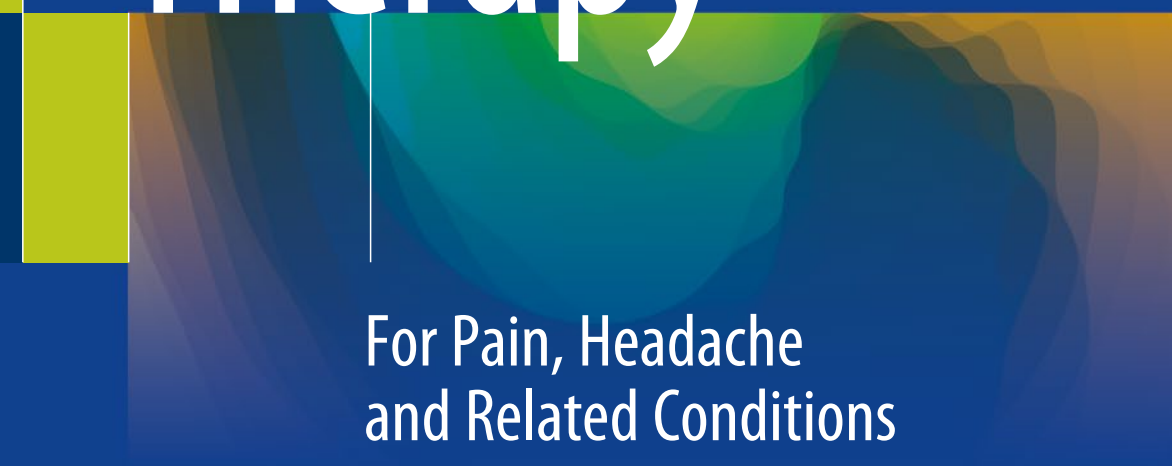
Infusion Therapy



For Pain, Headache and Related Conditions

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Editor

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I would like to dedicate this book to my parents, my wife and my two beautiful kids Maro and George

Preface

Dear Reader:

I have found various infusional therapies to be increasingly useful in my pain management practice, and many patients who had failed other types of treatments responded to this modality. As my use of infusional treatments for pain has expanded, so has my awareness of the limitations on guidance for this type of treatment. In many cases, the use of a specific drug as an intravenous or subcutaneous is not a part of the FDA-approved labeling of the drug. In other instances, the use of a drug parenterally may be accepted and approved, yet the reason for the use of the drug is not part of the labeling. An example is the increasing use of intravenous lidocaine for the treatment of pain instead of its formally approved use for cardiac arrhythmias. Rigorous blinded and controlled studies may not be supported for drugs that are generic and relatively inexpensive, so in many cases one's off-label use of an infusional therapy is based upon reported cases or case series. In addition, the novel application of drugs to diseases outside of our typical practice may provide insight into how the drugs might have application to our own patient population.

The goal of this book is to provide an overview of various intravenously infused medications that can serve as a summary of current practice. In many examples in this book, the applications and use of the drugs are familiar and FDA-approved. In others, often with the same drugs, the authors seek to provide a summary of less formalized, yet hopefully useful applications of the medications. A brief overview of the pharmacology of the drugs is provided, which may provide both useful review and education on newer mechanistic discoveries that support the use of the medication. Monitoring guidelines, typical doses and titration processes, and cautions are included as well, with the intent of providing the practitioner a useful resource for their practice.

It should be cautioned that the off-label use of infusional therapies may meet resistance by insurers of health care. While a publication such as this may provide support for reimbursement for the off-label use of a medication, consideration of the financial impact of novel infusional treatments may be necessary on an individual basis.

Finally, like all publications, this is a work that reflects practice at a point in time. While the authors here present their best interpretation and recommendations for

the use of medications covered in the various chapters, it must be recognized by the reader that much of this practice will change over time. Professional judgement must prevail on behalf of the individual patient.

Madison, WI, USA Alaa Abd-Elsayed

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Paul R. Hutson and Alaa Abd-Elsayed

Introduction

Lidocaine is an amide local anesthetic that was found in the 1950s to have antiarrhythmic effects when infused intravenously. Lidocaine is still used for this purpose but is usually reserved for patients with ventricular arrhythmias who fail to adequately respond to amiodarone [1]. In current practice, intravenous infusions of lidocaine are more commonly used for the treatment of neuropathic pain. Local infiltrations are obviously used for pre-procedural anesthesia and may be used post-procedure to decrease pain and the need for opioid analgesics. Lidocaine may also be used topically, such as with cutaneous patches, or as an oral rinse for patients with pain from mucositis.

Lidocaine is metabolized by CYP1A2 and CYP3A4 in the liver to its active metabolites MEGX, glycinexylidide (GX), and N-ethylglycine (EG) [2, 3]. MEGX is considered to have slightly less activity than lidocaine as an inhibitor of the Na-channel [2]. MEGX and the other metabolites are considered to have greater analgesic effects on other pathways of neurotransmission such as the glycine receptor than does the parent drug.

Dosing adjustments are not needed in the presence of mild-moderate renal impairment, and even patients who demonstrate severe impairment of kidney function may benefit from a single dose of systemic lidocaine for neuropathic pain that has been reduced by 50% [4, 5].

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Mechanism of Action

Lidocaine is known to be an inhibitor of the voltage-gated sodium (Na) channel (VGSC) of both peripheral nociceptive and dorsal root neurons [6, 7]. The action of lidocaine and its active metabolite (MEGX) upon the VGSC leads to an inhibition of depolarization and hence an inhibition of neurotransmission. It is this inhibition of the VGSC that is considered to provide the antiarrhythmic action of lidocaine [2]. MEGX is considered to have approximately 80% of the activity of lidocaine in inhibiting the VGSC. The potency of the GX and N-ethylglycine (EG) in inhibiting the VGSC is less well characterized, but is considered to be minimal.

In addition to the inhibition of the VGSC, other mechanisms of action may be responsible for the anti-nociceptive and analgesic effects of lidocaine. MEGX, GX, and EG were all found in *in vitro* models to inhibit the uptake of the neurotransmitter amino acid glycine by the GlyT1 glycine transporter [8]. The inhibition of GlyT1 by GX and EG was shown to be competitive, whereas the concentration-dependent inhibition by MEGX was more mechanistic. The increase in synaptic glycine is suggested to decrease hyperalgesia and neuropathic pain by action at spinal inhibitory glycine receptors [8].

Lidocaine also demonstrates anti-inflammatory effects, but it is not clear to what extent the parent drug is responsible for these effects as opposed to the action of the metabolites. Doses of lidocaine have been shown to decrease granulocyte adhesion, migration, and activation [9]. Effects upon cyclooxygenase are not well described.

Indications

FDA-approved labeling includes its use for local and regional nerve blocks by local infiltration. Lidocaine hydrochloride injection administered intravenously or intramuscularly is also indicated in the acute management of ventricular arrhythmias such as those occurring in relation to acute myocardial infarction, or during cardiac manipulation, such as cardiac surgery [1, 10]. There is no formal FDA-approved indication for the intravenous administration of lidocaine for the treatment of pain. Although this does not prevent the use of lidocaine for this purpose, it may complicate the reimbursement for such use.

Post-herpetic and Peripheral Neuropathic Pain

The use of short IV infusions of lidocaine has been shown to decrease pain scores or the area of allodynia in patients with nerve injury or host-herpetic neuralgia [11–15]. A 2005 Cochrane review found that the preponderance of the evidence from evaluable studies indicated that systemic (IV) lidocaine provided statistically significant improvement in pain [16]. The Cochrane review was impaired by a variety of sources of neuropathic pain that included post-herpetic pain, traumatic nerve injury, neuropathy secondary to cancer, and diabetes. No studies with extended

infusions have been reported for this use, and the duration of any benefit appears to be short, often returning to baseline within 24 hours.

Wallace found that concentrations of at least 1.5 mcg/mL were associated with an analgesic response (pain VAS and mechanical allodynia) with a multi-dose concentration-targeted infusion study [17]. This was an unusual approach to dose escalation, contrasting with other studies that tested different doses or infusion rates [18]. None of the clinical trials reviewed by Challapalli et al. in the Cochrane meta-analysis [16] appeared to administer a sustained, multiple-day infusion of lidocaine.

Attal and colleagues compared the effect of 5 mg/kg lidocaine infused over 30 minutes to placebo in 22 adults with post-herpetic neuralgia or peripheral nerve injury and found a significant difference in relief from spontaneous pain that lasted up to 6 hours [19]. The response to lidocaine was greatest in patients with substantial mechanical allodynia. Attal et al. also found that the administration of oral mexiletine yielded a higher analgesic benefit in patients with mechanical allodynia associated with their neuropathy [19]. Similarly, an analgesic response to IV lidocaine predicts a benefit from orally administered mexiletine used as a form of outpatient maintenance of the analgesia [20].

In a double-blind comparison of placebo vs lidocaine doses of 1 and 5 mg/kg infused over 2 hours, Baranowski found that there was no difference in either spontaneous or evoked pain between any of the three treatment arms [14]. However, the area of any allodynia decreased after the lidocaine treatments, and there was not a significantly greater effect with the higher dose of lidocaine. In contrast, Tremont-Lukats et al. noted that there appeared to be a significant difference in the response to peripheral nerve pain or CRPS when lidocaine was infused over 6 hours at 5 mg/kg, but not at 1 or 3 mg/kg [18]. This was a double-blinded but parallel arm study, and it is not known what impact the longer, 6-hour infusion may have played in the response.

Some patients find relief from post-herpetic neuralgia using 5% lidocaine patches or plasters that can correctly be assumed to deliver lidocaine at a rather constant rate similar to an IV or subcutaneous infusion. Pharmacokinetic sampling in patients with varying numbers of such topical dosages of lidocaine suggests that plasma concentrations are substantially lower than those achieved by typical doses of intravenous lidocaine infusions [21].

Complex Regional Pain Syndrome

Several case series suggest a benefit from more prolonged exposure to systemic lidocaine in some patients with Complex Regional Pain Syndrome (CRPS) [11, 22]. Linchitz reported a series of nine patients with a duration of CRPS of 30–96 months [22]. Four of the nine subjects were not able to complete the treatment, two for lidocaine hypersensitivity, and two for what were termed unrelated causes. The five remaining patients received a subcutaneous infusion of lidocaine at an initial rate of 200 mg/hr for 1 hour, followed by an infusion of 100–190 mg lidocaine per hour.

The SC lidocaine was continued for 4–5 days after the maximal decrease in pain expressed by the subject. Durable responses were found with these prolonged infusions, and patients could restart the infusions at home if pain recurred. The authors suggest that the response and durability of the response was due to the extended duration of the infusion compared to the typical 30–60 minute IV infusion. There was no apparent benefit of the subcutaneous route other than the convenience and safety of this route compared to IV dosing.

Similar to the 5-day subcutaneous lidocaine infusion reported by Lipchitz, Schwartzman et al. published a retrospective case series of 49 patients suffering from CRPS who received a 5-day IV infusion of lidocaine titrated to a concentration in plasma of 5 mg/L [23]. Seventy-six percent of the subjects reported at least a 25% reduction in pain score on the 0–10 NRS, and 31% reported more than a 50% reduction in NRS pain score. Other components of CRPS such as allodynia, cold sensitivity, and muscle weakness and spasms also improved to a statistically significant degree. The improvement in the pain and other CRPS-associated symptoms was maintained for 3 months, but after 6 months was no longer statistically significant. The intent was to establish a plasma lidocaine concentration of 5 mg/L, yet at the end of the 5-day IV infusion the mean lidocaine concentration was only 3.4 ± 1.3 mg/L. The concentrations of MEGX and other lidocaine metabolites were not mentioned [23].

Erythromelalgia

Erythromelalgia is a rare disease characterized by red, painful extremities. The symptoms may be intermittent, and affected patients will often try to decrease the pain and burning sensation by immersing the extremity in cold or iced water. Various pharmacologic interventions have been reported in multiple case series. Intravenous lidocaine has been reported to be helpful in an 11 year old boy for whom other drug treatments had failed [24]. Lidocaine infusion was begun at 16.5 mcg/kg/minute, and titrated upward to establish plasma lidocaine concentrations of 2–5 mg/L. After the pain was suppressed so that he had 4 nights of restful sleep, the lidocaine infusion was stopped and replaced with oral mexiletine, another inhibitor of the VGSC. The child is described to have had a durable remission of the pain with mexiletine concentrations of 0.7–1.4 mg/L. Recent data suggest that the responsiveness of erythromelalgia pain to lidocaine and mexiletine may be a function of the specific polymorphisms of the sodium channels associated with this disease [25].

Fibromyalgia

Three reports of the use of intravenous lidocaine suggest benefit in some patients diagnosed with fibromyalgia. A study of 5 mg/kg lidocaine infused over 30 minutes in 12 adult patients showed a durable reduction in pain for 4–7 days in patients who had a response [26]. The drug was well tolerated, and in some cases allowed

improvement in muscle strength. Raphael et al. prospectively and retrospectively reviewed the cases of 156 fibromyalgia patients who received lidocaine as short infusions over 6 consecutive days in increasing doses [27]. There were 42 minor side effects noted, most commonly hypotension, and one patient in the 106 subjects evaluated prospectively developed supraventricular tachycardia. Another experienced pulmonary edema, yet all the adverse events resolved with no long term sequelae. Only 4 of the 50 patients studied prospectively felt that the lidocaine was not a worthwhile treatment, with 32 indicating that it was very worthwhile. NRS pain scores decreased from an average of 9 to 5, and the median duration of any pain relief was 11.5 weeks, ranging from 0 to 36 weeks.

Schafranski [28] reported a series of 23 adult patients treated with daily, increasing infusions of lidocaine increasing from 2 to 5 mg/kg administered over 2 hours. In contrast to the Raphael series, no side effects were observed after any of these doses, and all subjects appeared to have received all five intended doses. Significant improvement in the Visual Analog Pain Scale and in the Fibromyalgia Impact Questionnaire was found and persisted for at least 30 days.

Peri-operative Pain

Systemic infusions of lidocaine have been administered peri-operatively with the intent of decreasing post-operative pain, opioid needs, and ileus. Weibel and colleagues recently provided an updated Cochrane review of this use of lidocaine [29]. Their review included 68 trials with 4525 randomized participants. The analysis was complicated by a multiplicity of surgery types, lidocaine doses and infusion durations. Most lidocaine infusions were in the familiar range of 1–5 mg/kg. Some trials used a bolus at the induction of anesthesia or at first incision, and others started the lidocaine at the end of the surgery. Some infusions did not continue beyond the end of anesthesia, others were maintained from 1 to 24 hours postoperatively [30].

These and other reviewers found the clinical studies of perioperative lidocaine to be generally small and of poor methodologic quality [29, 31]. In cases wherein a decrease in pain or post-operative opioid demand were noted, the magnitude of any benefit was considered clinically non-significant. The average 8 hour reductions in the time to first defecation as a marker of effects on ileus was not considered to be of substantial clinical significance. There was no effect of peri-operative lidocaine on the time to discharge following either outpatient or inpatient surgical procedures.

Sickle Cell Pain

Only one report was found that reported benefit of treating the pain of sickle cell crisis with intravenous lidocaine. Nguyen [32] and colleagues retrospectively identified 11 patients who had received IV lidocaine for pain for a total of 15 courses. Eight of the 15 treatment trials decreased pain scores by at least 20% and reduced

opioid needs by over 30%. Rather than a short infusion (30–60 minutes), these infusions of lidocaine were run over 2–8 days at rates of 0.5–1.9 mg/kg/hour. Two patients experienced reversible confusion and dizziness.

Pediatric Use

The use of systemic lidocaine for the treatment of pain in children is not common, but appears to be safe and similarly effective as in adults. The previously mentioned report of benefit of a prolonged IV lidocaine infusion in an 11 year old boy included titration of rate to a target concentration of 2–5 mg/L with no reported side effects [24]. After demonstrating a response to lidocaine the child was successfully transitioned to an outpatient regimen of oral mexiletine. Massey et al. reported a case of a child with refractory cancer-related pain who was treated with a continuous lidocaine infusion [33]. The infusion of lidocaine initiated at 2.1 mg/kg/min was able to displace a sufentanil infusion of 18 mcg/kg/hour, and was continued at rates up to 3.8 mg/kg/hour after discharge to the patient's home with no significant adverse effects.

Gibbons, et al., reported four cases of children with severe, opioid-refractory pain who responded to prolonged IV lidocaine infusions that averaged 2.2 days in length and ranged from 5 hours to 17 days [34]. Lidocaine infusions were started at a rate of 1.8 mg/kg/hour and adverse effects were mild and reversible. As is described by others, the relief from pain was greatest in those patients who had the most severe pain prior to the treatment, and relief was durable for weeks to months.

In a recent review, Lauder reported on the experience of using intravenous and subcutaneous lidocaine in children suffering from chronic pain [3]. Of the 45 children considered appropriate for a trial of intravenous lidocaine (73% with neuropathic pain or CRPS), 73% had a significant reduction in pain and improvement in function. The response of different types of pain to lidocaine was not described, but the children tolerated the escalating infusions well.

Emergency Department Use

Silva and colleagues performed a systematic review of reports of the use of lidocaine in the Emergency Department [35]. In general, most studies were small, inconsistent in their reporting of doses and of rescue doses of opioids or nonsteroidal anti-inflammatories (NSAIDs), and unblinded. Of the 61 articles meriting close examination, only 6 were considered sufficiently randomized and blinded to provide insight into the utility of IV lidocaine for severe pain. Their review and others suggests that lidocaine was not better than placebo for the treatment of migraine headaches [35, 36]. IV lidocaine was found to have good analgesic benefit in patients with renal colic or critical limb ischemia, equaling or exceeding the benefit of opiates or ketorolac. A separate Cochrane review found equivalent benefit of opioids and NSAIDs for renal colic [37]. The Silva review suggests that IV lidocaine can be considered as first line analgesia in such patients who may have a

relative or absolute contraindication to receive opioids or NSAIDs, but larger, well-controlled studies are needed to support this premise.

Subcutaneous Infusion

The use of extended subcutaneous infusions of lidocaine have been reported in several case series [22, 38, 39]. The limited number of published case series have, in some instances, utilized an intravenous bolus to demonstrate benefit of the lidocaine, followed by a subcutaneous infusion to simplify outpatient treatment with the drug. The use of subcutaneous infusions provides the convenience and safety of avoiding the need for a permanent venous catheter or changing peripheral venous catheters.

The rate of subcutaneous infusion is the same as for intravenous infusions, typically starting at 100 mg/hr. The 10% w/v lidocaine concentration in the infusate for subcutaneous infusions is higher than that used for intravenous infusions to minimize the volume required for drug delivery. This higher lidocaine concentration poses a risk if the bag intended for subcutaneous infusion is mistakenly infused intravenously at flow rates appropriate for the typical IV infusion concentrations of 0.8% (2 gm lidocaine in 250 mL). Preservative-free lidocaine must be used for both intravenous and subcutaneous infusions.

Durations of subcutaneous infusions have varied from days to weeks, and even months. The infusions are generally well tolerated, with the nature and incidence of adverse effects similar to that of intravenous infusions. Once discontinued, the duration of benefit of the prolonged lidocaine infusion upon improved analgesia can be very durable [22, 39].

Contraindications

Lidocaine is contraindicated in FDA-approved labeling in patients with a known hypersensitivity to amide-type local anesthetics. A 12-lead electrocardiogram (ECG) is usually performed to rule out abnormal conduction pathways prior to the first administration of an intravenous infusion of lidocaine for the purpose of treating neuropathic pain. Although not formalized, the use of intravenous lidocaine should be avoided in patients for whom administration of mexiletine or flecanide is contraindicated. These drugs are contraindicated in patients in whom an ECG demonstrates pre-existing second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block) unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur [6]. Continuous cardiac telemetry is not a standard of care for lidocaine infusions for the treatment of pain [40, 41].

Formulations of lidocaine containing epinephrine must not be administered by IM or intravenous injection and are intended only for local anesthesia. Similarly,

only preservative-free formulations of lidocaine can be used for systemic administration.

Hepatic impairment and heart failure can be expected to decrease the clearance of lidocaine to its metabolites. The decrease in elimination rate is reported to be as much as 40% [42]. This decrease in clearance does not prohibit the use of lidocaine, but if extended infusions are intended beyond 60 minutes the initial infusion rate should be decreased and then escalated based upon combined plasma concentrations of lidocaine and MEGX.

Side Effects

Acute adverse events with systemic lidocaine infusions for the treatment of neuropathic pain or hyperalgesia are common and concentration dependent [43–45]. Commonly the initial side effects are peri-oral numbness, altered taste, and slurring of speech. Mental confusion can occur, and if concentrations are sufficiently high, cardiac arrhythmias, hypotension, loss of consciousness and even seizures may be precipitated. Fortunately, such severe effects are uncommon in patients treated with systemic lidocaine for pain and resolve with supportive care [46].

The anti-arrhythmic, systemic analgesic, and adverse effects of systemic lidocaine are considered to be related to the concentration of lidocaine and of its metabolites. The rate of lidocaine infusion (e.g., delivery of the same dose over 30 minutes vs 60 minutes) is therefore expected to affect the incidence of side effects. This is illustrated in Fig. 1.1 comparing the effect of infusing a 500 dose of lidocaine over 30 minutes (blue, dashed line) instead of 60 minutes (solid orange line).

Using published pharmacokinetic parameters to estimate the concentration time curve [47], the initial, rapid decline in concentration from the distribution phase of

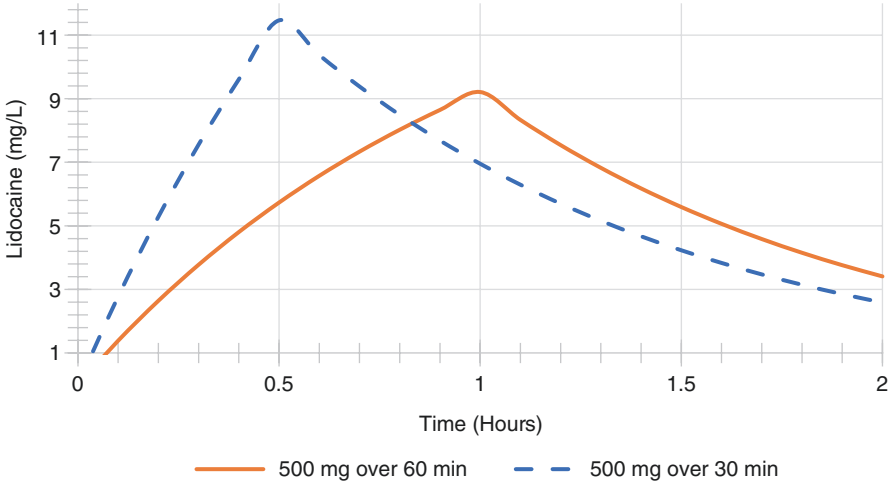

Fig. 1.1 Effect of increasing duration of infusion on peak lidocaine concentration

lidocaine is noticeable for both infusion times. The peak concentration of lidocaine is lower with longer infusions because the slower infusion rate permits both more metabolism and distribution of the drug from plasma to tissue. Decreasing the rate of lidocaine infusion can be expected to reduce the incidence of adverse events, and stopping an infusion that is causing unwanted effects usually leads to prompt dissipation of minor side effects such as confusion and peri-oral numbness. Table 1.1 lists the adverse effects noted in a retrospective chart review of adult patients receiving lidocaine for the treatment of pain at an initial, fixed dose of 500 mg infused over 30 minutes (16.7 mg/min, or approximately 14 mg/kg/hour) [43].

Adverse effects reported in Table 1.1 are given as the percentage of 69 lidocaine-treated patients who experienced each side effect. The starting infusion rate was 16.7 mg/min, and was reduced in patients who experienced adverse effects as this dose. Side effects were reported by the either the patient or the administering nurse. The same patient may be represented multiple times at different infusion rates. The average infusion rate of the infusion that the patient experienced the adverse effect is also reported in mg/min. No ECG monitoring was performed during any infusions [43].

At the onset of symptomatic side effects of lidocaine and its metabolites, the usual policy should be to stop the infusion until the adverse effects dissipate. If the side effects were not serious, the remainder of the lidocaine infusion can be re-started at 50% of the previous rate. If patients demonstrate an analgesic benefit from lidocaine infusions, they may be willing to tolerate some level of dysgeusia and

Table 1.1 Lidocaine side effect incidence

Side effect	Percentage of patients affected	Average infusion rate at which side effect occurred (mg/min)
Total	79.7	13.1
Lightheadedness	44.9	14.5
Other	39.1	14.4
Dizziness/vertigo	30.4	13.0
Peri-oral numbness	23.2	13.7
Speech disturbance	23.1	15.3
Clumsiness/ incoordination	18.8	11.1
Nausea/vomiting	15.9	11.6
Sedation/lethargy	13.0	13.4
Headache	8.7	13.5
Peripheral numbness/ dysesthesias	8.7	13.4
Tinnitus	5.8	16.7
Confusion	2.9	12.8
Tingling	2.9	16.7
Delirium	1.4	11.7
Metallic taste	1.4	16.7
Muscle twitching	1.4	7.8
Arrhythmia	0	N/A

peri-oral numbness in later infusions, but ideally a rate can be found that provides analgesic benefit without bothersome side effects.

Serious events such as seizures, coma, and/or cardiac arrhythmia and collapse have been described with lidocaine infusions or by local infiltration. These are typically idiosyncratic events, or the result of excessive doses. Seizures are rare and are usually preceded by more common prodromal signs and symptoms, yet 20% of patients experiencing a seizure associated with lidocaine did not demonstrate a prodrome [46]. Airway support and oxygenation must be assured if a seizure occurs. Seizures can be treated with a benzodiazepine such as lorazepam, since the use of benzodiazepines are not expected to affect the risk of cardiac arrhythmias. In cases of cardiovascular collapse, the intravenous administration of small (10–100 mcg) boluses of epinephrine are preferred to a larger bolus. Vasopressin and calcium channel blockers are not recommended [46].

Intravenous infusion of 20% lipid emulsion is recommended in cases of severe lidocaine toxicity [46]. The lipid emulsion is presumed to sequester the lidocaine in the lipid emulsion, removing it from the aqueous plasma phase. The ASRA guidelines recommend an IV bolus of 1.5 ml/kg of 20% lipid emulsion, followed by an infusion of 0.25 ml/kg/min for at least 10 minutes after the return of cardiovascular stability. It is obvious that in such instances the infusion of lidocaine should be halted. The administration of subsequent doses of lidocaine after resolution of the adverse effects should only be allowed if the patient showed substantial analgesic benefit, and if the reason for the adverse event can be adequately explained and subsequently avoided.

Monitoring

In addition to inquiring about adverse events arising from prior exposure to lidocaine or other amide anesthetics, a 12-lead ECG should be performed before deciding to implement an intravenous infusion of lidocaine. The presence of second- or third-degree conduction defects or right bundle branch block are usually contraindications for lidocaine infusions. The administration of lidocaine in such patients with continuous, monitored cardiac telemetry may be an option, but the literature to date does not provide a useful guide to the safety and utility of lidocaine infusions for pain in these higher risk patients. Although continuous cardiac telemetry is likely performed at some sites infusing lidocaine and is considered “essential” in the FDA-approved labeling of its use as an anti-arrhythmic [6], it is not a routine component in most reports of lidocaine for neuropathic pain [6, 7]. A physician or other qualified health care professional should be immediately available to diagnose and treat serious adverse events arising from lidocaine infusions regardless of whether telemetry is used.

The timing of blood sampling for lidocaine concentrations is problematic in that such patients are commonly treated as outpatients. There is an eagerness on the part of the patient to depart the infusion center after the completion of a short infusion, and for the facility to cycle the chair for the next patient. As can be seen in Fig. 1.1, there is a rapid decrease in the concentration of lidocaine after the conclusion of the

infusion. Inconsistency in the timing of blood samples after the end of the infusion will therefore lead to dramatically different drug concentrations. Waiting for 1 hour to allow distribution of the drug to the tissue compartment should result in more reproducible results, but may not reflect the utility of the dose as manifested by the peak concentration of the infusion. It is also much more inconvenient for the patient who is asked to stay for a blood sample. Blood sampling just prior to the end of the infusion or collected during the infusion after the onset of adverse events may be informative, but if possible, should be collected from the arm opposite the lidocaine infusion. Blood samples collected from the same IV catheter and tubing as was used for the infusion itself are likely to yield inappropriately high drug concentrations due to the desorption of drug from the tubing.

Lidocaine concentrations of at least 1–2 mg/L are considered necessary for the anti-arrhythmic effect of the drug, and concentrations of at least 5 mg/L have been reported to be needed to control arrhythmias. Lidocaine and MEGX concentrations are not routinely obtained during short infusions of lidocaine for the treatment of neuropathic pain, and no systematically-collected concentrations of both lidocaine and MEGX have been reported for the treatment of neuropathic pain. Modification of the lidocaine infusion rate based upon drug concentrations is impractical when administered as a 30–60 minute intermittent infusion but may be useful in assuring an adequate therapeutic trial and minimizing adverse effects during a more prolonged infusion. Blood sampling to obtain lidocaine and MEGX concentrations may be useful in patients experiencing unusual adverse effects, but usually adverse events are empirically addressed by a decrease in the infusion rate of their subsequent doses of lidocaine. Conversely, blood samples for lidocaine and MEGX concentrations may be helpful in determining whether an unsuccessful treatment with lidocaine for neuropathic pain failed because the usual, empiric dose yielded atypically low concentrations in a given individual. Many clinical laboratories will report both lidocaine and MEGX concentrations, since both are considered roughly equivalent in their inhibition of the voltage-gated sodium channel. Although they may play an active role in the analgesic effects of lidocaine infusions, assays of the GX and EG metabolites of lidocaine are not typically available.

Lidocaine and MEGX are bound to alpha-1-acid glycoprotein (AAG), a heat-shock protein that can demonstrate substantial variation in concentration after burns, trauma, surgery, and other acute events [48]. Higher concentrations of AAG lead to higher total concentrations of lidocaine and MEGX, yet the unbound, active concentrations may not vary substantially with AAG concentration. High AAG concentrations and associated higher plasma lidocaine and MEGX concentrations may be misinterpreted and lead to inappropriate reduction in lidocaine infusion rates. Furthermore, the relative contribution of lidocaine, MEGX, EG, and GX for the treatment of neuropathic pain has not been described.

Inhibition of the metabolism of lidocaine can arise from interactions with various drugs and by decreased hepatic blood flow. Patients with heart failure or severe hepatic cirrhosis can be expected to have a slower clearance of lidocaine to its metabolites [8]. Similarly, propranolol and other drugs that decrease cardiac output have been shown to decrease lidocaine clearance [49]. Drugs such as fluvoxamine

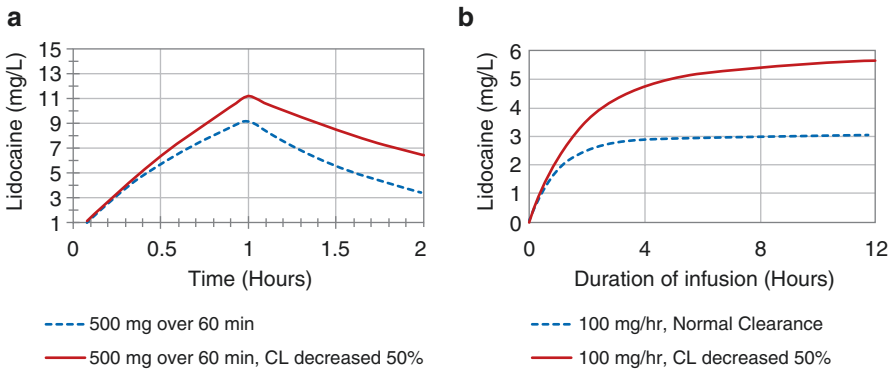

Fig. 1.2 Comparison of the effect of decreased lidocaine clearance on a short vs prolonged infusion. *Note: Panel A shows the effect of a decrease in lidocaine clearance upon the maximum (end of infusion) concentration after a 60 minute infusion of 500 mg. Panel B shows the greater effect of the same decrease in clearance upon lidocaine concentrations from an extended IV infusion of 100 mg/hr*

and ritonavir are examples of drugs that will inhibit the metabolism of lidocaine by inhibiting CYP1A2 and CYP3A4, respectively [50]. In addition to slowing the removal of lidocaine after a single, short infusion, such enzyme inhibitors may decrease the efficacy of lidocaine for hyperalgesia or neuropathic pain by decreasing the amount of active lidocaine metabolites.

The effects of analgesic effects of multiple-day IV lidocaine infusions are noted at infusion rates (1–3 mg/kg/hour) that are substantially lower than the more common rapid, intermittent IV dosing of drug (5 mg/kg over 30–60 minutes, or 5–10 mg/kg/hour). The clinical relevance of disease- or drug-related slowing of lidocaine metabolism during and after 30–60-minute infusions is not clear. Toxicity arising from reductions in lidocaine clearance to its active metabolites is of much greater importance during longer infusions of lidocaine (1–5+ days) in which substantial accumulation of drug and metabolites may occur. In contrast, the peak concentration of the intermittent infusions of lidocaine administered for the treatment of neuropathic pain is more a function of the rate of distribution. As illustrated by the solid, red line in Panel A of Fig. 1.2, a 50% decrease in lidocaine elimination rate can be expected to only slightly increase the end-of-infusion peak concentration of a 60-minute infusion of 500 mg. In contrast, the same 50% decrease in lidocaine clearance would be expected to increase the steady-state lidocaine concentration of an extended, multi-day infusion by two-fold, illustrated in Panel B.

Algorithms for Lidocaine Infusion Regimens

The following table summarizes proposed algorithms for infusion regimens based on current published literature (Table 1.2)

The duration of any analgesic response will guide the frequency of subsequent infusions. These repeat infusions may occur multiple times weekly, or several times

Table 1.2 Algorithm for lidocaine infusion regimens

Indications	Lidocaine infusion
All discussed indications	Loading dose: 1 mg/kg [3] Day 1: 5 mg/kg over 60 minutes Day 2: 7 mg/kg over 90 minutes Day 3: 9 mg/kg over 90–120 minutes
	No loading dose [7, 48] 5 mg/kg over 60 minutes
	No loading dose [13, 43] 500 mg over 30 minutes

monthly. If a patient responds for only a short time, a continuous IV or subcutaneous infusion may be helpful. Unless other findings suggest them, 12-lead ECGs are not required after the screening for the first infusion. If side effects occur during the lidocaine infusion the infusion should be stopped, and if the symptoms were minor and resolve, the infusion can be re-started at 50% of the original rate. Blood sampling for lidocaine and MEGX is not typically indicated but may be helpful to guide continuous infusion rates. Such continuous infusions may be titrated to achieve a combined lidocaine + MEGX concentrations of approximately 5 mg/L, although higher concentrations may provide additional benefit. Case series in CRPS, erythromelalgia, and sickle cell disease suggest that the infusion of lidocaine over several days may provide greater, more durable analgesia than short infusions: this has not been confirmed in controlled clinical trials and may be associated more with accumulation of the EG and GX metabolites than of the parent drug lidocaine. With this in mind, if the effects of lidocaine are dramatic but dissipate quickly, continuous intravenous or subcutaneous infusions may be considered.

Summary

Systemic infusions of lidocaine in general will often reduce the severity of peripheral neuropathic pain, although the duration of benefit may be modest. Although specific case series demonstrate some variability in regimens, most converge on an infusion of 5 mg/kg lidocaine delivered over 30–60 minutes intravenously. If patients do not respond to their first dose, an escalation to 7.5 mg/kg may be tested.

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Ketamine Infusion Therapy

2

Matt Fischer and Alaa Abd-Elsayed

Introduction

Ketamine, an analog of phencyclidine that antagonizes the N-methyl-D-aspartate (NMDA) receptor, is not a novel medication. It has long been employed for induction of general anesthesia, a role that continues to this day given its favorable hemodynamic profile as well as its preservation of independent ventilation. Recently, however, it has seen an explosion in use across a variety of clinical subspecialties including anesthesiology, critical care, emergency medicine, pain medicine, and psychiatry.

Consensus Statements and/or Guidelines have been issued by the American Society for Regional Anesthesia (ASRA), the American Academy of Pain Medicine (AAPM), the American Society of Anesthesiologists (ASA) and the American Psychiatric Association (APA), on the use of ketamine for acute pain ("Acute Pain Guidelines" [1]), chronic pain ("Chronic Pain Guidelines" [2]), and mood disorders ("Mood Disorders Consensus Statement" [3]). Although these documents do not embody all possible indications for ketamine use, they do provide comprehensive evaluation of the current state of evidence surrounding ketamine as infusion therapy. As such, they feature prominently in this chapter.

Mechanism of Action

Ketamine exerts its effects through multiple pathways. Most notably, it is an antagonist at the NMDA receptor in the central nervous system, a glutamate receptor involved in both pain and mood. However, it is not the effect at the NMDA receptor

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alone that mediates ketamine's analgesic and antidepressant effects; for example, investigation of other NMDA antagonists has not shown antidepressant effects similar to ketamine's [4]. In fact, ketamine has activity at myriad other pathways ranging from direct channel receptors to downstream gene expression. Selected targets include anticholinergic effects, increased levels of norepinephrine and dopamine leading to sympathomimetic effects, modulation of opioid pathways, and suppression of pro-inflammatory cytokines [5]. Its interaction with opioid receptors is especially interesting: Williams et al. (2018) showed that pre-treatment with the opioid-receptor antagonist naltrexone can eliminate the short-term antidepressive effect of ketamine infusion as well as significantly attenuate long-term effects [6]. This echoes findings that opioid antagonism can also minimize analgesic effects of ketamine [7].

Indications

Evidence is available to support the use of ketamine in acute pain states, chronic pain states, mood disorders, and analgosedation in the critical care setting. Despite lack of high-level evidence, ketamine is likewise employed as adjunct to opioid taper. Although it can also be used in higher doses for induction of general anesthesia, and in lower doses for procedural sedation, these indications are not discussed in this chapter.

Perioperative Use/Acute Pain

Sub-anesthetic ketamine has been demonstrated as an effective contributor to multimodal analgesia in the perioperative period for numerous surgical procedures. Multiple randomized controlled trials have evaluated the impact of ketamine in such scenarios, with endpoints often including pain scores as well as cumulative opioid requirements as compared to control therapies. Based on the results of these analyses, the Acute Pain Guidelines identify several classifications of patients who are likely to benefit from perioperative ketamine as adjunctive analgesia [1]:

- **Patients undergoing painful procedures**. It seems reasonable that the greatest opportunity for marginal pain relief will occur when there is a significant pain burden in the perioperative period. Put another way, a patient undergoing relatively painless surgery is not likely to derive much marginal analgesia from perioperative ketamine because there is not much effect size available to garner. One review of 70 randomized controlled trials identified service lines including thoracic surgery, abdominal surgery, and major orthopedic surgery as most likely to realize benefit from perioperative ketamine therapy [8].
- **Opioid-tolerant patients**. The largest randomized controlled trial investigating the impact of ketamine on postoperative pain scores and opioid consumption in opioid-tolerant patients demonstrated significant reductions in opioid consumption

both 48 hours and 6 weeks following major spine surgery [9]. Despite more modest results from smaller studies of similar patient cohorts, the summation of available evidence in this population has led ASRA and AAPM to label this cohort as mild-moderate benefit in its Acute Pain Guidelines [1].

- **Patients with obstructive sleep apnea**. Although most studies of perioperative ketamine as adjunctive analgesia do not specifically include postoperative respiratory depression among their endpoints, there is a demonstrated negative association between ketamine use and perioperative opioid requirement, and positive association between perioperative opioid requirement and incidence of respiratory depression in patients with obstructive sleep apnea. Therefore, the Acute Pain Guidelines recommend that ketamine may be considered as an adjunct to limit perioperative opioid consumption in patients with obstructive sleep apnea [1].
- **Patients with sickle cell disease**. Case series have reported improved analgesia during pain flares for patients with sickle cell disease who receive ketamine. Part of this benefit may be due to ketamine's effectiveness for opioid-tolerant patients, as opioids are commonly used by individuals with sickle cell disease. Despite the lack of randomized controlled trials addressing this clinical scenario, the Acute Pain Guidelines recommend that ketamine may be considered for opioid-tolerant patients with sickle cell disease [1].

Dosing protocols vary widely in the literature, but usually include a larger bolus dose followed by a smaller continuous infusion. The Acute Pain Guidelines note that rarely does a study of ketamine for acute pain use a bolus dose greater than 0.5 mg/kg and hourly infusion greater than 0.5 mg/kg/h. As such, recommended dosing includes bolus doses not exceeding 0.35 mg/kg and infusions not exceeding 1 mg/kg/h, with caveat that lower doses (e.g. 0.1–0.5 mg/kg/h) may be required to avoid untoward side effects especially in patients who are at increased risk due to various comorbid diseases [1]. Protocols vary as to whether ketamine is continued beyond the operating room, however the addition of ketamine infusion as adjunct to opioid patient-controlled analgesia (PCA) has been shown to improve pain scores and decrease cumulative opioid dose for up to 72 hours following surgery [10].

Chronic Pain

Ketamine's popularity for use in chronic pain states largely stems from the theory that it can reverse deleterious central sensitization and decrease opioid-induced hyperalgesia [11]. Use of ketamine in chronic pain states has been the subject of multiple blinded randomized controlled trials as well as review articles including, notably, the recent Chronic Pain Guidelines [2]. The specific trials will not be described here in detail but have explored the use of ketamine in such pain conditions as traumatic spinal cord injury, postherpetic neuralgia, phantom limb pain, migraine headache, complex regional pain syndrome (CRPS), and fibromyalgia, among other conditions. The Chronic Pain Guidelines summarize the evidence for indications as follows [2]:

- There is moderate evidence for medium-term improvements in pain (up to 12 weeks) related to complex regional pain syndrome. Specific protocols include ketamine infusions of 22 mg/h for 4 days, or 0.35 mg/kg/h for 4 hours repeated in 10 consecutive days.
- There is weak evidence for short-term improvements in pain related to spinal cord injury. One such protocol included ketamine total dose of 80 mg infused over 5 hours, although other investigators used varying approaches.
- There is weak or no evidence to support immediate improvements in pain for mixed neuropathic pain, phantom limb pain, postherpetic neuralgia, fibromyalgia, cancer pain, ischemic pain related to peripheral vascular disease, migraine headache, or low back pain.

Optimal dosing strategies are difficult to infer from such a heterogenous literature. In totality, the evidence suggests that duration of effect appears to be, at least in part, dose-dependent. For example, the Chronic Pain Guidelines contrast the duration effect of a single, low-dose bolus in fibromyalgia which results in only 3 hours of benefit, [12] to an intermediate dose of 80 mg/d for 1 week in spinal cord injury which results in 2 weeks of benefit [13], to a high dose of 0.35 mg/kg/h over 4 hours for 10 days in CRPS which results in sustained benefit through 12 weeks [14]. However, investigations in other chronic pain states have failed to show a dose-response relationship, and the marginal benefit from higher dose protocols must be weighed against the marginal risk of increased adverse effects, many of which are also proposed to be dose-responsive. At the far end of the dosing spectrum, ketamine has even been employed in anesthetic doses – to achieve a so-called "ketamine coma" – for treatment of refractory CRPS; while this had yielded some positive outcomes, its use is grounded in case reports [15] and an uncontrolled trial [16] and is not a widely accepted protocol at present. Given the totality of evidence, the Chronic Pain Guidelines recommend a starting point of at least 80 mg ketamine infused over at least 2 hours, with subsequent therapies, if warranted, based on clinical response [2].

Mood Disorders

Ketamine has been investigated as treatment for multiple psychiatric conditions, however the most promising results have occurred in treatment of major depressive disorder. A recent review [17] of seven randomized controlled trials investigating ketamine in this context is referenced in the Mood Disorders Consensus Statement. A recurrent theme in this Statement is that the current evidence is based on small, short-term investigations of its effects which leave several large gaps in the current knowledge base. However, although more and larger investigations will be required to fully elucidate safety features and optimal dosing strategies, the Mood Disorders Consensus Statement did propose several best practices for use of ketamine in treatment resistant depression.

The standard dosing for treatment resistant depression is 0.5 mg/kg actual body weight administered as intravenous infusion over 40 minutes, which is significantly lower than dosing regimens commonly employed for treatment of chronic pain states. Other strategies have been investigated with some evidence to suggest that lower doses were less efficacious than the standard of 0.5 mg/kg, however the quality of evidence is not sufficient for the Mood Disorders Consensus Statement to recommend dosing algorithms different than this standard regimen [3]. Much of the excitement surrounding ketamine's use in major depression is due to its rapid and reliable effect, however the benefit is transient, lasting only up to 7 days [18] or 2 weeks [17] following a single dose.

Opioid Use Disorder

By similar rationale as its application to chronic pain states, ketamine is also employed as adjunctive therapy for opioid tapering in settings of tolerance, side effects including neurotoxicity, or addiction. This theory has been tested in a controlled setting: Freye et al. (2006) demonstrated that ketamine could diminish central nervous system hyperactivity, as measured by EEG, during rapid opiate detoxification in otherwise-healthy subjects under general anesthesia [19].

In a case report, Strickler et al. (2018) describe use of ketamine infusion (at doses titrated from 5–20 mg/hr) to allow rapid inpatient tapering of a chronic opioid regimen; this individual's daily morphine equivalents decreased more than 66% over 1 week from his baseline daily dose of 400 mg without worsening pain scores or apparent withdrawal symptoms [20]. Quinlan (2012) describes 15 patients who underwent 100% taper of their chronic opioid regimen over 5 days while receiving subanesthetic ketamine infusion as inpatients, however doses are not specified in this report [21]. The evidence for ketamine as primary therapy for opioid taper is limited to case reports and case series, and pales in comparison to that supporting transition to methadone or buprenorphine-naloxone. Despite this absence of randomized controlled trials, its use as adjunctive therapy is supported by theory as well as these limited data.

Analgosedation in the ICU

Although not specifically the focus of this chapter, ketamine is also gaining popularity in the form of extended infusions to provide analgosedation in the intensive care unit and is included in the Society for Critical Care Medicine's 2013 Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in the ICU [22]. Reviews of randomized controlled trials have largely demonstrated the effectiveness of ketamine in this scenario, specifically related to reduction in opioid consumption and stable cardiorespiratory profile as compared to other medications classically used for analgosedation; caution remains given the possible

psychomimetic effects of ketamine and the potential impact to delirium in the intensive care unit [23]. The authors of this review suggest dosing via continuous infusion in the range of 0.06–1.2 mg/kg/h, with bolus doses available as needed in the range of 0.5–1 mg/kg for agitation, though they note that no consensus exists as to the maximum dose for continuous infusions [23].

Contraindications

At doses that are relevant in the context of this review, ketamine is well tolerated despite its sympathomimetic and neuropsychiatric effects. However, many of the trials investigating use of sub-anesthetic ketamine as adjunctive therapy have excluded individuals who may be high risk for untoward effects based on clinical history. Based on the totality of evidence, certain relative contraindications have been identified in the Acute Pain Guidelines, Chronic Pain Guidelines, and Mood Disorders Consensus Statement including [1–3]:

- Based on sympathomimetic effects:
  - cardiovascular conditions including unstable angina, uncontrolled hypertension, or high-risk coronary atherosclerosis
  - endocrine disorders including hyperthyroidism or pheochromocytoma
  - elevated intracranial or intraocular pressure
- Based on psychiatric effects, including potential for abuse with prolonged therapy
  - Delirium or psychosis
  - Active substance abuse
- Based on reports of transient, reversible hepatotoxicity
  - Severe liver disease
- Based on a lack of data on safety
  - pregnancy

Side Effects

The most commonly encountered adverse effects can be categorized as cardiovascular or neuropsychiatric [24]. Importantly, these effects tend to be transient, with >95% resolution following cessation of ketamine infusion by one investigation [25]. Caution must be taken for obese individuals and consideration given to dosing based on ideal bodyweight, as some reviews have determined that certain adverse effects are dose-dependent [26].

Administration of ketamine will generally produce side effects consistent with stimulation of the sympathetic nervous system. This can include bronchodilation and increased airway secretions which can increase risk for aspiration events if patients become obtunded, though loss of protective airway reflexes is rare at the subanesthetic doses reviewed in this chapter. More relevant is the propensity for

relative tachycardia and hypertension which could effect cardiac ischemia in predisposed patients. Central nervous system effects include perceptual or behavioral disturbance such as vivid dreams, hallucinations, or dysphoria, as well as impaired cognition and memory during acute exposure to ketamine. Investigations are conflicting as to the likelihood of these effects, however, with some authors finding no increase in psychiatric effects compared to placebo [27]. Reports have also demonstrated transient reversible elevations of liver enzymes following exposure to ketamine [24]. In addition, investigations of recreational users of ketamine have identified ulcerative cystitis as a potential adverse effect [28].

Patient Monitoring

Ketamine can induce a state of general anesthesia when used in high doses and, when used for this purpose, the American Society of Anesthesiologists standard monitoring of oxygenation, ventilation, circulation, and temperature should be employed. However this degree of monitoring is not typically required when ketamine is used in subanesthetic doses, as it produces a generally stable respiratory and hemodynamic profile in persons who are otherwise medically healthy. In studies of healthy volunteers reviewed in the Chronic Pain Guidelines, low-dose exposures to ketamine yielded no adverse respiratory events; observed adverse effects were rare and limited to cardiovascular (i.e. tachycardia and hypertension) or neuropsychiatric (i.e. related to ketamine's dissociative effect) systems. Based on these findings, consensus statements generally recommend that ketamine infusions be undertaken only with basic cardiorespiratory monitors including heart rate, blood pressure, and pulse oximetry. In addition, there should be individuals on site with the expertise and readily-available equipment to manage the potential adverse cardiovascular effects (e.g. training in Advanced Cardiac Life Support and advanced airway management) or behavioral effects of the infusions, as well as the ability to prescribe and dispense medications to counter these effects (e.g. benzodiazepines in the setting of severe dysphoria.) Because the doses employed in treatment of chronic pain states are typically higher than for treatment-resistant depression, the Chronic Pain Guidelines and Acute Pain Guidelines also recommend that administering providers be trained to administer conscious sedation [1, 2].

Despite its possible cardiovascular and hepatic adverse effects, randomized controlled trials have largely foregone laboratory or procedural interrogations prior to initialization of ketamine infusion therapy. For example, only one of 21 randomized controlled trials referenced in the Chronic Pain Guidelines obtained 12-lead electrocardiogram (ECG) prior to initialization of ketamine infusion therapy, and there were zero adverse cardiac events reported among the 20 patients studied [29]. And, despite reports of transient and reversible elevation in liver enzymes in response to ketamine infusion, no trials routinely obtain these as screening parameters prior to initiating therapy. Based on this data, the Chronic Pain Guidelines conclude that there is insufficient evidence for any laboratory or procedural investigation prior to initializing ketamine infusion therapy in healthy individuals, although selected

Table 2.1 Algorithm for ketamine infusion regimens

Indication	Dosing
Perioperative analgesia	0.35 mg/kg bolus, followed by 0.5 mg/kg/h infusion intraoperatively
Chronic pain states	80 mg infused over 2 hours
Mood disorders	0.5 mg/kg infused over 40 minutes
Inpatient adjunct to opioid taper	Continuous infusion 0.25–0.5 mg/kg/h
Analgosedation in ICU	0.5 mg/kg/h infusion, bolus dose 0.25 mg/kg PRN

investigations such as ECG or liver enzyme serologies may be considered on a case-by-case basis for those individuals deemed to be at elevated risk based on comorbidities [2].

Algorithm for Ketamine Infusion Regimens

The variety in dosing strategies present in the literature makes it difficult to identify any single approach as optimal (Table 2.1). As discussed above, there is some evidence supporting improved responses to higher dosages, but this dose-response relationship does not hold for all indications and consideration must also be given to the possibility of increased adverse effects at higher doses. It is critical that patients be continuously monitored by qualified personnel who have the expertise and authority to modify administration based on clinical response. Please review local protocols prior to initiating any infusion regimen.

Recommended minimum standard for outpatient infusion therapy include:

- Patient selection:
  - Thorough assessment of disease history as well as medical and psychiatric comorbidities
  - Obtain laboratory (e.g. liver function tests) or procedural (e.g. electrocardiogram) evaluations in high-risk candidates
  - Informed Consent
- Patient check-in on day of intervention:
  - Pre-intervention vital signs: heart rate, blood pressure, pulse oximetry, level of consciousness
  - Confirm appropriate nil-per-os (NPO) status
  - Ensure availability of qualified supervisory staff as related to:
    - Advanced Cardiac Life Support
    - Conscious sedation
    - Ability to manage possible adverse neuropsychiatric effects
- Intra-treatment
  - Periodic measurements of vital signs and level of consciousness
  - Continuous end-tidal CO_2 monitoring in patients deemed high risk for adverse respiratory events
- Post-treatment

– Vital signs and level of consciousness return to baseline prior to discharge

Summary

Ketamine as infusion therapy has seen increasing use across various conditions including acute pain, chronic pain, and mood disorders. Specific indications supported by literature include acute surgical pain of moderate-to-severe intensity, especially in those patients who are opioid tolerant or with known obstructive sleep apnea; sickle cell disease flares; chronic pain, especially in the context of neuropathic states such as complex regional pain syndrome and spinal cord injury; mood disorders, especially treatment resistant depression; and as adjunct therapy for opioid taper. The literature shows enormous variation in dosing strategies, and care must be taken to adjust doses based on patient characteristics as well as treatment response.

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Propofol Infusion Therapy

3

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Introduction

Propofol (2, 6 diisopropyl phenol) is a phenolic compound with a high lipid solubility and insoluble in water. Propofol is reformulated in an egg-oil-glycerol emulsion. Propofol is an in intravenous agent that leads to decreased level of consciousness and provides a lack of memory. Loss of consciousness is realized by the uptake of propofol into the central nervous system (CNS). It is used in general anesthesia as a part of total intravenous anesthetic (TIVA) regimen, as an induction agent, as a sedative agent for mechanically ventilated adults in the intensive care unit, and as a sedative for small procedures. It can also be used to treat severe postoperative nausea and vomiting and intractable seizures. Doses vary greatly based on its exact use, but induction doses range from 1.5 to 2.5 mg/kg. Maximum effect occurs in 2 minutes and lasts 5–10 minutes in duration.

Mechanism of Action

Propofol works via potentiation of the gamma-aminobutyric acid (GABA) receptor. It acts as a $GABA_A$ receptor allosteric modulator slowing down the channel closing time and at high doses in the absence of GABA it can act as $GABA_A$ receptor agonist. Propofol affects the chloride channels on the B_1-subunit of the GABA receptors [1]. GABA is an inhibitory transmitter in the central nervous system (CNS). Further, propofol analogs have been shown to act as sodium channel blockers.

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Propofol is roughly 98% bound to albumin, metabolized by the liver, and excreted via the urine. Propofol exhibits context sensitive half time for elimination; as a result, elimination time ranges from 2 to 24 hours. However, it's duration of action is much shorter than that because it is rapidly distributed into the peripheral tissues.

Indications

Acute Migraine Headaches

Acute migraine headaches can have debilitating effects. Acute migraine headaches account for roughly 2.1 million emergency department visits and incur over $600 million in annual healthcare costs [2, 3]. Therapy is often multimodal and includes agents that offer treatment of acute exacerbations and those that are for chronic maintenance to prevent exacerbations. Management is highly provider and patient specific with many different analgesic options, but no single best option [4]. Initial treatment may also utilize non-pharmacologic options such as oxygen and intravenous fluids.

Patients with migraines have a disturbance of serotonin metabolism. The antimigraine effect of potent agonists of the 5-HT receptors is via a reduction in neurogenic inflammation, and partially explained by the vasoconstrictive effect on meningeal, dural, cerebral, and pial vessels. The proximal parts of these large cerebral vessels carry nociceptive information to the thalamus and cortical pain areas. This is associated with a derangement of $GABA_A$ involved in causing migraine headaches [5]. Nishikawa et al. proposed that GABA exerts inhibitory control over central serotonergic neurons located in the raphe nuclei, which are involved in migraine pathology [5]. GABA receptors may also play a role in the regulation of the pain threshold in the trigeminal nucleus caudalis (TNC) [6]. Welsh et al. found that GABA was not detectable in the cerebrospinal fluid (CSF) during headache free periods, however, its metabolism was altered during migraine attacks [7]. These findings were confirmed in the saliva of a large group of patients who experienced migraines without aura [8]. Further, GABA receptors appear to have reduced activity in migraines [6]. One of the classic agents used is Valproic acid, which may work as an inhibitor of GABA aminotransaminase [6]. Due to inhibition of the enzyme, there is an increased level of GABA available in the synaptic cleft and an enhancement of the relative inhibitory neurotransmission [6]. Gabapentin, which is also used for treatment of migraine headaches, may also increase the level of brain GABA levels [6]. Propofol is a positive allosteric modulator of the GABA-A receptor and at high enough doses may behave as a GABA receptor agonist [9]. Further, propofol results in decreased cerebral blood flow and cerebral metabolic rate, which may assist in reducing the debility of headaches [10]. GABA also regulates cortical functions by circuits that modulate the activity of NMDA receptors post-synaptically [11].

Patients with treatment resistant migraines are tried on a variety of agents. Each of these agents have a varying level of efficacy in patients. One of the agents used is

sub-anesthetic doses of propofol. In a randomized controlled trial, which evaluated 77 patients, there was a reduction in headache intensity of 95.4% of those treated with propofol [12]. Further, 63 of the 77 patients reported complete resolution of the headache after receiving just 120 mg of propofol intravenous infusion delivered over 30 minutes [12]. Similar findings were also seen by Drummond et al. [13]. In this study, both patients were experiencing intractable treatment resistant migraines. Before trying propofol, patients were on tried numerous medications including morphine PCA, ibuprofen, promethazine, gabapentin, divalproex, clonazapine, trazadone and diphenhydramine [13]. Patients received doses of 0.5–1 mg/kg of propofol and headache scores declined significantly [13]. Despite the immediate improvement in headache severity, the headaches recurred a couple of months later [13]. Further, the dosing regimen is not as clear cut and is often provider and patient dependent requiring close titration to achieve the desired effects. Soleimanpour et al. [14] and Krusz et al. [15] performed randomized controlled trials comparing propofol with dexamethasone in its abortive role in treating headaches. The mean reported pain was lower with propofol and the onset of pain relief was faster [14, 15]. Krusz et al. found that 82% of patients were completely pain free after treatment with propofol. Propofol may also be effective in the management of acute exacerbations of migraine headaches lasting longer than 72 hours [16]. In this study, patients had an average VAS score of 8.8/10 prior to use of propofol, while 30 minutes after use of propofol the severity went down to 1.1/10 [16]. Compared to 6 mg of subcutaneous sumatriptan, 30–40 mg initial bolus of propofol followed by 10–20 mg boluses every 3–5 minutes of propofol lead to greater pain relief at 30 minutes [17]. Further, the length of stay for patients presenting to the emergency department with migrant headaches was 50% lower for those patients treated with propofol compared to those not treated with propofol [18].

Low dose propofol may also be used to improve the migraine headaches in pediatric patients [19]. In a small study, patients who received sub-anesthetic doses of propofol (3 boluses of 0.5 mg/kg) were compared to matched controls who received that standard abortive migraine treatment, which included non-steroidal anti-inflammatories, diphenhydramine, and prochlorperazine [19]. Others have recommended using 10 mg IV every minute with a maximum of 80 mg until the headache begins to improve to provide closer titration of propofol [20]. Those that received propofol experienced significantly greater reduction in pain scores and shorter stays in the emergency department [19]. There was also twice as many patients who received complete resolution of symptoms compared to the control [19]. However in a follow up randomized controlled trial, this same author team found that there was no better reduction in pain scores, but there was a statistically significant reduction in number of rebound headaches and a nonsignificant trend towards a shorter median length of stay [19].

The management of acute exacerbations of migraines is multifactorial and includes a number of agents including antidopaminergics, triptans, non-steroidal agents, acetaminophen, corticosteroids, antihistaminergic agents, valproic acid, ketamine, magnesium, and opioids. The evidence surrounding each of these agents varies greatly. Despite propofol showing some promising benefits in these

aforementioned studies, it is not a part of any official algorithm for headache management [4]. Propofol has shown some short-term benefits in headache management, but no sustained long-term benefits of prevention. The dosing regimen is not clearly delineated but is usually at sub-anesthetic doses.

Chronic Daily Headaches

Chronic daily headaches (CDH) is a common and disabling pain syndrome that affects approximately 5% of the overall population. CDH disproportionately affects women. CDH has been defined as headaches that lasts for >4 hours a day for >15 days a month [21]. CDH leads to significant loss of functional capacity and can be challenging to treat. CDH often begins as an episodic headache and progresses to being more symptomatic with time. GABA-ergic drugs are one of the first therapies tried because of their role in improving acute exacerbations of migraines. Because of the potential role of GABA in management of these headaches, propofol has been tried. Giampetro et al. [22] found that in 23/31 patients undergoing endoscopy with chronic daily headaches not in exacerbation using propofol as the primary anesthetic had improved headache symptoms [22]. About 74% of patients involved in this study suffered from chronic migraines [22]. Mean scores of headache severity and daily activity also improved with propofol use [22]. Patients received between 140 and 470 mg of propofol with an average dose of 276 mg [22]. In these patients, the headache severity and impact was lower 30 days after exposure to propofol compared to those not being treated with propofol [22]. However, Simmonds et al. has argued despite the statistical significance of propofol administration, its clinical impact is not significant [23]. Simmonds et al. administered 2.4 mg/kg intravenous infusion over 60 minutes, which led to reduced headache related disability 30 days after treatment, but no meaningful reduction in pain or medication use over this period [23].

Acute Postoperative Pain

Propofol is often thought of as having no analgesic properties. However, recent research has begun to suggest that propofol might have some modulatory effects on pain processing and perception. Propofol interacts with n-methyl-D-aspartic acid (NMDA) receptors [24–27]. NMDA antagonism is associated with pain relief. Bandschapp et al. [28] found that administration of propofol at a dose of 2 mg/mL was associated with smaller areas of hyperalgesia and allodynia when compared to a placebo. Further, Singler et al. [29] showed that propofol attenuated opioid induced post infusion anti-analgesia. Propofol inhibits pro inflammatory cytokines induced by lipopolysaccharides including: IL-B, IL-6, and TNF-a. These cytokines play a key role in pain signaling [30]. Further, propofol also acts as a scavenger of free radicals and thus protects the body [31]. Propofol has been shown to increase the antioxidant activity of human plasma and protect cells from oxidative stress by

impeding lipid peroxidation [32]. Propofol has also shown to have some neuroprotective effects [33]. Further, GABA also plays a role in the analgesic potential of propofol. The effect of propofol is associated with GABA accumulation and occupation of the GABA receptor [34]. Occupation of the receptors produce hyper polarization of the postsynaptic cell membrane and neuronal inhibition [34]. Propofol at low concentrations enhance the amplitude of response of GABA and prolong the duration of GABA mediated synaptic inhibition [34]. At supraclinical concentration, propofol directly activates the receptors [34].

Some argue that Propofol's effects occur due to a hangover effect from slower elimination compared to volatile anesthetics, and thus the perceived benefits stop quickly after the discontinuation of the propofol [28]. Thus, the benefits are seen in the first few minutes after discontinuation [35]. This reduced narcotic consumption isn't just explained by the theory of residual concentration of the propofol but also by the theory of central sensitization, which occurs with propofol treatment. Central sensitization is process dependent on NMDA activation, whereby pain modifies the CNS, so that the patient becomes more sensitive and gets more pain with less stimulation. This process can be prevented by giving patients NMDA antagonists. O'Connor et al. [36] observed that there is significant suppression of spinal sensitization in animal models associated with propofol use. Further in animal studies, propofol also decreases the nociceptive transmission in neurons and led to a reduction in the continuing nociceptive barrage [37, 38]. Nociceptive transmission is mediated by a slow ventral root potential (VRP) and a dorsal root potential (DRP). Slow VRP is mediated by glutamate and NMDA receptors [39]. The DRP is reflected by GABA-mediated depolarization of primary afferent nerve terminals that inhibit transmitter release [40]. In effect, the DRP is a form of feedback inhibition [37]. Jewett et al. [37] recorded these potentials in the rat spinal cord model to determine the extent of propofol depression of nociceptive neurotransmission. Propofol depresses the nociceptive-related slow VRP and enhanced the anti-nociceptive DRP by inhibiting their output [37]. These effects are seen at the concentrations of propofol offered by general anesthesia [37]. Further, some studies have shown the effects of propofol lasting up to 24 hours postoperatively [35]. And finally, some have argued the pain relief associated with propofol isn't seen till 24 hours postoperatively. Others have argued that despite the analgesic effects of propofol not being as clear cut, the benefits of propofol are more subjective and include improved overall well-being [41]. There is no clear consensus on the benefits of propofol, but at the same time no one has reported on the negative effects of propofol. In a experimental study by Briggs et al. [42] evaluating healthy patients, increasing pressure was applied to the anterior surface of the middle third of the tibia, and patients were asked to evaluate their pain after propofol at 2 mg/kg. Patients exhibited analgesic benefits associated with use of propofol [42]. However, if patients received thiopentone instead the authors found an increased sensitivity to somatic pain [42].

In a review article by Qiu et, al. that evaluated 14 clinical trials, the pain relief associated with propofol use lead to a small statistically significant reduction at 24 hours, however, this difference was not seen 2 hours post-operatively [31]. While the study as a whole didn't show any benefit to propofol based TIVA, there were

particular studies that showed some benefit. Making broad claims about all surgeries can be challenging as the surgical procedures vary so much. In a group of 80 patients undergoing open uterine surgery, those anesthetized with propofol reported less pain and utilized less morphine during the first day after surgery [35]. In particular, there was reduced pain in the first 4 hours after surgery in patients undergoing an open hysterectomy [43]. Similar findings were also found in patients undergoing a laminectomy or middle ear surgery [44, 45]. In patients undergoing hysterectomy, Ogurlu et al. [43] found that that there was reduced risk of persistent surgical pain at the 3-month mark. There was also reduced anxiety and depression scores at the 3 month mark [43]. However, at near anesthetic concentrations, this hyperalgesic effect is not seen [46].

In a retrospective study, Cho et al. [47] looked for the incidence of chronic pain after breast cancer surgery in 175 patients for greater than 2 years [47]. In patients with propofol used as an anesthetic, the risk of chronic pain was 44%, while in those treated with sevoflurane it was 67% [47]. Further, although not statically significant, patients treated with sevoflurane had severe pain more than twice as frequently [47]. Patients given sevoflurane anesthesia were also twice as likely to come back to the hospital for management of pain [47]. Further, if remifentanil is used in combination with volatile anesthetics then patients were more likely to develop hyperalgesia [48]. This hyperalgesia was not seen with use of a propofol infusion. The mechanism of action was like due to central sensitization, which is theorized to lead to chronic pain [49].

In patients undergoing a thoracotomy, the incidence of chronic post-thoracomy pain syndrome (CPTS) at 3 and 6 months was greater in patients who underwent general anesthesia with volatile anesthetics rather than propofol based TIVA [50]. The frequency of CPTS group was 30–40% while in the volatile anesthetic group it was 50–60% [50]. Further, the group of patients treated with volatile anesthetics also had an increased risk of new onset pain at 6 months [50]. Despite the difference in frequency, the intensity of pain was similar [50]. The etiology of this difference is likely multifactorial, but could be due to a combination of the antioxidant properties, the neuroprotective effects, and the GABA mediated effects. In all the aforementioned studies, propofol was dosed with different regiments, which may make comparison more challenging. But the main techniques of dosing included regimens utilizing a bispectral index (BIS) of 35–50, target continuous infusion, or rates of 1–2 mcg/kg/hr.

But other studies have found no difference between volatile anesthetic use and propofol intravenous infusion in laparoscopic surgery [51–53]. It theorized that volatile anesthetics have hyperalgesic effects at low doses, even as low as 0.1 minimum alveolar concentration, likely due to nicotinic acetylcholine receptor inhibition in the brain and spinal cord [46, 54]. It also appears that open surgical procedures may benefit more from the use of propofol as an analgesic in comparison with laparoscopic procedures. But these findings aren't conclusive either, in a study evaluating propofol based TIVA in laparoscopic cholecystectomy, patients who underwent propofol based TIVA had significantly less use of analgesic medicine postoperatively and reduced duration of hospitalization [55]. In this same study, there is an

association with improved patient satisfaction [55]. Further, there is some benefit to propofol anesthesia in patients undergoing planned gynecological laparoscopies with planned opioid free post-operative analgesia [56]. This was also associated with shorter durations of stay in the post-anesthesia care unit (PACU) [56].

The evidence regarding propofol use for improvement in pain control in the acute surgical setting is incomplete. Some trials show support and others show no evidence. If there is improvement, the exact time period of improvement is highly variable. It also appears there is a feeling of improved well-being associated with propofol use, while intangible this may help with patient satisfaction and also lead to reduced narcotic consumption. The mechanism of action is also highly variable but is likely due to a combination of GABA agonism and NMDA antagonism. However, there does appear to be more evidence to use propofol based TIVA in patients undergoing open surgical procedures rather than laparoscopic surgeries.

Opioid Induced Hyperalgesia (OIH)

Patients on long term narcotic therapies, suffer from desensitization to narcotics. Hyperalgesic states can be induced with chronic narcotic use. The mechanism for opioid induced hyperalgesia (OIH) Is unknown, but there may be components of excessive NMDA activation. NMDA antagonism has long been one of the multi-modal analgesic options to provide adequate pain relief in these individuals. It could also be due to interactions with GABA receptors at the supra spinal level [29, 57]. In patients where the hyperalgesia is worsened with fentanyl administration, propofol infusions can be used to help mitigate these effects [49]. As mentioned earlier, propofol at appropriate doses has shown to have some NMDA antagonism [24–27]. Further, in animal studies, propofol at sub hypnotic doses has shown to increase the latency of pain threshold and reduce pain in a dose dependent manner [58]. Similar effects found in these animal studies have also found in experimentally induced pain in human subjects [24].

Contraindications

Propofol is contraindicated in certain conditions including abnormal metabolism of fats and cholesterol, hardening of the arteries in the brain, abnormally low blood pressure, seizures, weakened patient, decreased blood volume, pancreatitis and allergy to Propofol.

Side Effects

Propofol causes a significant reduction in blood pressure, often more than 50% of preoperative level. The decrease in blood pressure is due to decreased systemic vascular resistance. Further, propofol produces venous dilation. There is an associated

fall in cardiac output that is manifested with a decrease in heart rate. Hypotension is more common in patients who are volume depleted. There is also significant respiratory depression and apnea associated with propofol. Propofol decreases the tidal volume and increases the respiratory rate. There is also a shift in the ventilatory response to carbon dioxide and hypoxia, but propofol does not depress hypoxic pulmonary vasoconstriction. Propofol also reduces cerebral metabolic rate of oxygen consumption, intracranial pressure, and cerebral blood flow. There is also often pain with injection, which can be reduced with lidocaine infiltration immediately prior to [59]. But at the dose administered in the above studies, the risk of major complications highlighted above is extremely rare. However, transient effects such as lethargy, drowsiness, and unintelligible speech were more prevalent [15].

With long term use, high dose propofol infusions can lead to propofol infusion syndrome (PRIS). It often occurs with doses of more than 4 mg/kg/hr. for more than 24 hours [59]. PRIS is a result of mitochondrial dysfunction that can lead to cardiac failure, rhabdomyolysis, metabolic acidosis, and kidney failure [59]. Risk factors include those patients on glucocorticoids and catecholamines. Treatment is supportive and involves discontinuation of the propofol, but early recognition is key to management. Further, despite being not as prevalent as narcotic dependence, some small studies have shown patients suffering from propofol addiction associated with repeat administration of propofol [60, 61].

Monitoring

Propofol infusions requires close monitoring of cardiac and respiratory status continuously with the ability to intervene if necessary. Recommended monitors include at least noninvasive blood pressure monitoring, electrocardiography, and pulse oximetry. Please review your institute guidelines for monitoring and needed support in places where you perform the infusion.

Algorithm for Propofol Infusion Regimens

This algorithm summarizes all proposed doses published in literature (Table 3.1). The goal of this algorithm is to provide a guide for practitioners, but different doses might be used depending on the setting and patient population.

Summary

While propofol is used in sedation and anesthesia on a regular basis, there are some applications for propofol beyond this setting. The primary uses of propofol outside of these settings include acute exacerbations of migraine headaches and for management of acute pain. Doses for migraine headaches range widely and include: 10 mg IV q5–10mins w/maximum of 80 mg, 30–40 mg bolus w/10–20 mg boluses ever

Table 3.1 Algorithm for propofol infusion regimens

Indication	Dosage
Adult migraine headaches	10 mg IV q5–10mins w/maximum of 80 mg, 30–40 mg bolus w/10–20 mg boluses ever 3–5mins, 120 mg bolus, or 0.5–1 mg/kg dose
Pediatric migraine headaches	3 boluses of 0.5 mg/kg
Chronic daily headaches	2.4 mg/kg (over 60 minutes) or 140–470 mg propofol
Post-operative pain, TIVA regimen	Maintenance of BIS scores of 35–50, target continuous infusion, or 1–2 mcg/kg/hr. infusion
Opioid induced hyperalgesia	150 mcg/kg/min

3–5mins, 120 mg bolus, or 0.5–1 mg/kg dose. No single indication is better than the rest. While dosing for preventing postoperative pain is at a higher dosing regimen and may utilize other agents. For this indication propofol should be dosed using a bispectral index (BIS) targeting 35–50, target continuous infusion, or rates of 1–2 mcg/kg/hr. Other uses also include in as an agent to prevent exacerbations in chronic headaches and in opioid induced hyperalgesia. However, the conclusions and evidence are not concrete. Propofol is not only a potent mediator of the GABA receptor, but also interacts with the NMDA receptor. We are still learning more about all the benefits of NMDA antagonism. More large-scale randomized controlled trials have to be done to evaluate the efficacy of propofol for analgesia or in headaches.

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Magnesium Infusion Therapy

4

Andrew J. Wendahl and Adam L. Weinstein

Introduction

Magnesium is a commonly used medication with many applications. Magnesium's uses range across numerous medical specialties such as obstetrics and various disciplines of surgery and anesthesia. It is also a valuable component in both the anesthesiologist's and pain physician's armamentarium of tools. It plays a vital role in many cellular processes. It is essential to a number of metabolic activities through association with a variety of metabolic enzymes that are dependent on it. Several studies report antinociceptive effects of intravenous magnesium. The following chapter aims to provide clarity and direction through providing mechanistic understanding, organ system relevance, indications, adverse effects, monitoring and administration protocols based on a thorough and up to date literature review on intravenous magnesium therapy.

Mechanism of Action

Magnesium is a naturally occurring element on the periodic table and is the lightest of any of the alkaline earth metals. Magnesium has an atomic number of 12 and weight of 24.305. Within the human body it is an endogenous ion critical to cellular function and homeostasis. Magnesium serves many roles: enzyme activation, protein formation, vascular tone, cellular signaling, and neurological transmission [1, 2].

After administration, about 40% of plasma magnesium is protein bound. The unbound magnesium ion diffuses into the extravascular-extracellular space including muscle and bone. Magnesium is 90% excreted in the urine. The pharmacokinetic

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profile of $MgSO_4$ after intravenous administration can be described by a 2-compartment model with rapid distribution (a) phase, followed by a relative slow beta phase of elimination [3]. Adult human bodies contain approximately 24 g of magnesium, 67% located in the skeleton, 31% intracellularly, and only about 1–2% extracellularly. As stated, one half is ionized, and the rest is nearly all protein bound. For this reason, a routine serum level is not representative of true total body stores [4].

Magnesium is known to play a role in prevention of central sensitization and decrease hyperalgesia through its natural affinity for antagonism at the N-methyl-D-aspartate (NMDA) receptors. It is known that NMDA receptors play a critical role in pain transduction and for this reason its association with acute and chronic pain has been studied in depth. Ketamine and magnesium are representative NMDA receptor antagonists. Paoletti et al. have investigated magnesium as an analgesic adjuvent through its function on regulation of calcium access into cells through the antagonistic effect at the NMDA receptor [5].

In the central nervous system with respect to pain signaling, magnesium acts as a voltage gated receptor channel blocker of the NMDA (*N* methyl D aspartate) receptor [1, 2]. The NMDA receptor is a membrane bound ion channel made up for four subunits. It controls influx of Na and Ca and efflux of K [6, 7]. In the clinical setting intravenous magnesium is prepared and administered as magnesium sulphate ($MgSO_4$). Magnesium itself is not an analgesic, but through NMDA inhibition, calcium is prevented from entering central nervous system cells [7, 8]. It is the accumulation of intracellular calcium that is largely responsible for generation and continuation of central sensitization [7].

In the muscular system magnesium also augments the properties of paralytic agents. Magnesium sulphate has the ability to act at the endplate where it inhibits the release of acetylcholine. When magnesium concentrations are significantly elevated, calcium binding is reduced at the vesicles containing acetylcholine, resulting in a reduction in the amount released at the neuromuscular junction [9]. This in effect potentiates the non-depolarizing neuromuscular blocking medications [9, 10]. Kussman et al. showed that the administration of magnesium did not necessarily change the onset of the muscle relaxant, but prolongs its effect [9].

In the cardiovascular system magnesium can cause hypotension and bradycardia. It serves to act as a calcium channel blocker in the cardiovascular system by reducing the release from and into the sarcoplasmic reticulum. It reduces systemic and pulmonary vascular resistance. Studies have shown magnesium to have a beneficial impact on coronary artery disease (CAD) through multiple other avenues including anti platelet effects, inhibition of vulnerability to oxygen free radicals, and coronary vasodilation to name a few [11].

In the pulmonary system magnesium reduces pulmonary vascular resistance. It achieves this through inducing bronchial smooth muscle relaxation in a dose-dependent manner by inhibiting calcium influx in to the cytosol, histamine release from mast cells, or acetylcholine release from cholinergic nerve endings. It may also increase bronchodilator effect of B2-agonist by increasing receptor affinity [12].

Indications

Intra- and Post-operative Pain

Kara et al. has described magnesium to be effective for treating intra- and post-operative pain and for blunting autonomic, somatic, and endocrine reflexes to noxious stimuli [13]. Many dosage regimens have been described some of which are mentioned in the infusion protocol section to follow. Oguzhan et al. studied the effect of magnesium sulphate infusion on postoperative requirements for opioids, intraoperative neuromuscular relaxants, volatile anesthetic consumption, and postoperative pain during and after lumbar disc surgery. Specific benefits are mentioned in a later section [14]. In other varieties of surgeries magnesium was also found to decrease the amount of morphine needed for postoperative pain control. Ryu et al. looked at remifentanil and magnesium during middle ear surgery in terms of postoperative pain and other complications. Patients in the magnesium group experienced more comfort postoperatively from an analgesic standpoint, less shivering, and less postoperative nausea. The amount of sevoflurane to maintain surgical anesthesia was significantly lower in the magnesium group than in the remifentanil group [15].

Pain impairs the daily activities of a significant proportion of patients long after the acute surgical phase ends and is termed persistent post-surgical pain (PPSP). It is defined as pain that develops from a surgical procedure that lasts at least 2 months, and where other causes (i.e., malignancy or chronic infection) have been excluded [16]. Some of the surgeries studied with significant rates of chronic pain include phantom limb pain, breast surgery, cesarean section, vasectomy, inguinal hernia repair, and thoracotomy to name a few with the highest incidence [17]. Kim et al. aimed to compare the effects of systemic lidocaine versus magnesium administration on postoperative functional recovery and chronic pain in patients undergoing breast cancer surgery in a prospective, randomized, double-blind, comparative clinical trial. Intraoperative systemic magnesium was only effective in reducing intraoperative opioid consumption and pain score in the early postoperative period. In their prospective study, magnesium was not found to have a significant effect on chronic pain control [16].

Remifentanil has been reported to induce dose-dependent hyperalgesia in humans. Sun et al. addresses remifentanil induced hyperalgesia characterizing it as stimulation evoked pain including allodynia and thermal hyperalgesia after remifentanil infusion. Remifentanil is widely used with general anesthesia especially for neurosurgical procedures in which a deep anesthetic is required. It has been shown that general anesthesia with remifentanil results in severe postoperative pain and an increase in analgesic consumption. Sun et al. concluded that remifentanil induced hyperalgesia/allodynia could be ameliorated by Mg-mediated blockade targeting the NR2B subunit in NMDA receptors when studied in rats [18].

Begon et al. presented data suggesting that magnesium amplifies the analgesic effect of low-dose morphine in conditions of sustained pain. Several published data

sets support co-administration of NMDA receptor antagonists in neuropathic pain, restoring the efficacy of opioids. This mechanism reverses what has been described as an excess of excitatory pathway activation via NMDA receptors leading to morphine resistant neuropathic pain [19].

In humans, incidence of magnesium deficiency increases with aging (poor diet, increased urinary loss, reduced intestinal absorption, etc.) and obesity. These are all associated with oxidative stress and low grade inflammation [20]. Cancer cells preferentially accumulate magnesium, which is used to activate or inhibit various metabolic and genetic pathways to promote cell survival and proliferation [21]. The correlation between magnesium level and cancer growth is beyond the scope of this chapter and no direct relationship has been found. The connection relates to the high incidence of neuropathic pain alongside chemotherapy regimens. Crosby et al. studied the safety and efficacy of a single dose (500 mg or 1 g) of intravenous magnesium sulfate in neuropathic pain poorly responsive to strong opioid analgesics in 12 cancer patients with malignant infiltration of the brachial or lumbosacral plexus. Both 500 mg and 1 g were well tolerated. Of those receiving 500 mg, three patients experienced complete relief and two experience partial relief for up to 4 hours duration. One patient had zero response. In the 1 gram group, similar results were obtained [22].

Complex Regional Pain Syndrome (CRPS)

Activation of NMDA receptor signaling has been proposed in induction and maintenance of CRPS with ketamine and magnesium infusions. Fischer et al. Set out to assess the effects of intravenous magnesium on complex regional pain syndrome type 1 (CRPS-1) in a randomized boule-blind placebo-controlled trial. Fifty-six patients received $MgSO_4$ 7 mg/kg or normal saline in 4 hours over 5 consecutive days. No significant differences were found between the groups [23]. In a literature review, IV ketamine has shown efficacy, however, different RCT's have yielded contradictory results of IV magnesium in CRPS with low evidence [24].

Menstrual Pain

Magnesium has been described to help prevent menstrual pain. Primary dysmenorrhea prevalence rates are as high as 90%. The mechanism through which this works is by relaxing the smooth muscle of the uterus and reducing the prostaglandins causing pain. Increased production of endometrial prostaglandin results in increased uterine tone and stronger, more frequent uterine contractions. This treatment is cited on the AAFP website as an alternative therapy for women who do not respond to NSAIDs or oral contraceptives. The studies are limited, however, in a study by Benassi et al. with 30 patients who received magnesium pidolate, up to 84% of patients had decreased symptoms [25, 26].

Migraine

Magnesium's role in migraine pathogenesis has been well described and is a well-tolerated, safe, and inexpensive option. Lipton et al. described migraine as the most common form of disabling primary headache that afflicts patients, affecting approximately 12% of Western populations [27]. Current theories on etiology of this disease focus on hyperexcitability of the cortex and trigeminovascular complex. Specifically, headache triggers stimulate release of neuropeptides including calcitonin gene-related peptide and substance P. Additionally, trigeminal ganglion increases cerebral blood flow due to release of vasoactive intestinal peptide by the facial nerve. This vasodilation and increased vascular permeability leads to meningeal neurogenic inflammation [28]. The accompanying aura is the presentation of characteristic neurological symptoms and is a phenomenon known as cortical spreading depression (CSD). This can be triggered by depolarization of a small region of brain tissue or direct activation of the NMDA receptor [29]. Studies examining IV magnesium use for this indication are conflicting. To name a few, Demirkaya et al. describes a single-blind placebo-controlled, randomized trial involving 30 patients with migraines randomized to magnesium sulphate 1 g or placebo. Treatment was superior to placebo in both response rate (100% for magnesium sulphate vs 7% for placebo. Those treated did not experience headache recurrence within 24 hours. Bigal et al. describes a double-blind placebo-controlled, randomized study evaluating the efficacy of magnesium sulphate 1 g on pain and associated symptoms of migraine with and without aura. No differences were observed in pain relief or nausea with the non-aura group, however, the aura group had significant improvement in pain [30].

Central Sensitization

Magnesium plays an important role in preventing central sensitization and pain hypersensitivity. It seems to attenuate or even prevent central sensitization after peripheral tissue injury or inflammation because of the inhibition of dorsal horn NMDA receptors [8]. The main mechanism by which this appears to function is through its involvement with the voltage-gated NMDA receptor antagonism [7]. Woolf et al. states that although magnesium doesn't have a direct analgesic effect, it produces an antinociceptive effect through its inhibition of calcium ions entering cells through NMDA receptors. Pockett et al. states intracellular calcium levels pay a major role in the initiation of central sensitization which can be attenuated by magnesium therapy [8, 31].

Fibromyalgia

Fibromyalgia is considered a stress-related disorder, with both the onset and exacerbation associated with intense stressful periods. It has been shown that there is an

inverse correlation between Mg levels and parameters in patients with fibromyalgia [32]. It is currently perceived by clinicians as the classic condition of central sensitization. Again, the beneficial role of Mg is based on NMDA antagonism. Studies have shown that patients with chronic fatigue linked to fibromyalgia exhibit chronically low Mg levels. These patients saw significant improvement following intramuscular weekly injections of 1 g of $MgSO_4$ seeing improvement in energy level, pain, and emotional reactions [33–35].

Postherpetic Neuralgia (PHN)

PHN is characterized by pain that persists for more than a month after the healing of acute herpes (HZ) lesions. It is a persistent clinic problem in the elderly, reaching 75% in patients over 70 years of age who have had HZ infection [36]. Brill et al. showed utilizing a double-blind, placebo-controlled, cross-over study in which seven patients with PHN were infused with either magnesium sulphate 30 mg/kg or saline that the NMDA receptor is involved in the control of PHN pain. The mean pain score during the magnesium infusion fell from 6.7 at baseline to 1.9 at 30 minutes and was significant as compared to placebo. Five out of seven patients reported complete pain relief after infusion at 1 hour. Unfortunately, all patients reported return of pain the next evening and the magnesium had no effect on dynamic allodynia [37].

Contraindications

Magnesium is a relatively safe medication to use for infusion. In certain instances, and at certain physical levels magnesium can be toxic and harmful. Magnesium should be withheld in patients at risk or suffering from hypotension, bradycardia, significant cardiac disease, over sedation, nausea, active emesis, confusion/delirium, or elevated serum magnesium levels (2.6 mEq/L) [38]. When levels of magnesium exceed 7 mg/dL cardiovascular impairment may occur. Levels between 2.6 and 7 can result in mild symptoms of hypermagnesemia [39]. Magnesium levels may be elevated with certain co-morbid conditions and should prompt testing. Care should be taken in patients currently suffering from: hypothyroidism, Addison's disease, milk-alkali syndrome, familial hypocalciuric hypercalcemia, and those currently undergoing lithium therapy [39].

Side Effects

Potential for magnesium related side effects are of concern particularly with more potent infusion protocols and in patients with renal impairment. A feeling of warmth is commonly felt at the IV site upon administration. Severe side effects are less

common. In a meta-analysis of randomized controlled trials by Gildasio et al., none of the included studies reported any clinical manifestations of magnesium toxicity related to high serum levels of magnesium. Of the symptoms reported in the aggregate studies, none were found to be statistically significant finding magnesium infusion as the cause. Those symptoms included dizziness, headache, postoperative nausea and/or vomiting, postoperative shivering, and cardiovascular side effects including perioperative bradycardia or hypotension [40]. Data outcomes are predominantly from obstetric literature. The clinical effect and toxicity of $MgSO_4$ can be linked to its concentration in plasma. The suggested plasma concentration for treatment of eclamptic convulsions is 1.8–3.0 mmol/L. The first warning of impending toxicity is loss of patellar reflex at between 3.5 and 5 mmol/L. Respiratory paralysis occurs at 5–6.5 mmol/L. Cardiac conduction is altered at greater than 7.5 mmol/L, and cardiac arrest is expected when concentrations exceed 12.5 mmol/L. The recommended intravenous regimen for severe pre-eclampsia and eclampsia is a 4 g bolus dose, followed by a maintenance infusion of 1–2 g/h [3].

Monitoring

Magnesium is predominantly an intracellular ion, and its serum level does not reflect intracellular concentrations or total body stores. Detailed accounts of errors with magnesium sulfate have been published, although mainly within the obstetric population when treating for preterm labor and pre-eclampsia as stated above. In a 2009 report, an ongoing review of mishaps in the U.S. accumulated 52 reports of accidental overdoses of magnesium sulfate. The patient's vital signs, oxygen saturation, deep tendon reflexes, and level of consciousness should be monitored. The patient should be assessed for signs of toxicity (e.g., visual changes, somnolence, flushing, muscle paralysis, loss of patellar reflexes) or pulmonary edema. During bolus administration, a staff member should remain at the patient's bedside to oversee continuous monitoring. Subsequent assessment intervals of 15 minutes are recommended for the first hour, 30 minutes for the second hour, and then hourly after [41]. Magnesium levels are difficult to assess with blood testing and serum levels are a poor reflection of body stores of the cation [42]. For this reason, replacement is often empirical, guided by symptoms, plasma magnesium, and renal function.

Algorithm for Magnesium Infusion Regimens

Magnesium infusions for pain therapy consist of a bolus dose followed by a continuous infusion (Table 4.1). Koinig et al. describes a possible protocol consisting of 50 mg/kg bolus over 10 minutes followed by an infusion maintained at 8–15 mg/kg/h [7, 15, 43]. While this protocol describes magnesium infusion through the entire surgical procedure and a higher initial bolus; Seyhan et al. in a trial using different magnesium regimens describes an ideal dosage protocol in which a bolus

Table 4.1 Algorithm for magnesium infusion regimens

Indication	Dosage
Severe intra-op surgical pain	IV 50 mg/kg bolus over 10 minutes followed by an IV infusion maintained at 8–15 mg/kg/h during surgery
Moderate intra-op surgical pain	IV 40 mg/kg is administered followed by an IV infusion of 10 mg/kg/h during surgery
Moderate intra-op surgical pain with prolonged post-operative pain	IV 30 mg/kg is administered followed by an IV infusion 500 mg/h for up to 20 hours
PHN	IV 30 mg/kg (proposed)
Fibromyalgia	IM 1 g $MgSO_4$ weekly
CRPS	IV 7 mg/kg over 4 hours for 5 days
Cancer pain	IV 500 mg–1 g

dose of 40 mg/kg is administered followed by an infusion of 10 mg/kg/h for only 4 hours [10]. This reduced dosage difference was due to larger quantities of magnesium leading to unintended hypotensive hemodynamic consequences and no further positive benefit with higher doses [7].

Summary

Magnesium plays a key role in human physiology and for this reason there has been interest in its application in clinical medicine. We have strong evidence for its use in the fields of obstetrics and cardiology. There is a wealth of literature describing its application and potential for benefit in pain management. However, many studies counter with conflicting results. The aim of this chapter was to summarize current knowledge surrounding the use of magnesium in clinical practice for pain related indications. As the fourth most abundant essential ion in the human body, we know magnesium has critical function in maintaining cell homeostasis. These functions include protein synthesis, adenosine 5′-triphosphatase regulation, neuromuscular function, and nucleic acid stability to name a few [44, 45]. This ion is known to modulate pain pathways and central sensitization through its endogenous antagonism at the calcium channel and NMDA receptor.

As a therapy, it has a well-known safety profile and deserves to be considered as an alternative and multimodal therapy [46]. Tramer et al. describes the first randomized, double-blind, clinical study to look at magnesium sulfate infusion and analgesic requirements. They showed that when compared to the control population, those given magnesium required less morphine and had less discomfort 24 and 48 hours after surgery [47]. In 2008 Oguzhan et al. showed that the use of magnesium did not affect experienced side, effects, Aldrete scores, or early recovery parameters. However, they did demonstrate a decrease in intraoperative opioid use, paralytic use, and more importantly post-operative opioid use [14]. In Seyhan's 2006 study looking at three dose regimens of magnesium they ultimately showed that when compared to the control group, those who received magnesium had reduced intraoperative propofol dosages, paralytic dosages, and in the post-operative setting a

reduced opioid requirement [10]. In addition to reduced doses of other anesthetic drugs magnesium has been studied in the use of regional anesthesia. Turan et al. showed that magnesium mixed with lidocaine in regional anesthesia resulted in quicker onset of sensory and motor block, reduced VAS scores, lower tourniquet pain, and longer time to postoperative analgesic requests [48].

Based on the data and above literature the efficacy of magnesium should be considered as an adjunct agent in any clinical practice.

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Opioid Infusion Therapy

5

Christi Ann Albert and Cory Sarver

Introduction

Opioids bind to the mu opioid receptor to produce analgesia and include synthetic (methadone, fentanyl, sufentanil, remifentanil), semisynthetic (hydromorphone, oxymorphone, heroin) as well as natural opiates (morphine, codeine, opium) which are derivatives of poppy/opium [1, 2]. Morphine was derived from opium in the early 1800s and was the first opioid available for medical use. They have been widely used in the medical, dental, and surgical settings for acute and chronic pain as well as in cancer pain, noncancer pain, and pain in end of life. Opioid medications are at the top of the WHO Pain Cancer Ladder to use adjunctively with non-opioid multimodal therapy [3]. Immediate release oral opioids, followed by addition of transdermal or long-acting oral opioids are preferred as first line opioids before intravenous (IV) or subcutaneous (SQ) opioids are prescribed to ambulatory patients if clinically appropriate [4–6]. Intravenous and subcutaneously administered opioids for the ambulatory setting are predominantly reserved for palliative pain and end of life care [4, 6, 7]. In hospital settings, intravenous opioids are routinely used for acute procedural pain as well as acute medical pain crises such as for cancer and sickle cell pain. They are administered most frequently as IV slow push, patient-controlled analgesia (PCA) and by IV continuous infusion, which is also an optional administration method used in combination with PCA.

Following the "Stamp Out Pain" and "Pain is the 5th Vital Sign" campaign(s) in the 1990s; an increase in oral opioid prescribing occurred worldwide for acute

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procedures as well as for chronic noncancer pain [2]. An unintentional increase in opioid exposure to the general public occurred and subsequently opioid overdose emergency room visits, hospitalizations, and deaths rose in the early 2000s. Patients chronically opioid dependent on prescription or illicit opioids have increased in frequency. Acute pain management becomes more difficult due to opioid tolerance but can oftentimes be overcome with more potent escalated doses of intravenous opioids or addition of adjunctive agents when clinically indicated. Since the opioid epidemic emerged, several guidelines recommend more stringent patient selection criteria for chronic opioid therapy (COT) in chronic noncancer pain (CNCP) conditions [8–10]. A decline in use of parenteral opioids for acute on chronic pain flares of chronic noncancer pain is being observed in hospital settings unless the patient is in severe pain unrelieved by other multimodal measures or has relative enteral contraindications.

Performing opioid drug and route conversions is problematic given the limited supporting evidence and lack of standardization studied with commonly cited opioid equianalgesic tables [11]. Interpatient variability increases opioid conversion complexity with comorbid disease states affecting opioid sensitivity such liver or renal dysfunction. IV to oral and oral to IV dose conversions are imperfect and can result in over or under treatment at time of conversion.

Opioids are used intravenously and subcutaneously as continuous infusions for acute and chronic analgesia for both inpatient and outpatient indications and adjunctively with other sedatives and anesthetics for operative procedures or for patients that require intensive care or mechanical ventilation [2, 4, 5, 12]. The purpose of this chapter is to discuss opioids available for pain management, thus opioid use reserved for anesthesia and medical induced sedation will be excluded.

Hydrocodone, oxycodone, codeine, and tramadol are not available for parenteral use in the United States (US) thus will be excluded from discussion in this chapter [13–15]. Oxycodone and tramadol are; however, available parenterally outside of the United States. Intrathecal and epidural infusion techniques using opioids are used as advanced measures to control pain but also fall outside the scope of this chapter. Meperidine is a parenterally available opioid, however guidelines recommend against its use for acute pain due to neurotoxicity, so will also be excluded [5, 13].

This chapter will focus on US available opioids for intravenous or subcutaneous use which are administered continuously or via intravenous patient controlled analgesia (PCA) and will focus on morphine, hydromorphone, and fentanyl as preferred opioids for infusion [9–12]. Oxymorphone and buprenorphine are available parenterally, but use is most often reserved for IV bolus dosing rather than for infusion therapy [13–15]. Methadone is a last line oral and parenteral opioid option, avoided due to complex kinetics and QTc prolongation [4, 6, 7]. Sufentanil and remifentanil are primarily approved and indicated in anesthesia but have been used off label with some limited evidence and thus use for acute pain management will be briefly discussed.

Target controlled infusions (TCI), while not used in the US, offer an opportunity for improved patient safety and monitoring for patients requiring opioid infusion therapy. They are infusions with frequent or continuous serum concentration

monitoring, of which a smart pump automatically adjusts the infusion rate based on a predetermined target serum concentration. This mechanism of infusion will be briefly discussed as an opportunity for future treatment options on the horizon for patients in the US.

Mechanism of Action

Opioid receptors are located throughout the body in the central nervous system (CNS), peripheral tissues, as well on immune cells and bind natural endorphins [1, 2, 5, 7]. They are subcategorized into mu (μ), kappa (κ), and delta (δ) receptors. Pharmaceutical opioids produce a majority of their analgesic and adverse effects by binding μ opioid G protein-coupled receptors as agonists specifically in the spine and CNS. Agonism at μ opioid receptors increases potassium influx into neurons resulting in hyperpolarization and thus inhibition of nerve transmission from the CNS and spinal cord to the periphery [1, 2]. Opioids do not alter the pain threshold nor cause changes at the site of stimulus where the pain signal originates nor affect transmission or transduction of nerve impulses in the peripheral nervous system (PNS).

Pharmaceutical opioids have been developed that are classified as weak (such as codeine, tramadol, tapentadol) versus potent (including morphine, oxymorphone, hydromorphone, methadone) opioids and also as full or partial agonists [1–3]. Weak opioids are not commercially available in the US for injection or infusion [13–15].

Buprenorphine is the only parenterally available partial μ agonist, given by slow intravenous (IV) push or intramuscularly (IM) owing to its longer half-life [5, 7, 13–15]. It is generally not infused continuously nor routinely used in acute pain because of its ceiling effect due to partial agonism as well as antagonism at higher doses. The partial effect of buprenorphine is used therapeutically in chronic maintenance of opioid addiction disease because overdose with buprenorphine is much less likely to result in respiratory depression and overdose death when compared to other pure μ agonists [5, 13–15]. The remaining potent parenteral opioids (hydromorphone, morphine, oxymorphone, fentanyl, sufentanil, remifentanil, and methadone) are full and potent μ agonists. Oxymorphone is available for parenteral use for IV/IM bolus dosing, despite being studied for PCA, is rarely continuously infused or use for PCA and will be excluded from review in this chapter.

Three commercially available opioids in the US market including tramadol, tapentadol and methadone in addition to binding the μ opioid receptor (weak: tramadol, tapentadol; potent: methadone) also act as norepinephrine re-uptake inhibitors (tapentadol) or combination serotonin and norepinephrine reuptake inhibitors (tramadol) [1, 2]. The non-opioid analgesic effect is helpful in chronic pain or neuropathic pain conditions. These ancillary mechanisms of action modulate pain signaling pathways in the spinal cord and PNS providing multimodal therapy in a single agent. Methadone also provides analgesia as an n-methyl-d-aspartate (NMDA) receptor antagonist [5, 7, 13–15].

Indications

Intravenous Continuous Infusion and Patient Controlled Analgesia

The most common indication for use of continuous infusion opioids is sedation for ventilated patients. From an analgesic standpoint, it is used when patients have severe intractable around-the-clock pain despite IV bolus opioids or the patient is unable to take their established around-the-clock opioids orally [16–20]. Continuous infusions, also called basal rates, can be added as an option to patient controlled analgesia (PCA) pumps for patients requiring around-the-clock opioids for analgesia [21, 22]. Continuous intravenous infused opioids are indicated following procedures for acute pain control, for severe acute exacerbations of chronic pain conditions such as sickle cell anemia, for acute severe cancer pain, and can be continued as an outpatient for patients in palliative care or end of life (EOL) care.

Efficacy of continuous infusion and PCA administered opioids in studies is measured by changes on the numeric rating scale (NRS) or visual analog scale (VAS) which is a challenging endpoint given it is subjective rather than objective [16–22]. Secondary endpoints commonly cite time to improved analgesia, hospital length of stay, and incidence of adverse drug reactions (ADRs). Most studies, no matter the indication, demonstrate that opioids can reasonably reduce pain scores by 30–50% from baseline in 1–2 days from initiation or dose escalation. Because intravenous opioid infusions and PCAs do not have an upper limit for dosing, more aggressive improvements in pain can be achieved, but are commonly plagued by adverse effects that are likely to interfere with clinical goals for improvement. Objective, measurable goals of analgesia should be established with the patient, caregiver, and/or family. Full pain relief or a pain score of 0/10 on NRS scale is generally not attainable as opioids do not change the baseline disease state causing pain. Goals of analgesia will vary greatly by indication but can include ability to perform activities of daily living (ADLs), instrumental ADLs, or physical therapy (PT) for noncancer pain. Comfort by reducing (rather than fully eliminating pain) at rest and reduction of air hunger are common goals of analgesia for palliative care and at EOL. Comfort defined at EOL is a manageable pain level that allows the patient to achieve their specific EOL goals (decrease pain that interferes with sleep, visiting with friends and family are examples).

The most commonly continuous intravenously infused opioids include morphine, hydromorphone, and fentanyl [16–20]. Parenteral use of oxymorphone and buprenorphine are limited to IV slow push [13–15]. There is emerging data with sufentanil and remifentanil being used outside of anesthesia as infusions for pain [1]. Many can be administered intramuscularly, however this is not a preferred route of administration [4, 6, 7]. IM administration is limited due to pain with injection, erratic absorption, and local injection site reactions.

Opioid continuous infusions and basal rates on PCAs are best reserved for opioid tolerant patients who have already been on established doses of opioids to prevent respiratory depression. The FDA's definition of opioid-tolerant is daily consumption

Table 5.1 Adult opioid equivalency table [5, 7, 11, 13–15]

Drug	IV	Oral
Morphine	10 mg	30 mg
Hydromorphone	1.5 mg	7.5 mg
Fentanyl	100 mcg	Not available
Oxycodone	Not available	20 mg
Hydrocodone	Not available	30 mg
Oxymorphone	1 mg	10 mg
Tapentadol	Not available	75–100 mg
Codeine	Not available	200 mg

Data supporting these conversions are from single dose finding studies of reported pain relief following minor procedures. Equianalgesic doses are approximate. To account for incomplete cross tolerance, a 25–50% dose reduction is recommended when converting between opioids

the following oral (unless otherwise specified) doses for 7 days or longer: 60 mg morphine, 30 mg oxycodone, 15 mg oxymorphone, 8 mg hydromorphone, or 25 mcg/hour transdermal fentanyl patch [23]. The basal rate method on the PCA can replace a long acting opioid formulation for patients that are unable to take oral (strict nothing by mouth, NPO). If the opioid the patient is tolerant to is available parenterally, using that same opioid simplifies conversion from PO to IV. Efficacy has been demonstrated with the same parenteral opioid as used orally in acute pain episodes [20]. Oral opioids lose potency with absorption and first-pass metabolism, thus all opioids when converted from PO to IV will need a dose reduction to account for 100% bioavailability of the IV formulation. Most sources cite a 1:3 conversion from IV to PO morphine, 1:5 from IV to PO hydromorphone, refer to Table 5.1 [5, 7, 13–15].

PCA: Patient Controlled Analgesia

Opioids infused via PCA without a basal rate are more routinely encountered than non-PCA opioid infusions due to their appropriate use in opioid naïve patients for acute pain. They have been routinely prescribed for analgesia while hospitalized following surgery or trauma since their development in 1968 [21, 22]. Contraindications for use include altered mental status, low cognitive ability (severe developmental delay), extremes of age (infants, toddlers, elderly) or any bilateral upper extremity physical impairments or injuries to hands/arms that prevents a patient's use of the PCA button [21]. Since PCA development, there have been dramatic improvements in the technology available for PCA administration, security for bedside storage, and use has moved from specialist prescribing to general physician prescribing. Locking devices on the smart pump and pump programing are routine to prevent pump or drug manipulation and misprograming that could result in medication errors. PCAs have been error prone in the past with the complexity of pump programing and transcribing orders into the pump. It is estimated the US healthcare system spent $12 million in 2010 related to PCA medication errors, excluding legal costs [24]. Given the risk for respiratory depression and cases of

PCAs leading to overdose deaths, the Institute of Safe Medication Practices (ISMP) classifies opioid infusions as "High Alert" and provides a series of recommendations for safe use [25–28]. Limiting the number of available standard concentrations, using tall man and bold lettering to differentiate sound-a-like look-a-like medications (example: **HYDRO**morphone versus morphine), nurse monitoring, and double check processes when programing the PCA infusion pump are some safety recommendations provided.

PCA dosing is complex and contains several variables that are opportunities for dose customization [21, 22, 24]. The loading dose provides analgesia during initial PCA setup after the tubing has been primed. The patient-initiated dose (PID) is that dose demanded by the patient and is associated with a PID lockout interval, of which doses are not administered by the pump despite demands that may be made by the patient during that interval. Patient lockout intervals dictated by half-life of the drug selected and are a safety mechanism to prevent over dosage. The shorter the half-life of the drug the shorter the PID lockout interval can be, refer to Table 5.2

Table 5.2 Adult pharmacokinetic comparison of IV bolus and continuous infusion opioids [13–15]

Drug	Onset	Peak	Duration of action[a]	Half-life ($T^{1/2}$)	Metabolism
Morphine	5 min	20 min	2–4 hours; longer with prolonged infusions or renal impairment	2–4 hours	Both hepatic glucuronidation to active and inactive metabolites and renal elimination of active metabolites and unchanged parent drug
Hydro-morphone	5 min	15–30 min	3–5 hours; longer with prolonged infusions or renal impairment	2–3 hours	Major: Hepatic glucuronidation to inactive metabolites Minor: 7% excreted unchanged parent drug in urine
Fentanyl	<1 min	3–4 min	30–60 minutes; longer with prolonged infusions, or obesity, concomitant CYP3A4 inhibitors, or renal impairment	2–4 hours; becomes extended, ~20 hours, with prolonged use due to lipophilicity and tissue accumulation	Major: Hepatic CYP 3A4 to inactive metabolites Minor: 10% excreted unchanged parent drug in urine Highly lipophilic and distributes widely to tissues. As slowly releases from the tissues may increase duration of exposure following drug elimination from plasma or cessation of therapy

[a]Duration of analgesia following IV bolus dose, duration of action becomes extended with prolonged infusions, duration of respiratory depression or other adverse effects may persist longer

for pharmacokinetic comparison of infused opioids. Most commonly used lockout interval at time of PCA initiation is 8–10 minutes. In addition to the PID, there is a nurse (RN)-initiated boluses dose option with a separate lockout interval. The nurse is able to bolus directly off of the PCA pump at the bedside when the patient's pain is severe and cannot be controlled with PID doses. Some PCA technology allows for a 1 hour and 4 hour maximum dose and if attained a lockout period will be applied. Lockout intervals equivalent to 20–30 mg IV morphine were used in clinical trials [21, 22]. Since there is less evidence to support hourly or four hour maximum doses their use is optional and at the discretion of the prescriber. For common PCA dosing parameters, please refer to Table 5.3.

For PCA drug selection, morphine is the gold standard for palliative and EOL care [4, 6, 7]. Hydromorphone and fentanyl are considered other first line alternatives based on indication for the PCA. Morphine is avoided in acute care settings due to adverse effects of hypotension, itching, and a high proportion of patients with chronic kidney disease or renal failure who would experience accumulation of active metabolites with prolonged use [21, 22]. Ten percent of morphine is converted via hepatic metabolism to an active metabolite, morphine-6-glucuronide (M6G), which is more potent and has a longer half-life than the parent compound and is renally eliminated. For these reasons, hydromorphone, albeit structurally similar to morphine, tends to be a preferred first line option over morphine for acute pain in procedural or trauma settings.

Fentanyl is commonly used in acute care as a second line agent for patients who demonstrate intolerance to hydromorphone or morphine and a 50% improvement in common adverse drug effects are seen (nausea, itching, sedation, urinary retention) [24]. Since morphine and hydromorphone are structurally similar, converting from one to the other may not offer a large improvement in side effects. Fentanyl, unlike hydromorphone or morphine does not have active metabolite(s) that have the potential to accumulate which may explain its improved tolerability. Downfalls to fentanyl include hepatic metabolism by CYP3A4 that could result drug-drug interactions, a short half-life and thus need for more frequent PCA PID administrations, and high lipophilicity resulting in tissue drug accumulation that can result in delayed sedation and respiratory depression if used for >4 days [21, 22].

See Table 5.3 for common opioid PCA dosing; it is recommended to start opioid naïve doses at the lower end of the PID range and the high end of the lockout interval upon initiation and use the reported ranges for titration of the PCA to avoid respiratory depression [21, 22, 24]. Lowest doses provided in the opioid naïve range are recommended for those with opioid sensitivity risk factors, such as elderly age or kidney or liver dysfunction. In studies, a lower PCA PID with a shorter lockout interval require less rescue naloxone than higher PID doses with longer lockout intervals [22]. From an efficacy standpoint, however, patients prescribed low PID doses will be more likely to have unmet PID attempts during the lockout interval. If the patient's pain is not controlled, adjustments to PCA dosing can be made to either the PID or lockout interval. If the patient's pain does not result in a 20–30% reduction on the NRS or VAS with each PID, increase the PID prior to decreasing the lockout interval. Lockout intervals can be shortened if the patient reports adequate

Table 5.3 Adult IV opioid PCA dosing [13, 21, 22, 24]

	Opioid naïve initial PID	Opioid naïve PID range	Opioid tolerant initial PID[a]	Opioid tolerant PID range[a]	PID lockout interval	RN initiated bolus dose	RN bolus dose lockout interval
Morphine	1 mg	0.5–2.5 mg	2 mg	2–5 mg	5–10 min	100–200% of the PID	30–60 minutes
Hydromorphone	0.2 mg	0.05–0.4 mg	0.4 mg	0.4–1 mg	5–10 min		
Fentanyl	12.5 mcg	10–25 mcg	25 mcg	25–50 mcg	4–10 min		

[a]Dose will vary based on patient's chronic opioid regimen

analgesia with each PID, but reports escalating pain before the end of the lockout interval.

Another PCA dosing strategy that has been studied successfully in the sickle cell disease population is determining the needed total daily dose of opioid and providing 33% of the dose as a basal rate infusion and reserving 66% of the daily dose as available PID doses (high demand dose, low infusion rate; HDLI) [29]. This small randomized-controlled trial compared this dosing strategy to the reverse dosing strategy of 66% of the total daily dose as a basal rate infusion and the remaining 33% available as PID doses (low demand dose, high infusion rate; LDHI). An 8 minute lockout was used in both treatment arms and 4 hour maximum was at the discretion of prescriber. The total daily dose (TDD) of opioid used and hospital length of stay (LOS) in the adult population was 2.5 times higher in the HDLI versus LDHI arms despite similar reductions in pain, time to improvement, and patient global impression of change scale. Study results are limited due to a small sample size and lack of characterization of chronic opioid use prior to study enrollment.

Basal rates are the last option to add to PCA for select patients only and are relatively contraindicated in opioid naïve patients. Risk of respiratory depression increases 6–20 fold with basal rate added to PCA, routine use is not recommended [30]. The risk of opioid-induced respiratory depression on PCA is the highest 8–24 hours after PCA initiation. Morphine basal rates of 0.5–2 mg/hour have been shown to increase exposure to active metabolites, accumulation proportional to rate of the basal infusion, demonstrated without kidney or liver dysfunction. While empiric dosing for basal rates for PCA for opioid naïve patients has been cited in older references for acute pain, it is not discussed in detail in this chapter since harm has been demonstrated and a practice change ensued. Since the basal rate setting of the PCA provides the same effect as an opioid continuous infusion, doses could be cross-referenced with those cited in Table 5.4.

For opioid-tolerant patients that require a basal rate on their PCA to replace a long-acting oral opioid, use of an opioid equivalency table and conversion, is instead recommended (until a better method can be developed) [21, 22]. For example, a patient stable on oral long acting morphine of 60 mg per day, would require 20 mg per day of intravenous morphine as a continuous infusion (or approximately 0.8 mg/hour as a continuous infusion.) A 50% dose reduction to account for incomplete cross-tolerance, is recommended if the intravenous opioid is not the same as the oral opioid. Lower dose reductions (25% instead of 50%) can be considered based on indication (EOL, palliative care) and severity of pain upon presentation. The timing of the substituted PCA basal rate is at the discretion of the prescriber but should be initiated at the end of the dosing interval of the last known dose of their long-acting opioid to prevent dose overlap for patients with controlled pain whom require a change in route due to NPO status.

Improved NRS/VAS and patient satisfaction is seen with the use of PCA rather than every 1–2 hour RN initiated bolus dosing as it prevents delays in care [31]. Older evidence suggests PCA superiority to RN initiated boluses; however, at the time PCA was compared to IM opioid injections, which are no longer a standard of care and are also painful [21, 22]. Since PCA dosing is focused on small frequent

Table 5.4 Adult opioid naïve IV and infusion dosing [12–15]

	Initial IV bolus dose[a,b]	IV Continuous infusion dose[c]
Morphine	**Pain:** 2.5–5 mg q3–4 hours PRN **Procedural:** 2–3 mg q5 min PRN until desired analgesic effect or adverse reaction up to 10 mg/dose **MI**: 2–8 mg q1–2 hours PRN **Critical illness:** 2–4 mg IV q1–2 hours PRN	**Pain:** 0.8–10 mg/hour titrated to desired effect; doses of ≥20–30 mg/hour have been reported in EOL **Critical illness:** 2–30 mg/hour
Hydromorphone	**Pain:** 0.2–1 mg q2–3 hours PRN **Critical illness:** 0.2–0.6 mg q1–2 hours PRN **ED:** 0.5 mg IV q15min ×2–3 doses until achieved desired analgesia	**Critical illness:** 0.5–3 mg/hour
Fentanyl	**Peri-procedural:** 50–100 mcg q1–2 hours PRN **Critical illness:** 0.35–0.5 mcg/kg q30–60 min PRN (25–35 mcg for 70 kg patient)	**Pain:** 10–50 mcg/hour when added to PCA settings **Critical illness:** 0.7–10 mcg/kg/hour; 50–700 mcg/hour for a 70 kg patient

Abbreviations: *CKD* chronic kidney disease, *ED* emergency department, *EOL* end of life, *KG* kilogram, *MCG* microgram, *MG* milligram, *mL* milliliter, *MI* myocardial infarction, *MIN* minute(s), *PRN* as needed

[a]Dose reductions are recommended for frail or elderly patients. Start at lowest dose recommended in ranges. Doses may listed for off-label indications, refer to package labeling

[b]Dose reduce for CKD/hepatic disease by keeping the same bolus dose but increase the interval between redosing to avoid accumulation and adverse effects

[c]Should be reserved for opioid-tolerant patients for an indication of pain. Dose reduce for CKD/hepatic disease by using a lower hourly rate of infusion. Hourly basal rate can be calculated by totaling q5–10min boluses that achieved desired analgesia. If pain is not controlled on maintenance basal rate, recommend adding IV bolus doses prior to increasing basal rate. If increased pain is persistent and IV boluses are required to maintain analgesia, then increase the rate of the continuous infusion once steady state has occurred. Changes in the basal rate should occur no more frequently than every 12–24 hours

doses in opposition to larger, less frequent RN administered boluses, lower CNS-type adverse effects with PCA are noted. Up to nine-fold improvements in confusion rates have been documented in patients treated with PCA in comparison to comparator parenteral (IV/IM) opioids. A more recent systematic review of more recently published data, however, indicates PCAs are associated with increased risk of pruritus without improvements in other adverse side effects or hospital length of stay [31].

Routine PCA utilization following surgery is declining with the use of enhanced recovery after surgery protocols (ERAS) that encourage early oral intake of both food and medications following surgery as well as multimodal therapy [32]. Opioid drug shortages have also impacted health-systems' ability to provide PCA universally to post-surgical patients, so initiating oral opioids immediately following surgery has been encouraged whenever possible [33].

To transition off of PCA, oral opioids have a longer duration of action due to slower absorption and onset in comparison to IV [13–15]. For patients on basic

PCA settings for acute procedural pain, improved analgesia with lower than equianalgesic oral doses may be observed, particularly if rotating to a new opioid. Initial package insert oral dosing can be trialed with as needed breakthrough IV RN-initiated bolus doses to replace the PCA if the oral transition provides inadequate analgesia. Oral opioids allow for longer intervals for redosing can be used which also facilitates longer sleeping intervals. Range orders are acceptable to allow the patient to use lower doses at rest and higher doses with activity. Patient education should be provided since oral opioid onset is slower than intravenous, which may require planning prior to known incidental pain such as ADLs or physical therapy (PT). Furthermore, if prolonged intervals between oral redosing are attempted and pain becomes severe, time to pain relief will be longer with oral in comparison to IV.

Opioid Continuous Infusions

Outside of basal rates on PCAs, opioid continuous infusions are generally reserved for palliative, comfort and EOL care, for critically ill patients requiring ventilation, and when the patient's mental status does not allow for PID usage on a PCA [12–15]. If a patient has a stable mental status and has the cognitive ability to deliver their own bolus doses, then PCA administration would be a preferred option when patients are unable to tolerate oral analgesia [4, 6, 7].

Initial dosing opioid continuous infusions will vary based on patient prior exposure to opioids in both the ambulatory and acute care settings [16–19]. Table 5.4 has commonly used opioid infusion ranges. Despite continuous infusion opioid being generally reserved for severe intractable pain that is around-the-clock, it is valuable to start the patient with bolus dose opioids every 5–15 minutes until desired level of analgesia is achieved or limiting adverse effects are noted. The total boluses required to achieve analgesia can be used to calculate an hourly infusion rate. If the patient is taking oral opioids as an outpatient, daily utilization can be used to calculate a total daily dose (TDD) that can be divided by 24 hours for the hourly rate by using an opioid conversion table.

Decreasing the calculated daily dose by 25–50% will be required based on patient's level of analgesia to account for incomplete cross-tolerance when converting between opioids. If a patient is being converted to intravenous therapy with the same opioid as used orally, a reduction for cross-tolerance is not needed, but the dose should be reduced due to improved IV bioavailability using standard oral to IV conversion ratios (see Table 5.1). If there is a change to the opioid drug when converting to intravenous infusion, sources recommend a 50% dose reduction upon initiation to be conservative as opioid equivalency conversion tables were developed using single doses trials and not with continuous infusions [11, 16–19]. Depending on severity of pain and level of monitoring available, it may be safer to under dose the infusion (with a 50% rather than 25% dose reduction) at time of initiation and have liberal availability of bolus doses. For example, a 25% dose reduction with conversion for a hospitalized hospice patient being transitioned from oral hydromorphone to IV morphine with poorly controlled pain due to the increased

monitoring is reasonable. Conversely, a 50% TDD reduction with conversion is reasonable in a homebound hospice patient in the same situation, where the conversion is taking place in the home setting with less monitoring available.

Bolus doses should accompany continuous infusions and are usually 10–20% of the total daily requirement (or approximately 100–200% of the hourly basal rate) [16–19]. Nurse-initiated boluses should continue to be available to be administered every 1–2 hours if needed for moderate to severe pain despite the ongoing infusion. Adjusting the hourly rate will require time to distribute to peripheral tissues and accumulate to produce a response at steady state. Therefore, a bolus dose should be used with rate adjustments for pain that is not controlled. Adjustments to the hourly rate should be avoided until the dose has infused for approximately five half-lives (approximately every 12–24 hours), and boluses should be used in the interim. If pain is not at desired goal, adjustments to the hourly rate should be made in increments of 10–20% (including the sum of the administered bolus doses) to achieve analgesia.

Indication for the continuous infusion will drive the goal infusion rate to minimal or no boluses. For acute procedural pain where incidental pain is expected with ambulation and other ADLs, boluses will be required to manage incidental pain. For palliative and pain at EOL, it is reasonable to up titrate the infusion rate until no boluses are required and analgesia is achieved without severe adverse effects. Bolus doses may later require adjustment depending on the final opioid continuous infusion rate that provides analgesia.

Opioid Continuous Infusion Product Selection

Morphine, Hydromorphone and Fentanyl

First line choice of opioid for infusion will be between morphine, hydromorphone and fentanyl. Morphine is the most commonly cited as it has been available longer and is has been more cost effective than alternatives in the past, although all products are now available as generics. Morphine continues to be the preferred primary opioid in EOL and palliative care but hydromorphone is a more common selection for acute noncancer pain in the perioperative or trauma setting [4, 6, 7, 16–19, 24]. Refer to page 7 in the PCA section to review the intra-drug variability to assist with drug selection for continuous infusions as those concepts also apply to continuous infusions. Unique to fentanyl as a continuous infusion, slower rates of infusion are recommended to avoid chest wall rigidity that may complicate ventilation and lead to respiratory distress [13–35]. Morphine active metabolite accumulation in renal insufficiency is also more likely with a continuous infusion than by PCA without basal rate.

Continuous infusion fentanyl has demonstrated a shorter return of bowel function and decreased length of stay in comparison to morphine following abdominal surgery [36]. Fentanyl recipients experienced a statistically lower diastolic blood pressure which resulted in more crystalloid administration; however, the difference

is likely clinically insignificant. Pain control and sedation scores during the hospital stay were clinically similar only with slight statistical differences on post-operative day (POD) 1. Continuously infused fentanyl at 100 mcg/hour in comparison to every 30 minute 100 mcg IV boluses appears to have similar efficacy for pain control with lower risk of respiratory depression, particularly when combined with benzodiazepines for procedural pain and conscious sedation. The total fentanyl dose administered in each of the groups was equal, suggesting respiratory depression is due to peak serum concentrations [36, 37].

Sufentanil and Remifentanil

Sufentanil and remifentanil are synthetic, ultra-potent, fentanyl analogues with ultrashort half-lives, their specific pharmacokinetic parameters are shown in Table 5.5. They are FDA labeled for anesthesia but have been used and studied off-label for pain indications as both PCA and by continuous infusion [38–40, 42, 43]. Since sufentanil and remifentanil do not accumulate, even in high doses, and undergo rapid tissue metabolism their effects can be reversed rapidly with infusion discontinuation, which offers an advantage over fentanyl [22]. For a pain indication, this can be problematic if additional drug is not readily available when the previous dose finishes infusing, however, may prove beneficial in labor and delivery and procedures where nociceptive pain has a distinct endpoint. Remifentanil's unique rapid tissue hydrolysis makes it a safer opioid for metabolically immature neonates and offers a niche in labor and delivery for women that do not qualify for epidural analgesia [41]. Remifentanil in labor and delivery was studied with a PID of 0.5 mcg/kg with a short 2 minute lockout interval or a combination continuous infusion at 0.05–0.1 mcg/kg/min with a 10 mcg fixed PID and 1 minute lockout interval. Low rates of common adverse effects were noted, and episodes of respiratory depression did not occur. Despite placental transfer of remifentanil, neonatal adverse effects were minimal and drug levels in the cord were low.

Sufentanil studied in the perioperative setting used PCA PIDs of 4–6 mcg combined with a range of lockout intervals between 1 and 10 minutes. Currently published studies use sufentanil and remifentanil in highly monitored post-surgical

Table 5.5 Pharmacokinetics of sufentanil and remifentanil [13–15, 22, 38–41]

Drug	Onset	Peak	Duration of action	Half-life ($T^{1/2}$)	Metabolism
Sufentanil	1–3 min	1–3 min	5 min	0.7–1.2 min, improves to 2.7 hours with redistribution and redosing	Hepatic and intestinal tissue N-dealkylation and O-demethylation
Remi-fentanil	1 min	1 min	3–10 min	3–10 min, improves to 10–20 min with redosing	Rapid by blood and tissue esterases. No hepatic metabolism

or labor and delivery settings with anesthesia trained personnel available, which is different than current US practice standards for monitoring patients on general wards prescribed opioid infusions or PCAs but offers an opportunity for future growth and study in the US.

Parenteral and Oral Methadone

Methadone when used parenterally is usually given by slow IV push, less commonly by PCA, and only by case reports of use as a continuous infusion. Continuous infusion methadone at steady state is not commonly required due to its long half-life (refer to Table 5.6). Intravenous methadone should be a last-line option for patients requiring opioid infusion therapy, although methadone does have a unique niche in palliative care [4, 6, 7, 44]. Methadone's NMDA receptor antagonism provides inherent multimodal therapy in addition to its μ receptor agonism [2, 7, 44]. Opioid rotation to methadone can provide symptomatic relief of opioid-induced neurotoxicity such as myoclonus, allodynia and hyperalgesia seen at very high infusion rates of other opioids.

Methadone has a black box warning due a known fatal arrhythmia called torsades des pointes induced by a prolonged QTc interval seen on electrocardiogram (EKG) [44–46]. A normal QTc interval is <450 milliseconds (ms) and as it extends to ≥500 ms is strongly associated with arrhythmia. The FDA has reported methadone's incidence of QTc ≥500 ms and torsades des pointes is >16% and 3.6%; respectively. Risk of prolonged QTc and torades des pointes is linearly dose-related and a significant increased risk has been noted at oral methadone doses ≥100 mg/day. Guidelines now recommend a baseline EKG prior to initiating methadone, follow-up EKG 2–4 weeks after therapy initiation or dose adjustments, and if other QTc prolonging medications or conditions are prescribed or diagnosed concomitantly with methadone therapy [45, 46].

Table 5.6 Pharmacokinetics of methadone [13–15]

Drug	Onset	Peak	Duration of action	Half-life ($T^{1/2}$)	Metabolism
Methadone	10–20 min (IV) 30–60 min (PO)	1–2 hours	4–8 hours (single dose) 22–48 hours (repeated doses, steady state), longer with concomitant CYP inhibitors	8–59 hours	Hepatic CYP 3A4, 2B6, 2C9, 2C19, and 2D6 to inactive metabolites Highly lipophilic and distributes widely to tissues. As slowly releases from the tissues may increase duration of exposure following drug elimination from plasma or cessation of therapy

If the patient can take oral methadone by tablet or solution, the enteral formulation is preferred [44–46]. The bioavailability of oral methadone ranges from 36% to 80% [13, 47]. The standard of practice for oral methadone to IV conversion is to dose reduce methadone by 50% (2:1, PO to IV) [44]. The parenteral formulation of methadone has an increased propensity of causing QTc prolongation due to a preservative called chlorobutanol that independently prolongs the QTc. Reversing hypokalemia and hypomagnesemia, converting to oral methadone, avoiding antiemetics known to prolong QTc are management strategies to help reverse the elevated QTc associated with IV methadone.

With methadone's niche use in palliative and EOL care, most often the benefit of analgesia and reversal of opioid-induced neurotoxicity outweighs the risk of QTc prolongation. Since methadone is not a standard opioid for infusion therapy, there are not any recommended or standard initial doses for infusion or PCA therapy. Successful dosing by infusion and PCA in case reports have been obtained by conversion methods from other opioids which is another challenge [48, 49].

Methadone has a nonlinear conversion from morphine [47, 50]. The most commonly accepted method to convert to oral methadone is cited below in Table 5.7. However, there are case reports where this conversion method results in an increased adverse effects due to too aggressive of an initial methadone dose [52]. Initial oral methadone doses should not exceed 30–40 mg/day and should be divided every 8–12 hours. Some sources cite a 4:1 rather than 3:1 initial conversion ratio as cited in Table 5.7 [47, 50]. Toombs suggests a dosing algorithm using the conversions shown in Table 5.7, but conversion is more conservative [47]. As always, with opioid conversions, it is better to start a lower dose and allow liberal use of short acting, as needed, breakthrough medication during the titration. Avoiding rapid titration of methadone will help reduce the risk of delayed respiratory depression due to its long half-life [5, 7].

Transitioning from other infused opioids to intravenous methadone is complex as it will require several drug and route conversions and is recommended only under the care of a pain or palliative care expert. Admission to an inpatient palliative care

Table 5.7 Conversion to oral methadone [46, 47, 51]

Average daily ORAL morphine usage	ORAL morphine to ORAL methadone conversion ratio
≤100 mg	3:1
101–300 mg	5:1
301–600 mg	10:1
601–800 mg	12:1
801–1000 mg	15:1
≥1001 mg	20:1

[a]Methadone total daily dose to be divided q8–12 hours. Initial methadone doses >30–40 mg/day is not recommended following conversion

[b]Adult initial dose for oral methadone starts at 2.5 mg q12 hours [47]

[c]These conversions should not be used to convert patients off of methadone to other potent opioid analgesics; methadone to morphine conversions are recommended in reference [51]

unit for titration and frequent nurse monitoring of vitals and assessment of adverse effects is recommended. Advanced planning for discharge from the hospital on parenteral methadone may be required as its use for outpatients with home health infusion or at hospice is rare.

Transitioning from an Opioid Infusion to Oral Opioids

Many patients following a hospital admission for an opioid infusion for pain control, will discharge home on oral or transdermal rather than parenteral opioids [4, 6, 7]. Transitioning off the parenteral opioid to a regimen for ambulatory use is more successful if planned a day or two prior to hospital discharge to ensure the transition is successful. Advanced planning is advised to allow for breakthrough IV bolus dosing if under dosing occurs and additional nursing monitoring and assessments if overdosing occurs. Either situation is likely given limited patient population opioid equivalencies were studied [11]. If the parenteral opioid is available orally, transitioning to that opioid will be less complex than converting to a new opioid via a new route of administration.

Converting from parenteral to oral opioids (morphine, hydromorphone, oxycodone are examples) is recommended as follows: ensure nonopioid multimodal medications are scheduled and maximized, calculate the total average IV 24 hour dose utilized, use an opioid equivalency conversion table to convert to desired opioid, then decrease total daily dose by 25–50%. If using short-acting opioids only, then divide total daily dose by 6 for an every 4 hour regimen to get the prescribed dose [16, 17]. Each dose for the first 24 hours following IV to oral conversion should be given scheduled. Use of immediate-release versus long-acting is at the discretion of the provider based on the indication. In cancer, palliative care, and EOL would recommend a combination of long and short-acting opioids to provide pain control around-the-clock as well as for incidental pain [4, 6, 7]. In acute pain, given new guidelines and risk for harm associated with long-acting opioids, would recommend short-acting opioids first line and the addition of long acting opioids a second line option [8–10, 22]. Alternatively, a more simple approach to parenteral to oral opioid conversion, for patients using only minimal to moderate opioid naive parenteral doses, just iniate the oral opioid with the recommended initial range cited as opioid naive in the package insert.

At the time of this chapter being written, a paradigm shift in outpatient opioid prescribing was underway by increasing prescription restrictions for patients without cancer, palliative or EOL conditions. Additional prior authorization paperwork was instituted by Centers for Medicaid and Medicare Services (CMS) as well as a majority of private pay insurers for >42 doses as a 7 day supply [53]. Previously, using a combination of both short-acting and long-acting opioids was recommended for acute pain management but efficacy data to support this recommendation for long term use are lacking. Data does suggest harm by respiratory depression and increasing risk of death with opioid requirements exceeding 50 and 90 MME (milligrams of morphine equivalents) per day [8–10]. Guidelines recommend to maximize scheduled non-opioid multimodal medications and nonpharmacologic therapy to titrate down opioid doses if possible to <50–90 MME for acute or chronic

noncancer pain. A naloxone rescue kit is encouraged (≥50 MME) and strongly recommended (≥90 MME) to be co-prescribed with the high dose opioid prescription. Careful counseling is needed as some naloxone kits have fixed doses that will also reverse analgesia. Careful patient selection is warranted, and the risk/benefit ratio in palliative care and EOL is less clear.

Transdermal Fentanyl Patch Transitions

The ratio when converting from IV or SQ fentanyl to long-acting transdermal fentanyl is 1:1 [13–15, 54–56]. There is a 6–12 hour delay in fentanyl plasma concentrations with application and removal of the fentanyl patch; intravenous continuous infusions should overlap by 6 hours with when transitioning to fentanyl patches. A 50% dose reduction in the IV continuous infusion should occur 3 hours after patch placement, then the IV infusion can be discontinued 6 hours after patch placement. An extended the overlap period from 6 to 12 hours was studied and found an 11-fold increase in adverse effects [54]. A pharmacokinetic study evaluating fentanyl serum concentrations has supported the 6 hour overlap conversion from IV or SQ to fentanyl patch [55, 56]. See Table 5.8 for fentanyl transdermal patch dose conversions recommendations by the manufacturer [57]. Note these recommendations already account for incomplete cross-tolerance and thus further reductions are not needed unless immediate release oral opioids will be used in addition to the patch for analgesia.

Intravenous Opioid Infusions and PCA at Hospital Discharge

Depending on severity of pain, availability of oral route, IV/SQ access, availability of infusion pumps and home health nursing, expected length of life, continuous infusion of opioids have been continued into the ambulatory setting instead of being converted to an oral or transdermal opioid regimen [18, 19, 34]. Subcutaneously (SQ) administered opioids are preferred to intravenous opioids and will be discussed in the next section [4, 6, 7]. Maintaining the opioid infusion intravenously into the ambulatory setting or into hospice requires maintaining intravenous access,

Table 5.8 Infusion conversion to fentanyl patch [57]

Morphine IV/SQ[a]	Hydromorphone IV[a]	Transdermal fentanyl dose
<10 mg	<1.5 mg	12 mcg/hour
10–22 mg	1.5–3.4 mg	25 mcg/hour
23–37 mg	3.5–5.6 mg	50 mcg/hour
38–52 mg	5.7–7.9 mg	75 mcg/hour
53–67 mg	8–10 mg	100 mcg/hour

[a]Average 24 hour opioid utilization. Recommend overlapping the infusion and patch for 6 hours for delayed onset of the patch. IV Fentanyl infusions can be converted 1:1 to fentanyl patch. Intermediate patch sizes are available. Table should not be used to determine reverse equianalgesia from fentanyl to other opioids. Additional reductions for incomplete cross-tolerance are not necessary; they are already factored into above recommendations from the manufacturer

access to an infusion pump and a home infusion pharmacy. The latter two requirements are also needed for subcutaneous infusion in the home. However, there are increased infectious risks associated with chronic intravenous access, making SQ preferred to IV. An established venous access device, however, is commonly already present in patients undergoing cancer treatment. Patient and family education is required from a safety standpoint and expectations need to be set if patient-initiated bolus doses (PID) via patient controlled analgesia (PCA) are prescribed for the home setting. Drug delivery, drug storage, IV access care, and pump education are additional pieces of education the patient and family will need for success in the home. A locking mechanism on the pump is recommended to prevent pump manipulation, diversion, or accidental or intentional overdose.

Subcutaneous Opioid Infusions and PCA at Hospital Discharge

For patients intolerant of oral or transdermal opioid formulations, subcutaneously infused opioids is preferred and as efficacious to intravenous opioids [4, 6, 7]. Limitations to subcutaneously infused opioids includes slower time to onset (although faster than oral), possibility of skin irritation, and an average 2–3 mL hourly volume restrictions at the administration site. Subcutaneous PCA for the home setting is also an option now that improvements to ambulatory PCA technology has been available. Subcutaneous opioids have been studied post-operatively in acute care settings, however, intravenous opioids are more convenient given IV access devices are routine standard of care for post-operative hospitalized patients [58].

The most common opioid for SQ administration is morphine; 75% of prescriptions dispensed for SQ opioids are for morphine [59, 60]. Palliative and EOL care represents 95% of indications for SQ morphine dispensed by hospice or home infusion pharmacies. Commercially available morphine concentrations are as high as 50 mg/mL to concentrate the volume of drug for subcutaneous infusion [13]. Hydromorphone is also available as concentrated as 10 mg/mL. Hydromorphone and fentanyl are second line alternatives to morphine; both more lipophilic than morphine with faster absorption and onset of action. SQ fentanyl is reserved for patients with a history of allergic reaction or adverse drug reactions to morphine and hydromorphone [61]. Subcutaneous methadone has been used in the past for palliative care but is now avoided due to local tissue irritation and availability of other opioids [60, 62].

Conversion from another oral or IV opioid follows the same convention of dose conversions as previously discussed in other parts of this chapter. The ratio when converting a TDD from oral to SQ morphine is the same for oral to IV morphine; 3:1. An example calculation is provided in the cited reference [60, 63]. If a PID dose is prescribed in addition to an infusion, 50% of the hourly infused dose is the recommended PID starting dose [59, 60]. Nearly all palliative patients converted SQ morphine will remain on therapy until death or a pain exacerbation that requires IV opioids or more advanced techniques [61].

Because a majority of SQ opioid use is reserved for palliative care, continuous basal rate infusions are commonly used to provide around-the-clock analgesia. SQ opioid PCA PID doses can be prescribed in addition to the basal rate. The SQ PID

dose should have a longer lockout interval in comparison to IV attributed to the long absorption time, commonly set at 20–30 minutes [59]. Time to onset from SQ may vary based on the patients' available adipose tissue, but averages 20 minutes. As patients' health and abilities decline in palliative and EOL care, PCA can be continued with PCA by proxy, where the surrogate caregiver (with training) can initiate doses based on patient's signs and symptoms of pain [60].

Preferred infusion sites are chest and abdomen [63–66]. Thigh, flank, and back can be considered as alterative infusion sites. If high doses are required beyond the hourly volume limits of 2–3 mL/hour higher volumes up to 7 mL/hour can be attempted but waning absorption and efficacy may be seen. If a higher concentration of infused drug is not alternative, then dual infusion sites with the same pump may be an option. Adverse effects to subcutaneous opioids, outside of local tissue irritation, are the same as intravenous opioids.

Monitoring requirements for SQ infused opioids are no different than IV for hospitalized patients. Rapid SQ titration is best completed in the hospital setting or can be titrated with IV while hospitalized then transitioned to SQ prior to being discharged for home. Slower titration and dose adjustments are feasible in the home setting with the assistance of a home health nurse or infusion pharmacy. For the home setting, another individual should be present in the home to help monitor for adverse effects. The infusion site should be checked twice daily and dressing changed at minimum once weekly [59].

Contraindications

The only absolute contraindication to infused opioids is severe hypersensitivity, such as anaphylaxis [12–14]. The incidence of anaphylactic reactions to opioids is rare. Cross reactivity between opioids may be seen with codeine and morphine as well as hydrocodone and hydromorphone as these parent opioids are metabolized to those listed subsequently. Itching due to histamine release seen with more natural opiates such as codeine and morphine are not hypersensitivity reactions, rather adverse effects of the drug itself. Other disease states in which opioid avoidance is recommended include acute respiratory syndromes with hypercarbia (if ventilator support is not available or not desired) and gastrointestinal obstructive conditions such as paralytic ileus. The opioid adverse effects can be additive to these disease states and prevent or delay resolution of the underlying disease state. Opioid addiction disease is not a contraindication to opioid infusion therapy in the hospitalized acute care setting, however the necessity of prescribing an oral opioid upon discharge may increase the patient's risk for relapse if not done in a highly monitored or supported setting.

Side Effects

While most opioids do not have a maximum ceiling dose, efficacy can be limited due to adverse effects. A majority of common opioid adverse effects are attributable to effects from binding in CNS include sedation, mental clouding, confusion,

dizziness, pinpoint pupils, urinary retention, and respiratory depression [1, 7]. Miosis, pinpoint pupils, is due autonomic stimulation of the oculomotor nerve and is sustained despite tolerance or chronicity of opioid use and is present nearly universally in patients prescribed opioids no matter the route of administration [2, 13–15]. Sedation, confusion, and delirium is more common when opioid infusions are prescribed to the elderly, in palliative care, and at EOL and reported as often as in 20–30% of cases, likely an additive side effect with waxing and waning mental status with advanced age, worsening end organ function and other underlying comorbidities [2, 7, 18–20, 34]. Sedation can be managed with dose reduction, slower titration, opioid conversion, or addition of CNS stimulants such as methylphenidate.

Less common CNS-related adverse effects from opioids include hallucinations, hyperalgesia, and myoclonus [7]. Hallucinations occurs <5% of patients and hyperalgesia and myoclonus are even less prevalent and are most often seen in very high intravenous doses most often seen in palliative care [7, 48–50, 52]. Hyperalgesia and myoclonus are best managed with opioid rotation; success has been cited with conversion to methadone in these situations [48–50, 52].

Euphoria from opioids result from modulation of the dopaminergic reward pathways deep in the brain in the nucleus accumbens and amygdala [2]. The euphoric, unintended anxiolytic, and reward effects provided by opioids can trigger aberrant behaviors and lead to misuse, abuse, and/or addiction in at-risk individuals. These adverse effects are less problematic with provider monitored infusion therapy and more often reported with orally prescribed outpatient opioids with an incidence ranging 1–8% [13–15]. Prior to the initiation of chronic opioid therapy (COT), and while maintaining ongoing COT, guidelines now recommend using screening tools to assess for risk factors [8–10]. Risk factors for misuse can include younger age (age 16–45), history of sexual abuse, uncontrolled psychiatric illness (including depression), substance use disorder (excluding tobacco) or family members with substance use disorder. COT, opioid use disorder, or heroin abuse can make acute pain management due to trauma or surgery with opioid medications more challenging due to the risk of opioid under treatment, need of escalating opioid doses, increasing risk for adverse effects, potential for underlying poor coping skills for recovery, and risk for ongoing or future misuse or abuse of therapeutic opioids in the latter two conditions.

Mu agonism exerted on peripheral smooth muscle such as bowel results in delayed peristalsis, constipation, and possibly ileus [67, 68]. Incidence of ileus following colorectal surgery is ranges 10–30% compared to ≤10% in non-abdominal surgeries and cause is multifactorial but opioids are strongly associated as a main contributor. Mu receptors in the gut block parasympathetic (cholinergic) neurotransmitter acetylcholine and also have antisecretory effects; both effects are dose related and can be prevented with opioid sparing or low dose opioid pain regimens following surgery. Oral, epidural, intravenous, and intramuscular opioids all cause constipation. There has been conflicting evidence that epidural opioids may have a lower incidence or lesser severity of constipation as they are administered directly to the CNS and limit peripheral and thus bowel opioid exposure [69, 70]. Epidural-based

pain regimens are still preferred for efficacy and to possibly avoid opioid effects on the gut for patients undergoing abdominal surgery. Constipation is the most commonly cited side effect associated with the use of intravenous and subcutaneous infusions in EOL care, with rates as high as 40–50% [18–20, 34].

The cause of opioid-induced nausea and vomiting is multifactorial. It is mediated both in the periphery by increased smooth muscle tone of the digestive tract (causing delayed peristalsis, delayed gastric emptying, and constipation) as well as centrally due to the undesired stimulation of the chemoreceptor trigger zone (CTZ), stimulation of the vagal nerve, and altering the vestibular system of the inner ear [67, 68]. If opioid-induced constipation (OIC) and delayed gastric emptying can be controlled, nausea from opioids diminishes with repeated dosing, lower doses, slower titration, timed with concomitant food intake, and with premedication with antiemetics. Hydromorphone may be better tolerated than morphine from a nausea standpoint [7]. When opioids are used for procedural sedation, premedication with steroids and antiemetics is used as anesthetics also cause post-operative nausea and vomiting (PONV) and have an additive effect [13, 68].

Urinary retention is mediated mainly by the CNS; increased parasympathetic activity results in impaired contraction of smooth muscles in the detrusor muscles, ureters and urinary sphincter [68]. The loss in smooth muscle tone also decreases urge to void. Rates of urinary retention due to opioids and following procedures vary widely in the literature (2–70%) due to a lack of a standardized definition but is strongly associated with opioids and is dose, route, and drug dependent. Epidural or intrathecal infused opioids do have a higher incidence of urinary retention. Lower lumbar placed epidurals have a higher severity and incidence of urinary retention. Addition of non-opioid multimodal pain drug regimens, removing epidural catheters, and lower doses of opioids improve urinary retention rates.

Opioids bind to mast cells and release histamine resulting in vasodilation, decreased blood pressure and opioid-induced itching that tends to be refractory to traditional antihistamine medications [24, 68]. The severity of the hypotension is proportional to plasma histamine levels and confounded by underlying disease states (shock, blood loss) and concomitant medications (anesthesia). This histamine release is more prevalent with natural opiates (morphine, codeine) and less common with semi-synthetics (hydromorphone, oxymorphone). Despite a lack of an effect on mast cells, pruritus is still reported with fully synthetic opioids such as fentanyl, sufentanil, and remifentanil with an incidence of 3–10% and as high as 18–25% with neuraxial administration or higher doses for anesthesia suggesting μ receptors play a role in pathophysiology of pruritus even without affecting histamine levels [7, 13–15, 69]. Morphine via neuraxial administration has the highest incidence of pruritus, up to 80%. Management of pruritus with antihistamines produces mixed results and sedation from concomitant use is additive to that opioids. Nalbuphine is a partial μ antagonist and kappa agonist and is indicated for acute pain control [71, 72]. It is more often used off-label at lower 2.5–5 mg intermittent IV push doses to prevent and treat opioid-induced itching. Due to nalbuphine's kappa agonism, unlike naloxone, it can be used more successfully in combination with opioids to treat itching without compromising analgesia nor increasing severe adverse effects.

Some opioid-induced adverse effects can be reversed with the use of other opioid receptor antagonists as naloxone, naltrexone, and methylnaltrexone [13–15]. Naloxone binds and antagonizes the μ receptor and is used for reversal of opioid-induced respiratory depression, oversedation, or opioid overdose/intoxication. Naloxone will reverse opioid-induced analgesia, so when administered it is recommended to administer frequent 0.1 mg doses until clinical effect has been achieved for patients with chronic cancer pain or following surgery. Continuous infusions of naloxone are recommended for patients with exposure to opioids with longer half-lives such as methadone or fentanyl patches, as the half-life of naloxone is very short when administered IV, IM or subcutaneously (SQ). Very low dose naloxone infusions have been studied in combination with opioids for opioid-induced itching with mixed results as it's effect is limited by worsened analgesia [71, 72]. Naloxone is also co-formulated with abuse deterrent oral or sublingual opioids without in vivo activity unless crushed and/or injected.

Naltrexone is available orally and by long-acting, monthly, intramuscular injection to maintain opioid abstinence, which has the potential to be problematic from a pain management standpoint with unanticipated acute trauma or unplanned surgery [13–15]. Methylated naltrexone (methylnaltrexone) is available by subcutaneous injection or by oral tablet to treat opioid-induced constipation via competitive antagonism to peripheral μ receptors without losing analgesia mediated by the therapeutic opioid the in the spine or CNS. Since the methyl group on methylnaltrexone has a positive ionic charge; it gives the drug polarity and is unable to cross the lipophilic blood brain barrier to affect μ receptors in the spine or CNS. Lastly, naloxegol is another peripherally acting μ antagonist with drug properties similar to methylnaltrexone. Both naloxegol and methylnaltrexone carry warnings about use in conditions such as Ogilvie's, peptic ulcer disease, invasive gastrointestinal (GI) malignancies where GI continuity is a concern and perforation has occurred. For these reasons, management of constipation with over-the-counter stimulants and laxatives such as polyethylene glycol, senna combined with docusate sodium, bisacodyl, and milk of magnesia are all preferred to peripheral μ antagonists.

Target Controlled Infusion (TCI)

Target controlled infusion (TCI) is a method of infusing drugs that is used with several intravenous drug classes most often by anesthesiologists [73–76]. Established drug doses for infusion are traditionally developed from pharmacokinetic studies where each dose or infusion rate produces an acceptable range of serum concentrations to produce a desired clinical effect and minimal adverse effects. Since patient pharmacokinetic parameters may vary greatly between patients and also from the study population, a range of dosing is cited to produce the desired clinical response. With target controlled infusions, patient specific pharmacokinetics are adjusted for continuously during the infusion. An established goal infusion serum concentration is established and a closed-loop computer or smart pump technology adjusts the infusion rate to produce the desired serum concentration to provide more targeted infusion therapy. Many opioids have been studied with TCI techniques outside of

the US in anesthetic and postoperative acute care settings. The technology for closed-loop smart pump adjustments has not yet been FDA approved to allow for use in the United States, but offers an opportunity for improved and more patient-tailored opioid infusion dosing to help reduce adverse effects with customized dosing for opioid infusions.

Opioid Infusion Monitoring

Patients prescribed opioids as a continuous infusion should be monitored no less frequently than every 30 minutes during initial titration of the infusion to monitor depth of respirations, respiratory rate, level of sedation, vital signs, oxygen saturation, and previously described adverse effects [16, 17]. Once titration is complete and goal analgesia has been achieved, nursing assessments and vital signs no less than every 4 hours is recommended. If adverse effects are noted, additional pharmacotherapies can be used to treat adverse effects, or the opioid can be converted to an alternative opioid, then more frequent every 30 minute nursing assessments should recommence.

Algorithm for Opioids Infusion Regimens (Fig. 5.1 and Table 5.9)

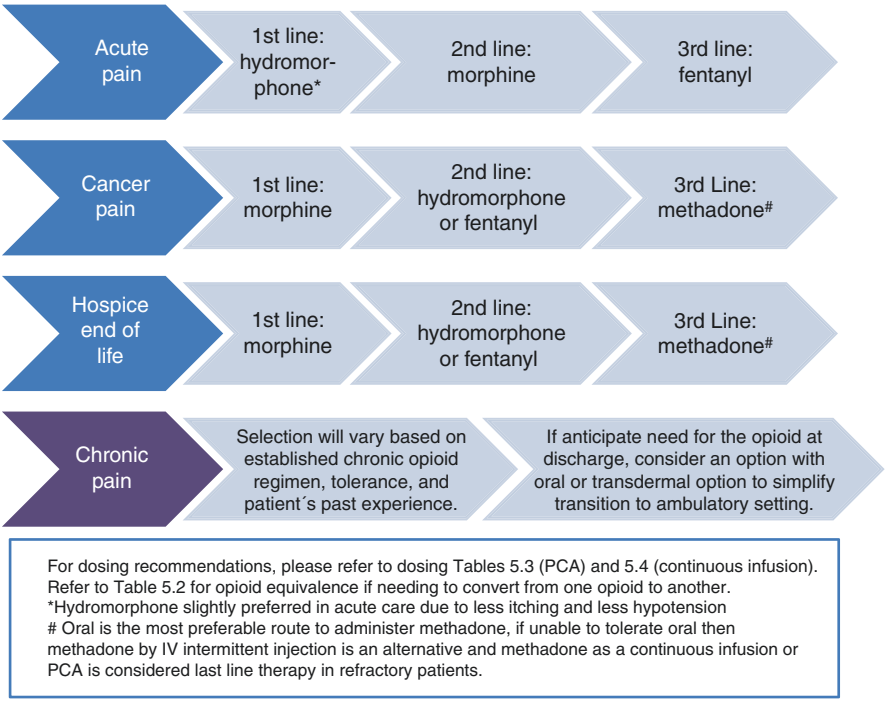

Fig. 5.1 Different opioids used for treating different tyes of pain

Table 5.9 Summary: Adult opioid naïve IV and infusion dosing [12–15]

	Initial IV bolus dose[a,b]	IV Continuous infusion dose[c]
Morphine	**Pain:** 2.5–5 mg q3–4 hours PRN **Procedural:** 2–3 mg q5 min PRN until desired analgesic effect or adverse reaction up to 10 mg/dose **MI**: 2–8 mg q1–2 hours PRN **Critical illness:** 2–4 mg IV q1–2 hours PRN	**Pain:** 0.8–10 mg/hour titrated to desired effect; doses of ≥20–30 mg/hour have been reported in EOL **Critical illness:** 2–30 mg/hour
Hydromorphone	**Pain:** 0.2–1 mg q2–3 hours PRN **Critical illness:** 0.2–0.6 mg q1–2 hours PRN **ED:** 0.5 mg IV q15min ×2–3 doses until achieved desired analgesia	**Critical illness:** 0.5–3 mg/hour
Fentanyl	**Peri-procedural:** 50–100 mcg q1–2 hours PRN **Critical illness:** 0.35–0.5 mcg/kg q30–60 min PRN (25–35 mcg for 70 kg patient)	**Pain:** 10–50 mcg/hour when added to PCA settings **Critical illness:** 0.7–10 mcg/kg/hour; 50–700 mcg/hour for a 70 kg patient

Abbreviations: *CKD* chronic kidney disease, *ED* emergency department, *EOL* end of life, *KG* kilogram, *MCG* microgram, *MG* milligram, *mL* milliliter, *MI* myocardial infarction, *MIN* minute(s), *PRN* as needed

[a]Dose reductions are recommended for frail or elderly patients. Start at lowest dose recommended in ranges. Doses may listed for off-label indications, refer to package labeling

[b]Dose reduce for CKD/hepatic disease by keeping the same bolus dose but increase the interval between redosing to avoid accumulation and adverse effects

[c]Should be reserved for opioid-tolerant patients for an indication of pain. Dose reduce for CKD/hepatic disease by using a lower hourly rate of infusion. Hourly basal rate can be calculated by totaling q5–10min boluses that achieved desired analgesia. If pain is not controlled on maintenance basal rate, recommend adding IV bolus doses prior to increasing basal rate. If increased pain is persistent and IV boluses are required to maintain analgesia, then increase the rate of the continuous infusion once steady state has occurred. Changes in the basal rate should occur no more frequently than every 12–24 hours

Summary

Opioids as infusions by PCA or by continuous infusion offer relief from pain for those going through acute procedures, injury from trauma, pain crises for cancer and noncancer pain, and for both pain and suffering in palliative and end of life care. Their analgesic effect is plagued by adverse effects that at the worst are life threatening and thus monitoring during use is recommended. Depending on the indication and intensity of therapy, rescue antagonists are available for reversal of adverse effects which can be administered by heath care professionals or in the home setting by caregivers if needed. Infusions of opioids by intravenous or subcutaneous routes are now possible in the home setting with the use of smart pump technology by offered by home infusion pharmacies and by hospice.

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Vitamin Infusion Therapy

6

Peggy Y. Kim and Ann Stumpf

B Vitamins

Introduction

The B vitamins are a group of water-soluble vitamins that are thought to support metabolism. Vitamin B_1, also known as thiamine, assists in carbohydrate metabolism and may have a role in nerve function. Vitamin B_2, also called riboflavin, is involved in the release of energy via the electron transport chain, the citric acid cycle, and in beta oxidation of fatty acids. Vitamin B_{12}, or cobalamin, is involved in the metabolism of carbohydrates, proteins, and lipids, and is involved in the production of nerve sheaths.

Mechanism of Action

The mechanisms of action of the B vitamins in the treatment of pain are not well characterized. However, it is thought that they may improve the function of mitochondrial respiration in tissues [1] and increase mitochondrial energy metabolism [2]. Methylcobalamin may promote nerve regeneration or remyelination and suppress ectopic nerve firing, as well [3].

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Indications

Mitochondrial Encephalomyopathy

Mitochondrial encephalomyopathies (MEM) are a group of disorders associated with defects in respiratory chain substrate utilization and/or mitochondrial oxidative phosphorylation coupling errors [1]. Treatment of these disorders involves decreasing toxic metabolite production, stimulating beneficial enzyme activity, and administering electron acceptors, such as cytochrome c (CC). However, it appears that combining CC with vitamins B_1 and B_2 may confer additional improvements [1].

One combination of CC and vitamins B_1 and B_2, Cardiocrome®, was administered intravenously to nine patients with MEM, with an two-fold dose increase if there was insufficient improvement. Two patients exhibited improvements in headaches and one patient's thalamic pain improved [1].

Uremic and Diabetic Neuropathy

Uremic neuropathy is a disabling symptom associated with hemodialysis patients [3]. The mechanism of nerve damage from uremia is unknown, but this polyneuropathy involving both sensory and motor systems starts in the distal lower extremities and can ascend as the polyneuropathy progresses. The pain is experienced as burning with dysesthesias. Renal transplantation can improve symptoms, but alterations in hemodialysis frequency have yielded mixed results [3]. In rat models, repeated ultra-high dose methylcobalamin, a vitamin B_{12} analogue, promoted nerve regeneration [4]. Excess vitamin B_{12} is typically excreted via the kidneys, but in hemodialysis patients, the serum concentration would be expected to be higher than patients with normal renal function, even after a typical dose.

In a pilot study, 192 dialysis patients were screened for polyneuropathy via a neuropathic symptom questionnaire, nerve conduction study, and neurological examination [3]. Ten patients were administered 500 μg methylcobalamin intravenously (IV) after each hemodialysis session. Clinical severity, nerve conduction studies and vitamin B_{12} assays were performed at baseline and at 6 months after initiating therapy. Vitamin B_{12} serum concentrations increased greater than 100 times baseline levels, neuropathic pain ratings significantly decreased, and ulnar and median nerve conduction velocities were significantly increased [3].

Postoperative Pain

Improving postoperative pain control and patient comfort while reducing adverse effects is a goal of many hospitals. Thus, infusions of various analgesic medications with adjuncts are periodically used, particularly if there are opioid-sparing benefits without significant side effects. One hospital evaluated the infusion combinations utilized at their institution, to determine which, if any, were effective for postoperative pain [5]. Four of their infusions included B vitamins as an adjunct. However, this study found the addition of B vitamins to be of "questionable" value [5]. Another placebo-controlled, double-blind study of diclofenac infusions with the addition of B vitamins did not detect any additive effects of the B vitamins [6]. Therefore, little evidence exists suggesting that B vitamin infusion combinations are effective for postoperative pain.

Contraindications

Allergies/anaphylaxis to the vitamins themselves are a contraindication. Allergies/anaphylaxis to beef is also a contraindication for the CC and vitamins B_1 and B_2 combination (Cardiocrome®), as the CC is extracted from beef heart muscle.

Contraindications to vitamin B_{12} infusions include hypokalemia, history of complete gastrectomy, atrophic gastritis, Leber's hereditary optic atrophy, and allergies to cobalt or cobalamin and its derivatives.

Side Effects

No detectable side effects were reported from the CC and vitamins B_1 and B_2 combination (Cardiocrome®), and it appeared to be stable and non-toxic even in large doses [1]. No adverse effects were noted from methylcobalamin administration, even when doses were in excess of 100 times the normal range [3]. Side effects of the B vitamins in general can include diaphoresis, warmth, cyanosis, restlessness, edema, pruritis, urticaria, pulmonary edema, weakness, nausea, and throat tightening.

Monitoring

Pre-infusion evaluation for the CC and vitamins B_1 and B_2 combination treatment included serum lactate levels, urinalysis, and CSF studies in one trial, but it is unlikely that this level of monitoring would be required for clinical use [1]. Baseline and 6-month post-treatment vitamin B_{12} serum concentrations may be advisable for monitoring deficiencies and treatment effect [3], as well as routine pre- and post-infusion vital signs.

Algorithm for Vitamin B Infusion Regimens

This table summarizes various doses published in the literature (Table 6.1). The goal of this table is to provide a guide for practitioners, but different doses might be necessary depending upon the setting and the patient.

Table 6.1 Algorithm for Vitamin B Infusion Regimens

Indication	Dosage
Mitochondrial encephalomyopathy	Cytochrome C + vitamin B_1 + vitamin B_2 (Cardiocrome®): 1 ampoule IV daily for 2 weeks, then 1–2 ampoules IV q1–3 days for 2–4 weeks
Uremic polyneuropathy	Vitamin B_{12} (methylcobalamin): 500 μg IV 3 times a week (after each hemodialysis session) for 6 months
Postoperative pain	B vitamins were NOT shown to be effective in combination with other analgesics, including diclofenac

Summary

The B vitamins are popular over-the-counter oral supplements, but the use of intravenous infusions for pain have been trialed on a more limited basis. Vitamins B_1 and B_2 in combination with cytochrome C (Cardiocrome®) may be helpful in treating symptoms of mitochondrial encephalomyopathy in children, including headaches and multifocal thalamic pain, at a dose of 1 ampoule IV daily for 2 weeks, then 1–2 ampoules IV every 1–3 days for 2–4 weeks. Vitamin B_{12} (methylcobalamin) may also be helpful in treating the pain and dysesthesias associated with uremia and hemodialysis, at a dose of 500 mcg IV 3 times a week (after each hemodialysis session) for 6 months. Intravenous treatment with B vitamins appears to be well tolerated, with few side effects. Little special monitoring is likely to be necessary, though baseline labs to determine potential deficiencies and treatment effect may be helpful, as well as routine vital signs. Additional research, including larger randomized controlled trials, is needed to ascertain the efficacy of vitamin B IV infusions for treating pain.

Vitamin C

Introduction

Vitamin C, also known as ascorbic acid, has been utilized as an intervention for multiple conditions. Spinal and musculoskeletal pain have been associated with vitamin C deficiencies, such as scurvy [7, 8]. There is some suggestion that vitamin C might exert analgesic properties beyond merely correcting deficits. In rat models of painful peripheral neuropathy due to chemotherapy, IV vitamin C was shown to reverse oxaliplatin-induced mechanical hyperalgesia [9]. Though data obtained from animal models do not always yield similar results when applied to humans, there is evidence that vitamin C may be helpful in treating pain from a variety of etiologies.

Mechanism of Action

As a water soluble antioxidant, vitamin C is thought to provide antinociceptive properties via both neuromodulation and neuroprotection. Its neuromodulating properties are important in three main ways. Vitamin C mediates glutamate and dopamine neurotransmission to ultimately inhibit the NMDA receptor [10]. It also serves as a cofactor of dopamine b-monooxygenase, which helps convert epinephrine to norepinephrine [11]. In addition, it is required for the release of synaptic vesicles filled with norepinephrine and acetylcholine, which are important for inhibitory pain pathways [12].

Vitamin C also serves a role in neuroprotection. As an antioxidant, vitamin C acts as an inhibitor in the formation of reactive oxygen species (ROS), an

established intermediary in neuropathic pain [10]. Furthermore, ROS generated by arterial walls have been linked to endothelial dysfunction, and vitamin C may also have beneficial effects on reducing coronary vasospasm [13]. Vitamin C may also be involved in the release of free oxygen radicals, which may exert cytotoxic activity on cancerous cells [14].

Indications

Cancer-Associated Pain

There has been considerable interest in vitamin C as a treatment for cancer-associated pain, whether the pain is caused directly by the cancer itself, such as with bony metastases, or from anti-cancer treatment. As noted above, in a rat model, vitamin C (50 and 100 mg/kg IV) was found to decrease oxaliplatin-induced hyperalgesia in a dose-dependent manner [9]. In a case report, a 45-year-old-female with recurrent breast cancer undergoing chemotherapy was administered 50 g IV vitamin C, 2 days before each chemotherapy cycle and 2 days afterwards for 2 months [15]. She reported noticeable improvements in fatigue, quality of life, and pain.

Vitamin C may also be helpful in treating pain from deficiency secondary to anti-cancer treatment. A 2-year-old boy with gastritis secondary to neuroblastoma treatment necessitating enteral feeding began reporting bilateral lower extremity pain [8]. The resulting malabsorption from his enteritis had led to a vitamin C deficiency, despite adequate vitamin C in his enteral feeds. Once this was replaced intravenously, he made a full recovery [8].

Pain from bony metastases may also be improved with vitamin C infusions. Metastases can cause edema in the bone due to increased vascular permeability and inflammation [16]. In a clinical trial of 50 consecutive cancer patients administered high-dose IV vitamin C for up to 10 days, several patients reported dramatic improvement of their pain and decreased opiate requirements within days of starting this treatment [17]. In a retrospective pilot study of 11 cancer patients with bone metastases status post radiotherapy and unresponsive to standard anti-cancer treatments, pain increased in intensity, often with an increase in metastatic sites and decrease in overall health [16]. These patients received 2.5 g ascorbic acid IV every week. The average reduction in pain scores on a visual analog scale (VAS) was 48.5%, with a mean follow up time of 10 months [16]. In a follow up retrospective study, 15 patients with bone metastases unresponsive to radiotherapy undergoing chemotherapy received IV vitamin C at the same dose, whenever their pain increased [14]. Fifteen other patients received chemotherapy but no vitamin C, and 9 patients did not receive vitamin C or chemotherapy (control group). Though no formal statistical analyses were performed, 8/15 patients in the vitamin C + chemotherapy group reported ≥50% reduction in pain, compared with 2/15 in the chemotherapy only group and 0/9 in the control group. Incidentally, the vitamin C group was found to have a median survival time of 10 months, whereas the chemotherapy only group and the control group had median survival times of 2 months each [14].

There is also evidence that vitamin C infusions may improve cancer patients' quality of life, including their pain. An 81-year-old male with inoperable recurrent angiosarcoma received 30 g of IV vitamin C, and reported a "complete cessation of pain" and his function and quality of life improved, as he became ambulatory again after previously requiring a wheelchair [18]. In a prospective study of 39 terminal cancer patients who were administered 10 g IV vitamin C then 4 g oral vitamin C, patients reported significant improvement in pain, fatigue, nausea/vomiting, sleep disturbance, appetite, and physical and emotional functional scales [19]. In a retrospective, multicenter cohort study of breast cancer patients undergoing chemotherapy and radiation, 53 patients received 7.5 g of IV vitamin C for at least 4 weeks, compared with 72 patients who did not receive vitamin C [20]. Unfortunately, the two groups were not equal in anti-cancer treatment; significantly more patients in the control group underwent chemo-, radio-, and hormonal therapy. The vitamin C treatment group exhibited significantly decreased intensity of cancer-related symptoms, though tumor pain by itself did not achieve statistical significance [20].

Another multicenter, open-label, prospective, observational study examined the quality of life of 63 cancer patients receiving high-dose IV vitamin C [21]. Patients received increasing doses to achieve serum concentrations of 350–400 mg/dL. Oral vitamin C was concomitantly administered. By the 4 week follow up, patients reported significantly decreased pain, as well as other symptoms such as fatigue, insomnia, and constipation; functional scales and global health status were also significantly improved [21].

A phase I clinical trial of high-dose IV vitamin C in 17 cancer patients reported improved pain scores from 36/100 down to 0/100 by week 4, but there was significant participant attrition [22]. In a retrospective study of 86 cancer patients who received IV vitamin C, 11/24 patients reported improved pain relief [23].

Virus-Associated Pain

Postherpetic Neuralgia Intravenous vitamin C infusions have also been utilized in the treatment of both acute and persistent virus-associated pain, such as that from varicella zoster virus reactivation, which results in a painful neuralgia in a dermatomal distribution known as postherpetic neuralgia (PHN). The virus typically remains dormant in a dorsal root ganglion, but may be reactivated during times of physical or emotional stress. After the vesicular eruption heals, pain may continue for weeks or months, which may significantly impact the patient's life. There are a few case reports which describe the use of IV vitamin C to treat acute PHN. A 67-year-old female with a 10-day history of zoster reactivation received 2 g IV vitamin C, which did not improve her pain, but additional doses of 4 g IV daily resulted in a complete resolution of her pain for at least 3 months [24]. A case series of two patients who were administered 15 g IV vitamin C treatments starting the day after vesicle eruption, reported that the rash and pain resolved by the 12th day of the illness [25]. Another case report described a patient treated with cantharidin patches, containing a poisonous compound secreted by the Spanish fly, and 7.5 g of IV vitamin C reported being "pain-free" 8 weeks later [26]. However, given that these were acute episodes, and the natural history of this disease is to improve within a few weeks, it

is difficult to know whether or not these acute episodes might have resolved on their own without the IV vitamin C treatments. An additional case report describes a 78-year-old male who experienced PHN for 8 months; he received 2.5 g IV ascorbic acid and his PHN pain improved within 1 week, with continued improvement at the 3-month follow up [27].

In a randomized, double-blind, placebo-controlled study of 41 patients with PHN for at least 3 months, patients received either an IV infusion of normal saline, with or without IV ascorbic acid 50 mg/kg [28]. Spontaneous pain and allodynia elicited by mechanical stimulation (brush-evoked pain) were measured before and after the infusions. Spontaneous pain decreased significantly in the vitamin C group by day 7, but there was no difference in brush-evoked pain [28]. Another multicenter, prospective cohort observational study of 67 patients with symptomatic herpes zoster were administered IV infusions of 7.5 g [29]. Improvement in pain scores, number of affected dermatomes, number of vesicles, and the presence of hemorrhagic lesions were statistically significant at the 2 and 12-week follow up visits. The risk of developing PHN was deemed to be reduced by the authors, since 6.4% of their participants developed PHN, as compared to 24.1% of participants in a similar study [29]. In a randomized controlled study of 87 patients admitted for herpes zoster, participants were administered IV normal saline with or without 5 g of ascorbic acid [30]. There was no difference in acute herpes zoster pain between the two groups, but by week 8, pain was significantly lower in the vitamin C group and there was a significantly decreased incidence of PHN compared to the control group, which potentially suggests a role of IV vitamin C in preventing PHN [30]. Since the appropriate dose for this indication has not been established, it is possible that a higher cumulative dose may have resulted in improved pain relief, as case reports have suggested [31].

Chikungunya Viral Disease Another viral disease associated with the onset of pain is Chikungunya fever, an acute, mosquito-borne viral illness which can develop into chronic arthralgias in up to 33% of patients, lasting several years [32]. Treatment is largely supportive. One 54-year-old patient with Chikungunya, increased immunoglobulin M (IgM) titer and elevated CRP experiencing severe arthralgias was treated with 100 g/day IV vitamin C. His acute viral symptoms of pain, fever, and rash resolved in 2 days, and his CRP also decreased [33]. However, it is possible that the patient's symptoms and CRP might have resolved in this time frame without treatment, as the natural course of the acute phase of the disease is typically 5–7 days.

In an observational study, 56 Chikungunya patients received IV infusions containing hydrogen peroxide, magnesium chloride, and methylcobalamin, followed by either an isotonic solution or 20–50 g IV ascorbic acid and various B vitamins [32]. Many patients reported a 60–71% reduction in their pain, with 9% reporting complete resolution and 5% with no improvement [32]. However, it is difficult to ascertain the contribution of vitamin C, as there were multiple other substances concomitantly infused.

Postoperative Pain

The effect of IV vitamin C infusions on post-surgical pain has also been investigated. It is hypothesized that perhaps there is an anti-nociceptive effect of the anti-oxidant and neuromodulating properties of this vitamin, which could result in opioid-sparing [12]. In a randomized, double blind study of 100 patients with colon cancer undergoing elective laparoscopic colectomy, patients either received 50 mg/kg vitamin C IV or placebo, immediately after induction of anesthesia [12]. Morphine and rescue tramadol consumption, as well as VAS pain scores were assessed at 2, 6, and 24 hours after surgery. Postoperative pain scores at rest were significantly lower in the vitamin C group, though there was no difference in post-operative pain while coughing. Morphine use was only significantly lower in the vitamin C group at the 2 hour postoperative timepoint. Rescue analgesics were required significantly more frequently in the placebo group [12].

In another randomized, double blinded trial, 40 patients undergoing uvulopalatopharyngoplasty (UPPP) with tonsillectomy were evaluated to determine if vitamin C infusions might reduce postoperative pain and analgesic requirements [34]. Patients received 3 g of IV vitamin C or normal saline within 30 minutes after the start of surgery. VAS pain severity scores at 0, 6, 12, and 24 hours after the procedure and analgesic requests were recorded. The vitamin C group reported significantly better pain scores at all measured timepoints, requested significantly fewer rescue analgesic doses, had a significantly longer time to first dose of analgesic use, and required a significantly lower total dose of analgesics [34]. Thus, there is some suggestion that IV vitamin C may reduce postoperative analgesic requirements.

Rheumatological/Inflammatory Pain

The anti-oxidant and anti-inflammatory properties of vitamin C have also been trialed in treating rheumatological/inflammatory pain. A case report examined the use of IV vitamin C in a 47 year old female with rheumatoid arthritis and mononeuritis multiplex secondary to central nervous system (CNS) vasculitis, likely due to adverse effects from her chronic hepatitis C infection treatment [35]. She underwent a trial dose of 12 g IV vitamin C, then was administered 50 g IV. The patient reported markedly improved overall global health status, including dramatic decreases in fatigue, and reported that her pain, initially reported at 100% before treatment, had completely resolved [35]. Thus, it is possible that parenteral vitamin C infusions may have a role in improving rheumatological pain.

Contraindications

There are no standard contraindications to vitamin C infusions. People with an allergy/anaphylaxis to vitamin C should not undergo such infusions. It has been suggested that hemochromatosis, renal dysfunction/history of nephrolithiasis, existing ascites/edema, and glucose-6-phosphate dehydrogenase (G6PD) deficiency (due to increased risk of hemolysis) are relative contraindications [16, 19, 23, 35].

Side Effects

Vitamin C IV infusions appear to be generally well tolerated. There have been reports of mild side effects including up to 40% GI and 30% urinary symptoms in one trial, but the patients were also undergoing chemotherapy, and it is difficult to ascertain whether the side effects were from the vitamin C or from the chemotherapy [16]. Fluid retention, oliguria, GI issues (colic, diarrhea, constipation dyspepsia, GERD, nausea, vomiting), increase in urinary oxalate excretion, headache, vascular pain/phlebitis, dry mouth, tumor site pain, and dysuria have been noted in various studies, though these side effects were generally noted to be mild and relatively infrequent, affecting <3–9% of study patients [14, 17, 21]. A few patients in a clinical trial of cancer patients receiving chemotherapy had worsening ascites and/or edema and renal issues, but it is difficult to ascertain if this was from their cancer treatment, disease progression, or vitamin C [23]. There does not appear to be an increased bleeding risk in post-surgical patients [12, 34].

Monitoring

Serum screening for G6PD deficiency and hemochromatosis is recommended prior to infusion [16, 19], as well as baseline ECG, renal function tests and screening for history of current or prior nephrolithiasis, ascites, and edema [23]. Routine vital signs are recommended at least prior to and after the infusion, if not periodically during the infusion.

Algorithm for Vitamin C Infusion Regimens

This table summarizes various doses published in the literature (Table 6.2). The goal of this table is to provide a guide for practitioners, but different doses might be necessary depending upon the setting and the patient.

Summary

Collectively, there is some evidence that vitamin C infusion therapy can be helpful in several pain conditions. Vitamin C's antioxidant, neuromodulative, and neuroprotective properties are thought to confer antinociceptive properties. It has been used for various indications, including chemotherapy-associated pain, at doses of 50 g IV 2 days prior to and 2 days after chemotherapy, over the course of 2 months. There is some suggestion that vitamin C infusions may also be helpful for pain from bony metastases, at doses of 2.5 g IV infused for 60 minutes, up to daily for 3–10 infusions as needed. More diffuse cancer-associated pain has also been successfully treated with vitamin C infusions, at doses of 7.5–50 g IV up to twice a day for up to 4 weeks, with or without concomitant oral vitamin C at doses of 2–4 g per day.

Table 6.2 Algorithm for Vitamin C Infusion Regimens

Indication	Dosage
Chemotherapy-associated pain	50 g IV twice a week (2 days prior and 2 days after chemotherapy) for 2 months
Pain from bony metastases	2.5 g IV over 1 hour, weekly for 3–10 infusions or PRN up to daily
Cancer-associated pain	7.5–50 g of IV twice a day to weekly for up to 4 weeks, with or without oral vitamin C 2–4 g/day
Acute postherpetic neuralgia	2–15 g IV up to daily for up to 2 weeks
Chronic postherpetic neuralgia	2.5–7.5 g (or 50 mg/kg) every other day for up to 2 weeks
Chikungunya viral arthralgias	20–100 g/day IV for up to 2 days, possibly in combination with other B vitamins, magnesium, and hydrogen peroxide
Postoperative pain	3 g or 50 mg/kg IV within 30 minutes after the start of surgery
Rheumatoid arthritis/mononeuritis multiplex	50 g IV over 30 minutes ×3 infusions in 2 weeks

Vitamin C infusions have also been utilized to treat postherpetic neuralgia; treatment doses for acute PHN range from 2–15 g IV as frequently as daily for up to 2 weeks, while chronic PHN has been treated with doses of 2.5–7.5 g (or 50 mg/kg) every other day for up to 2 weeks. Patients with another viral neuralgia, Chikungunya viral disease, have responded to vitamin C infusions, at doses of 20–100 g/day IV for up to 2 days, with or without other adjuncts such as B vitamins, magnesium, and hydrogen peroxide. Vitamin C may also reduce postoperative pain in doses of 3 g (or 50 mg/kg) IV within 30 minutes after starting surgery. Other inflammatory/rheumatoid disorders, such as rheumatoid arthritis/mononeuritis multiplex, may also respond to vitamin C infusions at a dose of 50 g IV infused over 30 minutes, given 3 times over a 2 week period. Pre-infusion serum testing for G6PD deficiency and hemochromatosis is recommended, as well as baseline ECG, renal function tests, and screening for history of nephrolithiasis, ascites, or edema. Routine vital signs are also advised prior to and after the infusion. With proper screening, side effects appear to be mild and relatively infrequent, and even at high doses, vitamin C appears to be generally well tolerated. The data is somewhat limited for the analgesic effect of vitamin C infusions, and additional randomized controlled clinical trials are sorely needed to solidify the potentially diverse role vitamin C plays as a pain modulator.

Vitamin Combinations

Introduction

Various combinations of vitamins have been trialed as infusions, purporting to improve health, alertness, and pain. However, most of these cocktails have not been rigorously empirically tested, and there is very little peer-reviewed, published data

for the efficacy and safety of these vitamin infusion mixtures. There are often other medications added into the infusion, which are less controversial analgesic treatments, which makes the additional contribution of the included vitamins difficult to assess. One popular combination, consisting of magnesium, calcium, vitamin C, and some B vitamins, is known as the "Myers' Cocktail," after John Myers, MD, a physician from Baltimore. It is said that many of his patients improved after receiving this infusion, but the documentation regarding his patients' reported benefit was incomplete [36].

Mechanism of Action

It is thought that the various vitamins included exert anti-oxidant effects and assist metabolism and energy, but there is little evidence in the literature to this effect [36, 37].

Indications

Fibromyalgia

Fibromyalgia is a syndrome of unknown etiology (or perhaps multiple etiologies), which are associated with fatigue, sleep disturbances, cognitive effects, and widespread pain [37]. This syndrome can be quite debilitating, and various treatments, including exercise, cognitive behavioral therapy, non-steroidal anti-inflammatories, tricyclic antidepressants, selective serotonin-norepinephrine reuptake inhibitors, and anticonvulsants have been somewhat effective. However, many people still are affected with significant adverse symptoms despite multi-modal treatment.

In one case report, a 48-year-old woman with a 6-month history of diffuse myalgias and arthralgias underwent a Myers' cocktail IV trial [36]. Immediately after the infusion, she reported that her pain was "gone" for the first time in 6 years. She repeated these treatments periodically for 3 years, noting that her pain would start to return if she went longer than 1 month between treatments. The author stated that he has treated 30 patients with Myers' cocktail, half of whom have dramatically improved, usually after 3–4 treatments [36].

In a small, open-label pilot clinical trial, seven patients with chronic, therapy-resistant fibromyalgia were administered a modified Myers' cocktail IV infusion once a week for 8 weeks [38]. Baseline and weekly pain levels, as well as subjective fatigue levels were obtained. Over the 8-week treatment period, participants' pain and fatigue levels significantly improved. Participants also reported increased energy in the 1–2 days after the infusion [38]. It has been speculated that more rapid infusion rates may result in higher peak serum concentrations, which may improve the therapeutic effect [39].

In a randomized, double-blind, placebo-controlled pilot study of 34 adults with fibromyalgia, participants were infused a treatment mixture with similar components, with the addition of benxyl alcohol [37]. Participants' baseline medication use was recorded, then they received either placebo or the vitamin infusion weekly

for 8 weeks. Both groups significantly improved from baseline, but there was no significant difference between the intervention group and the placebo group in change in tender points, VAS scores, physical function, depression, subjective mood, or general well-being. It was noted that participants experienced a strong placebo effect, and the efficacy of the intravenous solution above and beyond the placebo is indeterminate [37].

Contraindications

Patients who are hypotensive, have hypomagnesemia, hypokalemia, arrhythmias or cardiac conduction blocks, are taking digoxin or potassium-depleting medications (such as certain diuretics), have diarrhea or vomiting, or are malnourished should not undergo these combination infusions, as they can exacerbate these conditions [36]. If a person is allergic to or experiences anaphylaxis from any of the components of the infusion, they should not be administered this cocktail.

Side Effects

Patients may experience sensation of heat or flushing with intravenous therapy combinations, often beginning in the chest and spreading to the genital/rectal area, especially with large doses or rapid administration, though this may be due to the magnesium and/or calcium [36]. Visual changes may also occur for up to 2 days post-infusion, such as increased visual acuity and color perception [36]. Hypotension, lightheadedness and syncope can also occur, in which case it is advisable to stop the infusion and possibly restart when symptoms resolve, though some patients do not tolerate restarting. Vasovagal symptoms, muscle cramps, arrhythmias, pruritis, burning at the injection site, dyspepsia, insomnia, depression, increased blood pressure, and anaphylaxis have also been reported [36, 37].

Monitoring

One author reported that he has administered approximately 15,000 combination infusions, and that these have been generally well tolerated without serious adverse reactions [36]. Two small pilot studies with a combined total of 41 patients reported that there were no serious adverse events and patients tolerated the infusions well [37, 38]. No special monitoring appears to have been used, though it might be prudent to obtain magnesium, potassium, calcium, and vitamin levels prior to these infusions, and ensure that vital signs are within normal limits prior to and after administration.

Table 6.3 Algorithm for Vitamin Combination Infusion Regimens

Indication	Dosage
Fibromyalgia	Various dosages used of the following components: vitamin C 1332–3000 mg; vitamin B_{12} 1000 mcg; vitamin B_6 100–102 mg; vitamin B_5 250–252 mg; riboflavin 2 mg; thiamine 100 mg; niacinamide 100 mg; magnesium 400–1000 mg; calcium 40–250 mg. Administered IV over 5–30 minutes, typically q1wk for up to 8 weeks.

Algorithm for Vitamin Combination Infusion Regimens

This table summarizes various doses published in the literature (Table 6.3). The goal of this table is to provide a guide for practitioners, but different doses might be necessary depending upon the setting and the patient.

Summary

Various vitamins, including vitamin C and various B vitamins, have been used in combination with other substances, including calcium, magnesium, and other analgesics, in the hopes of augmenting any potential beneficial effect. These combinations have been used most often for the treatment of fibromyalgia, with mixed results; it is unclear that they are helpful for post-operative pain. Doses for fibromyalgia vary, and include vitamin C 1332–3000 mg; vitamin B_{12} 1000 mcg; vitamin B_6 100–102 mg; vitamin B_5 250–252 mg; riboflavin 2 mg; thiamine 100 mg; niacinamide 100 mg; magnesium 400–1000 mg; and calcium 40–250 mg. This combination is often known as a "Myers' cocktail," though various modifications to its components are sometimes made. The infusion is administered IV over 5–30 minutes, typically once a week for up to 8 weeks, though ongoing periodic monthly infusions for maintenance has been reported without ill effects. No special monitoring has been specifically recommended, however, pre-infusion labs such as magnesium, potassium, calcium, and vitamin levels; screening for history of arrhythmias or cardiac conduction blocks, digoxin use, potassium-depleting medications, diarrhea or vomiting, or malnourished status; and routine pre- and post-infusion vital signs may be helpful. The data is not terribly robust in support of the effectiveness of such vitamin combinations, and additional, large-scale, randomized controlled trials would be very helpful to further characterize the efficacy of these infusions.

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Dihydroergotamine Infusion Therapy

7

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Introduction

Migraine headaches and other chronic headache conditions are extremely disabling conditions that affect a significant proportion of the general population [1, 2]. Dihydroergotamine (DHE) administration for persons with migraine and cluster headaches is an evidence based management option [3–6]. Of note, all four of the common DHE routes of administration formulations – intranasal, subcutaneous, intramuscular, and intravenous – were designated by the American Academy of Neurology as having a high level of substantial and supportive clinical evidence [7]. Despite the extent and strength of clinical data in support of DHE for the aforementioned indications, it is a relatively lesser-utilized medication, attributed largely to its unfamiliarity by many clinicians [4–7]. This is especially unfortunate as DHE is thought to have comparable if not superior efficacy to several standard of care medications [5–7]. Delineated below is an overview of DHE, specifically as an intravenous agent.

Mechanism of Action

Pharmacokinetics

DHE is mostly cleared by the hepatic circulation [4, 8–10]. Therefore, oral administrations are heavily susceptible to first pass clearance and have an estimated

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bioavailability of <1%. The bioavailability of intramuscular administrations is 47% and, expectedly, 100% for intravenous administration. Thus, intravenous therapy allows for practitioners to administer DHE reliably at therapeutic dosages. DHE is 93% bound to plasma proteins and has a half-life of approximately 9 hours. Pharmacokinetic studies have found that the volume of distribution is 800 liters. Following its metabolism, almost 99% of DHE and its metabolites are excreted via the bile into feces. A small percentage of DHE excretion occurs via renal clearance. There exist five major metabolites of DHE. Of note, it is thought that the major metabolite, 8′-β-hydroxydihydroergotamine, may have equally efficacious agonistic activity at α-adrenergic, 5-hydroxytryptamine (5-HT), and D_2 dopamine receptors. However, well designed pharmacological data are lacking.

Although the precise molecular mechanisms responsible for DHE metabolism in the liver have yet to be clearly elucidated, the CYP-4503A cytochrome pathway appears to be heavily involved. Consequently, the concomitant use of DHE with other medications metabolized through the CYP-4503A mechanism may increase circulating concentration of DHE to unsafe levels and possibly increase the risk of ergotism – the pathological vasocontriction of peripheral structures such as fingers and toes that can lead to infarction and gangrenous necrosis. There have been several case reports of macrolide antibiotics, which are also catalyzed via the CYP-4503A pathway, producing ergotism in persons also receiving ergot based medications [11]. In particular, clarithromycin, erythromycin, and troleandomycin have been implicated. Moreover, protease inhibitors, bromocriptine, dexamethasone, ethinyloestradiol, ketoconazole, nifedipine, omeprazole, and verapamil have also been suggested to confer an increased risk of ergotism with coadministration of ergot derivatives like DHE [4, 8–12].

Pharmacodynamics

DHE is an ergot alkaloid compound that acts as an agonist at numerous receptors, which include α-adrenergic, 5-hydroxytryptamine (5-HT), and D_2 dopamine receptors [8–10]. It binds with particular affinity to the α_1-adreneceptor and the 5-$HT_{1B/1D}$ receptor at the level of the blood vessel and produces vasoconstriction. Although this physiological vasoconstriction is thought to be relatively widespread, large arteries are notably affected. The constriction of meningeal arteries, which are dilated in the setting of migraines, is thought to normalize perfusion pressures and confer the primary therapeutic effects of DHE. Additionally, DHE reduces the release of noxious neurokinins such as Substance P by way of 5-HT_{1D} receptor activation. This reduction in Substance P delivers analgesia because it in turn reduces the neurokinin driven sterile inflammation of the dura mater, which is thought to underlie migraine pain pathophysiology [8–13].

Indications

Acute Migraines and Status Migranosus

Migraines comprise a primary headache disorder with a high prevalence in the United States and across the world [1, 2]. Additionally, they are even implicated as being one of the largest causes of disability worldwide. Consequently, the appropriate diagnosis and management in these persons is instrumental in preventing poor outcomes. Migraines are dichotomized into *migraine without aura* and *migraine with aura* subtypes, which are grossly characterized by the absence or presence, respectively, of transient and focal neurological symptoms accompanying the headache [14].

Per the International Headache Society (IHS), a person is diagnosed with a migraine without aura if they endorse recurrent severe intensity headaches, each lasting 4–72 hours, that are characterized as unilateral and throbbing [14]. Affected persons also exhibit nausea, vomiting, photophobia, or phonopobia [14, 15]. In contrast, migraines with aura are usually shorter and are associated with one or more transient and focal neurological deficits. These neurological symptoms can range from visual disturbances to speech disturbances to numbness and tingling to motor weakness. Additionally, those with migraines can experience prodromal and/or postdromal symptoms ranging from hours to days that precede and follow the migraine headache, respectively. These symptoms are varied and can include nausea, yawning, insomnia, muscle stiffness, fatigue, depression, irritability, concentration deficits, craving foods [14, 15]. A person who endorses a migraine, either with or without aura, that has features typical of their prior migraine headaches except that it is intractable and lasts for greater than 72 hours is defined as having status migranosus if not otherwise accounted for by a different headache diagnosis.

Many migraines, especially if severe or associated with focal neurological deficits, can prompt the effected persons to seek emergency medical care [2]. Those with status migranosus can especially have debilitating symptoms that preclude them from engaging in any activity. By this time, a vast majority of persons affected by acute migraines will have tried and failed conservative measures and over the counter analgesic medications [2, 16]. Thus, these persons often warrant early and judicious analgesic therapy in conjunction with supportive measures like intravenous fluids.

DHE administration, via intranasal or intravenous forms, has been shown to be highly efficacious in this context [3, 17]. Despite this, data suggest that emergent care of persons presenting with migraine headaches is largely variable [18, 19]. In addition to this, a study by Gupta et al. found that migraine specific medications, such as triptans and DHE, were largely underutilized [20]. Approximately less than 10% of patients received these medications in their emergency room care. A review by Kelley et al. highlights several studies that found that DHE infusion, either with

or without an anti-emetic, was comparable or more efficacious to intramuscular or other intravenous medications, which included dexamethasone, valproid acid, ketorolac, butorphanol, and meperidine [6]. Addtionally, there exists data to suggest that the administration of an anti-emetic with DHE treatment may be a superior than DHE alone in ameliorating side effects of nausea [21]. However, there does not appear to be any superiority of this combination for conferring analgesia relative to DHE alone [6, 21].

Chronic Migraine

Approximately 1% of the general population in the United States suffers from chronic migraines [22]. A majority of affected persons are appropriately managed in the outpatient setting with prophylactic pharmacotherapy, which includes medications from the beta blocker, anti-convulsant, tricyclic antidepressant, and calcium channel blocker drug classes [23, 24]. Unfortunately, there exists a sizable proportion of those affected by chronic migraines who are not optimally responsive to this standard of care regimen. These persons affected by refractory chronic migraines confer a large burden to healthcare costs, as accrued by repetitive emergency room visits and diagnostic testing [1, 2, 23, 24]. More importantly, this condition may also lead to chronic pain, suffering, and disability.

Following a pathophysiological understanding of migraine disorders, several studies found DHE infusion therapy to be an effective rescue therapy for persons affected by acute migraines [3, 25, 26]. However, there lacked a standardization in DHE infusion protocols and dosages. One unique protocol was detailed by Raskin et al. who describe a repetitive dosing regimen across 2 days [3]. Interestingly, they found that their patients were headache free from their chronic migraines long after their DHE infusions with a majority of patients reporting analgesic benefits at an average follow up period of 16 months. Silberstein et al. report their experience with DHE infusions for persons with chronic daily headaches, of whom most were diagnosed with migraine headaches [27]. They found that a majority of patients, 59% of 50 patients, had an excellent response (defined as greater than a 90% reduction in headache intensity or frequency, or >75% reduction in both) at 2 years following the infusion. It is theorized that repetitive infusion practices, with dose dependence, serve to chronically attenuate pathologically sensitized central neural mechanisms [21, 28, 29].

Medication Overuse Headache

According to the IHS guidelines, a diagnosis of a medication overuse headache is made in persons with a pre-existing headache disorder who endorse headaches for greater than 15 days in a month that have developed or worsened as sequela of medication overuse not otherwise accounted for by a different headache diagnosis [30]. The overuse of medication is defined as the regular overuse of acute or symptomatic headache medications for greater than 3 months, with ergotamine, triptans,

opiates, and combination analgesics being used for 10 or more days per month or simple analgesics being used for 15 or more days per month. Simple analgesics are non-opiate medications that include non-steroidal anti-inflammatory and acetaminophen medications. Lastly, a medication overuse headache often reverts to the prior pattern of the initial headache disorder after the implication medication is weaned.

The prevalence of medication overuse headaches largely varies based on epidemiological data from across the world. In the United States, up to 80% of new patients presenting to a headache clinic may be diagnosed with a medication overuse headache [31]. This large prevalence is not surprising considering that simple analgesic medications are readily available without a prescription or physician oversight [30–32]. Moreover, because the early management of a headache disorder can often be challenging to patients, they may not fully understand the consequences of overusing their acute or symptomatic headache medications in worsening their headache symptoms across a chronic time frame.

The current treatment paradigm for treating this condition is to wean the offending acute or symptomatic headache medications and possibly initiating headache prophylactic medications, if reasonable and appropriate for the clinical context [33]. Although data suggest that drug withdrawals are general well tolerated in these persons, there also exists some data to suggest that relapse rates may be high [34, 35]. When initiating medication weaning for medication overuse headaches, a bridge therapy is often indicated to ensure that these patients have the necessary analgesia to completely wean the offending agent(s). The American Academy of Neurology endorses DHE as an efficacious bridge therapy, largely in part to DHE overuse having a very low likelihood of developing a medication overuse headache [4, 7, 33, 34]. DHE infusion is notably well studied for this indication with findings, including those from Raskin et al., suggesting that a vast majority of patients achieve complete analgesia within 48 hours of initiating the infusion [3, 4, 7]. Additionally, most of those persons who were administered DHE infusion as a bridge therapy were also found to have sustained benefits across a 2 year period. Lastly, there is also some thought that those persons with initial headache presentations who exhibit risk profiles suggestive of acute or symptomatic pain medication abuse may be appropriate candidates for early introduction to DHE treatment, with the hope that medication overuse headaches may be prevented in this population [4, 36].

Cluster Headache

The IHS definition of a cluster headache is a headache disorder, not otherwise accounted for by a different headache diagnosis, characterized by severe, strictly unilateral pain that is orbital, supraorbital, and/or temporal lasting between 15 and 180 minutes [8]. Associated symptoms include ptosis, miosis, conjunctivitis, lacrimation, eyelid edema, and nasal congestion and/or discharge [8, 9]. Additionally, they usually occur in frequency clusters, which range from every other day to eight times a day across several weeks to months. Epidemiologically, these headaches tend to disproportionately affect young men between 20 and 40 years of age [8].

Unfortunately, managing cluster headaches is often challenging, with many patients being refractory to prophylactic monotherapy [29, 37]. DHE is well evidenced and recommended as an efficacious management strategy in persons with refractory cluster headaches. In particular, Magnoux et al. share their clinical experiences with elective DHE infusions in 70 persons with episodic or chronic cluster headaches across an 8 year span [29]. They found that DHE produced partial or total analgesia in a majority of patients at the 1 month post-infusion time point. There was also some increased efficacy noted for persons with the episodic phenotype of cluster headache. Interestingly, they also found that persons with the chronic phenotype exhibited a degree of remission or conversion to the episodic phenotype. Nontheless, their data, congruent with those of others, deem DHE infusion as efficacious for persons with cluster headaches [4, 5, 29].

Contraindications

As DHE has potent vasoconstrictor effects, particular to large arteries, it is contraindicated in persons with severe cardiovascular comorbidities [8–10]. In particular, DHE is contraindicated in persons with severe or uncontrolled hypertension, angina pectoris, coronary artery vasospasm, a history of a cerebrovascular accident or myocardial infarction, ischemic cardiomyopathy, basilar artery migraine, recent vascular surgery, peripheral vascular disease, or sepsis. Moreover, concurrent use of DHE with other potent vasoconstrictor agents, either peripheral or central, is not recommended.

Studies have shown that DHE use may be associated with adverse pregnancy outcomes, namely prematurity [12]. For this reason and fears of risks that may be related to fetal hypoperfusion, DHE is listed as a Category X medication by the Food and Drug Administration and must not be used in pregnant women [4, 9, 12]. Given a possibility for neonatal risks, breastfeeding mothers should also be excluded as possible candidates for DHE infusion.

DHE infusion should also not be administered in persons who have recently received serotonin agonist medications, both selective and non-selective [8–10]. Implicated serotoninergic agents include triptans, which like DHE selectively act agonistically upon 5-$HT_{1B/1D}$ receptors, buspirone, trazodone, metoclopramide and cisapride. Medications that increase serotonin concentrations – such as those in the selective serotonin reuptake inhibitor, serotonin norepinephrine reuptake inhibitor, or tricyclic antidepressant drug families – may predispose towards serotonin syndrome. Of course, other formulations of DHE, such as intranasal and oral forms, also preclude persons from safely receiving DHE infusion therapy until cleared from systemic circulation. Similarly, persons also taking medications metabolized via the CYP-4503A pathway – protease inhibitors, azole antifungal medications, and macrolide antibiotics in particular – may be at risk for developing threatening vasoconstriction associated adverse events including myocardial infarction, ischemic strokes, and peripheral ischemia leading to gangrenous necrosis of fingers and toes.

Lastly, DHE infusion in persons with hepatic or renal impairments is not recommended, should be considered judiciously depending on the particular patient and clinical context.

Side Effects

While receiving DHE infusion therapy, a majority of patients – some studies found a prevalence of approximately 90% – can experience at least one side effect [4, 6, 21]. Common side effects are constitutional symptoms and include nausea, dysphoria, flushing, sedation, worsened headaches, light headedness, and new headaches. Nausea is reported by several studies by far the most common side effect and has a prevalence ranging from 33% to 67% [38, 39]. Most patients have reported relief of nauseous symptoms with anti-emetic medications such as ondasetron or metoclopramide. Premedication with anti-emetics has also been effective in promoting DHE infusion tolerance [4, 6, 21].

Fortunately, most patients tolerate DHE infusions relatively well. Only a small minority of patients requires dose reduction; infusion termination because of side effects is thought to be a rare occurrence. For the most part, side effects are thought to be mild and transient. Although most side effects were thought to resolve across subsequent infusion sessions, the prevalence of leg cramps is thought to increase with repeated exposure. Other reported constitutional side effects are gastrointestinal in nature and include abdominal cramps and diarrhea.

Despite its favorable safety profile, DHE infusion can be associated with severe and threatening physiological effects, which are often sequela of arterial vasoconstriction. Common cardiovascular effects can include bradycardia, tachycardia, hypertension, coronary vasospasm. Therefore, complaints of chest pain must be approached with a healthy understanding and concern for angina and myocardial ischemia, especially in patients with other predisposing cardiovascular comorbidities. Likewise, focal neurological deficits must also be analyzed with a degree of suspicion for a cerebrovascular accident. Lastly, peripheral perfusion deficits may result in pallid and/or cold distal extremities with possible tingling, which may collectively propagate ischemia of fingers, toes that can lead to gangrenous necrosis.

Monitoring

Pre-infusion Screening

Given the aforementioned risk for detrimental cardiovascular adverse effects with DHE infusion therapy, a comprehensive pre-infusion diagnostic screening must be conducted to risk stratify patients and ensure favorable safety profiles. Screening tests include a cardiovascular physical examination, blood pressure measurement, electrocardiogram, urine toxicology testing, and echocardiography if indicated [4, 6, 21]. Given its Category X designation in pregnancy, all women of reproductive

age should receive a urine pregnancy test. Moreover, standard laboratory testing including a complete blood count with differential, a comprehensive metabolic panel with magnesium and phosphate levels – to assess for hepatic and renal dysfunction-, and standard coagulation studies including the prothrombin time, partial thromboplastin time, and international normalized ratio should be collected.

Peri-infusion Monitoring

Before, after, and if provoked by symptomology, vitals signs recordings are essential to ensure that the patient is not at risk for hemodynamic compromise in the setting of the DHE infusion. Careful attention must also be paid to constitutional side effects that may be present, pronounced especially with earlier initial infusion sessions. While most of the aforementioned constitutional sessions can be managed conservatively and supportively, a healthy index of suspicion must be maintained for presenting sequela of myocardial ischemia, cerebrovascular accidents, and even peripheral limb ischemia. Additionally, a small subset of patients may have allergic reactions to DHE and may require termination of the infusion, especially if at risk for developing anaphylaxis.

Post-infusion Monitoring

Serial cardiovascular monitoring, laboratory testing, and even pregnancy screening is essential, notably in persons receiving recurrent infusions of DHE. This repeated monitoring is indicated to screen for any manifestations of chronic DHE administration or interval changes that now preclude patients from receiving additional DHE infusions. These changes may include but are not limited to uncontrolled hypertension and hepatic or renal impairments. Recurrent DHE exposure with chronic infusions is also associated with non-specific tissue fibrosis [40]. Notably, cases of cardiac valvular, pleural, and retroperitoneal fibrosis have been reported. If prompted by symptomology of cardiopulmonary decompensation, diagnostic investigation including echocardiography, pulmonary function tests, and computerized tomography imaging of the chest may be appropriate and indicated.

Algorithm for DHE Infusion Regimens

The table below delineates the dosage and algorithms for DHE infusion as previously published in the literature (Table 7.1). Clinicians should note that these algorithms are only intended to serve as guidelines and that different dosing regimens may be indicated for different settings and patients populations. All algorithms denote protocols for intravenous infusion in adults weighing more than 50 kg unless otherwise specified. DHE infusions should not exceed a maximum administered dose of 2 mg across a 24 hour period or 6 mg across a 1 week period [8–10]. Of note, inpatient monitoring is required if DHE infusion for greater than 48 hours is

Table 7.1 Algorithm for DHE infusion regimens

Indication	Dose
Acute Migraine *From Pryse-Phillips et al.* [41]. **Status Migranosus**	0.5–1.0 mg every 1 hour. If the initial migraine persists or does not yield effective analgesia, a subsequent infusion can be administered, not to exceed maximum daily or weekly dosages.
Chronic Migraine *From Evans* [42] *and Nagy et al.* [21]*., as adapted from the Raskin protocol* [3]*. It must be noted that the use of intravenous DHE for chronic headache conditions is off-label.* **Medication Overuse Headache** *From Paremeleire et al.* [43]*. and Nagy et al.* [15]*., as adapted from the Raskin protocol* [3]. **Cluster Headache** *From Nagy et al.* [15]*., as adapted from the Raskin protocol* [3].	Pre-treatment with ondasetron 4 mg intravenously approximately 30 minutes prior to DHE infusion is to be administered every 8 hours if clinically appropriate, namely in those with risks for QTc prolongation. **Day 1** First dose: 0.5 mg in 100 mL of normal saline administered across 1 hour. Second dose (if first dose is well tolerated): 0.75 mg in 250 mL of normal saline across 1 hour, to be administered 8 hours following the following the first dose. **Day 2–5** Third, subsequent doses: 1 mg in 250 mL of normal saline administered intravenously across 1 hour every 8 hours for a total of 10 doses. Administer for a goal of 11.25 mg of DHE (+/−) across 5 days. Do not use triptan medications within 24 hours of DHE use.

required. This is instrumental as inpatient monitoring allows for close observation with the logistical and procedural mechanisms in place to intervene in the setting of any threatening adverse events. Infusions should be stopped if any threatening side effects, as those aforementioned, are encountered.

Summary

DHE has extensive evidence towards its usage across numerous headache contexts. Intravenous DHE therapy has notable indications for treating several headache conditions including acute migraines, status migranosus, medication overuse headaches, and cluster headaches. Moreover, repetitive dosing of DHE infusions appears to confer chronic benefits for persons suffering from chronic headache conditions. It operates at the level of the α-adrenergic, 5-hydroxytryptamine (5-HT), and D_2 dopamine receptors to not only normalize meningeal artery vasodilation, but also to reduce noxious neurokinin release to ameliorate sterile inflammation of the dura mater. Given its vasoconstrictive effects, often specific to larger arteries, DHE is contraindicated in persons with cardiovascular comorbidities at risk for myocardial or cerebral ischemia, pregnancy, and those taking other vasoconstrictive medications. When utilized with evidence-based algorithms, DHE infusion therapy can be comparable if not superior to many standards of care medications across several headache conditions.

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Bisphosphonate Infusion Therapy

8

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Introduction

Bisphosphonates (e.g., pamidronate, clodronate, alendronate) are pyrophosphate analogs, traditionally used in the treatment of pathologic conditions associated with abnormal bone metabolism, such as osteoporosis, Paget's disease, and cancer-related bone pain [1]. Additionally, bisphosphonates seem to have an analgesic efficacy in complex regional pain syndrome (CRPS). Bisphosphonates act by directly inhibiting osteoclasts and shortening their lifespans [1]. Osteoclast activity has been found to be upregulated in CRPS, and propagate the pain cycle by activating nociceptive nerve fibers in bone. The mechanisms by which osteoclasts act and outcomes bisphosphonates are shown to inhibit are: low pH environment, releasing inflammatory cytokines and prostaglandins, and production of nerve growth factor [1]. Nerve growth factor is of particular importance as it is a known inducer of hyperalgesia via upregulation of gene transcription for pain receptors [1].

Mechanism of Action

Bisphosphonates come in two distinct types that determine important differences in their potency and toxicity [2]. The nitrogen-containing bisphosphonates (zoledronic acid, risedronate, ibandronate, alendronate, neridronate, and pamidronate) are more potent inhibitors of bone resorption than the simple bisphosphonates (etidronate,

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clodronate, tiludronate). The nitrogen-containing bisphosphonates act primarily by inhibiting the enzyme farnesyl pyrophosphate (FPP) synthase in the mevalonate pathway (cholesterol biosynthetic pathway) [2]. Inhibition of FPP synthase disrupts protein prenylation, which creates cytoskeletal abnormalities in the osteoclast, promotes detachment of the osteoclast from the bone perimeter, and leads to reduced bone resorption [2]. The relative antiresorptive potency of the individual nitrogen-containing bisphosphonates is related to the potency with which they inhibit FPP synthase [2]. When FPP synthase is disrupted, there is an accumulation of a precursor, isopentenyl pyrophosphate (IPP), which can bind to a receptor and cause the release of tumor necrosis factor (TNF)-alpha. This pathway, leading to the production of TNF-alpha, is hypothesized to cause the acute-phase reaction, a well-recognized side effect of intravenous bisphosphonates [2]. The second type of bisphosphonates are referred to as simple bisphosphonates [2]. These do not contain nitrogen and have a different mode of action. They are metabolized by osteoclasts to metabolites that exchange with the terminal pyrophosphate moiety of adenosine triphosphate (ATP), resulting in an ATP that cannot be used as a source of energy [2]. The osteoclasts then undergo apoptosis [2].

Bisphosphonates are poorly absorbed orally (1–5% of an oral dose), and absorption is best when they are given on an empty stomach [3]. Patients tolerate oral bisphosphonates better with water and when the patient waits at least 30 minutes before ingesting food or other medications [3].

Bisphosphonates are not metabolized and are exclusively eliminated by the kidney [3]. Approximately 70% of the absorbed bisphosphonate is cleared by the kidney, and the remaining 30% is taken up by bone [3]. Relative bone uptake is increased in conditions of high bone turnover, with less of the drug being excreted by the kidneys [3]. Bisphosphonates are cleared rapidly from the plasma (half-life is approximately 1 hour) but may persist in bone for the patient's lifetime [3].

Indications

CRPS

Various trials and case studies report the use of bisphosphonates for the treatment of CRPS. A systematic review by Brunner et al. [4] reviewed randomized trials comparing bisphosphonates with placebo with the goal of improving pain, function, and quality of life in patients with CRPS-I with bone loss, and demonstrated in these patients that bisphosphonates have the potential to reduce pain associated with bone loss. All trials show efficacy and patients experienced clinically significant improvement in their symptoms with minimal adverse effects. Most studies showed improvement in pain symptoms and increased functionality both in the immediate period [4]. Though the findings were encouraging, the sample sizes for most of these trials were small and further research was needed. Some studies of particular interest are detailed below.

One study of particular interest was Maillefert et al., in 1995. They reported on 7 of 11 patients with CRPS, who experienced clinically significant improvement from

IV infusion of pamidronate therapy (30 mg over 4 hours daily for 3 days) in an open prospective study. In this study, the same observer assessed the patients at baseline and after one and 3 months [5]. This evaluation included a VAS and a physician global assessment based on objective signs on clinical evaluation (hyperhidrosis, vasomotor changes, and joint stiffness). The mean VAS decreased from 58.8/100 before therapy, to 41.1/100 at 1 month ($P < 0.05$; Wilcoxon paired test) and 33.8/100 at 3 months ($P < 0.01$) [5].

Another open prospective study in 1997 examined the effects of IV infusion of pamidronate on 23 patients with CRPS [6]. Intravenous pamidronate was infused at a dose of 1 mg/kg/day over 3 hours for 3 consecutive days in 14 cases, 2 consecutive days in 7 cases, and only one day in the last 2 cases. All the patients were unable to receive the pamidronate throughout the 3 consecutive days due to adverse effects. The authors of this study assessed the efficacy of treatment by a decrease of pain VAS, verbal scale (PVS), and the patient and the observer estimated the efficacy of the treatment based on a verbal scale (EVS), all measured before treatment, and 7, 30, 60, and 90 days later. A significant decrease of VAS and PVS were observed between day 0 and day 30 ($p = 0.0002$ and $p = 0.0002$, respectively), day 0 and day 60 ($p = 0.0004$, $p = 0.0004$, respectively), and day 0 and day 90 ($p = 0.00003$, $p = 0.0001$, respectively) [6]. A significant increase of EVS was only observed between day 0 and day 90 ($p = 0.03$) [6].

In 2001, Kubalek et al. [7] treated 29 patients with CRPS/ RSD. Twenty-five of the patients experienced excellent pain relief from IV pamidronate at a dose of 60 mg/day over 4 hours for 3 consecutive days. Patients were evaluated at 15 and 45 days after pamidronate treatment, with effective treatment defined as a complete disappearance of pain (stopping of analgesics). Functional improvement was rated as favorable if the increase in range of movement was more than 20° compared with the range of movement prior to treatment. On day 15 after the beginning of the treatment, total pain disappearance was obtained in 17 patients (58.6%) and functional improvement was observed in 9 cases (45% of 20) [7]. On the 45th day after the beginning of the treatment, total disappearance of pain was obtained in 25 patients (86.2%) and functional improvement was obtained in 14 out of 20 patients (70%) [7].

A 2004 study by Robinson et al. [8] examined the efficacy of IV pamidronate infusion (single infusion of 60 mg) in a double-blind, placebo-controlled study of 27 patients with CRPS. Patients' pain scores were measured via VAS, global assessment of disease severity scores, and functional assessment (SF-36) scores were documented at baseline and at one and 3 months. The active treatment group ($n = 14$) reported significant improvement in pain and physical function at 3 months after pamidronate infusion [8]. However, at one month there was no significant difference in pain score or in global assessment of disease between the pamidronate and placebo (normal saline) groups.

In 2008, Breuer et al. [9] administered IV ibandronate, 6 mg infused over 2 hours to 10 CRPS patients over 3 consecutive days and assessed treatment results at 4 weeks post-infusion [9]. The authors reported significant improvement in average and worst pain ratings; the neuropathic pain qualities of "unpleasant," "sensitive,"

"deep," "intense," "sur- face," "hot," "cold," "sharp," and "dull"; and hyperalgesia and allodynia [9].

A 2017 meta analysis of four studies, including 181 patients, reported VAS pain in the blinded phase within 30–40 days [10]. At the end of this phase, short-term VAS pain was statistically lower in the bisphosphonate group versus the placebo group by an average of 2.6 points with $p < 0.001$ [10]. Two of the studies in this analysis reported VAS pain after 2–3 months with statistically significant lower VAS scores in the bisphosphonate groupe by an average of 2.5 points with $p < 0.001$ [10].

This same meta analysis found conflicting result regarding disability and quality of life [10]. One found no change in motion range while another did [10]. One found better outcome in the physical functioning section of SF-36, while another found improvements at day 40 in all items of SF-36 except for role limitations due to emotional problems. None were statistically significant in the meta analysis [10].

Mechanical Back Pain

Pamidronate has been reported to have a clinically significant analgesic effect in patients with painful osteoporotic vertebral fractures, erosive degenerative disk disease, and degenerative lumbar spinal stenosis. The first case series suggesting the efficacy of intravenous pamidronate in the management of the acute back pain of osteoporotic vertebral fractures were published in 1999 and 2000 [11, 12]. Subsequently, two small RCTs comparing pamidronate with placebo and parenteral calcitonin, respectively, were conducted. The placebo-controlled study on 32 patients demonstrated statistically significant superiority of 90 mg of intravenous pamidronate (given in 3 daily infusions of 30 mg each), which decreased pain as assessed by visual analog scale (VAS) at day 7 by 42 mm in the treatment group versus 23 mm in the placebo group. Twelve of 16 pamidronate-treated patients achieved 50% improvement a week after treatment, with the analgesic effect persisting at least for a month [13]. In another RCT, conducted on 37 patients with back pain due to osteoporotic vertebral fractures, pamidronate (1 mg/kg) decreased VAS pain scores by 1.1 points in days one to four, and by by 2.3 points by day 30 [14]. The second study [14], however, enrolled patients with more prolonged (mean duration of 41 days versus less than 21 days) and less severe (59 mm versus 71 mm on pain VAS) disease.

Pamidronate (two daily infusions of 90 mg each) was effective in ten patients with chronic back pain resulting from erosive degenerative disk disease with mean duration of 15 months. Mean VAS pain score improved gradually over several months, with eight patients rating their improvement as excellent or good [15]. However, this study was uncontrolled. In another uncontrolled trial, three to six monthly infusions of 60 mg of pamidronate led to improvement in 75% of 24 patients with symptomatic refractory degenerative lumbar spinal stenosis, with mean VAS pain score improved by 40%, as well as amelioration of neurogenic claudication [16]. Ninety-one percent of 25 patients with intractable chronic back pain and diffuse degenerative vertebral disease (with no mention of spinal stenosis)

showed 36 mm (41%) improvement in VAS pain score after 3 monthly infusions of 90 mg of pamidronate in another open trial.

In 2014, a study of 11 subjects (that has not since been further pursued with a large randomized control trial) found clinically significant decreased pain intensity for 6 months in subjects with chronic low back pain (CLBP) with IV pamidronate, administered as two 90 mg infusions [17]. A statistically significant overall treatment difference in pain scores was observed, with clinically meaningful effects persisting for 6 months in the 180 mg pamidronate group. Least square mean changes in daily average pain score were −1.39 for placebo, and −1.53, −1.26, −1.42, and −4.13 for pamidronate 30, 60, 90 and 180 mg, respectively ($p = 0.012$ for pamidronate 180 mg versus placebo) [17]. The proportion of responders, changes in worst pain and pain interference of daily function were also significantly improved for pamidronate 180 mg compared to placebo [17].

Contraindications

Contraindicationsto bisphosphonate infusion therapies include allergy to the medication, pregnancy (category D), nursing mothers, and use in pediatric patients.

Side Effects

Alendronate is administered either orally with a high dose of 40 mg/d across 8 weeks, or intravenously with a dosage of 7.5 mg for 3 consecutive days. Clodronate is administered intravenously with a dosage of 300 mg for 10 consecutive days; pamidronate with a single dosage of 60 mg, and neridronate 4 times with 100 mg every third day [18]. A barrier to therapy might be those chronic pain patients who cannot sit or stand for 30 minutes to tolerate the infusion.

Overall, bisphosphonates are generally well tolerated [10]. A 2017 meta analysis found that among 181 patients (90 in the bisphosphonate group and 91 in the placebo group), there were no serious adverse events in either group and the Number Needed to Harm was 4.6 [10]. The most common adverse events were acute phase reactants consisting of mild fever for less than 3 days, gastrointestinal intolerance, erythema and discomfort at infusion sites that resolved within 48 hours, and asymptomatic hypocalcemia [10]. These symptoms were successfully treated with over the counter regimens such as nonsteroidal anti-inflammatory drugs [10].

Monitoring

It is recommended that patients who receive bisphosphonates should have serum creatinine assessed prior to any treatment and if having multiple, before each one [19]. Other baseline labs such as serum calcium, electrolytes, phosphate, magnesium, and CBC, differential, and hematocrit/hemoglobin must be closely monitored

in patients treated with pamidronate disodium [19]. Patients who have preexisting anemia, leukopenia, or thrombocytopenia should be monitored carefully in the first 2 weeks following treatment [19].

Additionally, bisphosphonates have potential for renal toxicity and pamidronate specifically carries warnings for renal deterioration and progression to renal failure and dialysis [18]. However, renal safety risks of pamidronate are mitigated by restricting use in patients with renal impairment, limiting any single administration to 90 mg, slow infusion over at least 2 hours, and an interval of at least 3–4 weeks between doses [18]. We used 4 hour infusions up to a maximum of 90 mg, separated doses by 4 weeks for the 180 mg dose level, and did not observe any clinically significant changes in renal function [18].

Rare, serious adverse effects of intravenous bisphosphonates such as osteonecrosis of the jaw have been reported in patients on bisphosphonate therapy for multiple myeloma or bone metastases from other primary malignancies [19]. However, no cases were reported in the previously mentioned studies. A larger sample size will be needed to determine the risk of such events [19]. There are no human pharmacokinetic data for drug interactions. Other contraindications would be pregnancy (category D), nursing mothers and use in pediatric patients [19].

Algorithm for Bisphosphonate Infusion Regimens

This algorithm summarizes all proposed doses published in literature (Table 8.1). The goal of this algorithm is to provide a guide for practitioners, but different doses might be used depending on the setting and patient population.

Summary

Overall, though the evidence is sparse, it is encouraging. Further studies on intravenous bisphosphonate therapy are certainly warranted, as CRPS and CLBP can be a very difficult conditions to treat. The benign nature of these medications will likely propagate their future use chronic pain field. However, not enough evidence exists at this time to formally recommend bisphosphonates as a tool in the chronic pain

Table 8.1 Algorithm for bisphosphonate infusion regimens

Indication	Medication	Dosage (IV in number of total infusions, frequency and miligrams)
Complex regional pain syndrome (CRPS)	Pamidronate Ibandronate Alendronate Clodronate Neridronate	Three daily 30 mg or single 60 mg Three daily 6 mg Three daily 7.5 mg Ten daily 300 mg Four 100 mg infusions every 3 days
Mechanical low back pain	Pamidronate	Three daily infusions of 30 mg or two daily infusions of 90 mg

practitioners often limited toolbox. Further studies are needed to confirm these findings and assess the overall risks/benefits in this population before any medical recommendation can be made for use of pamidronate in the medical therapy of CLBP.

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Phentolamine Infusion Therapy

9

Michael J. Suer and Alaa Abd-Elsayed

Introduction

Phentolamine is available in various formulations for intravenous administration. The US product, a lyophilized powder with mannitol, requires reconstitution with sterile water and does not store [1]. The Sandoz Canada product is a liquid formulation that does not require constitution and can be stored at 2–8 °C if protected from light [2]. By acting on both venous and arterial vessels, it decreases total peripheral resistance and venous return. It may also stimulate beta-adrenergic receptors, causing cardiac stimulation. As such, traditional indications include peri-operative hypertensive crisis associated with pheochromocytoma as well as hypertensive crises associated with interaction between monoamine oxidase inhibitors and tyramine or other sympathomimetic amines and sudden withdrawal of sympatholytic antihypertensive drugs (e.g., clonidine) [3, 4]. It has also been used as an adjunct for cocaine-induced acute coronary syndrome to reverse coronary artery vasoconstriction. The phentolamine-blocking test has also been described for the diagnosis of pheochromocytoma although this has largely been supplanted by measurement of catecholamines and their metabolites [5]. It has also been used in the treatment of erectile dysfunction through self-injection of small doses combined with papaverine hydrochloride into the corpus cavernosum [6]. In the dental realm, it has been used as a reversal agent of oral soft tissue anesthesia [7]. Dosages vary by use, but typically vary from 1 to 5 mg (with the exception of dental uses which are typically less than 1 mg and are dependent upon the amount of local anesthetic used).

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Mechanism of Action

Phentolamine works via non-selective competitive blockade of both pre- and post-synaptic alpha-adrenergic receptors producing brief antagonism of circulating epinephrine and norepinephrine. It has also been found to have a positive inotropic and chronotropic effect on the heart. Phentolamine is approximately 72% protein bound [8] and is metabolized by the liver. Excretion is 80% in the urine (approximately 13% as unchanged drug) and 20% in feces [8]. Half-life elimination is 19 minutes for IV administration and 2–3 hours of submucosal injection. Its onset of action is 1–2 minutes for IV administration and duration of action is 10–30 minutes [9].

Indications

Sympathetic-Mediated Pain (SMP)

Complex regional pain syndrome is the most well-known pain disorder associated with sympathetic nervous system pathology. Other conditions include central and peripheral neuropathic pain, orofacial pain, fibromyalgia, cancer, pancreatitis, and phantom pain. CRPS, a disorder of unknown pathophysiology and usually of the distal limbs, is characterized by pain; swelling; diminished range of motion; vasomotor instability; and skin changes. There are several other names in the medical literature for CRPS, most commonly reflex sympathetic dystrophy (type I CRPS), causalgia (type II CRPS), and Sudeck atrophy. Treatments are multimodal including physical and occupational therapies, pain medications, sympathetic ganglion blocks, and neuromodulation [10]. Management is both patient and provider-specific as there are no single best options for treatment. However diagnosis of SMP is most frequently made by positive response to sympathetic blockade.

Although the pathophysiology of CRPS remains unknown, there are several theories regarding the pathogenesis. Multiple studies have suggested an increase in proinflammatory cytokines (IL-1beta, IL-2, IL-6, and TNF-alpha) in affected tissues, plasma, and CSF [11]. A hallmark of CRPS with persistent pain and allodynia is the release of inflammatory mediators and pain-producing peptides by peripheral nerves [10]. Central sensitization, increased activity in nociceptive afferents due to peripheral noxious stimuli, tissue damage, or nerve injury leading to increased synaptic transmission at somatosensory neurons in the spinal cord dorsal horns offers another possible explanation for pain and allodynia [10]. Pertinent to phentolamine, the role of the sympathetic nervous system in CRPS remains unclear. Autonomic manifestations, formerly attributed to sympathetic overactivity, could be in fact due to catecholamine hypersensitivity. The reflex arc following the inciting event follows the routes of the sympathetic nervous system and is modulated by cortical centers to produce peripheral vascular changes [12]. In response to pain sensation, injured neurons may have increased sensitivity to epinephrine and other substances released by local sympathetic nerves [12]. Further, other mechanisms by which derangements in the sympathetic nervous system can interact with pain include increased expression of alpha-1 adrenoreceptors on primary afferent nociceptors

[13], hyperalgesic skin of CRPS [14], central sensitization rendering A-beta mechanoreceptors algogenic [15], and enhance discharge and sympathetic sprouting in the dorsal ganglia [16]. This enhanced sensitivity can be blocked by the administration of sympatholytic agents.

Although described early in the scope of intravenous infusions, phentolamine infusion offers a paucity of literature for SMP. In two studies comparing intravenous phentolamine test to respective sympathetic blockade of the upper or lower extremities, phentolamine was found to be more specific though less sensitive in diagnosing SMP. Further, in comparison to lumbar sympathetic blockade and stellate ganglion blocks, IV phentolamine was not found to provide sustained analgesic response lasting longer than 12 hours with peak effect at 1–2 hours post infusion [17–19]. In an evaluation of the activity of the central nervous phenomenon in SMP, Moriwaki *et al.* [20] measured the size of the receptive fields of low threshold spinal neuron in response to IV phentolamine infusion in physiological and painful pathological conditions in a rat model. After confirmation of the phentolamine-induced reduction in the size of the receptive field in low threshold spinal neurons, they studied the degree of maximal reduction in the size of the receptive field and reversibility of the change. This study provided the first evidence that IV phentolamine produced a reduction in low threshold neuron receptive field size indicating that sympathetic blockade results in inhibitory modulation of spinal neuronal activity. In another rat model, Ogon *et al.* [21] evaluated sympathetic nerve sprouting around the dorsal root ganglion in a lumbar radiculopathy model. They found phentolamine administration around the dorsal root ganglion could suppress neural plastic changes in the early phase (within 4 days) after nerve injury but had no effect if not administered in the early stages. While these latter two animal model studies have not been replicated in humans, they provide insight into future directions that could be taken by phentolamine administration.

As is oft done with other intravenous therapies, two studies have attempted to correlate pain relief with IV phentolamine with analgesia obtained by a prolonged treatment course with a sympatholytic agent (eg clonidine). Davis *et al.* [22] subjected six patients with CRPS to sympathetic ganglion blocks and IV phentolamine infusions to identify those with SMP in the first open-label prospective study. A clonidine patch was applied to the hyperalgesic skin. In the four patients with SMP, the patch significantly reduced cold and mechanical hyperalgesia. In three of these four patients, the beneficial effects were confined to the area beneath the patch. In the two patients with sympathetically independent pain, topical clonidine failed to relieve pain or reduce allodynia. A subsequent double-blind, placebo-controlled study of 41 patients with diabetic peripheral neuropathy, Byas-Smith *et al.* [23] treated all with either transdermal clonidine or placebo patch. The responders (12 patients) then enrolled in a second 3-phase study to identify consistent responders of whom 8 were identified. None of the consistent responders received benefit from intravenous phentolamine or saline infusions and all 8 obtained benefit from continued transdermal clonidine. Park *et al.* [24] evaluated the involvement of selective alpha-2 adrenoreceptors in SMP in a randomized, prospective, double-blind, crossover study of 20 patients. While they did not find a statistical difference between yohimbine (alpha-2 selective) and phentolamine IV infusions, they did find

significant improvements in almost all measures and sub-tests of pain (VAS, short-form McGill pain questionnaire, and neuropathic pain score) except affective scores of phentolamine. In an observational study to evaluate the ability of phentolamine infusions to predict response to IV regional guanethidine, a post-ganglionic adrenergic blocking agent, Arner [19] evaluated 104 patients with CRPS. Of the 53 phentolamine responders, all obtained relief after regional guanethidine treatment. In the 51 patients who did not respond to IV phentolamine, 25 experienced excellent or partial relief with guanethidine and 26 experienced no relief. Given the limited, conflicting data examining IV phentolamine, there is no evidence to suggest that pain relief during phentolamine infusion can be used to predict response to subsequent treatment with other agents.

Abdominal Visceral Cancer

Multiple treatment regimens have been established in the treatment of cancer pain, the most well-known being the World Health Organization analgesic ladder [25]. Treatments must balance benefits of analgesia with side-effects of the therapeutic agents of procedures. While the WHO ladder focuses on oral medications, invasive blocks such as celiac plexus blocks are utilized to provide analgesia. Such blocks of sympathetic ganglia target those mechanisms mentioned in the previous section on SMP. However, there remains a relative paucity of information regarding IV phentolamine in treatment of such conditions.

A sentinel case report by McCleane [26] demonstrates initial efficacy of such an approach. A single patient with inoperable pancreatic cancer underwent initial bolus infusion which provided 36 hours of relief. Subsequent 48-hour infusion produced complete relief of pain for 26 days. A third infusion of 36 hours (stopped due to phlebitis) provided 12 weeks of complete pain relief. A case series by Yasukawa *et al.* [27] described eight patients (four with pancreatic carcinoma and one with each hepatocellular carcinoma, gastric and rectal carcinoma, sigmoid colon cancer, and rectal cancer). Following a similar protocol of 48-hour infusions at 80 mg/day, complete analgesia was obtained in three patients, decrease in pain was noted in four (only sustained in two patients), and one patient was ultimately excluded from the study due to use of intrathecal morphine in conjunction with the IV phentolamine infusion. Of these patients, two remained pain free for 40 and 30 days until their respective demise. A third patient remained pain free without analgesics for 96 days. Two patients underwent subsequent infusions and had excellent relief of pain for several months.

Other Indications

Prior to his aforementioned case report, McCleane published other such case reports that have not since been duplicated with larger studies. Using intravenous phentolamine, potentially useful analgesic effects were noted with chronic pancreatitis [28], visceral pain associated with acute intermittent porphyria [29], and as an

anti-emetic in those with liver metastases [30]. However, as these case reports did not generate further study, one cannot comment further on the efficacy of IV phentolamine for such uses.

Contraindications

Phentolamine is contraindicated in individuals with hypersensitivity to phentolamine, any component of the formation, or related compounds; MI (or history of MI), coronary insufficiency, angina, or other evidence suggestive of coronary artery disease [31]. Use with extreme caution in patients who have intracranial hemorrhage or ischemic stroke as excessive lowering of blood pressure may aggravate brain injury [32].

Side Effects

Phentolamine can cause both bradycardia and hypotension during infusion although the incidence is unknown for prolonged infusions. The decrease in blood pressure is due to competitive blockade of alpha-adrenergic receptors producing brief antagonism of circulating epinephrine and norepinephrine. It has also been shown to have positive inotropic and chronotropic effect on the heart thought to be due to presynaptic alpha-2 receptor blockade which results in release of presynaptic norepinephrine [31]. But at the dose administered in the above studies, the risk of major complications highlighted above is extremely rare. Contraindications to phentolamine infusion include hypersensitivity to phentolamine, myocardial infarction, coronary insufficiency, angina, or other evidence suggestive of coronary artery disease [31].

Monitoring

Phentolamine infusions requires close monitoring of cardiac status with the ability to intervene if necessary. Recommended monitors include at least noninvasive blood pressure and heart rate monitoring. For boluses, blood pressure should be monitored immediately after the injection, every 30 seconds for 3 minutes, then every minute for 7 minutes, and every 10 minutes for 30 minutes after the bolus [33]. For prolonged infusions, more periodic monitoring may be implemented. Please review your institute guidelines for monitoring and needed support in places where you perform the infusion.

Algorithm for Phentolamine Infusion Regimens

The following table summarizes proposed doses as published in literature (Table 9.1).

Table 9.1 Algorithm for phentolamine infusion regimens

Indications	Dose
Sympathetic mediated pain Abdominal visceral cancer And All other pain indications	Phentolamine is administered as intermittent boluses or as continuous infusion though a combine approach is recommended. Initiate treatment with a bolus of 2.5–5.0 mg given repeatedly (at 5–10 minute intervals) for total dosage of 10–20 mg very slowly via intravenous line. When initial phentolamine challenge shows decrease in pain of 40%, it is considered positive and patients can undergo 48-hour infusion should they have continued pain. Infusion of 80 mg (8 mL) per day is given with 112 mL normal saline (infusion speed, 5 mL/hr) for 2 days. Lactated Ringer's solution at 500 mL/day can be infused with via phentolamine via 3-way stopcock. Should patients experience negative cardiac effects, infusion can be slowed or stopped

Summary

While most commonly used extravasation of norepinephrine, pheochromocytoma diagnosis and hypertensive management, erectile dysfunction, and in reversal of oral soft tissue anesthesia; there exist applications for intravenous infusion of phentolamine for pain management. The use of phentolamine is primarily sympathetic-mediated pain and secondarily abdominal viscera cancer. Infusions are typically 80 mg/day infused over 2 days at 5 mL/hr with most common adverse effects noted to be hypotension and bradycardia with infusions titrated to these effects. The literature and evidence for these infusions are sparse and there is a need for further basic science research and larger randomized, clinical trials to evaluate the efficacy of phentolamine infusions for the treatment of chronic pain.

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Dexmedetomidine Infusion Therapy

10

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Introduction

Dexmedetomidine, or 4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole, is a potent and selective α_2-adrenoceptor agonist used for its sedative, analgesic and anxiolytic properties [1, 2]. It was initially approved in the United States in 1999 (Precedex®; Hospira, Lake Forrest, IL, USA) for intravenous (IV) sedation of mechanically ventilated adult patients in the intensive care unit (ICU), at doses ranging from 0.2 to 0.7 mcg/kg/h for up to 24 h [3]. In 2008, it received additional approval for procedural sedation of non-intubated adult patients in perioperative and non-surgical settings [2]. In Europe it has been approved since 2011 (Dexdor®; Orion Corporation, Espoo, Finland), for sedation in adult ICU patients who are required to remain easily arousable to verbal stimuli [4, 5].

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Mechanism of Action

As the pharmacologically active dextro-isomer of medetomidine (a commonly used agent in veterinary medicine) [2], dexmedetomidine binds to transmembrane G_i-coupled α_2-adrenergic receptors in the periphery (α_{2A} subtype) and centrally within the brain and spinal cord (α_{2B} and α_{2C} subtypes) [6, 7]. It does not have action at gamma-aminobutyric acid (GABA), opioid or N-methyl-D-aspartate (NMDA) receptors as do benzodiazepines, opioids and propofol. Sedative and antinociceptive actions are mediated through α_{2A} stimulation [8, 9], vasoconstrictive effects are produced by α_{2B} activation, and α_{2C} stimulation modulates dopaminergic neurotransmission, hypothermia and numerous behavioral changes [9]. The suppression of neurotransmission seen with α_2-agonists is due to activation of pre- and postsynaptic potassium ion channels. Subsequent potassium efflux and membrane hyperpolarization inhibits norepinephrine release and leads to decreased excitation, particularly in the medulla within the locus coeruleus [6, 9]. This area of the brain is the key site of noradrenergic functions including arousal, sleep, anxiety, and withdrawal from CNS depressants including opioids [6, 9, 10]. Additionally, dexmedetomidine interacts with imidazoline type 1 (I_1) receptors, which are not G-coupled, and have roles in memory [11], neuroprotection [12], central hypotension and display antiarrhythmogenic qualities [13, 14]. These receptors are found centrally in the medulla, and peripherally within the cardiac tissue [15]. Overall, α_2-agonists have sedative, sympatholytic, and opioid sparing properties [6, 16]. Importantly, dexmedetomidine-based sedation resembles natural sleep, with patients remaining quickly and easily arousable [17–20].

As compared to the prototypic α_2-agonist clonidine, dexmedetomidine has a dose-dependent seven to eight-fold higher α_2-receptor selectivity (α_2:α_1 ratio of 1620:1 vs. 220:1) [2, 16, 21]. Both α_1- and α_2-receptor activity was found in early preclinical studies with slow high dose infusions (>1000 mcg/kg) or following rapid IV bolus administration [3]. This proclivity for α_1-activity at very high plasma concentrations, in addition to the expected α_2-receptor actions at recommended plasma concentrations, explains the main hemodynamic side effects of dexmedetomidine. Main among them are transient hypertension, bradycardia and hypotension. The onset of action of dexmedetomidine infusion is 5–8 min when given with a loading dose, with a peak effect after 10–20 min [1]. It is 94% albumin-bound in plasma and has a weight-dependent volume of distribution of 1.3–2.5 L/kg [2]; thus, reduced doses are not required in pediatric patients. Dexmedetomidine undergoes hepatic biotransformation via direct glucuronidation and hydroxylation by cytochrome P450 enzymes (mainly CYP2A6) and is excreted unchanged in the urine (95%) and feces (5%) [2, 3, 5]. There are no active or toxic metabolites, and the elimination half-life ranges between 2–4 h [2]. As with clonidine, a dependence potential has been demonstrated in preclinical studies, however, this has not been researched in clinical trials [22].

Despite the seemingly narrow list of approved indications, numerous off-label uses and routes of administration, including intra-auricular [23], intranasal [24], buccal [25], and epidural [26] have been described in the literature. Indications

which include therapeutic IV infusion for pain associated conditions will be the focus of this chapter.

Indications

Perioperative and Intensive Care Unit

Overall, dexmedetomidine is primarily used in perioperative and ICU settings. Its use for sedation in the ICU has been thoroughly researched and is well established [3, 6]. The approved dosing regimen in adults is 1 mcg/kg over 10 min as a loading dose, followed by a 0.2–0.7 mcg/kg/h maintenance infusion for a maximum of 24 h [3]. Studies have described safe infusions in mechanically ventilated ICU patients for upwards of a week in duration [27, 28]. The most recent RCT from 2018 by Skrobik et al. demonstrated that low-dose nocturnal dexmedetomidine infusion can prevent delirium in adult ICU patients [29]. Furthermore, in light of the current opioid epidemic [30], as increasing numbers of patients are admitted to the ICU for the management of withdrawal or acute detoxification [31], dexmedetomidine has shown value in both adult and pediatric patients [32–35]. It has been approved for awake fiberoptic intubation (AFOI) since 2008 [2], and as per the most recent meta-analysis, remains a suitable agent alongside remifentanil [36]. In a recent trial comparing these two agents, Hu and colleagues found that dexmedetomidine (loading: 1.5 mcg/kg, infusion: 0.7 mcg/kg/h) reduced the incidence of recall to 40%, in comparison to 70% in the remifentanil group, indicating that it may be preferable [37]. The easily arousable nature of dexmedetomidine sedation renders it a common agent for procedures where conscious sedation is required. A large RCT with 326 patients undergoing varied procedures found that dexmedetomidine at 0.5–1.0 mcg/kg loading dose, followed by continuous IV infusion at 0.2–1.0 mcg/kg/h, reduced the need for supplemental midazolam and overall dose required to achieve adequate depth of sedation [38]. However, where dexmedetomidine has been successful in orthopedic, vascular, diagnostic and dental procedures, it is inappropriate for outpatient colonoscopy [39]. This is due to possible vagal stimulation during colonoscopy, which may potentiate the bradycardic side effects of dexmedetomidine. Indeed, due to its shorter duration of action and less hemodynamic disturbance, propofol remains the drug of choice in such scenarios [39]. Furthermore, recent meta-analyses have concluded that, dexmedetomidine-infused patients experience significantly lower rates of postoperative nausea and vomiting (PONV) and shivering, compared to placebo controls [40, 41]. Alone and in combination with other agents, dexmedetomidine has been shown to attenuate the incidence of emergence delirium in children [42–44]. The agent may in fact, be the drug of choice to achieve opioid-free total IV anesthesia [45], as studies have demonstrated its effectiveness when combined with propofol and/or ketamine in bariatric [46] and spinal surgery [47]; however, more RCTs are needed in this field and further discussion is outside the scope of this chapter.

Opioid-Sparing and Acute Postoperative Pain

Alleviating the acute postoperative pain seen in up to 80% of patients after surgery is paramount to increasing patient satisfaction, reducing time in recovery and curbing the incidence of chronic postsurgical pain [48]. A multimodal analgesic approach is recommended by the American Society of Anesthesiologists [49]. Due to its inherent antinociceptive qualities, dexmedetomidine has demonstrated promising results in the perioperative period [50, 51].

Initial studies evaluated dexmedetomidine for its opioid-sparing properties [52, 53]. Lin et al. randomized 100 post-hysterectomy patients to receive either morphine or morphine plus dexmedetomidine as part of patient-controlled analgesia (PCA) over the first 24 h after surgery [52]. The investigators found that patients in the combined group required one-third less morphine compared to those who received morphine alone, without any higher incidence of bradycardia, hypotension or respiratory depression [52]. Similarly, Wahlander and colleagues investigated dexmedetomidine as an adjuvant IV infusion (loading dose: 0.5 mcg/kg over 20 min, maintenance infusion: 0.4 mcg/kg/h) in patients following thoracic surgery [53]. Twenty-eight patients with epidural bupivacaine catheters for regional anesthesia at T4 were randomized to receive dexmedetomidine or placebo in the 24 h after surgery [53]. The pain scores were similar in both study arms, however, the placebo group required more epidural rescue fentanyl to maintain adequate analgesia.

A more recent RCT included patients after laparoscopic gynecologic surgery and compared postoperative dexmedetomidine PCA versus fentanyl PCA [54]. Again, no difference in pain scores was seen; however, patient satisfaction was significantly higher in the dexmedetomidine group [54]. Indeed, Peng et al. who performed a meta-analysis of 18 RCTs including 1284 heterogeneous surgical patients, and determined that combined opioid-dexmedetomidine PCA decreased postoperative pain, opioid consumption and related adverse events [55]. Doses of dexmedetomidine were generally low, and ranged from 0.045 to 0.2 mcg/kg/h [55].

Following from these and other studies, the intraoperative use of dexmedetomidine for postoperative pain was investigated. In a study from 2017, Fan et al. analyzed intraoperative dexmedetomidine infusion versus placebo in 45 patients undergoing radical mastectomy [56]. General anesthesia was maintained with propofol, remifentanil and Ringer's lactate or propofol, as well as remifentanil and dexmedetomidine, followed by morphine-based PCA for 24 h after surgery [56]. The dexmedetomidine group exhibited lower pain scores, a longer time to initial morphine dose postoperatively, and decreased morphine consumption overall [56]. Similar findings were documented in several studies in patients undergoing abdominal surgery [57–59]. Ge et al. delivered intraoperative dexmedetomidine at 0.4 mcg/kg/h in hysterectomy [58] and colectomy [59] patients, and found reduced opioid consumption within the first 24 h following surgery. These results were comparative to those seen by Tufanogullari et al. after bariatric surgery; however, in these patients, opioid consumption was not decreased on postoperative days 2 and 7 [57]. Furthermore, the authors concluded that the optimal dose to achieve pain control and reduce the incidence of adverse cardiovascular events was 0.2 mcg/kg/h [57].

Analogous to its use in AFOI, remifentanil is a common agent used in neurosurgical cases where rapid emergence is required. In two trials investigating intraoperative remifentanil versus dexmedetomidine, Rajan et al. [60] and Hwang et al. [47] determined that dexmedetomidine provided superior pain relief and decreased postoperative opioid consumption for up to 48 h. Such results were not seen in a trial by Naik et al. where intraoperative dexmedetomidine (1 mcg/kg loading dose, followed by 0.5 mcg/kg/h infusion) was compared to placebo (normal saline) in patients undergoing major spinal surgery [61]. No differences were seen in postoperative opioid consumption or pain scores; however, dexmedetomidine did reduce intraoperative opioid consumption [61].

Such discrepancies were examined in a 2018 meta-analysis of 11 RCTs involving 674 neurosurgical patients [62]. The investigators concluded that dexmedetomidine reduces perioperative and post-surgical opioid consumption, in addition to reducing postoperative pain intensity [62]; optimal intraoperative doses were, however, not given. Meta-analyses including nasal [63] and general surgery [64] found comparative results, however, further trials for clarifying dosing regimens are required. Additionally, studies in pediatric surgery are lacking.

Chronic Pain Conditions

Studies investigating dexmedetomidine infusion in the treatment of chronic pain conditions are limited. Clinical evidence comes from a case report by Nama et al. [65]. The patient was a 47-year-old female with complex regional pain syndrome-1 (CRPS-1) of the upper left extremity, refractory to conventional therapy [65]. At admission, her pain was 10/10 on the pain scale and a sub-anesthetic IV infusion of ketamine (100 mcg/kg/h) was initiated. After 6 h, with pain at 7/10, a single dexmedetomidine dose of 8 mcg was given as a one-time IV bolus [65]. This led to a decrease of pain to 3/10. At the end of the 19-h infusion the patient reported pain 0/10 and was discharged [65]. The authors concluded that ketamine with adjunct dexmedetomidine is a promising treatment of acute exacerbation of CRPS [65]. Although the extract pathophysiology of CRPS remains unknown, activation and upregulation of NMDA receptors in the spinal cord leading to chronic pain has been implicated through a mechanism termed central sensitization [66]. Ketamine with its NMDA receptor antagonism is a rational agent for decreasing central sensitization. Dexmedetomidine has analgesic activity through activation of α_{2A}- and α_{2C}-adrenoceptors, located on C-fiber primary afferent nerve terminals and the superficial dorsal horn of the spinal cord [8]. Furthermore, dexmedetomidine has been shown to attenuate neuropathic pain by inhibiting purinergic receptor 7 and extracellular signal-regulated kinase signaling in a recent animal model [67]. Chronic constriction injury of the sciatic nerve created neuropathic pain which resolved following 2.5 mcg of intrathecal dexmedetomidine for 3 days [67]. This antinociceptive and sympatholytic effect is distinct from opioids. Indeed, this distinctive mechanism of action has proven effective in cases where opioids or ketamine are unsuccessful. Sheehy and colleagues presented a case series which included 11 adolescent patients

with severe vaso-occlusive episodes due to sickle cell disease [68]. All patients were receiving morphine or hydromorphone PCA at rates of 0.02 mg/kg/h (0.02 mg/kg boluses up to every 8 min) or 0.003 mg/kg/h (0.003 mg/kg additional boluses up to 10 min apart), respectively [68]. Furthermore, the patients were receiving ketamine infusions at sub-anesthetic doses less than 1.0 mg/kg/h, in addition to non-steroidal anti-inflammatory drugs as needed. In this report, the authors identified 3 patients who required escalating doses of opioids and ketamine without sufficient pain relief. The patients, aged between 15- and 18-years, reported pain 8/10 or greater despite morphine equivalents up to 9 mg/kg/day. The first patient received a continuous dexmedetomidine infusion at 0.2–0.4 mcg/kg/h over 5 days and subsequently discontinued opioids and ketamine with a pain score 6–7/10. After a 3-day dexmedetomidine infusion at 0.5 mcg/kg/h, the second patient discontinued ketamine, reduced their opioid requirement to 2.1 mg/kg/day and reported a pain score of 2/10 [68]. The third patient reported a pain score of "14" (pain scale 0–10) on the 5th day of hospitalization and was initiated on a 1.0 mcg/kg/h continuous dexmedetomidine infusion over 5 h; this dose was decreased to 0.5 mcg/kg/h for the next 12 h and then maintained at 0.2–0.4 mcg/kg/h over the subsequent 6 days [68]. After the infusion, the patient had a pain score of 6–7/10, with an oral morphine-equivalent of 0.17 mg/kg/day. Important to note, all three patients received a transdermal clonidine patch (0.1–0.2 mg) upon completion of the dexmedetomidine infusion, which was continued for 14, 7 and 7 days, respectively. The authors suspected that these patients may have developed opioid-induced hyperalgesia (OIH) and thus dexmedetomidine may have attenuated their response to opioids. In comparison to those patients who did not receive dexmedetomidine, the marked reduction in opioid requirement and improved pain scores, nevertheless, warrants further research before solid conclusions may be reached. Indeed, as of late 2018, there are very few active or completed trials examining dexmedetomidine in chronic pain conditions including chronic postoperative and cancer pain [69].

Opioid-Induced Hyperalgesia

Patients receiving high dose short-term [70] or long-term opioids are prone to developing opioid-induced hyperalgesia (OIH). Whether through pharmacologic tachyphylaxis and tolerance, or central sensitization by NMDA receptor activation, OIH is characterized by a paradoxical increase in pain intensity and distribution [71]. Where propofol infusion has shown benefit by way of NMDA antagonism [72], the exact mechanism how α_2- receptors act synergistically with opioids remains unclear. Nevertheless, limited studies have emerged that show the benefit of dexmedetomidine infusion in the treatment of OIH. The first report, a case series of 11 patients by Belgrade and Hall, demonstrated a decrease in the average pain intensity from 6/10 to 1/10 following dexmedetomidine infusion [73]. The doses ranged from 0.1–0.2 mcg/kg/h over 3 days, to 0.2 mcg/kg/h titrated up to a maximum of 0.7 mcg/kg/h over 24 h [73]. The majority of the patients continued their pre-OIH opioid therapy after infusion, however, at reduced doses. Indeed, the mean oral morphine

equivalent of the 11 patients prior to infusion was reduced from 648 to 122 mg following discharge; two of the patients ceased opioids altogether. The authors concluded that dexmedetomidine "rebooted" the opioid sensitivity of these patients [73]. In a similar fashion Patch III et al. presented a case report where dexmedetomidine infusion was successfully utilized as part of a controlled multimodal analgesic plan to treat OIH [74]. The patient was a 55-year-old female with a long history of chronic pain syndrome receiving up 19,702 mcg per day of fentanyl via an intrathecal drug delivery device. Following unremarkable exploratory laparotomy, she was diagnosed with acute pain crisis and OIH secondary to uncontrolled and disproportionate abdominal pain [74]. After consultation with the pain service, a continuous dexmedetomidine infusion was initiated at 0.8 mcg/kg/h, in addition to ketamine at 0.7 mg/kg/h with 10 mg IV boluses every 30 min as required, alongside extra ketorolac, and acetaminophen doses, and lidocaine patches around the incision [74]. Over 48 h both infusions were weaned, as hydromorphone (1 mg) and ketamine IV boluses were increased to 4-h intervals. Her pain subsided on the third postoperative day and she was transferred to the ward, where oral hydromorphone (4 mg) was prescribed every 6 h as needed until discharge; at 3-month follow-up her intrathecal fentanyl dose had reduced to 11,000 mcg per day [74]. Although dexmedetomidine was successfully used in this case, it remains only the second report published on OIH in patients with chronic pain syndromes.

High-dose remifentanil has been increasingly associated with the development of OIH in the acute postoperative setting [75]. To date however, few clinical trials have examined the antihyperalgesic effect of dexmedetomidine. In the first RCT from 2013, Lee and colleagues recruited 90 patients aged 20–65 years who were scheduled for laparoscopically assisted vaginal hysterectomy, to investigate whether dexmedetomidine could attenuate remifentanil-induced secondary hyperalgesia in the initial 24 h postoperative period [76]. The patients were randomized to three groups: placebo (normal saline) and 0.05 mcg/kg/min remifentanil, placebo and 0.3 mcg/kg/min remifentanil, and dexmedetomidine (1.0 mcg/kg over 10 min loading dose, followed by 0.7 mcg/kg/h) and 0.3 mcg/kg/min remifentanil [76]. Patients in the second group (with high dose remifentanil and placebo) were suspected to have developed OIH due to higher postoperative VAS scores, reduced mechanical hyperalgesia thresholds, and greater utilization of morphine PCA [76]; on the contrary, these findings were not seen in the third group who had received dexmedetomidine in addition to high dose remifentanil [76]. The authors concluded that intraoperative dexmedetomidine alleviated OIH symptoms in these patients, adding that it may have preventative properties [76]. Following on from this in 2016, Yu et al. conducted a similar RCT in the same subset of patients, to investigate whether dexmedetomidine combined with flubiprofen axetil (cyclooxygenase inhibitor) had comparable results [77]. Ninety-five female patients were included and randomized to similar groups as the aforementioned RCT; first group only high-dose remifentanil, second group high-dose remifentanil and dexmedetomidine, with the third group receiving high-dose remifentanil, dexmedetomidine (0.5 mcg/kg over 10 min loading dose, followed by 0.6 mcg/kg/h continuous infusion) and flubiprofen axetil [77]. The primary outcome was mechanical pain threshold in the first 24 h after

surgery. In this study the patients who received dexmedetomidine, with or without flubiprofen axetil experienced higher pain thresholds ($p < 0.05$) [77]. Furthermore, the postoperative VAS scores were significantly lower in the two dexmedetomidine groups ($p < 0.05$). This RCT concluded that when used in combination with flubiprofen axetil, dexmedetomidine provided the most significant attenuation of remifentanil-induced hyperalgesia [77]. Whether gender differences exist between patients was investigated in the most recent RCT from 2018 [78]. Forty-eight patients undergoing thyroidectomy were included and randomized into six male and female groups: control (0.2 mcg/kg normal saline), low-dose and high-dose dexmedetomidine injection (0.2 mcg/kg and 0.6 mcg/kg, respectively) [78]. Dexmedetomidine was given preoperatively and all patients received intraoperative remifentanil at 0.2 mcg/kg/min [78]. No significant differences were seen amongst the genders, and expectedly the dexmedetomidine groups demonstrated less PONV and shivering, in addition to lower pain scores by VAS and significantly higher mechanical hyperalgesia thresholds ($p < 0.05$) [78]. The underlying mechanism behind the preventative nature of dexmedetomidine on remifentanil-induced hyperalgesia has been attributed to regulation of the NMDA receptor-protein kinase C-calmodulin-dependent protein kinase II pathway in a recent rat model, however, human studies have not been performed [79].

Nevertheless, these few RCTs show that dexmedetomidine is a promising agent for remifentanil-induced hyperalgesia in the postoperative period. However, more studies are required to further our knowledge of its effect in OIH in patients with chronic pain conditions not undergoing surgical procedures.

Contraindications

There are no absolute contraindications to dexmedetomidine infusion. Nevertheless, it is an in vitro inhibitor of CYP2D6, CYP2C9, CYP1A, CYP3A and CYP3A4 [80]. In vivo, however, it does not inhibit the pharmacokinetics of midazolam, a CYP3A4 substrate [81]. Inhibition of CYP2D6 may affect the metabolism of opioids including oxycodone and tramadol, diminishing their analgesic effect [82]; however, this remains unproven. In contrast, dexmedetomidine has been shown to reduce the requirements of other anesthetics including sevoflurane [83], isoflurane [84], propofol [85], and thiopental [86], in addition to having opioid-sparing properties as discussed earlier. Perhaps the most well-known interactions were investigated in pre-registration studies. Antihypertensive agents such as β-blockers may increase the hypotensive and bradycardic effects of dexmedetomidine [5]. These effects may be further exaggerated with concomitant vagal stimulation as seen during sternal separation, colonoscopy and laparoscopic insufflation [39, 87, 88].

Renal impairment does not warrant dose reduction [3]. Hepatic impairment and/or hypoalbuminemia, however, necessitate dose reductions due to diminished clearance and an increase in unbound plasma concentration favoring toxicity [3, 89].

Side Effects

The side effect profile of dexmedetomidine is largely predictable and based on its receptor binding pharmacology. The most common adverse events are hemodynamic in nature, namely transient hypertension, bradycardia, and hypotension [5, 38, 90, 91]. It demonstrates a biphasic effect on blood pressure, producing hypertension at high plasma concentrations and hypotension at lower plasma concentrations [92, 93]. Rapid IV bolus or fast loading dose administration has been associated with progressive increases in mean arterial pressure [2, 93]. These effects are thought to occur due to α_{2B}-receptor activation in vascular smooth muscle, resulting in peripheral vasoconstriction accompanied by a baroreceptor-mediated reduction in heart rate [92, 93]. This increase in systemic and pulmonary vascular resistance may lead to systemic and pulmonary hypertension, which can limit its use in patients with serious cardiac morbidity. At plasma concentrations between 1.9 and 3.2 ng/ml these hypertensive effects prevail, and may be mitigated by decreasing and slowing loading doses and avoiding IV bolus administration [5, 93]. The hypotensive phase occurs at lower plasma concentrations and for a prolonged time after the initial dose, with an average decrease in mean arterial pressure of 13–27%, mediated by presynaptic α_2-receptor inhibition of catecholamine release and increased vagal activity [92, 93].

These side effects are to be expected, however, the most serious and life-threatening adverse events are difficult to predict. Numerous case reports and series describing severe bradycardia and/or atrioventricular block precipitating cardiac arrest have been reported in the literature [87, 94–98]. Ingersoll-Weng et al. were the first to report an episode of asystole during intraoperative dexmedetomidine infusion in a 52-year-old patient with myasthenia gravis undergoing thymectomy via median sternotomy [94]. Dexmedetomidine infusion was started prior to induction of general anesthesia, with a loading dose of 1 mcg/kg over 10 min followed by a rate of 0.2 mcg/kg/h. Asystole occurred immediately after sternotomy, lasted for 2 min and resolved following internal cardiac massage and 300 mcg/kg IV epinephrine [94]. The authors concluded that caution should be taken when dexmedetomidine is used in conjunction with other cardiac depressants [94]. Vagal stimulation caused by sternotomy may have also potentiated the bradycardia, which preceded cardiac arrest. Shah et al. reported cardiac arrest and subsequent death during procedural sedation with dexmedetomidine in a 76-year-old patient undergoing exchange of an infected permanent pacemaker [87]. An infusion of 1 mcg/kg was initiated and intended for 20 min duration (total dose 95 mcg). After 15 min, however, having received 71.25 mcg of dexmedetomidine, the patient began to cough, became dyspneic and lost consciousness; pacing spikes without capture were seen on the electrocardiogram [87]. Although these doses are acceptable loading doses, the plasma concentration immediately after the infusion began would have been 1.7 ng/ml, with cardiac depression induced at concentrations exceeding 1.2 ng/ml [92]. Takata et al. reported dexmedetomidine-induced atrioventricular (AV) block and cardiac arrest in a 56-year-old patient under sedation in the ICU on the first

postoperative day following a Bentall procedure [95]. As part of the postsurgical regimen the patient was receiving atrial pacing at a rate of 90 bpm [95]. In the ICU a dexmedetomidine infusion was initiated at a rate of 0.3 mcg/kg/h without a loading dose. Five hours and 30 min into the infusion, the interval between a pacing spike and a Q wave increased to 340 ms, and the patient subsequently developed complete AV block without an escape rhythm (asystole) [95]. The authors concluded that even low-dose dexmedetomidine may disturb AV conduction in addition to having an inhibitory effect on cardiac pacing autoregulation, above all, in patients with conduction abnormalities [95]. They added that ventricular pacing alongside standard atrial pacing may be prudent in similar patients [95].

Bharati et al. reported a series of six instances of intraoperative bradycardia leading to asystole [96]. Most were given loading doses of 1 mcg/kg, however, over less than 10 min, which led to plasma concentrations ranging from 0.77 to 1.8 ng/ml [95, 96]. The authors concluded that dexmedetomidine should be used with extreme caution when combined with negative chronotropes and inotropes, furthermore stating that dexmedetomidine should be avoided in elderly patients and those with cardiac disease.

Similar adverse reactions have been seen in pediatric patients. Shepard et al. presented a case of a 3-year-old patient with a history of repaired congenital heart disease, and a permanent pacemaker. On the second day following a mitral valve replacement surgery, the patient developed atrial standstill with a loss of capture after 21 h of dexmedetomidine infusion at a rate of 0.6 mcg/kg/h [98]. Immediate cessation of dexmedetomidine led to resolution without sequela. Similarly, Zhang et al. reported 10 s bouts of asystole in an 18-year-old patient with cystic fibrosis and a history of double-lung transplant in the ICU during mechanical ventilation [97]. On the 22nd postoperative day following laparoscopic fundoplication for gastroesophageal reflux disease, the patient, already on a propofol (0.5–2.5 mg/kg/h) and fentanyl infusions (up to 4 mcg/kg/h), was started on dexmedetomidine with a loading dose of 1 mcg/kg over 10 min followed by an infusion of 0.4–0.7 mcg/kg/h with the intention of weaning from propofol [97]. Over the following hours, propofol and fentanyl infusions were reduced but not stopped. After 8 h of dexmedetomidine (infused at a maximum rate of 0.7–0.8 mcg/kg/h), the patient developed a bradycardia which progressed to a 10-s period of asystole [97]. Over the subsequent 24 h, four additional episodes occurred, three during and one after the dexmedetomidine infusion. These instances of asystole were not pharmacologically treated, and the patient was uneventfully discharged on the 32nd postoperative day [97]. The authors concluded that changes to cardiac autonomic innervation that can occur after double-lung transplant place such patients at increased risk for these phenomena [97].

The consensus of the aforementioned cases is that dexmedetomidine, at any dose, should be used with extreme caution when combined with other common anesthetic agents, and in patients with cardiac abnormalities. Nevertheless, these severe adverse events are exceedingly rare.

The specific α_2-andrenoceptor antagonist atipamezole has been shown to rapidly reverse the sedative and hemodynamic effects of dexmedetomidine [99–101]. Although widely used in veterinary medicine, to date this agent has not been approved for use in humans [102].

Monitoring

The use of dexmedetomidine requires continuous monitoring of the cardiovascular and respiratory systems. Non-invasive or continuous blood pressure monitoring, electrocardiography and pulse oximetry are the minimal recommendations. BIS targeted between 60 and 80 may be beneficial in neonates and infants. As hepatic impairment may necessitate dose adjustment, liver function tests should be ordered before initiating the infusion. Please review your local monitoring and support guidelines regarding the use of dexmedetomidine.

Algorithm for Dexmedetomidine Infusion Regimens

The following algorithm summarizes the IV infusion dosing regimens published in the literature (Table 10.1). Differing settings and patients may require different doses.

Table 10.1 Algorithm for Dexmedetomidine infusion regimens

Indication	Dosage
Acute postoperative pain	Intraoperative: 0.1–0.7 mcg/kg/h IV continuous infusion PCA when combined with opioid: 0.045–0.2 mcg/kg/h IV
Acute exacerbation of CRPS-1	Adjuvant to ketamine infusion (60–120 mcg/kg/h), dexmedetomidine given as single bolus 8 mcg IV
Opioid-induced hyperalgesia	0.1–0.2 mcg/kg/h IV over 3 days or 0.2 mcg/kg/h titrated up to maximum 0.7 mcg/kg/h IV over 24 h
Sedation in the ICU	Loading dose: 1.0 mcg/kg (0.5 mcg/kg – geriatric pts) IV over 10 min Maintenance: 0.2–0.7 mcg/kg/h IV for up to 24 h Hypotension avoided by titrating less than q30mins
Prevention of delirium in adult ICU patients	Nocturnal dose: 0.2 mcg/kg/h IV, titrated 0.1 mcg/kg/min every 15 min to reach RASS < -1 or max 0.7 mcg/kg/h
Drug withdrawal and weaning	Loading dose: 0.5–1.0 mcg/kg IV over 10–20 min Maintenance: 0.2–1.0 mcg/kg/h IV for duration as needed, until clinical symptoms resolve
Awake fiberoptic intubation	Loading dose: 1.5 mcg/kg IV over 10 min Maintenance: 0.7 mcg/kg/h IV continuous infusion
Procedural sedation	Loading dose: 0.5–1.0 mcg/kg IV over 10 min Maintenance: 0.2–1.0 mcg/kg/h IV continuous infusion
Prevention of PONV	Continuous intraoperative infusion: 0.1–0.7 mcg/kg/h IV

Summary

Dexmedetomidine has numerous uses outside of the approved indications. Doses vary; however, most include a 1 mcg/kg/hr. IV loading dose over 10 min followed by a maintenance infusion of 0.2–0.7 mcg/kg/hr. Duration may safely extend beyond 24 h. Due to the risk of hemodynamic adverse events, careful monitoring of the cardiovascular and respiratory systems with non-invasive blood pressure measurement, electrocardiography, and pulse oximetry are the minimal recommendations. For the management of acute postoperative pain, optimal intraoperative doses range from 0.1–0.7 mcg/kg/h, and 0.045–0.2 mcg/kg/h when combined with an opioid for PCA. When given in the context of an acute CRPS exacerbation, dexmedetomidine as a single 8 mcg IV bolus has shown benefit when used as an adjunct to ketamine infusion. Infusion at 0.1–0.2 mcg/kg/h over 3 days, or 0.2 mcg/kg/h titrated to 0.7 mcg/kg/h over 24 h has shown benefit in alleviating OIH. Dosing for the prevention of delirium in adult non-surgical ICU patients includes a low-dose nocturnal infusion at 0.2 mcg/kg/h titrated by 0.1 mcg/kg/min every 15 min until the desired level of sedation is reached. The doses for alleviating emergence delirium in children vary greatly from intraoperative infusions of 0.2 mcg/kg/h to single IV doses of 0.5–1.0 mcg/kg. Slower loading doses over 10–20 min and longer infusions (up to 10 days) may be necessary when used for mitigating drug withdrawal. For AFOI and procedural sedation doses are also varied, however, 0.5–1.0 mcg/kg over 10 min loading dose followed by 0.2–1.0 mcg/kg/h maintenance infusion is optimal. For preventing PONV a continuous intraoperative infusion at 0.1–0.7 mcg/kg/h is advised.

Most dosing regimens do not differ greatly from those recommended upon registration. However, the data on numerous indications remains scarce and further studies are required.

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Clonidine Infusion Therapy

11

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Introduction

Clonidine (N-(2,6-dichlorophenyl)-4,5-dihydro-1H-imidazol-2-amine) is an imidazoline compound that consists of a heterocyclic five membered ring containing two N atoms within the ring [2, 3]. This is bridged with an Amine (NH) group to an aromatic ring with two Chloride (Cl) atoms substituted in the 2, 6 positions [1]. It has a half-life of 12–16 h. It is highly lipophilic and able to distribute into extravascular spaces, notably the central nervous system [4]. Clonidine is renally excreted with a variable half-life ranging 17.5–41 h depending on renal function [4].

Clonidine comes in multiple drug formulations. Oral forms come in extended and immediate release tablets as well as an oral solution. It also exists in a transdermal patch formulation which can be applied to the skin for 7 days. Parenteral forms of clonidine are available to allow the drug to be given intravenously, intrathecally, epidurally, and perineurally (regional block).

Mechanism of Action

Clonidine is primarily a central sympathetic α_2 receptor agonist [3, 5], but also has action on the imidazoline-1 and α1 receptors [5, 6]. Clonidine partially exerts its hypotensive effects by activating the imidazoline-1 receptor in the rostral

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ventrolateral medulla which works in concert with the α2 receptor causing decreased sympathetic outflow [5–8]. The imidazoline-1 receptor also has a role in causing bradycardia by inhibiting the baroreflex [7]. Clonidine activates the sympathetic α1 receptor, but it has less affinity for the α_1 than the α2 receptor. In fact, it has a selectivity ratio for the α1:α2 receptors of 1:200 [9]. Activation of peripheral sympathetic α1 receptor causes vasoconstriction, which partially contributes to the initial transient hypertension seen with clonidine as well as the drying of nasal mucosal [6].

The α2 receptor is a Gi coupled protein complex located on both presynaptic and postsynaptic regions of sympathetic nervous system [10, 11]. It is further divided into 3 subclasses: α2a, α2b, and α2c. α2a is responsible for clonidine's sympatholytic and antinociceptive properties [9–12]. The presynaptic α2a receptors act as a feedback inhibitor, decreasing release of endogenous catecholamines [10]. In the nucleus tractus solitarius and locus coeruleus, activation presynaptic α2a receptors decreases norepinephrine release, reduces sympathetic activity, and ultimately inhibits vascular tone [12, 13]. Agonism of postsynaptic α2a receptors in locus coeruleus leads to sedation and analgesia [10, 13]. A majority of α2b receptors are found on peripheral blood vessels. Activation of the α2b receptors results in vasoconstriction, leading to initial hypertension [10, 12]. Agonism of the α2c receptor further reduces sympathetic outflow by inhibiting catecholamine release from the adrenal cortex [12, 13]. Clonidine also causes bradycardia, which is a result of its ability to inhibit sympathetic cardiac accelerator nerves and its vagomimetic action [12, 14].

Indications

Acute Postoperative Pain

The pain experienced immediately following a surgical procedure up to postoperative day 7 is classified as acute postoperative pain [15]. If inadequately controlled, it is associated with delayed mobility, decreased function, increased opioid use, prolonged hospital stay, and increased morbidity leading to an impaired quality of life while increasing the overall cost to the health system [15, 16]. The incidence of poorly controlled acute postoperative pain is estimated that over 80% of patients in the United States [16]. The mechanism of acute postoperative pain involves the release of nociceptive mediators from local tissue, which triggers the A-delta and C pain fibers. After the signals enter dorsal horn of the spinal cord, they are modulated by other pain neurotransmitters as they make their way up the spinothalamic and spinoreticular tracts to cause thalamocortical projections [17–19].

In the current effort to decrease opioid use in treating acute postoperative pain, clonidine has been shown to be an effective analgesic while decreasing opioid requirements [20]. In addition to improved pain control, clonidine has many other benefits in the perioperative period including decreasing postoperative nausea and vomiting (PONV), suppressing postoperative shivering, optimizing cardiovascular stability by decreasing hypertension, as well as decreasing opioid adverse effects such as opioid induced hyperalgesia [20–22]. α2 receptor activation causes

antinociceptive action by inhibiting neuronal action potentials in superficial laminae of the dorsal horn via the suppression of voltage gated Na^+ and K^+ channels [23, 24]. α2 receptor agonism can also attenuate release of substance P from the A-delta and C fibers as they propagate signals towards second-order neurons and cortical regions [24, 25].

In a systematic review and meta-analyses, Munoz et al. found in 57 trials with 14,790 patients that clonidine significantly improved postoperative pain control, decreased anesthetic demand, attenuated postoperative nausea and vomiting (PONV), and decreased postoperative shivering [22]. Postoperatively, clonidine significantly decreased total pain medication requirements with a 24% decrease in analgesic use in the first 24 h [22]. In 18 trials, clonidine has showed a significant decrease in administration of anesthetics including propofol, sevoflurane, isoflurane, enflurane, alfentanil, sufentanil, and remifentanil [22]. Studies have found a significant decrease in incidence of PONV with a risk ratio of 0.35 in patients receiving clonidine and some report a decrease in rescue antiemetic use [22]. In several trials clonidine was found to decrease postoperative shivering with qualitative data placing the risk ratio at 0.17 [22]. A majority of the trials found significantly lower circulating levels of plasma epinephrine and norepinephrine in the clonidine groups [22]. In another systematic review and meta-analysis of 30 trials with 1792 subjects, there was significant evidence of improved postoperative pain control in patients who received systemic α2 agonists [20]. In this review, Blaudszun et al. concluded that clonidine reduced morphine equivalents by approximately 25% at the 24-h mark post-operatively [20]. Visual analog scale (VAS) pain scores decreased with the clonidine groups. Incidence of PONV within the first postoperative 8 h decreased with a number need to treat of 8.9 [20]. The study also found significant risk of postoperative hypotension in clonidine groups with number needed to harm of 9.0 [20].

Continuous intravenous (IV) infusions have been used to treat post-operative pain with varying results. The majority of these studies show that clonidine significantly decreases opioid consumption with some reporting improved analgesia. Most studies were limited by the adverse effects of clonidine. In one study, Bernard et al. found postoperative IV infusions of clonidine lead to decreased rescue morphine administration [26]. In this study 50 patients undergoing spinal surgery with fusion received a clonidine infusion with a loading dose of 5 μg/kg/h for 1 h followed by a maintenance dose at 0.3 μg/kg/h for 12 h [26]. There was a decrease in intramuscular morphine administration (10.8 mg) versus placebo to 3.8 mg [26]. In addition, lower pains scores were seen with the clonidine group (26/100) than compared to placebo group (42/100) even though less morphine was given [26]. The clonidine group had a delay in initial onset of pain as well as first request of morphine [26]. Despite positive results, the study was hampered by hypotension in clonidine group.

Comparable findings were seen with shorter intraoperative infusions of clonidine. De Kock et al. randomized 200 patients undergoing major abdominal surgery to receive IV clonidine [27]. A loading dose of 4 μg/kg was started prior to incision and infused over 30 min followed by a maintenance dose of at 2 μg/kg/h until the

peritoneum was closed [27]. Postoperatively, patients were administered a morphine patient-controlled analgesia (PCA) for additional pain control. At 36 h postop, morphine PCA use in the clonidine group (45.1 mg) was decreased compared to placebo (55.4 mg) [27]. Improved analgesia was reported, but interestingly, no hemodynamic limitations were encountered [27].

Other studies have looked into differences in route of clonidine infusion. Bharti et al. found that IV infusions and local injections of clonidine can improve postoperative analgesia and lower opioid consumption compared to placebo [28]. This study followed 60 patients undergoing open cholecystectomy, all of which received a local wound infiltration of 30 ml of 0.25% bupivacaine at the completion of the procedure [28]. In addition to the bupivacaine injections, patients were randomly assigned in to two additional groups one group received an IV clonidine at 3 μg/kg clonidine in 100 ml of saline infused over 10 min whereas another group received the local injection with 3 μg/kg clonidine added to the solution [28]. The study found significantly lower pain scores for both clonidine arms as well as decreased opioid requirements in both groups whereas 47% of the infusion and 42% of the wound injection group required no morphine at all, using only additional NSAIDs [28]. Conversely, all the placebo arm subjects required additional opioids. The IV infusion group had higher rates of hypotension and sedation compared to the two other groups [28].

Marinangeli et al. sought to find the "optimal intravenous dose" of clonidine in 80 patients undergoing lumbar laminectomy for disc herniation [29]. Patients were randomized into four groups: placebo or three different loading doses of clonidine (2, 3, or 5 μg/kg) over last 30 min of the case [29]. Afterwards, all except for the placebo group received a maintenance dose of clonidine at 3 μg/kg/h for 12 h. Additional postoperative pain was treated with a morphine PCA. For the placebo, 2, 3, and 5 μg/kg clonidine groups, the total number of PCA demand doses (0.3 mg/kg) given were approximately 29, 19, 11, and 5 doses respectively [29]. Total morphine administered was 32, 21, 12, and 5 mg respectively [29]. Pain scores were significantly higher for placebo and 2 μg/kg group within the first 5 h [29]. There was significant dose dependent hypotension with some subjects in the 5 μg/kg group ultimately developing hypotension requiring medical intervention [29]. Bradycardia was modest in all groups. Sedation was significant only the for the 5 μg/kg group [29]. It was concluded that loading infusions of clonidine 3 μg/kg over the 30 min was the optimal dose to treat postoperative pain while minimizing side effects [29].

Clonidine has been shown in repeated studies to lower patient's total opioid requirement while also increasing the time of first administration. In some studies, it has also been shown to decrease pain scores. Although clonidine's use can be limited by hypotension, bradycardia, and sedation, other potential benefits include decreased PONV and shivering.

ICU Sedation and Analgesia

Patients are often admitted to the intensive care unit (ICU) for a higher degree of monitoring and treatment which can involve many invasive techniques. One study

found that 20.7% to 38.9% of ICU patients were intubated and on mechanical ventilation [30]. An overwhelming number of patients have reported that discomfort and pain are the most negatively recollected experiences while admitted to the ICU [31]. Sedation, as well as analgesia, is needed in these patients in order to limit hemodynamic stress responses, allow for the tolerance of endotracheal intubation, decrease the incidence of self-extubation, and allow for ventilator synchrony [32, 33].

Sympathetic α2 receptor agonists like clonidine induce sedation by acting on the locus coeruleus (LC) [9]. Located at the floor of the fourth ventricle, the LC is the primary site of norepinephrine synthesis in the central nervous system [34]. It plays a major role in the regulation of arousal and wake states [35]. The LC is densely populated with α2-ARs [35]. The agonism of the α2-receptor in the LC decreases the release of norepinephrine leading to a sedative effect [10, 13]. Clonidine's analgesic properties are a result of its effect on the dorsal horn of the spinal cord as alluded to previously.

In a double blinded randomized control study, Hall et al. concluded that IV infusions of clonidine induce dose dependent levels of sedation with no significant hemodynamic or respiratory effects [36]. Eight healthy ASA class 1 22–30 years old participants had multiple infusions of different dosages of clonidine separated by 7–10 days [36]. Each had clonidine infusions at 1, 2, or 4 μg/kg loading dose over 15 min with maintenance doses of 1, 2, and 4 μg/kg/h respectively for 45 min [36]. After the 60-min infusion, clonidine produced significant sedation with the 2 higher infusion rates, but the subjects were easily arousable for evaluation tests [36]. At the highest infusion rate there was a significant decrease in pain response, memory, and coordination [36]. There were significant decreases in MAP with all clonidine groups of at least 13% but with insignificant changes in heart rate [36]. Furthermore, there was no change for either group in EtCO2, SpO2, and respiratory rate confirming preserved respiratory function [36]. Despite being underpowered and limited to a short infusion with healthy young subjects, the study showed clonidine could provide sedation with acceptable hemodynamic changes and limited respiratory depression.

Multiple systemic reviews and meta-analyses looked into the utility of clonidine in the ICU as sedation drug. Wang et al. reviewed 8 randomized control studies containing over 160 study subjects where infusions of clonidine were used as the stand-alone drug for sedation and analgesia (1 study) or as an adjunct with other medications (7 studies) [37]. Overall, there was a significant decrease in the total amount of opioid administered in patients where clonidine was administered. Clonidine had no influence on length of stay in the ICU, patient mortality, duration of infusion, or time spent on mechanical ventilation [37]. The study did find increased incidences of significant hypotension requiring medical interventions in the clonidine groups. However, incidence of bradycardia needing intervention or rebound hypertension was not increased in the clonidine groups [37]. The study concluded that clonidine could be employed as a sedative which decreases narcotic demand but could support routine use due to its hypotensive action [37]. Another review study assessed the long-term effects of intravenous infusions of clonidine for sedation and analgesia. Zeeman et al. looked at 3 prospective trials with over 70

subjects where mechanical ventilation was needed for at least 24 h [38]. The study found that clonidine provided dose-dependent sedation with decreased pain intensity and reduced opioid administration [38]. Moreover, the clonidine arms had less delirium associated with the sedation which facilitated ventilator weaning [38]. There were higher incidences of hypotension and bradycardia in clonidine groups with some isolated reports of heart block and cardiac arrest [38].

The efficacy of clonidine was tested against dexmedetomidine in regards to patient sedation in the ICU [39]. Srivastava et al. randomized 70 patients needing mechanical ventilation for 12–24 h to receive an infusion of clonidine or dexmedetomidine [39]. The clonidine infusions started at 1 μg/kg/h and titrated to a maximum of 2 μg/kg/h [39]. The dexmedetomidine arm started with a loading dose of 0.7 μg/kg given over 10 min followed by a maintenance dose starting at 0.2 μg/kg/h titrated up to an allowable 0.7 μg/kg/h [39]. Both infusions were titrated until patients achieved a Ramsay sedation score (RSS) of 3–4 as a surrogate of adequate sedation [39]. If sedation was not achieved with the maximum infusion rate or the infusion rate could not be increased due to adverse effects (i.e. hypotension or bradycardia), a bolus of 0.1 mg/kg of IV diazepam was administered [39]. Of the 35 patients in each arm, diazepam was given to 14 subjects in the clonidine group, 11 of which were due to hypotension limited infusion rate increases [39]. The dexmedetomidine arm had 8 patients requiring diazepam boluses with 3 instances due to rate halting hypotension [39]. The clonidine arm had statistically significant decreases in heart rate [39]. In addition, four patients in the clonidine group experienced rebound hypertension with two patients of systolic blood pressures above 180 mmHg. Rebound hypertension was not noted in the dexmedetomidine arm [39]. Overall, dexmedetomidine was found to provide superior hemodynamic stability allowing the authors to conclude that it is a better choice for sedation over clonidine [39].

Clonidine's efficacy as a sedative agent has also been assessed in the pediatric population. In the SLEEPS (Safety profile, Efficacy and Equivalence in Pediatric intensive care Sedation) study, Wolf et al. evaluated the utility of clonidine versus midazolam as a sedation agent in the pediatric intensive care unit (PICU) [40]. Midazolam is a widely used sedation agent in PICU. Some limiting factors include a high rate of patient agitation, development of patient tolerance, and increased incidence of withdraw as well as unknown risk of benzodiazepines on a neonatal brain development [40]. The SLEEPS study evaluated if these concerns were limited with the use of clonidine [40]. The multicenter prospective trial in the UK randomized 129 children between 30 days to 15 years of age requiring mechanical ventilation for longer than 12 h to have sedation with infusions of either clonidine or midazolam [40]. Patients were also administered a morphine infusion for analgesia [40] and were then evaluated hourly by the COMFORT score – a multiple point scoring system for pain and sedation in mechanically ventilated children [41, 42]. Both arms were titrated to COMFORT scores for adequate sedation. The study found that clonidine was essentially equivalent to midazolam in regards to ability to achieve sedation with >80% COMFORT score [40]. Children receiving midazolam were sedated for longer periods of time but required less time to emerge from deep

sedation [40]. Both drugs were also very similar in time to reach sedation, number of treatment failures, and incidence of withdrawal symptoms [40]. More patients in the midazolam group needed medical intervention for withdrawal symptoms [40]. One patient in the clonidine group had rebound hypertension not requiring medical management [40]. Only 2 patients (3.1%) from the clonidine arm experienced hypotension needing intervention [40]. It was concluded that was clonidine was a non-inferior alternative to midazolam.

In another multicenter prospective randomized control trial, Hunseler et al. randomized 219 infants (aged from birth to 2 years old) requiring mechanical ventilation to receive either a clonidine infusion or placebo as an adjunct to a fentanyl and midazolam infusion for sedation [43]. It was found that an infusion of clonidine at 1 μg/kg/h in neonates (up to day 28) lowered fentanyl and midazolam requirements allowing for a deeper degree of sedation and analgesia [43]. There were also significantly lower incidences of withdrawal symptoms in neonates in the clonidine groups with no significant adverse effects [43]. These results could not be applied to the older infant groups. Kleiber et al. found clonidine infusions added to morphine created more hemodynamically stability in neonates after surgery [44]. In a retrospective cohort study, 23 infants less than 2 months old recovering from cardiac surgery received morphine with clonidine or midazolam for analgesia and sedation [44]. The clonidine infusion was first administered at a mean of 12 h postoperative with an infusion rate of 0.5–2 μg/kg/h for a mean of 30 h [44]. The study found a stability or improvement in multiple cardiovascular parameters in the clonidine group [44]. Additionally, the infants had decreased length of stay in the PICU as compared to those receiving midazolam [44]. Ambrose et al. sought to find at optimal rate of clonidine infusion for sedation in children with regard to cardiovascular changes [45]. They studied 30 children under 10 years old requiring sedation for mechanical ventilation [45]. The subjects were given midazolam at 50 μg/kg/hr. with varying dosages of clonidine (0.1–2 μg/kg/h) [45]. In addition, 10 post cardiac surgery patients were administered clonidine 1 μg/kg/h and each patient's cardiac index was monitored [45]. Clonidine administration resulted in no significant changes in heart rate, MAP, or cardiac index [45]. The study found that clonidine lead to dose dependent sedation at an infusion rate of 2 μg/kg/h without failure [45]. It was concluded that a variable infusion rate of clonidine 0.2–2.0 μg/kg/h with a low dose benzodiazepine infusion was a viable form of opioid free sedation in children requiring mechanical ventilation [45].

Research has shown that clonidine can be used to provide adequate sedation and analgesia with less respiratory depression compared to other agents. It may be used to avoid side effects of other sedatives such as opioid or benzodiazepines. Routine use of clonidine to provide sedation has been limited due to its side effects.

Neonatal Abstinence Syndrome

Neonatal abstinence syndrome (NAS) is usually due to fetal dependence upon an illicit substance acquired while in utero [46]. Although NAS may be iatrogenic, the

most common setting is maternal opioid use in the antepartum period [47]. Recent statistics show a troubling rise in the United States of newborns with NAS. According to the National Institute on Drug Abuse, the data from 2012 shows 21,732 neonates born with NAS which is a five-fold increase from 2000 [48]. The CDC found in 2013 incidence occurred at 6.0 per 1000 hospital births from states with reported data [49]. The most notable characteristics of NAS are neurological hyperactivity such as hyperirritability, agitation, and restlessness [46, 50, 51]. Sympathetic manifestations involve impaired temperature regulation, diaphoresis, tachycardia, and hypertension [46, 50, 51]. Other symptoms include vomiting, diarrhea, high pitched cry, and poor feeding [46, 50, 51]. As opioids activate the μ-opioids receptor on neuronal surface, there is a decrease in cyclic adenosine monophosphate (cAMP) production resulting attenuation of norepinephrine release in the LC [52]. Abrupt opioid cessation causes excessive noradrenergic outflow that can help explain the clinical features of NAS [53]. Treatment for NAS involves substituting the abused drug with another longer acting opioid then gradually tapering administration as well as adding adjuncts [54].

With its ability to decrease norepinephrine release in LC, clonidine has been shown to be effective in ameliorating the symptoms of opioid withdrawal [53–57]. In a retrospective review study of 133 neonates with NAS, Esmaeili et al. examined intravenous infusions of clonidine with adjunctive chloral hydrate versus oral morphine with adjunctive phenobarbital [58]. In this study, the clonidine arm infusion was started at 0.5 μg/kg/h and titrated up to a maximum of 3 μg/kg/h depending on severity of NAS based the Finnegan NAS score (target below 8–10) [58]. If maximum clonidine dose was achieved, chloral hydrate was administered as adjuvant [58]. In the morphine group, 0.3 mg/kg/day was given orally in 3 dosages, which were titrated up to a maximum of 0.8 mg/kg/day if Finnegan scores were high at the end of the day [58]. Phenobarbital was added if symptoms were consistently high during the day [58]. The study found that a decrease in the median length of treatment and hospitalization in the clonidine/chloral hydrate (14 days, 32 days respectively) versus the morphine/phenobarbital arm (35 days, 44 days respectively) [58]. There was a significant decrease of withdrawal symptoms in the clonidine/chloral hydrate group without report of hypotension [58].

Clonidine has proven to be able decrease NAS symptoms and treatment duration. It is a viable option for other mainstays such as benzodiazepines and opioids with shorter taper periods.

Opioid Induced Myoclonus

Opioid induced myoclonus is associated with patients on high dosages of opioids for long durations of treatment such as cancer or palliative patients [59–61]. It has been suggested that certain opioids have neuroexcitatory metabolites which generates the myoclonus opposed to the actual opioid [60, 61]. IV infusions of clonidine have been reported to treat this adverse opioid effect in infants. In a case report by McClain et al., a 96 day old 4 kg neonate with gastroschisis requiring staged repair

on mechanical ventilation had increasing opioid requirements to 25 mg/kg/day [62]. The patient later developed facial twitching, clonic arm movements, and worsened agitation as well as increased peak inspiratory pressure of 40 cm H2O, pulse oximetry (SpO2) of 81% to 94%, and a high fraction inspired oxygen (FiO2) of 90% [62]. In an attempt to wean opioids, a loading dose of IV clonidine 1 μg/kg/h was given, followed by an infusion at 0.3 μg/kg/h [62]. This was eventually titrated to 0.5 μg/kg/h and multiple boluses of clonidine were needed for bouts of agitation and tachycardia [62]. It was determined that clonidine had decreased the facial and arm myoclonus, stabilized sympathetic symptoms, and achieved sedation to eventually allow for tapering of opioids without precipitating withdrawal [62].

Contraindications

Clonidine is generally contraindicated for administration through epidural at a level above C4 or in patients allergic to it [63]. There is a black box warning for epidural clonidine in the obstetrical setting due to increased risk of hypotension and bradycardia [64]. With systemic administration, multiple studies show similar concentrations between maternal plasma and umbilical cord samples reflecting free passage [65]. Clonidine has been shown to be excreted in breast milk and should be used with caution in nursing mothers [63]. The reduction of sympathetic outflow from clonidine may worsen AV block, sick sinus dysfunction, hypotension, bradycardia, or risk of syncope [63]. Clonidine's ability to lower blood pressure may exacerbate ischemia especially in patients with recent myocardial infarct, severe congestive heart failure, or cerebrovascular disease [63]. Extreme caution should be used in patients with hemodynamic instability or severe heart disease. Due to clonidine's excretion in the urine, patients with abnormal renal function should be monitored carefully and renally dosed to decrease the risk of accumulation [63].

Side Effect

Most common adverse effects are profound sedation, hypotension, and bradycardia. In the Perioperative Ischemic Evaluation 2 (POISE-2) trial, Devereaux et al. found starting low dose clonidine in patients undergoing noncardiac procedures increased risk of significant hypotension and nonfatal cardiac arrest [66]. Conversely, abrupt cessation of clonidine can precipitate withdrawal causing an acute surge of plasma catecholamines that can lead to severe hypertension resulting in hypertensive encephalopathy, strokes, and even death [63]. Cardiovascular monitoring is highly recommended when either commencing or discontinuing clonidine. In the pediatric population, acute stoppage has been associated with abdominal pain and emesis [64]. Due to its sedative qualities, clonidine is not advised for patients who operative heavy machinery. Bailey et al. found no changes in respiratory drive with patients on clonidine [67]. Other more common side effects include mouth dryness, anxiety, drowsiness, pruritus, headache, dizziness, and gastrointestinal disturbances [63].

Monitoring

Clonidine infusions can lead to multiple cardiovascular and neurological derangements. Monitoring for such changes should include electrocardiography, noninvasive blood pressure, and pulse oximetry. Caution should be noted during starting and discontinuation of clonidine as this is the time period during which most hemodynamic changes have been shown to be most likely to occur.

Algorithm for Clonidine Infusion Regimens

This table below summarizes the suggested doses published in literature for the different indications for Clonidine use (Table 11.1). Different doses may be used in various settings and patient populations.

Summary

Clonidine has been used extensively as an antihypertensive agent. The use of clonidine as an α2 receptor agonist has far outgrown the original intention. In the endeavor to curb opioid administration, clonidine can be a valuable tool in treating acute postoperative pain. It is usually administered prior to surgical closure in the perioperative period and continued postoperatively. Dosages have ranged from loading doses of IV 3–5 μg/kg over 30–60 min with maintenance doses of IV 0.3–3 μg/kg/h up to 12 h postoperative. Infusion doses below 2 μg/kg/h have demonstrated to be the most cardiovascularly stable. The efficacy of clonidine for ICU sedation has been shown to be most promising in the pediatric population. Clonidine has also shown promise in the treatment of NAS symptoms, causing less sedation and leading to shorter weaning periods than traditional treatment modalities. Doses are similar to those used for sedation in the ICU (0.5–3 μg/kg/h). Despite all that is known about sympathetic α2 receptor agonists, more research is needed to explore and confirm all its possible applications.

Table 11.1 Algorithm for clonidine infusion regimens

Indication	Maintenance dosage
Acute postoperative pain	Loading dose: Prior to closure IV 3–5 μg/kg over 30–60 min Maintenance dose: IV 0.3–3 μg/kg/h up to 12 h post-surgery
ICU sedation and analgesia	IV 0.5–2 μg/kg/h Titrated to adequate sedation scores
Neonatal abstinence syndrome	IV 0.5–3 μg/kg/h titrated to adequate NAS scores
Opioid induced myoclonus (neonate)	Loading dose: IV 1 μg/kg bolus Maintenance dose: IV 0.3–0.5 μg/kg/h

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Benzodiazepine Infusion Therapy

12

Thomas Ng, John Akhnoukh, and Neel Mehta

Introduction

The first benzodiazepine was chlordiazepoxide, a drug that had similar sedative properties to chlorpromazine, but superior anxiolytic and muscle relaxant properties to existing barbiturates [1]. Diazepam was synthesized shortly thereafter, principally designed for its enhanced effects on muscle relaxation, but its popularity grew from its ability to induce a state of calm and relaxation [2]. By the mid-1960's, benzodiazepines became the mostly widely prescribed class of medications, marketed as an anxiolytic and hypnotic with a high level of safety. Its decline in popularity came about a decade later as reports of dependence and withdrawals symptoms emerged.

Benzodiazepines continue to be widely used today for its treatment of panic and anxiety disorders, insomnia, alcohol withdrawal, seizures and as an amnestic. While it continues to be used as treatment for pain associated with muscle spasms and spasticity, its presence in the management of pain far exceeds its muscle relaxant properties. Approximately 25–30% of patients who were prescribed opioids for pain were concurrently prescribed benzodiazepines [3, 4], even though benzodiazepines have no known analgesic properties [5] or effects on the nociceptive system [6]. Instead, its widespread use in the clinical management of pain has depended on its adjuvant role of making existing pain more tolerable – by mollifying the associated anxiety and as a sedative. This strategy has been criticized due to its mixed results on efficacy, lack of strong clinical trials to support its use in the pain population and concern for dependency, cognitive impairment and increased morbidity and mortality.

Few high-quality studies exist that look at the practicality of benzodiazepine infusions for pain management. As benzodiazepines are considered to have no

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analgesic properties, much of the literature involving pain patients and infusions of benzodiazepines focus on its role as a sedative and anxiolytic. Nonetheless, a small number of studies have found that infusions of midazolam and diazepam are can be used to reduce a patient's overall pain experience, pain scores, anesthetic requirements and opioid requirements.

Mechanism of Action

In the 1950's, Leo Henryk Sternbach synthesized the first commercial benzodiazepine at Hoffmann-Roche Inc. in Basel, Switzerland. His goal was to develop a compound with neuroleptic properties like that of the recently commercialized drug, chlorpromazine. His creation was chlordiazepoxide, a drug that had similar sedative properties to chlorpromazine, but superior anxiolytic and muscle relaxant properties to existing barbiturates [1]. Diazepam was synthesized shortly thereafter, principally designed for its enhanced effects on muscle relaxation, but its popularity grew from its ability to induce a state of calm and relaxation [2]. Even though benzodiazepines have no known analgesic properties [5] or effects on the nociceptive system [6]. Instead, its widespread use in the clinical management of pain has depended on its adjuvant role of making existing pain more tolerable – by mollifying the associated anxiety and as a sedative. This strategy has been criticized due to its mixed results on efficacy, lack of strong clinical trials to support its use in the pain population and concern for dependency, cognitive impairment and increased morbidity and mortality.

Indications

Acute Pain

Acute pain is often associated with an underlying injury or disease that disturbs neighboring nociceptive receptors. Therapy usually involves treatment of the underlying disease and interruption of the nociceptive pathway [10]. Benzodiazepines, without any known anti-nociceptive effects, therefore, would seem particularly ill suited for the management of acute pain, however, there is evidence for a psychological component that plays an important role in the perception of pain. While the psychological component is often recognized to be a contributor to chronic pain, stress, and anxiety associated with recent injury, it can affect the severity of the pain experience in the acute setting. When exposed to acute stressors, subjects are less able to regulate their pain, with increases in pain intensification and decreases in pain inhibition correlating with increasing stressors [11]. Thus, addressing the psychological component with benzodiazepines may help reduce the severity of the pain experience and may help reduce the overall opioid requirements.

While oral and intravenous boluses of benzodiazepines are commonly used in the acute setting, infusions of benzodiazepines are less commonly seen. In the

emergency department, benzodiazepine infusions are used to treat seizures and as a sedative for intubated patients, but rarely for the treatment of pain-related conditions. The acute setting usually requires medications with rapid onset and short duration, limiting the number of benzodiazepines that can be used. Long-lasting anxiolytic effects are often desired, but the excessive sedation and amnesia are not ideal for most acute pain settings. Midazolam is the most frequently used benzodiazepine for this purpose, with infusions of this medication used in the perioperative, critical care and occasionally, outpatient setting. Diazepam infusions are less commonly seen, owing to its long duration, precipitate formation when diluted in IV fluids and adherence to IV tubing. As a result, outside of the perioperative setting, limited literature is available on the use of benzodiazepine infusions for the treatment of acute pain and no specific dosing range is provided.

Anecdotal reports suggest that midazolam has mild analgesic properties and reduces some aspect of the pain experience, but objective measures are complicated by the inherent subjective nature of pain. An individual's pain perception is affected by their genetics, gender, ethnicity and psychological state [12]. In the setting of acute pain, where the pain stimulus tends to be sharper, more rapid onset and more severe in nature compared to chronic pain, the brain's response to the stimulus can be measured by somatosensory evoked potentials (SEPs). SEPs are measured by scalp probes overlying the somatosensory cortex of the brain and amplitude changes in the late phase of these SEPs are correlated with application of painful stimuli and negatively correlated with opioid administration [13]. To determine whether benzodiazepines infusions provide an analgesic effect, mildly painful noxious stimuli in the form of electrical impulses were applied along the median nerve of subjects receiving moderate sedation by midazolam infusion of 2 mg/ml bolus and then 1 mg boluses in 30 s intervals to achieve a sedation end point or 0.07 mg/kg body weight. Results showed suppressed late phase SEP amplitudes that did not return to baseline levels within the 60-min experiment. This suggests that midazolam infusions provide some form of analgesia by way of suppression of higher-order brain function [14].

Muscle spasms are one of the original indications for benzodiazepines when this class of medication was first developed. Recently, however, other medications such as baclofen, tizanidine and cyclobenzaprine have been more commonly prescribed for its treatment. Diazepam is the only benzodiazepine approved by the FDA for the treatment of muscle spasms and is not typically considered a first-line treatment due to excessive sedation and risk of abuse [15]. It is most commonly given as a scheduled oral medication or IV bolus, but for severe spasms due to tetanus infections, infusions of benzodiazepines have been used.

While there were over 56,000 deaths from tetanus worldwide in 2015, by comparison, tetanus infections are rare in the United States, with 29 reported cases and 2 deaths in 2015 according to the CDC [16]. This disparity is due to widespread use of tetanus-toxoid vaccines and post-exposure use of tetanus immune globulin (TIG) the United States [17]. Treatment involves antibiotics, tetanus vaccination, TIG administration, control of muscle spasms and ventilator support. Spasms are initially controlled with sedation, which may include benzodiazepines, before

neuromuscular blockers are used. Diazepam may initially be given as a regular IV bolus, typically at a dose of 10–30 mg every one to 8 h, however, high doses of diazepam increases the risk of lactic acidosis from the propylene glycol solvent [18]. One study found that diazepam could be administered as an infusion, maintaining serum concentrations between 400–500 ng/ml for appropriate sedation and spasm control, when diluted to a maximum concentration of 5 mg per 40 ml of normal saline, 5% dextrose or lactated ringers, kept in glass bottles and administered with minimal IV tubing to prevent precipitation and adherence to the polyvinyl chloride tubing [19]. Midazolam infusions of 5–15 mg/h are equally effective and do not encounter the problems of lactic acidosis and precipitation. In an effort to maintain spontaneous breathing in these patients, midazolam epidural infusions at a rate of 2 mg/h have been successfully used to treat tetanic spasms [20].

Perioperative Pain

The perioperative setting is a unique for environment for acute pain where benzodiazepine infusions may have a fitting role due to significant patient preoperative anxiety that can extend into the postoperative recovery period. Thus, amnesia leading up to and including the procedure is often desirable. Infusion of benzodiazepines is effective at maintaining sedation and has an additive effect when used in conjunction with opioids, but debate remains whether benzodiazepine infusions contribute to the management of perioperative pain. Perioperative anxiety and depression are correlated to higher reports of postoperative pain intensity and higher opioid requirements [21]. Therefore, the use of benzodiazepine infusions would be expected to play a role in the patient's overall pain experience.

The pediatric population is particularly vulnerable to anxiety in the perioperative setting, where children are subjected to lengthy wait times in unfamiliar environments, unaccustomed NPO requirements, fear of separation from their parents and anticipation of post-surgical pain. High levels of anxiety are seen in up to 60% of children awaiting surgery with anxiety peaking in the operating room, and in some children, persisting up to 2 weeks after the procedure [22]. This anxiety is associated with increased postoperative pain scores [23]. This additional dimension of acute pain in the pediatric population may be poorly responsive to traditional analgesic medications. In some institutions, standing and as-needed doses of alprazolam, lorazepam and diazepam have been found to be effective adjuvants, allowing for dramatic reduction in pain scores and opioid administration [24]. No specific dosing guidelines were provided, but low pediatric anxiolytic doses were used, likely due to concomitant opioid administration.

In some circumstances, children may have difficulty expressing their emotional state and inappropriately reporting affective symptoms as pain, but this interplay between anxiety and the pain experience persists in adults and is supported by more objective testing. In the setting of adult trauma and orthopedic surgery, both known to have significant nociceptive stimulation, predictors of postoperative pain was positively correlated with preoperative anxiety and negatively correlated with age

[25]. Younger adult patients with high anxiety were the greatest predictors of increased pain in the immediate postoperative period. As no causation was established, there were no recommendations to treat the perioperative anxiety, but allowed for postsurgical teams to better anticipate patient pain intensity and tailor pain management regimens.

As both anxiety and pain are subjective experiences, measurements of these experiences rely on questionnaires, pain scores and patient reports. Objective measures include postoperative consumption of opioid equivalents, although this varies largely on the extent and type of injury or surgery and other multimodal analgesics techniques that are employed. One study examined the effects of anxiety on intraoperative anesthetic requirements, where anesthesiologists were blinded to patient's preoperative anxiety scores and patients had no control of their intraoperative medication consumption; they found that those with high preoperative anxiety scores based on the Spielberger State-Trait Anxiety Inventory required quantifiably higher doses of propofol and sevoflurane anesthetics to reach minimal (anxiolytic), moderate and deep levels of sedation, as determined by bispectral index (BIS) monitoring (BIS levels 85, 75 and 65, respectively). The same study found that those with high preoperative anxiety were more likely to experience immediate postoperative pain. The mechanism of higher anesthetic demands were attributed to anxiety-provoked increases in neuroendocrine and cardiovascular activity, resulting in higher baseline hemodynamics [26].

The combined anxiolytic, amnestic and sedative effects of benzodiazepines make it a fitting choice for some novel forms of procedural sedation. Midazolam infusions combined with local anesthesia were found to be effective at maintaining minimal sedation in patients undergoing extensive periodontal and dental implant surgery. In this setting, a target controlled infusion (TCI) pump was used, which attempts to maintain a level effective-site concentration of midazolam by taking into account the pharmacokinetics of the drug and provides a variable infusion that adjusts for the initial drug bolus, distribution and elimination. Using a 0.75 mg/ml midazolam solution, the researchers set the TCI pump to target a site effect concentration of 30 ng/ml, increasing to 40 ng/l after 90 s, then an additional 10 ng/ml every 60 s. The drug was further titrated to maintain BIS values between 80 and 90, corresponding to minimal sedation. One-week postoperative patient feedback indicated high satisfaction and strong amnesia of the procedure, including more painful periods of the procedure prior to additional local anesthesia administration [27].

Even in the acute setting, the representation of pain involves a complex interaction between nociceptive pathways and higher-order brain function, combining sensory, cognitive and affective systems [28]. While this interaction may complicate the treatment of pain, it also provides additional pharmacological targets for analgesia outside of the nociceptive pathway. Benzodiazepines, particularly infusions of midazolam, have shown to improve pain perception in the acute setting. An argument can be made that benzodiazepines may be more appropriate in the adjunctive treatment of acute pain than in its more commonly observed treatment of chronic pain. Criticism of benzodiazepine usage in the treatment of pain has largely focused on its co-administration with opioids, resulting in over sedation and respiratory

suppression. Treatment of patients with acute pain often takes place in a monitored setting, where concerns for overdose can be observed. In the cases where midazolam infusion was used for periodontal surgery and SEP testing to achieve mild-to-moderate sedation, there were no incidences of respiratory compromise and patients were able to leave the facility with a caretaker. If an overdose were to occur in a monitored setting, reversal agents are available for both benzodiazepines and opioids. Concerns for delirium and increased fall risks still exist with acute administration of benzodiazepines, with the elderly particularly sensitive to its effects. Careful patient selection would be necessary to mitigate these risks.

Psychiatric Treatment

Benzodiazepines are indicated for a number of psychiatric conditions, including anxiety, insomnia, panic disorder, acute psychotic agitation and terminal restlessness. While benzodiazepines were consider superior over placebo for the treatment of depression, there is insufficient evidence the effect is superior to that achieved by antidepressants alone [29]. It is, however, indicated in the short-term treatment of severe anxiety associated with depression [30]. Despite the significant role that oral benzodiazepines play in the treatment of anxiety, there appears to be a limited role for benzodiazepine infusions for the treatment of other psychiatric conditions. This may be secondary to the concerns of mental disturbances associated with benzodiazepines, which include rebound anxiety and insomnia, psychosis, depression and mania from prolonged administration or its withdrawal effects [31]. Benzodiazepine infusions have been used for the treatment of procedural anxiety and catatonic states and have shown some effectiveness at treating mania and reducing suicidal ideations associated with depression [31].

Benzodiazepines are frequently used to control for perioperative anxiety, usually administered as a single IV bolus (Adults: midazolam: 2–5 mg; Children 6–12 years old: midazolam 0.025–0.05 mg/kg) or oral dose (Children: midazolam: 0.25–0.5 mg/kg) before surgery. For minor procedures where the patient remains conscious, midazolam has been found be effective in maintaining light sedation/anxiolysis (Adults: initial 0.3–0.35 mg/kg, followed by additional doses up to 0.6 mg/kg; Children 6 months to 5 years old: initial 0.05–0.1 mg/kg, followed by additional doses up to 0.6 mg/kg; Children 6–12 years old: initial 0.025–0.05 mg/kg, followed by additional doses up to 0.4 mg/kg) [32]. As discussed earlier in the perioperative section, infusions of midazolam are effective for minor oral surgery, such as implants and molar extractions. However, the degree of anxiolysis with midazolam infusion alone was inferior to that of propofol infusions and was associated with slower recovery and more amnesia. The anxiolytic properties are enhanced when midazolam was used as part of a multidrug regimen (midazolam-fentanyl, midazolam-fentanyl-methohexital), but had increased risk of transient respiratory depression [33]. Midazolam infusions compared more favorably than dexmedetomidine when used for regional anesthesia [34].

Catatonia is a syndrome consisting of mental and physical unresponsiveness to external stimuli, often presenting with mutism and stupor, though excitatory

catatonia exists. Under the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5), catatonia is associated with psychiatric conditions such as schizophrenia, bipolar disorder and depression. It may also be caused by drug abuse, drug withdrawal or general medical and neurological conditions, including multiple sclerosis and uremia [35]. Regardless the cause, treatment of catatonic states generally involves intramuscular lorazepam. IM lorazepam often provides improvement in symptoms, but for those patients with catatonia refractory to IM lorazepam, an infusion of benzodiazepines – frequently with midazolam, lorazepam and diazepam –` has been found to be effective. For catatonia in patients associated with general medical conditions and substance abuse, some clinicians employ a lorazepam-diazepam protocol consisting of an initial 2 mg lorazepam IM dose, followed by a second 2 mg lorazepam IM dose if the first dose fails to achieve relief, followed by an IV diazepam infusion at 1.25 mg/h until relief from catatonia is seen. In patients where benzodiazepines are ineffective, electroconvulsive therapy (ECT) would be the next stage of management [36].

Benzodiazepines in Chronic Pain

The experience of pain varies in patients, related to different categories of pain. It is evident that certain classifications of medication clearly target receptors that modulate pain perception, however, currently benzodiazepines do not fall into those classes of drugs but may warrant reconsideration after a basic description of classification of pain.

Nociceptive pain thought to be somatic or visceral in nature is the most common area of pain. A stimulus triggers nociceptors that send information to the spinal cord and brain for interpretation and response [37]. The second class of pain, neuropathic, is presumed to be caused by nerve disturbances and non-triggered spontaneous transmission of pain signals to the spinal cord and brain. The most common cause of neuropathic pain is tumor infiltration of the brachial and lumbar plexus [38, 39]. In regards to neuropathic pain, a study done on rodents and the effect of chronic constriction injury of the sciatic nerve from surgery found that GABA inhibition plays an important role in neuropathic pain [40]. Continuous systemic benzodiazepine administration, specifically midazolam (Adult: midazolam: 2 mg/kg/h), showed benefit in alleviating neuropathic pain by preventing a decrease in levels of GABA transporter 1 (GAT-1) in the lumbar spinal dorsal horn thus preventing thermal hyperalgesia. In addition the preventive effect of midazolam was blocked by co-administration of flumazenil.

Benzodiazepine infusions have been shown to have favorable effects in the human population but in case studies. A specific case study involving a female with intractable complex regional pain syndrome I (CRPS-I), showed that a midazolam infusion in conjunction with a continuous systemic ketamine tim spontaneous movement. Upon improvement of symptoms, medications were tapered and the patient emerged free of pain and associated CRPS signs and symptoms. An 8-year follow-up showed the patient maintained complete remission from CRPS [41]. The third class, which is not as well understood, known as psychogenic pain has been

attributed to psychological disorders, such as depression or anxiety. In reality, psychological disorders have physical complications, such as fatigue and muscle aches [42]. Given that psychogenic pain does not usually have a physical origin, it is more difficult to treat than nociceptive or neuropathic pain and may require a different treatment approach than the physical types of pain. Benzodiazepines and psychological medications play a more effective role than traditional approaches.

Benzodiazepines infusions may also play an important role in analgesia for the terminally ill. In a report done on nine individuals with terminal metastatic cancer with intractable pain, continuous systemic benzodiazepine administration was used as an adjunct to ketamine and fentanyl infusions with favorable results (Adults: Drug mixture consisting of ketamine: 2 mg/ml plus fentanyl: 5 μg/ml plus midazolam: 0.1 mg/ml run between 2–13 ml/h titrated to where the patient was alert and oriented with minimal to no pain) [43]. These patients also exhibited a degree of cognitive compromise and agitation. Qualitative improvement in pain control and agitation were manifest in all patients.

Benzodiazepines Infusion for Opioid Detoxification

Unfortunately, opioid dependence affects nearly 15 million individuals worldwide; and of those, 11 million are heroin addicts [44]. A major challenge in fighting the opioid epidemic is the risk of mild to severe clinical withdrawal symptoms associated with opioid discontinuation. These include but are not limited to restlessness, rhinorrhea, lacrimation, myalgias, arthralgias, nausea, vomiting, abdominal cramps, diarrhea, diaphoresis, dysphoria, agitation, anxiety, depression, tachycardia, hypotension, hypertension and severe rebound pain, and these can potentially discourage a patient from continuing with opioid discontinuation. Consequently, cases of severe clinical symptoms are preferably managed in a hospital setting [45]. Considerable concern should be taken when abruptly terminating high daily requirements of opioids; this can lead to severe anxiety, depression and possible psychotic episodes [46–48]. When a decision is made to withdraw from opioid use abruptly rather than gradually with opiate substitution drugs, acute withdrawal symptoms are often managed with adjunctive medications such as benzodiazepines. The mechanism of action in which benzodiazepines and other GABAergic drugs help control acute withdrawal symptoms is by reducing catecholamine release. Benzodiazepines in particular have been shown to reduce withdrawal symptoms in animal models [49, 50]. In mouse studies, pre-treatment/co-administration of diazepam 1–4 mg/kg during chronic morphine treatment suppressed the expression of naloxone(3 mg/kg)-precipitated withdrawal signs such as jumping, exploratory rearing and weight loss [50]. In order to manage opiate withdrawal appropriately, it is necessary to use multiple drug classes that allow for the control of a variety of symptoms; nevertheless, one must keep in mind that there is a high risk of drug-drug interaction and incomplete patient relief especially in those taking opioids for somatic disease.

Contraindications

Despite the value of benzodiazepine infusions in select settings, the use of benzodiazepines is contraindicated in certain patient populations. These populations include patients who are at risk for respiratory depression, pregnant patients and the elderly. Care must be taken to screen patients before administering benzodiazepine infusions, as adverse effects can be significant and alternative medications for anxiety, muscle spasms and sedation exists.

A relative contraindication exists for patient who have compromised respiratory systems, including patients who have sleep apnea, COPD and myasthenia gravis. Benzodiazepines may worsen apnea for patients with either obstructive sleep apnea (OSA) or central sleep apnea (CSA), as these patients have exaggerated respiratory depressant responses. Respiratory depression is worsened when the dose is administered too rapidly, in conjunction with opioids and in elderly patients, but apnea may occur even when benzodiazepines are used on its own [55]. Almost one third of patients with COPD are prescribed benzodiazepines for associated insomnia, depression, anxiety and breathlessness [56]. This occurs despite known respiratory compromise in this population and evidence that new users of benzodiazepines were at increased risk for adverse respiratory outcomes [57] and increased mortality [58]. For patients with myasthenia gravis, the muscle relaxant effects of benzodiazepines may exacerbate muscle weakness. Despite limited studies that did not show additional weakness in rats that were administered diazepam, the safety of benzodiazepines in this patient population remains unclear [59].

Women who are pregnant should not receive benzodiazepines due to evidence of teratogenicity and neonatal toxicity. The FDA categorizes the majority of benzodiazepines as pregnancy category D or X, indicating positive evidence of fetal risk [60]. When administered within the first trimester of pregnancy, there is evidence of increased risk of cleft lip and limited evidence of other malformations [52]. When benzodiazepines are administered during the late third trimester, some infants exhibit floppy baby syndrome with variable levels of lethargy, poor respiratory effort and poor feeding. Benzodiazepines are excreted into breast milk at low levels. While generally considered safe at these levels, infants with difficulty metabolizing the drug may exhibit increased sedation and feeding difficulty [61].

As mentioned in the section regarding side effects, benzodiazepine administration may affect a patient's mental status, even long after administration of the drug has ceased. The geriatric population is particular vulnerable to the cognitive effects of benzodiazepines, such that the American Geriatrics Society warns against first-line use of benzodiazepines for geriatric patients [61]. Benzodiazepines are associated with diminished cognitive abilities, including memory problems, disorientation and confusion, and increased risk of delirium. They are more likely to be involved in accidents after benzodiazepine administration, including higher frequency of motor vehicle accidents and hip fractures [61].

Other contraindications include risk of acute narrow angle glaucoma with certain benzodiazepines, such as diazepam and alprazolam. This is due to the muscle

relaxation of iris sphincter muscles [61]. Patients with known hypersensitivities to benzodiazepines or its frequently used solvents, such as propylene glycol, should also avoid infusions of the drug. Careful patient selection and history taking is necessary to avoid complications.

Side Effects

Benzodiazepines are not benign medications and are known to have certain adverse effects, especially when given in high doses for prolonged periods of time. It is well documented in the literature and has become common knowledge that long-term use of benzodiazepines may lead to tolerance, dependence, and withdrawal. Given the context-sensitive half-life of benzodiazepine infusions, significant accumulation in fatty tissues may occur. Aside from common side effects such as fatigue, drowsiness, and lethargy; continuous systemic benzodiazepine administration may cause impaired motor coordination, vertigo, slurred speech, blurry vision, mood swings, euphoria can occur and potentially hostile/erratic behavior [51].

Venoirritation is a potential adverse reaction that may specifically occur with diazepam and lorazepam [52].

Another concern is with drug-drug interactions. Simultaneous use of multiple drugs would be common for a patient population requiring continuous systemic benzodiazepine administration for analgesia. Benzodiazepines are metabolized in the liver via the cytochrome p450 system and renally excreted. Consideration should be given to drugs that attenuate or potentiate cytochrome p450 enzymes in order to monitor the elimination half-life of benzodiazepines and avoid either adverse reactions or an inadequate level of the benzodiazepine, respectively [53].

Special attention should be placed on co-administration of opioids, which may cause cardiovascular and hemodynamic instability in addition to respiratory depression [54].

Monitoring

There are no established guidelines regarding the appropriate use of benzodiazepines for the treatment of pain. Current CDC recommendations advise clinicians to avoid prescribing opioids and benzodiazepines concurrently, citing increased risk of potentially fatal overdose, but indicates that circumstances may exist where concurrent prescription are appropriate [7]. Some clinicians feel benzodiazepines play a key role in addressing the hyperarousal that is associated with pain and is "beneficial to the welfare and pain relief of many patients [8]." Therefore, responsibility falls on the pain management provider to determine whether benzodiazepines fit within an individual patient's pain-control regimen. Despite the lengthy history and prevalence of benzodiazepines, limited literature is available to provide guidance for its use in pain patients.

Benzodiazepines have several routes of administration, with administration in the form of an infusion most frequently seen in the intensive care unit (ICU) as a

sedative where the additional anxiolytic and amnestic properties are generally desirable. Diazepam and midazolam are most frequently used, as they have a short onset of action. Complications with hypotension and respiratory depression are rare, especially when used as an infusion, as lower peak plasma concentrations are attained compared to bolus dosing [9]. Benzodiazepine infusions may be less practical outside of the ICU, as active metabolites, fat absorption and renal and hepatic dysfunction can cause prolonged sedation, but it has been effectively used for outpatient procedures in some limited settings.

Algorithm for Benzodiazepines Infusion Regimens

The following table summarizes the proposed doses as published in literature (Table 12.1).

Table 12.1 Algorithm for benzodiazepines infusion regimens

Indication	Dosage
Tetanic spasms	Diazepam 10–30 mg IV every one to 8 h. Diazepam IV infusion with serum concentration target of 400–500 ng/ml. Midazolam IV infusion 5–15 mg/h Midazolam epidural infusion 2 mg/h
Procedural light sedation (anxiolysis)	Midazolam with target control infusion (TCI) with initial target site concentration of 30 ng/ml, increasing by 10 ng/ml every 60 s, with target BIS scores 80–90. Adults: initial 0.3–0.35 mg/kg, followed by additional doses up to 0.6 mg/kg Children 6 months to 5 years old: initial 0.05–0.1 mg/kg, followed by additional doses up to 0.6 mg/kg Children 6–12 years old: initial 0.025–0.05 mg/kg, followed by additional doses up to 0.4 mg/kg
Catatonia	Lorazepam 2 mg IM. If incomplete relief, administer a second lorazepam 2 mg IM dose. Follow with diazepam 1.2 mg/h IV infusion.
Sedation-agitation	Midazolam IV infusion 0.5–10 mg/h when sedation agitation scale (SAS) > 4 on three consecutive assessments despite q1hprn therapy. Titrate midazolam in 1 mg/h increments to a SAS of 3–4 to a limit of 10 mg/h
Chronic neuropathic pain	Clinically recommended IV infusion rate of 2 mg/kg/h midazolam.
CRPS Type-1	Bolus injections of 1 mg/kg ketamine and 5 mg midazolam followed by continuous infusions of 3–5 mg/h ketamine and midazolam dosed as clinically needed to provide stable and deep sedation.
Terminal life care	Intravenous infusion of the drug mixture consisting of 500 mg ketamine/1250 mg fentanyl/25 mg midazolam dissolved in 250 ml of 0.9% NaCl providing a solution of 2 mg/ml ketamine, 5μg/ml fentanyl, and 0.1 mg/ml midazolam run between 2–13 ml/h titrated to where the patient was alert and oriented with minimal to no pain.
Opioid detoxification	Pre-treatment/co-administration of diazepam 1-4 mg/kg during chronic morphine treatment

Summary

A patient's overall perception of pain involves an interaction between the nociceptive pathways, neuropathic pathways and higher-order brain functions. The medications that are used to treat most pain patients target the first two pathways. This has been effective in alleviating pain for many patients, but leaves the affective portion of pain perception unaddressed. In certain patient populations, the anxiety associated with pain and the prospect of pain augments the overall pain experience, leading to increased pain scores and medication requirements. Benzodiazepines may play an adjunctive role in the treatment of acute, perioperative and chronic pain.

Infusions of benzodiazepines currently hold a limited role in pain management, owing to the deficit of inquiry and research for its use in the pain population. It has a few established roles in pathologic states often associated with pain, including the treatment of tetanic muscle spasms, catatonic states and CRPS. Additional research has shown it to be effective for its anxiolytic and amnestic properties for procedural sedation and treatment of terminal pain. But its side effect profile, including excessive sedation, respiratory depression and delirium has limited the amount of research dedicated to benzodiazepine infusions and its role in analgesia.

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Immunoglobulin (IVIG) Infusion Therapy

13

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Introduction

First used as a replacement therapy for immunodeficiency disorders, human pooled immunoglobulin has since been increasingly recognized as a primary treatment in certain autoimmune and inflammatory disorders [1]. There are now a number of conditions for which their use is approved by the US Food and Drug Administration and over 150 off-label uses for immunoglobulin therapy. Different dosage forms of immunoglobulin, including intravenous, subcutaneous, and intramuscular preparations are being used. This blood product derivative, created from the plasma of donors is used in the treatment of immunodeficiency states, infections, autoimmune and inflammatory conditions, and alloimmune processes. In the setting of immunodeficiency states, the onset of action is immediate in providing concentrations of antibodies against a broad range of pathogens. Regarding its use in the suppression of inflammatory and autoimmune states, there are several mechanisms that contribute depending on the disease treated including, but not limited to, interaction with Fc receptors on phagocytic cells, neutralization/solubilization of antibodies and

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immune complexes [2–4], and suppression of cytokine production and neutralization of existing cytokines [5].

While the creation of all immunoglobulin products has specific standards set by the World Health Organization, individual manufacturers have continued to improve them to increase safety and efficacy. These minimum standards are set to include highly purified, mostly polyvalent IgG from a pooled set of at least 1000 healthy donors with the intent to maximize the array of specific IgGs and reduce the risk of transmission of viral infections. There are currently 10 brands of intravenous immunoglobulin (IVIG) commercially available in the United States. Among these, product specifics vary with respect to sugar content, sodium content, osmolality, IgA content, and methods of viral reduction. While it remains a relatively safe treatment, it is expensive with no currently available generic alternatives [6–9]. A workshop held in the UK allowed experts to present evidence supporting the use of IVIG for a range of disorders. Based on the conclusions of this expert workshop and results gathered from clinical trials, in addition to previously recognized indications, IVIG therapy may be a valid treatment option for peripheral neuropathic pain associated with certain diseases in patients that have been refractory to conventional treatments [10].

Mechanism of Action

While the precise pathogenesis for complex regional pain syndrome (CRPS) remains unknown, multiple mechanisms may contribute to the chronic pain that patients experience from central sensitization, inflammation and autonomic nervous system dysfunction. It is currently thought that at the site of traumatic injury of the involved tissue, an inflammatory response enables pre-existing autoantibodies to trigger a pain disorder. There are studies that have observed an increased concentration of pro-inflammatory cytokines, tumor necrosis factor-alpha, interleukin-1β, and IL-6, in not only the affected tissues, but also in plasma and cerebrospinal fluid. The use of IVIG treatment may reduce the immune activation and neutralize autoantibodies [11].

When it comes to neuropathic pain, There is currently no agreed upon mechanism that is the driving force of the pathophysiology of this process. It is thought to be immune-mediated with characteristics of ischemic damage due to a microvasculitis that involves peripheral nerves and nerve roots of the lumbosacral plexus [12, 13] The pain in diabetic amyotrophy may also be related to the presence of cytokines, growth factors, and antibodies to these neuronal structures. Higher cytokine content has been found to be associated with neuropathic pain; however, the exact role is currently unclear. There may also be heterogeneity regarding pathophysiology among patients with this disease as some patients have spontaneous resolution of symptoms and some patients respond to IVIG despite no previous response to corticosteroids [14].

It is hypothesized that the painful sensory neuropathy in Sjogren's Syndrome (SS) is caused by a continuum of the lesion at the sensory ganglion from T-cell infiltration, associated with the sensory ataxic form. The blockage of inflammatory

cytokines, inactivation of B-cell function leading to a reduction in autoantibodies by IVIG is thought to allow for the remaining dorsal root ganglion neurons to regain function in the ataxic form of SS. This mechanism could be extrapolated to work in a similar manner in the small dorsal root ganglion neurons in the painful neuropathy associated with SS [15].

Indications

Complex Regional Pain Syndrome

CRPS has been defined as "an array of painful conditions that are characterized by a continuing regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain usually has a distal predominance of abnormal sensory, motor, pseudo motor, vasomotor, and/or trophic findings." There are two subtypes of this syndrome based on the absence (Type I) or presence (Type II) of peripheral nerve injury [16, 17]. The pain and allodynia often come from complications after a fracture, surgery, or damage to the extremities. The pathophysiological mechanisms underlying the disorder are currently poorly understood, but it has been suggested that both central and peripheral mechanisms are involved regarding neurogenic and classic inflammation, autonomic nervous system dysfunction, and maladaptive neuroplasticity. These mechanisms change over the course of the disease where in early stages of CRPS I, primary afferent C-fibers release neuropeptides, and later stages are characterized by maladaptive cortical changes in the CNS. There are currently no diagnostic tests for the diagnosis of CRPS and it is purely a clinical diagnosis based on the Orlando or Budapest clinical diagnostic criteria. Treatment is generally a multidisciplinary approach primarily focused on physical therapy as first line treatment [18, 19]. There is limited evidence for the basis of pharmacological treatment; however treatment with NSAIDs [16], anticonvulsants, antidepressants [20], bisphosphonates in the early stages [11], and oral glucocorticoids have been studied with some efficacy being demonstrated for each [21–23]. Some patients have also benefitted from interventional procedures including trigger point injections, sympathetic nerve blockade [21], and spinal cord stimulator implantation [24].

Several studies have shown success in IVIG treatments for patients with complex regional pain syndrome with refractory pain despite conventional treatments including physiotherapy, bisphosphonates, corticosteroids, and opioids. In addition to two case reports that showed positive results with treatment [25, 26], the authors in a prospective cohort study with 11 patients showed that 27.3% of patients had a > 70% pain relief when followed over a period of 36 months [27]. In a follow-up trial by the same author, 12 patients completed a randomized, double-blind placebo controlled crossover trial in which 3 patients had a 50% or greater reduction in pain intensity when treated with IVIG as compared to placebo [28]. Additionally, a report on maintenance therapy in two patients showed that at a follow-up at 12 months, these patients were now in remission. However, a larger randomized,

placebo controlled, double-blind study with 111 patients who received 0.5 g/kg IVIG or placebo showed that 35(66%) patients in the placebo and 34 (68%) of patients in the IVIG group had lower pain scores. Four patients (three placebo, one IVIG) had a 30% pain reduction. Overall, over a 6-week period of treatment, patients showed no clinical benefit from IVIG infusion when compared to placebo. There is a need for repeated large RCTs with possible consideration for a higher dosing of IVIG at 2 g/kg [29].

Diabetic Lumbosacral Radiculoplexus Neuropathy

Diabetic amyotrophy, also known as diabetic lumbosacral radiculoplexus neuropathy among many other names, represents the most common cause of lumbosacral plexopathies. This condition typically occurs in patients with type 2 diabetes mellitus and symptoms include acute pain followed by weakness in the proximal lower extremity, autonomic changes, and weight loss [30]. Electrodiagnostic studies will show axonal degeneration typically in the lumbar and sacral nerve roots, plexuses, and peripheral nerves. While the condition typically progresses, patients experience clinical improvement over months; however, most do not completely recover and have residual weakness and neuropathic pain. There are no proven treatment options for diabetic lumbosacral radiculoplexus neuropathy or for the clinically similar idiopathic lumbosacral radiculoplexus neuropathy. There have been some regimens that employ immune suppression with some trials that have shown some associated clinical improvement. However, there are currently no randomized controlled trials that exist examining the use of immunomodulation [31, 32]. Positive results were found in some case studies and case series. Kawagashira et al. noted a pain reduction by 50% in a patient with proximal diabetic neuropathy treated with 0.4 g/kg × 5 days IVIG. His pain was reduced again from a 7 to a 2 on the Visual Analogue Scale (VAS) by a repeat treatment of IVIG after an exacerbation [33]. Another case report was done by Tamburin et al. on a patient with diabetic lumbosacral radiculoplexus neuropathy with repeated interval treatments of IVIG over 8 years when the patient had a relapse of symptoms. It was reported that IVIG was repeatedly effective on pain severity, and for other measures with each treatment [12]. In a follow-up small open label series with five patients over a follow-up period of 14–20 months, four patients were reported to have a positive response to treatment with a > 50% reduction of pain measured on the VAS [14]. An open label trial in 2010 with six patients reported positive results in half of the patients that had multifocal neuropathy versus the non-responders who had polyneuropathy [34].

Despite the improvement in pain noted in these reports, not all case series have shown positive results. In 2003, Zochodne et al. completed a case series of three patients with progressing symptoms of lumbosacral radiculoplexus neuropathy despite immunosuppression treatment. Two patients in the series were treated with 0.5 g/kg/day × 5 days of IVIG. The last patient in the series a developed a plexopathy while he was on an immunosuppressive regimen of cyclosporine A and mycophenolate after cardiac transplant. During follow-up all three continued to have progressive pain despite the described treatment [35].

Idiopathic Lumbosacral Radiculoplexus Neuropathy

There are a limited number of reports on idiopathic lumbosacral radiculoplexus neuropathy, a condition clinically similar to diabetic amyotrophy regarding pathology, clinical features, and management. Park et al. reported a case study of a patient who failed treatment with antibiotics and IV methylprednisone. After treatment with IVIG he had improvement in both pain and motor weakness without relapse in symptoms over a follow-up period of 6 months [36]. Two other small studies involving a total number of seven patients reported success in pain reduction after treatment with IVIG treatment [37, 38]. Further investigations with randomized controlled trials would better characterize the use of IVIG in diabetic amyotrophy and LRPN.

Sjogren's Syndrome

Sjogren's syndrome is a chronic inflammatory autoimmune disorder that primarily effects lacrimal and salivary glands. The most common clinical signs are resultant sicca symptoms of ocular and oral dryness. There is no singular diagnostic test for Sjogren's syndrome and the diagnosis is made based on a combination of clinical, histological, and laboratory findings. The presence of SSA/Ro and/or SSB/La antibodies may be suggestive, but not diagnostic of Sjogren's syndrome. Treatment is aimed at specific manifestations of the disease with current treatments for neuropathy primarily using GABAergic drugs, tricyclic antidepressants, corticosteroids, and IVIG in refractory cases [39].

There is published data on a limited number of patients that have benefitted from the use of IVIG in Sjogren's Syndrome. There are no direct comparisons regarding the different immunomodulatory medications; however, the response rate to IVIG appears promising. In a case study, Kizawa et al. treated a patient with severe pain and dysesthesias in all extremities with 0.4 g/kg/day × 5 days followed by a second course for relapse of symptoms. He showed improvement on the VAS scale from 10 to 2 in 2 weeks after the first course of treatment. After the re-treatment he showed a similar improvement in response with a VAS score of 10–2 [40]. Morozumi et al. included this patient with 4 other patients that showed an improvement of the VAS score reduction by 73% from 7.6 ± 2.9 to 2.2 ± 1.5 within 2 weeks of treatment. This improvement lasted for 2–6 months. Four patients had relapses in pain with repeated treatments of IVIG proving to be effective; however, one patient did note a less pronounced effect after 6 years of treatment [15]. Additionally, Wakasugi et al. published a case report on a patient who developed small fiber neuropathy after a diagnosis of Sjogren's syndrome. The pain was refractory to an increased dosage of corticosteroids and anticonvulsant therapy. The patient was treated with IVIG 20 g for five consecutive days. Her pain on the VAS decreased from an 8 to 4. She had an increase in symptoms 2 weeks later, but after a second course of treatment with IVIG, her VAS score was reduced to 2. She needed a third treatment 7 weeks later, which completely resolved her pain and improved her paresthesias [41]. Finally, in a

multicenter observational study, Mori et al. described three patients diagnosed with Sjogren's syndrome that had painful sensory neuropathy without sensory ataxia who were treated with 0.4 g/kg ×5 days. Two (67%) of these patients showed a favorable response rate measured by "definite improvement" in the modified Rankin scale in pain and painful dysethesias when evaluated 1 month after treatment [42].

Fibromyalgia

With an unknown etiology and pathophysiology, as well as being a common cause of widespread pain, fibromyalgia remains a diagnosis of exclusion. Clinical signs and symptoms will show only pain in muscles and joints and tender points in characteristic bilateral points. Treatment is typically a multidisciplinary approach aimed at improving sleep and mood, physical therapy, and pharmacological therapy using specific antidepressants and anticonvulsants.

There is a very limited data on the use of IVIG in fibromyalgia syndrome. In an open label pilot study, Caro et al. found that a subset of these patients that demonstrated chronic inflammatory demyelinating polyneuropathy (CIDP) using electrodiagnostic techniques benefitted from the infusion therapy. From their original 58 fibromyalgia patients, they treated 15 patients with CIDP, with a pre-treatment of intramuscular methylprednisolone acetate 40 mg followed by IVIG 400 mg/kg × 5 days. The patients showed an improvement in pain, tenderness, and strength [43].

Contraindications

IVIG is contraindicated in patients who have had an anaphylactic reaction to a previous administration of immunoglobulin. Patients with selective IgA deficiency can be given IVIG, however, treatment with a product low in concentration of IgA may be considered with monitoring for anaphylaxis. There is no correlation to the presence of anti-IgA antibodies and adverse reactions [44–46]. While there are no known drug interactions, IVIG should be avoided at the time of administration of an attenuated live vaccine or within 3 months following the vaccine [47].

Side Effects

Adverse reactions have been reported to occur in approximately 5–15% of infusions, affecting up to 50% of individuals receiving IVIG. The severity of reaction (ranging from mild to severe) and timing (immediate, delayed, or late) varies based on the individual. Most reactions are mild and include headache, chills, fever, abdominal pain, nausea, shortness of breath, and joint/muscle pain. These mild reactions are likely due to activation of the complement system, antigen-antibody,

or reactions from contaminants by accumulated immunoglobulin molecules [1]. Slowing the infusion rate or stopping the infusion can reverse these mild reactions. Pre-treatment hydration in addition to NSAIDs, acetaminophen, diphenhydramine, or a corticosteroid can prevent these reactions. A reduction in the number of leukocytes, neutrophils, and monocytes can also be seen, but is self-limited and is not associated with predisposition to infection. More severe adverse events include acute renal failure, aseptic meningitis neurodegeneration, and exacerbation of pre-existing cardiac disease, thromboembolic events, severe dermatitis, and anaphylactic shock [44–46].

Monitoring

A recommended set of safety labs prior to consideration for treatment with IVIG includes a complete blood count, serum immunoglobulin levels, creatinine, urea, electrolyte, liver function, viral hepatitis screening, and pregnancy test. Monitoring should include a set of vital signs prior to the infusion, every 15 min for the first hour of the infusion followed by every 30 min afterwards [29, 47].

Algorithm for IVIG Infusion Regimens

Due to the presence of several different regimens for IVIG infusion, we will be discussing the proposed algorithms for each disease condition separately and we will be citing the different literature proposing those algorithms (Tables 13.1, 13.2, and 13.3).

Summary

The use of IVIG has been a treatment choice in a variety of diseases treated based on immunomodulation. Knowledge of its use in the treatment of pain is continuing to emerge. The treatment of chronic pain can be challenging for both the provider and the patient. Based on current literature, a subset of patients with chronic pain that is associated with an immune mediated etiology as in the aforementioned conditions (Complex Regional Pain Syndrome, Lumbosacral Radiculoplexus Neuropathy, Sjogren's Syndrome, and Fibromyalgia) that have been refractory to conventional treatments, may benefit from treatment with IVIG. The dosing typically used is 0.4 g/kg/day for 5 consecutive days with repeated courses when symptoms relapse. The medication is high in cost, which may limit availability and payment coverage for its use, however, it is relatively safe with appropriate monitoring and associated with only mild side effects. IVIG is a promising treatment for pain; however continued research with larger randomized clinical trials is needed.

Table 13.1 Algorithm for IVIG infusion regimens for CRPS

Reference	Type of study	No. of Pts/ description of pt	Dosing of IgG	Control	Primary outcomes
Medlin (Clin J Pain 2013;29;e33–4)	Case report	19 yo male with CRPS s/p mandibular osteotomy with R foot drop. Pain refractory to pregabalin and tramadol	Total dose of 2 g/kg divided over 4 days	None	Pain decreased continuously within first day of treatment. Pain and skin manifestations resolved 2 weeks after CRPS onset.
Tachdjian, R. (Pain Ther, 2013. 2(2): p. 129–34.)	Case report	62-year-old white male patient with a history of longstanding CRPS	500 mg/kg monthly	None	Right leg pain decreased significantly from 7 out of 10 to 2 out of 10 following initial and subsequent reinfusions
Goebel (Pain Med, 2002. 3(2): p. 119–27)	Prospective multiple-dose, open-label cohort study	11	Initial dose of 9–18 g IVIG divided into 3 applications over 1 week After 28 days pt. had incomplete relief, gave 3 ×10 g IVIG over 1 week, retreated at 28 days intervals if needed	None	27.3% of patients had a > 70% relief of pain when followed over a period of 36 months
Goebel (Ann Intern Med, 2010. 152(3): p. 152–8.)	Randomized, double-blind, placebo-controlled crossover trial	12	IVIG, 0.5 g/kg, and normal saline in separate treatments, divided by a washout period of at least 28 days	Normal saline, cross over	Average pain intensity was 1.55 units lower after IVIG treatment than after saline (95% CI, 1.29–1.82; $P < 0.001$). In 3 patients, pain intensity after IVIG was less than after saline by 50% or more.
Goebel (Ann Intern Med 2017;167:476–483)	Double blinded randomized placebo-controlled trial	111	0.5 g/kg IVIG After blinded phase, all pts. offered open label IVIG on days 43 and 64 of 0.5 g/kg IVIG	0.1% albumin in saline on day 1 and 22	35 (66%) of patients in the placebo and 34 (68%) of patients in the IVIG group had lower pain scores 4 patients (3 placebo, 1 IVIG) with 30% PR 1 patient in placebo group with 50% PR

Table 13.2 Algorithm for IVIG infusion regimens for Neuropathy

Reference	Type of study	Disease	No. of Pts/ description of pt	Dosing of IgG	Control	Primary outcomes
Kawagashira (J Neurol Neurosurg Psychiatry 2007;78;899–901)	Case study	Proximal diabetic neuropathy	57 yo male with T2 DM × 10 years on PO glimepiride. He was wheelchair-bound due to bilateral LE muscle atrophy. He also had severe, burning, spasmodic pain in the bilateral LE. Eparestat, mecobalamin, mexiletine, and carbamazepine were given without benefit.	0.4 g/kg × 5 days after prednisone 250 mg × 3 days	None	Pain improved from 10 to 5 on visual analogue scale (VAS), gradually exacerbated in subsequent 3 weeks from 5 to 7, then after a repeat course of IVIG pain decreased from 7 to 2.
Tamburin (Pain Pract 2014;14:E85–90)	Case study	Relapsing diabetic lumbosacral Radiculoplexus neuropathy	65 yo male with 12-year h/o type 2 DM w/ subacute pain in L thigh and R abd wall and spread to right thigh and hip. Treatment with antidepressants, anticonvulsants, opioids, corticosteroids were not effective.	0.4 g/kg/day × 5 days for total ×9 treatments over 8 years when symptoms relapsed	None	Improvement of pain 10–20 days after therapy, repeatedly effective on pain severity, mechanical allodynia, and walking distance without an effect on muscle strength
Tamburin (Pain Med 2009;10:1476–80)	Open label clinical trial	Diabetic lumbosacral Radiculoplexus neuropathy	5	0.4 g/kg/day ×5 days Two patients had repeat infusion due to pain reappearance after 7 and 9 months with a positive response 1 patient had a third infusion 18 months after the second one, with positive response	None	After 1 month, 4 patients with positive pain response after IVIG, >50% reduction in VAS. 1 patient with 10% VAS reduction (−59% from 5.8 ± 2.0 to 2.8 ± 2.9; P = 0.04)

(continued)

Table 13.2 (continued)

Reference	Type of study	Disease	No. of Pts/ description of pt	Dosing of IgG	Control	Primary outcomes
Kawagashira (J Clin Neurosci 2010;17;1003–8)	Open label clinical trial	Diabetic neuropathy	6	0.4 g/kg ×5 days, with exacerbation of pain repeat treatment 1 month after initial therapy	None	Multifocal neuropathy: 3 patients with 80, 67, and 43% decrease in VAS Polyneuropathy: 3 patients with −13, −14, 0% change in VAS
Zochodne (Acta Neurol Scand, 2003. **107**(4): p. 299–301.)	Case reports	Diabetic lumbosacral Plexopathy	3	Patient 1: Cyclosporin A and mycophenolate mofetil Patient 2: 0.5 g/kg/day ×5 days, repeat course 3 months after Patient 3: 0.5 g/kg/day ×5 days	None	Continued progression of pain in all patients
Park (J Clin Neurosci 2005;12:313–5)	Case report	Idiopathic postoperative lumbosacral Plexopathy	66 yo male s/p decompressive subtotal laminectomy from L4-S1 for right sided pain. He developed L leg pain and subsequent R leg pain and weakness that did not improve with antibiotics or IV methylprednisolone.	0.4 g/kg/day × 5 days		Improvement in both pain and motor weakness

Verma (Neurology, 1994. 44(2): p. 248–50.)	Case reports	Lumbosacral Plexopathy	2	Patient 1: 0.4 g/kg/day × 5 days, 0.8 g/kg/day × 5 days followed by once a week 0.8 g/kg 9 months after first treatment Patient 2: 0.4 g/kg/day × 5 days, followed by 0.4 g/kg once a month	None	Improvement of pain in both patients
Triggs (Muscle Nerve, 1997. **20**(2): p. 244–6.)	Case reports	Idiopathic lumbosacral Plexopathy	5	Initial treatment of 0.4 g/kg/day × 5 days	None	Patients 1–4 had improvement following initial treatment In patient 5, IVIg at 0.2 g/kg/day, 0.4 g/kg/day, and 0.8 g/kg/day. Most patients relapsed within 1 month

Table 13.3 Algorithm for IVIG infusion regimens for Sjogren's syndrome

Reference	Type of study	No. of Pts/ description of pt	Dosing of IgG	Control	Primary outcomes
Mori (Brain, 2005. 128(Pt 11): p. 2518–34.)	Case series	3	0.4 g/kg ×5 days	None	2 (67%) patients showed a "definite improvement" in the modified Rankin scale in pain and painful dysesthesias 1 month after treatment
Kizawa (J Neurol Neurosurg Psychiatry, 2006. 77(8): p. 967–9.)	Case report	67 yo male with Sjogren's syndrome with severe pain and dysesthesiasin all extremities.	0.4 g/kg/day × 5 days followed by a second course 3 months later after relapse of symptoms	None	Improvement of pain 2 weeks after first course; VAS 10–2. Sensation to light touch, pinprick, and temperature were slightly improved. After relapse of severe pain that preceded treatment 3 months later, after second course improved a week later comparable to first response VAS 10–2.
Morozumi (J Neurol Sci. 2009 Apr 15;279(1–2);57–61)	Clinical series, open label	5 (1 patient in case report above)	0.4 g/kg/day × 5 days	None	VAS reduction from 7.6 ± 2.9 to 2.2 ± 1.5 over follow-up period. Reduced pain by 50–100% on VAS scale. Relapses in 4 patients, IVIG "effective at each relapse, but the effect of IVIG became less pronounced in patient 2 after 6 years of tx.
Wakasugi (Mod Rheumatol, 2009. 19(4): p. 437–40.)	Case report	40 yo female with Sjogren's syndrome who developed paresthesia and burning pain	20 g ×5 days, repeated courses when symptoms relapsed	None	VAS reduction of paresthesia from 8 to 4 and resolution of burning pain after first treatment Continued disappearance of burning pain and continued significant reduction in paresthesia

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Ketorolac Infusion Therapy

14

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Introduction

Ketorolac tromethamine is a potent, non-opioid, pyrrolo-pyrrole non-steroidal anti-inflammatory drug (NSAID) that provides anti-inflammatory, analgesic, and antipyretic effects in both the acute hospital and outpatient setting [1–4]. Ketorolac was first mentioned in the medical literature in the 1980s and was initially approved in 1989 for short-term pain management. Today, ketorolac is a widely used pharmacologic agent [5]. Currently, ketorolac is the only parenteral NSAID for clinical analgesic use in the United States. Ketorolac is thought to possess greater analgesia properties than other anti-inflammatory agents, making it a viable, non-opioid option for pain management [6]. Additionally, the various routes of administration,

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including oral, intranasal, intramuscular (IM), and intravenous (IV), makes ketorolac a readily available drug for acute and chronic pain syndromes [7]. It is typically used in the management of migraine headaches, renal colic, musculoskeletal pain, sickle cell crisis, cancer pain and postoperative pain management [7]. The use of ketorolac in some of the previous mentioned conditions will be outlined in this chapter.

Mechanism of Action

Ketorolac is non-selectively inhibits cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) enzymes. The inhibition of COX-1 prevents the normal production of prostaglandins and the inhibition of COX-2 prevents conversion of arachidonic acid to pro-inflammatory prostaglandins. Through both mechanisms, ketorolac decreases the formation of prostaglandins, a molecule which contributes to the nociceptive transmission in the spinal cord. Although ketorolac is known to non-selectively inhibit COX, there are reports indicating more than a 400-fold selectivity for inhibiting COX-1 compared to COX-2 [8]. This increased selectivity in inhibition of COX-1 correlates well with the toxicity associated with ketorolac. Ketorolac is a racemic mixture of [−]S- and [+]R- enantiomers, but only the S-form is noted to have analgesic activity [9]. Ketorolac has an analgesic effect within 30 min of administration, with a peak effect within 2–3 h and typically lasts for 4–6 h. In regards to pharmacokinetics, it is highly protein bound (99%), metabolized in the liver and renally cleared. About 92% of ketorolac is excreted via urine and about 6% is excreted via feces.

Indications

Migraine Headaches

Migraines are classically described as episodic, unilateral, pulsatile headaches that are often associated with nausea, vomiting, and sensitivity to light and sound [2]. Occurring in 8% of males and 12–15% of females, migraines are one of the most common encountered conditions in primary care and neurology practices [2]. This acute debilitating neurological disorder affects one in seven Americans annually and accounts for over one million emergency department (ED) visits in the United States annually, resulting in a cost of over 700 million dollars per year [10, 11].

The primary pain mechanism associated with migraines is considered to activate of the trigeminovascular system (TGV) [2]. Although the specific stimuli associated with the activation of the TGV is not well studied, the activation of the TGV results in the release of various neuropeptides including calcitonin gene-related peptide (CGRP), substance P, neurokinin A and nitric oxide [2, 12]. The release of these various inflammatory peptides directly act upon the trigeminal nucleus caudalis in the brainstem, which leads to central sensitization and results in the pain of migraine.

Ketorolac directly inhibits the vasoactive peptide–induced inflammation that occurs from the activation of the TGV thereby allowing symptom relief.

Traditionally, acute migraine exacerbations in the ED were managed primarily with the use of narcotics; however, with the increase in severity of the opioid epidemic, the use of other analgesic agents such as ketorolac have been more studied and favored. Ruzek et al. reviewed the treatment management for 290 ED visits between 1999–2000 and in 2014 to evaluate how the management for acute migraines in the ED setting has changed over the span of 15 years [11]. Based on the results, there was an increase in the use of ketorolac by 34% and a decrease in parenteral narcotics by 56% from 1999–2000 to 2014 [11].

Although there is an increased in the use of ketorolac in the ED setting for acute migraines, there is some conflicting evidence regarding its use. A systematic review by Taggart et al., which included 8 trials involving 321 patients showed ketorolac and meperidine to have similar pain score; however, in comparison to intranasal sumatriptan, ketorolac was found to be a more effective analgesic [13]. Even though ketorolac was not as effective as metoclopramie/phenothaizine agents in this review, it was found that the use of parenteral ketorolac is an effective in the treatment of acute migraine [13]. Given the low side effect profile associated with ketorolac in comparison to the other treatments, ketorolac is a viable option as an acute analgesic for migraines.

Renal Colic

Renal colic is defined as pain caused by urolithiasis, an urinary stone, and is known to be a common cause for emergency department visits in the United States. An estimated 12% of males and 6% of females will develop urolithiasis within a lifetime [14]. In 2000, the estimated claims for urolithiasis in the United States accounted for about $2.1 billion [15]. Renal colic typically results in acute severe flank pain which radiates to the groin and is most often accompanied by nausea, vomiting and microscopic hematuria. As the urinary stone progresses through the urinary tract, the location and intensity of the pain may change.

The mechanism of renal colic pain is due the obstruction of urinary flow by the kidney stone. This obstruction leads to increased wall tension in the urinary tract and the rising pressure result in the direct synthesis and release of prostaglandins [16, 17] . The release of prostaglandins induce vasodilation and diuresis, which further increases pressures, and spasm of the urethral smooth muscle [17].

The pain associated with renal colic is often severe and fluctuant in nature. For pain management, the use of parenteral ketorolac has been favored in many emergency departments. Specifically, ketorolac allows for pain relief by inhibiting the production of prostaglandins and subsequently decreasing the urethral smooth muscle tone [18]. This allows for targeted pain relief, serving as a preferred analgesic agent in the acute setting.

In 1996, Cordell et al. evaluated the use of 60 mg ketorolac IV versus 50 mg meperidine IV and found that ketorolac 60 mg IV and the combination of ketorolac

60 mg IV and meperidine 50 mg IV had better outcomes than meperidine 50 mg IV alone in pain relief and the time elapsed before the need for meperidine administration [19]. However, the combination of ketorolac 60 mg IV and meperidine 50 mg IV was not significantly superior when compared to the ketorolac 60 mg IV alone [19]. Based on the study, after 30 min of administration of the analgesia agents, 75% of the ketorolac group and 74% of the ketorolac-meperidine combination group had a 50% reduction in their pain score compared to the 23% in the meperidine alone group [19]. It is important to note that this study by Cordell et al. used a standard dose for meperidine IV rather than the preferred weight based dosing, which could have underdosed many patients in the study. A randomized, double-blind trial conducted by Larkin et al. compared the use of 60 mg of ketorolac IM and a weight based dose of meperidine IM and concluded ketorolac IM compared to meperidine IM was significantly more effective in reducing renal colic at 40, 60 and 90 min intervals based on the visual analogue scale [20]. Of those patients who were discharged to home and did not require admission to the hospital, the ketorolac IM group left the ED significantly earlier than the meperidine IM group (3.46 h vs. 4.33 h) [20]. Although, this study evaluated the use of ketorolac and weight based dosing for meperidine, the route of administration was IM, where the preferred route of administration in the acute setting is intravenous.

Based on the literature, there are no studies that compare the use of ketorolac IV and a preferred weight based dosing of meperidine IV in the management of acute renal colic pain. Although these studies evaluated the use of meperidine, morphine is often the preferred opioid of choice in the ED setting due to its greater potency and lesser side effect profile in comparison to meperidine. In 2006, Safdar et al. designed a randomized, double blinded study comparing the effectiveness of ketorolac 30 mg IV, morphine 10 mg IV and a combination of both in the setting of acute renal colic [21]. Based on the study, there was not a significant difference in pain relief with the use of either medication alone; however, through the combination of both medications, there was more effective pain relief than either medication alone [21]. Current literature shows that ketorolac is a preferred treatment option for management of pain in the setting of acute renal colic given the safer side effect profile and greater potency.

Sickle Cell Disease

One of the most common debilitating manifestations of sickle cell disease is vaso-occlusive crisis. Vaso-occlusive events result in recurrent episodes of pain caused by various triggers leading to tissue ischemia which may lead to severe multi-organ damage. Episodes can begin as early as 6 months of age and continue throughout life. The pain is often severe and debilitating, thus requiring adequate management of pain. Early and aggressive management of pain is key to management of episodes.

There is limited data regarding the use of ketorolac for acute pain management in sickle cell crisis. One study evaluated the role of ketorolac in management of pain during sickle cell crisis. Results indicated that patients who received continuous

infusion of ketorolac required 33% less total meperidine when compared to placebo group [22].

Although, ketorolac may be a good non-opioid treatment option for pain during vaso-occlusive crisis, it has been shown to be a major cause of acute kidney injury (AKI). A 2-year retrospective study by Baddam, et al. recommends against its use due to association with AKI [23]. Results showed that among participants who received at least one dose of ketorolac, the odds of developing AKI increased by 63% for each additional day receiving a dose of 0.5 mg/kg IV ketorolac every 6 h for 5 days [23].

Analgesia

Pain is one of the most undesirable consequences of surgery and often is undermanaged in the postoperative setting. Inadequate postoperative management can lead to increased length of hospital stay, reduced mobilization, increased rehabilitation, and an increased risk of developing a postoperative complication [24–26]. A survey conducted by Rawan et al. reported about 35% of surgery patients experienced moderate to severe pain despite having analgesia medications [27]. This inadequate management of acute pain can be detrimental to postoperative recovery and can lead to the development of chronic pain with the reduction in quality of life [24]. Due to the high impact inadequate management of pain has on physiological and psychological benefits, the monitoring of pain postoperatively has become an important quality measure in the hospital setting.

Despite enhancement in postoperative pain management, the mainstay of therapy in many settings is still the use of opioids [24]. Opioids pose many postoperative side-effects including sedation, nausea, vomiting, urinary retention, constipation, postoperative ileus and respiratory depression [28, 29]; thus limiting its use has been highly favored. Given the multifactorial mechanism of postoperative pain, a multimodal analgesia concept has been classified as the gold standard when managing postoperative pain [24, 30]. The multimodal analgesia model allows for the achievement of sufficient analgesia due to synergistic effects among different classes of analgesia [30, 31]. Through the use of different classes of analgesics, different mechanisms of pain are targeted, which allow for an overall lower dose of each analgesic thus resulting in a reduction of side effects [30, 31].

In a randomized double-blind trial, Cepeda et al. compared the efficacy of 0.1 mg/kg IV morphine and 30 mg IV ketorolac in postoperative pain in 1003 patients [32]. At 30 min post infusion of analgesics, if pain intensity remained at a pain score 5 or more out of 10, the patient received an additional 2.5 mg of morphine every 10 min until the pain intensity decreased to less than 5 out of 10. It was found that 50% of the patients in the morphine group achieved 50% of greater pain relief at 30 min, compared to 31% of patients in the ketorolac group, suggestive that morphine is more efficacious at pain relief than ketorolac [32]. Additionally from this study, Cepeda et al. reported the morphine group required 6.5 mg more of morphine to achieve the desired pain intensity level compared to the ketorolac-morphine

group [32]. With the reduction in morphine requirement, the ketorolac-morphine group had a lower incidence of opioid-related side effects including dizziness, sedation, and pruritus; however, the occurrence of nausea and vomiting was similar in both group [32]. Similarly, De Oliveria et al. conducted a meta-analysis to evaluate the efficacy of a single dose of perioperative ketorolac on postoperative analgesia [33]. This meta-analysis included 13 randomized clinical trials, which concluded that ketorolac 60 mg, compared to ketorolac 30 mg, was an effective multimodal strategy to reduce postoperative pain and opioid consumption [33]. Additionally, this meta-analysis reported that the IM route of ketorolac compared to the IV route showed to provide a greater opioid sparing effect [33].

In addition to postoperative pain, another common complication postoperatively includes the formation of an ileus, especially in those patients who undergo abdominal surgery. The rate of postoperative ileus varies significantly depending on the type of surgery; however, there has been a correlation that the use of opioids increase the risk of postoperative ileus development due to the known inhibitory effect on the gastrointestinal tract [28]. Chen et al. developed a study to determine the opioid-sparing effects of ketorolac when added to IV patient-controlled analgesia (PCA) morphine in patients who underwent major colorectal surgery [34]. Based on the study, the patients who received both ketorolac and morphine required 18.3% less morphine than the morphine alone group [34]. Due to the increased use of morphine in the morphine group, there was a 5.25 times greater risk of developing postoperative ileus [34]. Although this study focused on the postoperative ileus side effect, the opioid sparing effects of ketorolac are evident and can greatly reduce the other side effects associated with the use of opioids in the postoperative setting.

As discussed, ketorolac can be used as a bolus administration in the management of pain. However, the use of continuous ketorolac intravenous infusion has also been documented in the literature for analgesia in the postoperative setting. One of the earliest double-blind, randomized, multicenter studies on continuous intravenous ketorolac evaluated analgesic efficacy and safety. Patients received either continuous ketorolac infusion of 5 mg/h IV with an initial 30 mg IV bolus, initial ketorolac bolus of 30 mg IV with 15 mg IV bolus every 3 h, or placebo 24 h after a major surgery. All three groups in this study had access to a morphine PCA. Results showed that patients who received continuous ketorolac infusions required less morphine compared to the placebo group. In addition, both ketorolac groups reported less pain and experienced less postoperative vomiting than the patients receiving PCA morphine alone [35].

Continuous infusions of ketorolac have been studied as analgesic agent for orthopedic cases. In 1995, Etches et al. designed a study looking at the use of continuous infusion of 30 mg IV bolus ketorolac over 15–30 s followed by continuous infusion of ketorolac 5 mg/h for 24 h in postoperative total hip or knee arthroplasty [36]. Compared to the placebo group, the ketorolac group reported better analgesia and required the use of less morphine [36]. Similarly, a 2017 retrospective, cohort study showed the continuous ketorolac infusion group, who received 30 mg bolus followed by continuous infusion of 3.6 mg/h, to have significantly lower pain scores and reduced opioid consumption following an unilateral total knee arthroplasty [37].

The use of continuous ketorolac infusion has been widely documented in the setting of orthopedic cases; however, the literature on its use in cardiothoracic procedure is limited mainly due to the associated black box warning. Despite the black box warning, the use of continuous ketorolac infusion is often utilized for analgesia after a coronary artery bypass graft (CABG). Howard et al. evaluated the risk associated with the use of continuous ketorolac infusion in postoperative CABG patients and determined there was not an increased risk of mortality, myocardial infarction, or bleeding with the use of continuous ketorolac infusion [38].

One study by Russo, et al. evaluated the differences in postoperative pain management with ketorolac doses as a continuous infusion or scheduled bolus. The first group received a continuous infusion of 0.02 mg/kg/h morphine with 90 mg ketorolac and the second group received 0.02 mg/kg/h morphine with subsequent administration of ketorolac bolus every 8 h for 24 h. Postoperative pain scores showed greater pain relief in patients who received schedule ketorolac bolus in comparison to continuous infusion of ketorolac [39].

In addition to continuous intravenous infusions of ketorolac, continuous subcutaneous infusions have been used as a medication delivery method for analgesia. This method of delivery has shown to be advantageous in patients in whom intravenous access is difficult [40]. Additionally, continuous subcutaneous infusions have been associated with lower incidence rates of infection [40]. Blackwell et al. published the first case series on the use of continuous subcutaneous ketorolac infusions of 90 mg over 24 h for analgesia, which showed significant analgesia, reduction in opioid use and no adverse effects despite a prolonged infusion time, up to 31 days [41]. Although Blackwell and colleagues were able to report reduction in opioid use, an updated case series by Duncan et al. did not report similar findings [42]. Although the recommended duration of ketorolac therapy is not to exceed 5 days, a case series by Hughes et al. reported infusion therapies for periods up to 185 days with only 2 of 25 patients experiencing complications from the continuous infusion of 60 mg over 24 h which was increased to 90 mg as needed [43]. This is reported to be the longest duration for continuous subcutaneous ketorolac infusions in the setting of cancer-related pain. As a follow up to Blackwell et al., Meyers et al. conducted an observation study with 36 patients and reported significant improvement in pain and a reduction of opioid use with the use of continuous subcutaneous ketorolac infusion of 60 mg over 24 h in the management of cancer pain [44]. Of note, a subset of patients received a 30 mg SQ bolus prior to the initiation of CSI to assess the likely response [44]. Similarly to Hughes et al., the longest tolerated infusion period in this study was 115 days with 5 patients experiencing complications from the continuous infusion [44].

The cases and studies outlined by Vacha et al. have shown to provide significant analgesia benefit with small rate of complication, of which majority experienced gastrointestinal complications and there was no indication of a renal complication [7]. Dosage range for continuous subcutaneous infusion used was 30–120 mg over 24 h [7]. Although continuous subcutaneous ketorolac infusions is a viable treatment option for cancer pain that is refractory to other modalities, the limited research and the lack of longitudinal studies makes it difficult to justify its use on a routine basis.

Due to the opioid sparing effects of ketorolac, it is recommended to use ketorolac in conjunction with opioids when managing pain. When able to, clinicians should optimize the multimodal approach in the setting of pain management.

Contraindications

Ketorolac has been associated with an increased risk of gastrointestinal events including stomach or intestinal bleeding, ulceration, and perforation. Symptoms can be sudden and severe. For this reason, ketorolac is contraindicated in patients with history or active peptic ulcer disease or bleeding. A study by Gonzales et al. evaluated the variability of gastrointestinal bleeding and perforation risk amongst patients taking various NSAIDs [45]. Results indicated that ketorolac was associated with a higher relative risk compared to ibuprofen and other NSAIDs [45].

Ketorolac injections are contraindicated in patients with previous hypersensitivity reaction to aspirin or NSAIDs due to the risk of life-threatening anaphylactic responses. One case study found life-threatening asthma exacerbation after administration of intravenous ketorolac [46].

Due to the risks of impairing fetal circulation and inhibiting uterine contractions, the use of ketorolac in labor and delivery is contraindicated.

Side Effects

Ketorolac has a varied side effect profile of varying levels of severity. The risk of having an adverse effect from ketorolac is greater with increased dose administration and length of treatment. For this reason, the use of ketorolac should not exceed 5 days. Additionally, concomitant use of ketorolac with other NSAIDs is contraindicated due to the risk of cumulative adverse effects. The most significant adverse effects consist of dysfunction to the hematologic, renal, gastrointestinal, cardiovascular, and immune systems.

Ketorolac has been documented to inhibit platelet function by decreasing platelet adhesion and aggregation resulting in increased bleeding time. For these reasons, a US Boxed Warning exists and recommends against the use of ketorolac in patients with increased risk of bleeding including cerebrovascular bleeding, hemorrhagic diathesis, and incomplete hemostasis. A study by Sukmawan et al. evaluated the bleeding time of various non-aspirin NSAIDs [47]. Results showed that ketorolac had the highest elevation in bleeding time by 108.7% compared to all other non-aspirin NSAIDs. This elevation in bleeding time was statistically significant in comparison to the control group [47]. Due to the effects of ketorolac on bleeding time, it is recommended that patients with coagulopathies managed with anticoagulants need to be monitored closely.

NSAID use may impact renal function due to the dose-dependent decrease in prostaglandins which subsequently reduce renal blood flow and possibly cause

renal decompensation. To prevent renal dysfunction it is important to rehydrate patients prior to initiation of treatment.

NSAIDs, including ketorolac, cause increased risk of cardiovascular thrombotic events including myocardial infarction and stroke. For this reason, ketorolac is contraindicated in patients with history of coronary artery bypass graft (CABG) surgery [1]. In 2005, the FDA administered a black box warning recommending against the use of NSAIDs after cardiac surgery. Despite the FDA warnings, NSAIDs have been used postoperatively. A retrospective cohort study by Howard et al. evaluated the primary risk of mortality and the secondary risk of bleeding and myocardial infarction in patients who underwent CABG with and without ketorolac administration [38]. Results indicated that there was no difference in mortality between ketorolac and control groups [38]. Additionally, there was no increased risk of MI or bleeding. The literature evaluating the risks of using ketorolac in patients with CABG surgery is unclear regarding the potential for cardiovascular thrombotic events and cases should be evaluated by comparing risks and benefits.

Monitoring

Given the renal, gastrointestinal, and hematological effects of ketorolac, it is recommended to obtain a baseline complete blood count and basic metabolic panel prior to administration to ensure there is not a preexisting renal dysfunction and/or anemia. Subsequent monitoring with daily blood work should suffice to monitor hematologic and renal function. Please be sure to review your institutional guidelines prior to initiating infusion.

Algorithm for Ketorolac Infusion Regimens

The following table summarizes the proposed doses as published in literature (Table 14.1).

Table 14.1 Algorithm for Ketorolac infusion regimens

Indication	Dosing
Acute migraine headache	30 mg IV or 60 mg IM with a maximum of 120 mg/day
Renal colic	60 mg IV bolus with a maximum of 120 mg/day
Sickle cell crisis	Recommend against using due to development of AKI – refer to sickle cell disease section
Postoperative pain	60 mg bolus IV or IM with a maximum of 120 mg/day; 30 mg IV bolus followed by continuous infusion of 5 mg/h for 24 h
Cancer-related pain	Continuous SQ infusion of 30–120 mg over 24 h; 30 mg SQ bolus dose can be used prior to the initiation of continuous SQ infusion

Summary

The anti-inflammatory, analgesic, and antipyretic properties of ketorolac have made it a widely used pharmacologic agent [1–4]. Appropriate indicated uses include, but are not limited to acute migraine headaches, renal colic, and postoperative pain management. Although ketorolac is sometimes used in the setting of acute sickle cell crisis, its dose should be limited due to the increased risk of developing acute kidney injury.

The preferred dose and route of administration of ketorolac varies per indication. Lower doses of 30 mg ketorolac are typically used for acute migraine headache. However, for renal colic and postoperative pain management higher doses of 60 mg ketorolac are recommended. The use of ketorolac should be limited to a maximum duration of 5 days due to potential side effects. Notable side effects include increased bleeding time, acute kidney injury, gastrointestinal bleeding, and hypersensitivity reaction. In regards to cardiovascular thrombotic events, the literature is unclear regarding increased risk in the setting of ketorolac administration. For these reasons, it is important to consider the side effect profile of ketorolac while weighing the risks and benefits prior to administering ketorolac.

Additionally, ketorolac has been primarily studied and used in conjunction with opioids due to the opioid-sparing effect of ketorolac, which its use is desired due to the rising opioid epidemic. The use of ketorolac as a single agent needs further evaluation in large-scale randomized controlled trials.

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Depacon Infusion Therapy

15

Greta Nemergut

Introduction

Valproate (2-propylpentanoic acid) has a simple eight-carbon branched-chain fatty acid structure. Valproate is usually used as its sodium salt and is quickly dissociated to valproic acid in the body [1, 2]. Valproate is typically used in its oral form, but the IV form can be used in acute situations or in patients who are not able to take oral medications. Doses for use in seizures and mood are dependent primarily on clinical effect and drug levels; however, for acute use in migraine, there is no set dosing recommendation. The studies that evaluated use in this indication varied in dose; however, all tried to administer as quickly as possible.

Mechanism of Action

Valproate sodium is thought to have at least three mechanisms of action. Gamma-aminobutyric acid (GABA) is an amino acid that is found in the central nervous system. There are GABA receptors in the nervous system, that when activated, inhibit neurotransmitter firing, reducing activity. $GABA_A$ receptor is a chloride channel that, when activated, there is an influx of chloride ions and a subsequent efflux of potassium ions, causing hyperpolarization at the synapse and inhibiting the postsynaptic neuron. Valproate increases GABA levels in the brain and enhances GABA-mediated activity, in part by inhibiting GABA aminotransaminase and blocking the degradation of GABA. A second suggested mechanism is blockage of voltage-dependent sodium channels, a common mechanism of anti-epileptic drugs. Blocking these channels reduces the amount of excitatory amino acids, like

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aspartate and glutamate, that are released. A third postulated mechanism is the suppression of protein kinase C, which regulates the glutamatergic system and suppresses neuronal membranes. Glutamate is an amino acid in the brain that has significant excitatory effects. All of the mechanisms reduce the excitatory mechanisms of the brain, decreasing activity, and therefore decreasing seizures and pain. The last two mechanisms have only been proven in invitro and animal studies [1].

Indications

Acute Migraine Headaches

About 18% of women and 6% of men were reported to have at least one migraine in the past year in the US. The overall prevalence of migraine is 4% before puberty and steadily increases after puberty, more quickly in girls than boys. At age 40, the prevalence begins to decline. One million adult patients in the US present to the emergency department annually for the treatment of migraines. There can be a genetic component to some migraines. There have been several mutations seen on the CACNA1A gene, which is associated with voltage dependent P/Q calcium channels. P-type calcium channels are involved in the release of serotonin and excitatory neurotransmitters. If impaired, the release of serotonin is affected, resulting in an increase in migraine headaches. Trigeminal sensory neurons that contain substance P, calcitonin gene-related peptide and neurokinin A are activated during headaches and cause neurogenic inflammation which sensitizes nerve fibers and causes pain [3].

Valproate sodium has been studied in the setting of abortion of acute migraine headaches given as a one-time infusion in several small studies and one large randomized trial. The American Headache Society lists valproate infusion as "may offer" to patients to treat acute migraine attacks based on available data [4].

In a small prospective study, 61 patients who presented to clinic with an acute migraine were given valproate 300 mg IV [5]. Sixty-six migraines were treated. The study population consisted primarily of women (n = 54), mean age of 40.8 for women and 34.0 for men. Most of the headaches (n = 44) were without aura. The mean duration of migraine history was 5.5 years and the mean duration of the current headache was 7 h. All treated patients had a headache severity score of 4 or more (moderate to severe). Valproate was administered over 10 min with mean time to onset of effect of 8 min and meaningful relief at 16 min. At total of 56% of the attacks were downgraded from moderate to severe to mild after administration. Complete relief was demonstrated at 25 min post infusion. A 50% reduction in headache pain was reported in an additional 17% of attacks, for a total of 73% (n = 48) of attacks having significant relief. No serious adverse events were reported. There was a recurrence in eight cases, with the headache returning in an average of 9.5 h. Valproate was shown to be safe and effective in this small trial.

Karimi et al. [6] and Mazaheri et al. [7] compared valproate IV to dexamethasone IV in the acute treatment of migraines in two separate trials. Both trials

demonstrated similar efficacy between the two treatment arms. The first was a double-blind, randomized trial in 80 adult patients with migraine without aura [6]. Patients were randomized to receive either dexamethasone 4 mg IV or valproate 400 mg IV. The primary outcome assessed was pain relief at 0.5, 1, 3, or 6 h after administration of the drug. Secondary outcomes included other migraine symptom relief and adverse events. After 0.5 h, 67.5% of patients in the dexamethasone group and 55% of patients in the valproate group showed a reduction in pain; this was not a significant difference between groups. Also, at 0.5 h the Visual Analog Scale (VAS) pain score reduced to 3.85 ± 3.09 from 9.05 ± 0.90 in the valproate group and to 3.14 ± 2.73 from 8.92 ± 0.79 in the dexamethasone group (p = .513). By 6 h post infusion, 90% of patients treated with valproate and 97.5% of patients treated with dexamethasone experienced significant improvement in pain. The second study evaluated 72 patients who presented to the emergency department with acute severe migraine [7]. Patients were randomized to receive either dexamethasone 16 mg IV or valproate 400 mg IV. Severity of headache was measured at baseline and 0.5 and 2 h post-infusion. The reduction in pain in both groups at both 0.5 and 2 h was statistically significantly better than baseline. In the valproate group, VAS pain scores were reduced from 8.20 before treatment to 5.31 and 3.66 at 0.5 and 2 h. In the dexamethasone group, pain scores reduced from 8.46 at baseline to 5.46 at 0.5 h and 3.59 at 2 h post infusion. There was no difference between groups.

Ghaderibarmi et al. compared valproate 15 mg/kg IV to sumatriptan 6 mg subcutaneous (SQ) for the treatment of acute migraine in an open-label, randomized study [8]. Thirty-seven patients were randomized evenly and were assessed for reduction in pain and presence of side effects. Only 7 patients (19%) were male. The mean age of patients was 37.42 ± 9.68. VAS pain scores reduced to a greater extent at 1 h in the valproate group (8.3–2.2) than in the sumatriptan group (8.3–4.7). More patients experienced relief from other symptoms of migraine (phonophobia, photophobia, nausea, vomiting) in the valproate group. No side effects were reported in either group.

Another study compared valproate 400 mg IV to metoclopramide 10 mg IM + sumatriptan 6 mg SQ. Sixty patients were randomized evenly to each treatment arm [9]. The primary endpoint was to assess pain relief from moderate-severe to none-mild. Pain was assessed at baseline and 20 min, 1, 2, 4 and 24 h after infusion/injection. Patients were observed in a quiet, dark room for 4 h after administration. Patients were allowed to take rescue medications in the case of incomplete resolution of headaches. Participants were called at 24 h to assess pain control at that time point. Baseline demographics were similar between groups, with about 70% of participants being female and 100% Caucasian. Patients in the valproate group had significantly better pain control at 1 and 2 h post infusion; however, VAS pain scores did not differ between groups at any other time points. At 1 h post infusion, 46.7% of patients in the valproate group still were experiencing moderate-severe pain, while 76.7% of patients treated with metoclopramide + sumatriptan still had pain. This difference remained at 2 h (40% of valproate patient and 70% of metoclopramide + sumatriptan patients experiencing moderate-severe pain). Nausea was improved more quickly and to a greater extent in the valproate group, with most

patients being nausea-free after 20 min. Photophobia and phonophobia decreased in both groups to a similar degree. Only three patients reported adverse events. One patient had dizziness after the valproate infusion and two patients experienced flushing and nausea in the metoclopramide + sumatriptan group.

Edwards et al. completed a study comparing valproate 500 mg IV and metoclopramide 10 mg IM plus dihydroergotamine (DHE) 1 mg IM in to abort a moderate-severe migraine in patients [10]. Forty patients were randomized to receive one of the treatments and pain was assessed on the VAS at baseline and 1, 2, 4 and 24 h after administration of study drug. Presence or absence of nausea, phonophobia and photophobia were also assessed at each timepoint. Reduction in pain between the two groups was similar, with 50% of patients in the valproate group reporting none-mild pain at 1 h and 45% of patients in the DHE-metoclopramide group with the same pain reduction. The difference was similar at 2 and 4 h; however, at 24 h, more patients (90%) in the DHE-treated group still had headache relief, than in the valproate-treated group (60%), suggesting longer lasting effects of DHE. Nausea, photophobia and phonophobia also decreased to a similar extent in each group over the first 4 h of the study. Valproate was better tolerated, with no adverse events reported. In contrast, 15% the DHE-treated group reported side effects, including nausea and diarrhea.

In a study comparing valproate to prochlorperazine in the treatment of acute migraine in the emergency department, prochlorperazine was found to be more effective [11]. Forty patients were randomized to receive prochlorperazine 10 mg IV or valproate 500 mg IV, given over 2 min. The primary outcome was change in pain score at 1 h. The median improvement in the pain scale for prochlorperazine treated patients was 64.5 mm, while the change was only 9 mm in the patients treated with valproate, and 79% of patients who received valproate required rescue medication to treat their headache.

In the largest trial, 330 patients were randomized to receive valproate 1 gm IV, ketorolac 30 mg IV, or metoclopramide 10 mg IV each given over 15 min [12]. The primary endpoint was the change in pain score at 1 h post infusion. Patients in the valproate group had the lowest change of a 2.8 reduction. Patients in the metoclopramide group saw a 4.7 point reduction and those getting ketorolac had a 3.9 point reduction. Headache relief was sustained, defined as not needing rescue medication for 24 h after infusion, in 4% of valproate treated patients, 11% of metoclopramide treated patients and 16% of ketorolac treated patients. No significant side effects were reported with use of valproate.

Contraindications

Valproate sodium is contraindicated for use in several populations. It is contraindicated in patients with severe hepatic impairment and is not recommended to be used in hepatic disease. It is also contraindicated in patients who have urea cycle disorders due to impairments in metabolism. Pregnant women should not use valproate sodium for the prevention of migraines due to risk of serious birth defects. Patients

who have DNA mutations of the mitochondrial polymerase gamma (POLG) gene are at increased risk for acute liver failure and death with valproate sodium and use is contraindicated [13].

Side Effects

Valproate sodium is related to several rare but serious side effects. Hepatic failure has occurred, although generally after repeated use. Valproate causes major congenital malformations, most commonly neural tube defects (spina bifida), and can also cause decreased IQ scores in children who were exposed to the drug in utero. Life-threatening pancreatitis has also occurred in patients taking valproate. Less serious side effects include drowsiness, dizziness, nausea, and injection site reactions [13].

Monitoring

When using as a single acute treatment of migraine abortion, no specific monitoring is required. When valproate is used a more regular basis, liver enzymes need to be periodically monitored to assess any change in liver function and, for women who are of child-bearing age, pregnancy testing may be warranted.

Algorithm for Depacon Infusion Regimens

The following summarizes the doses administered in published trials (Table 15.1). There is no defined dose for use in migraine.

Summary

The primary use of valproate sodium is for seizures and mood disorders, and generally in its oral form. Valproate IV is used in acute settings and has been studied for the acute abortion of migraine headache. Doses for acute use in migraine headaches vary across trials, with the most common being 300 mg, 400 mg or 500 mg IV. Dose of 1000 mg and weight-based dosing of 15 mg/kg have been used as well. The

Table 15.1 Algorithm for Depacon infusion regimens

Indication	Dosage
Adult acute migraine	300 mg IV over 10 min 400 mg IV over 10–15 min 500 mg IV over 2 min 1 gm IV over 15 min 15 mg/kg

evidence for use of valproate in acute migraine is mixed and most of the studies are on small populations. However, overall it appears that use of an IV dose of valproate in the acute setting may be effective in aborting a headache with minimal to no side effects. Valproate potentiates GABA in the nervous system and likely has activity on sodium channels and protein kinase C. Larger scale trials would be beneficial to help determine the most effective dosing for acute migraine therapy. The current guidelines for treatment of migraine in the emergency department reference valproate as "may offer", which corresponds to level of evidence C (small benefit, low confidence in evidence, strength of principle-based inferences-plausible); primarily due to small trial size and mixed outcomes.

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Intravenous Hydration Therapy

16

Maxim S. Eckmann and Chad C. Parvus-Teichmann

Introduction

Classification of Intravenous Fluids

Intravenous fluids (IVF) are generally classified as colloids or crystalloids based upon their composition and membrane permeability [1]. This categorization portends differential ability of the fluid to diffuse between the intravascular and extra vascular spaces. Colloids include preparations containing serum globular proteins, such as human albumin solutions, or nonionic starch derivatives, as seen in hydroxyethyl starch (HES) solutions. Crystalloids are aqueous solutions of mineral salts or other water-soluble molecules, such as 0.9% sodium chloride a.k.a. normal saline (NS), as well as balanced salt solutions that include lactated Ringer's (LR) solution, Normosol, Plasma-Lyte.

Colloids

Colloids are typically administered in the setting of rapid resuscitation efforts given their hypothesized tendency to remain within the intravascular compartment, maintaining intravascular volume status and perfusion to organs and tissues; this characteristic is attributed to colloids' relative hyperosmolarity in comparison to plasma. Though the selection of colloid fluids during rapid resuscitation is rational in the setting of critical conditions such as trauma, intraoperative hemorrhage, or septic shock, there is controversy over whether overall outcomes are improved compared to the use of so-called balanced crystalloid solutions [2, 3]. In fact, there is a

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growing appreciation of the unique complications caused by colloids, including coagulopathy, volume overload, and allergic reactions.

Colloid-associated coagulopathy presents a serious concern and should be considered during selection of an appropriate fluid. In the case of massive resuscitation, rapid administration of large volumes of colloids results in a dilutional coagulopathy [4]. In the case of HES preparations, those with high molecular weight (Mw > 550 kD), and high molar substitution (MS > 0.7) are associated with coagulopathy secondary to effects on coagulation factors and clot formation. Factor VIII and von Willebrand factor (vWF) are negatively impacted by high-MS HES preparations, and fibrinogen activation of the platelet glycoprotein IIb-IIIa receptor is impaired, inhibiting a crucial precursor to the clotting cascade [5].

The ability of colloids to remain within the intravascular space, as well as the effects their constituent molecules exert on interstitial fluid, underlie their impact on volume status. For example, high-Mw HES solutions may increase intravascular volume by an additional 70–80% of their infusion volume over 90 min. Further, low-mW and low-MS HES solutions may cause an even greater effect on intravascular volume secondary to the oncotically active molecules produced by their metabolism. Cautious administration, therefore, is recommended to avoid the cardiovascular and pulmonary complications associated with volume overload.

Allergic reactions to colloids, though very rare, have been described and represent another serious possible complication. Less serious but potentially concerning to patients is the fact that HES molecules may cause pruritis as a result of accumulation in the skin.

In general, colloids are infrequently used in the ambulatory setting due to the potential for adverse effects, lack of demonstrated therapeutic benefit, and high cost.

Crystalloids

Saline Solutions

Crystalloid solutions contain sodium chloride as the dominant salt in order to approximate the physiologic composition of human plasma. These ionic solutions exist in an electrically neutral state in which positively charged ions are equally balanced with negatively charged ones. Physiologically, any remaining ions are electrically balanced by so-called “unmeasured” plasma components such as proteins and lactate. Each liter of human plasma contains approximately 141 mEq of sodium, 103 mEq of chloride, 4–5 mEq of potassium, 2 mEq of magnesium, and 26 mEq of bicarbonate, and have a normal pH of 7.4 and osmolality of 289 mOsm/L. [6] Normal saline (NS), or 0.9% sodium chloride, is a commonly used crystalloid with similar osmolality of 308 mOsm/L. NS however contains a moderately higher concentration of sodium (154 mEq/L) and dramatically higher chloride concentration (154 mEq/L) than plasma, and exists at a relatively acidic pH of 5.5–5.7. In addition to isotonic saline, hypotonic and hypertonic crystalloid solutions are sometimes

employed in the management of specialized clinical scenarios such as cerebral edema and correction of hypernatremia.

Balanced Salt Solutions

Another common category of crystalloid solutions is referred to as "balanced" salt solutions in light of their closer approximation to plasma electrolyte concentrations. In particular, these fluids contain similar chloride content to that of plasma and include Ringer's lactate solution, Normosol, and Plasma-Lyte.

These solutions contain a variety of alternative anions with which to supplement chloride content and maintain electric neutrality with fluid cations, in particular sodium. The presence of lactate, acetate, and gluconate allow for maintenance of an isoelectric state in Lactated Ringer's, Normosol, and Plasma-Lyte, respectively. By limiting the concentration of exogenously administered chloride ions, these solutions may avoid the adverse effects on acid-base status associated with NS.

One liter of Lactated Ringer's has a pH of about 6.4 and composition of 130 mEq sodium, 109 mEq chloride, 4 mEq potassium, 3 mEq calcium, and 28 mEq lactate. By comparison, Normosol is composed of 140 mEq sodium, 98 mEq chloride, 5 mEq potassium, 3 mEq magnesium, and 27 mEq acetate. In lieu of acetate, Plasma-Lyte contains gluconate (23 mEq), but includes the same composition and pH of Normosol (7.4). For comparison, Table 16.1 lists the composition of frequently administered solutions.

Table 16.1 Composition of frequently administered crystalloids

	Human plasma	Normal saline	Ringer's lactate	Normosol	Plasma-lyte
pH	7.35–7.45	4.5–7.0	5.0–7.0	4.0–8.0	4.0–8.0
Sodium[a]	136–145	154	130	140	140
Potassium[a]	3.5–5.0		4	5	5
Chloride[a]	98–106	154	109	98	98
Lactate[a]			28		
Acetate[a]				27	
Gluconate[a]					23
Calcium[a]	2.2–2.6	0	3	0	0
Magnesium[a]	0.8–1.0	0	0	1.5	1.5
eSID[b]	42	0	28	50	50
Theoretical Osmolarity[c]	291	308	273	295	295
Measured osmolality[d]	287	286	256	271	271

Modified from Reddy et al. [21]. Published 2016 Mar 15
[a]Measured in mmol/L
[b]Estimated strong ion difference, measured in mEq/L
[c]Measured in mOsmol/L
[d]Measured in mOsmol/kg H_2O

Dextrose-Containing Solutions

Though not commonly used in IVH, 50% dextrose solution (D5W) bears mentioning. The most commonly encountered clinical scenario in which D5W is the fluid of choice involves patients at risk of fasting-induced hypoglycemia, in particular the pediatric population, to supplement caloric needs and avoid ketosis [7]. For patients with free water losses, such as those with diabetes insipidus, D5W may be chosen for its ability to increase free body water. While isotonic to plasma, D5W has this effect *in vivo* secondary to rapid glucose metabolism by the liver which results in a dilutional hyponatremia.

Intravenous Fluid as Secondary Treatment

Conditions for which IVH is itself the sole treatment are generally limited to a small group of headache syndromes. Infusions for the majority of painful conditions, therefore, involve an active medication as the primary therapy. In this setting, intravenous fluid infusion occurs as a secondary "treatment" since, by definition, it is administered concurrently with any infusion therapy. In light of this fact, it is prudent for the provider to calculate the total volume of the infusion therapy to ensure it aligns with the patient's physiologic needs. Particular attention should be paid to volume deficits in the peri-procedural period. Fluid restriction and fasting often precede sedating infusions that include hypnotic agents such as ketamine. Lastly, the chemical compatibility of the active medication with its carrier solution, while rarely a concern with most relevant analgesic and anesthetic agents, should be confirmed by the provider.

Intravenous Cannulation

To maximize patient comfort, the smallest gauge catheter required to achieve clinical goals should be selected. The major factors that determine flow rate include catheter length and, more importantly, lumen radius [8]. Simply stated, lower flow rates are associated with long, thin catheters, while higher flow rates are associated with short, large-caliber catheters. This relationship is described by the Hagen–Poiseuille equation which addresses flow of fluid through a cylinder. Using this model, flow is found to be inversely proportionate to the length of the cylinder and exponentially proportional to the radius, which exerts greater effect given it is raised to the exponent of four. Achieving infusion rates higher than those estimated through this equation becomes increasingly more difficult as flow dynamics convert from laminar to turbulent flow.

In clinical practice, a 24-gauge, 0.75-inch catheter is often the smallest available size outside of specialized settings. This size catheter has a nominal flow rate of approximately 20 mL/min and would require roughly 1 h to deliver 1 L of fluid, additional resistance from extension tubing, valves, or dynamic kinking notwithstanding. In contrast, a 14-gauge, "large-bore" catheter, considered the mainstay of

Table 16.2 Flow rate estimates of common catheter sizes

Color	Gauge size	External diameter(mm)	Length(mm)	Water flow rate(mL/min)
Orange	14G	2.1	45	~240
Gray	16G	1.8	45	~180
Green	18G	1.3	32	~90
Pink	20G	1.1	32	~60
Blue	22G	0.9	25	~36
Yellow	24G	0.7	19	~20
Purple	26G	0.6	19	~13

Gorski [22]

rapid resuscitation efforts, can deliver fluid at roughly 240 mL/min, and therefore 1L in less than 5 min. For the majority of cases, a 20-gauge catheter is sufficient, permitting flow rates of up to 60 mL/min, or 1 L of fluid in almost 17 min, while causing minimal distress and pain to the patient. A comparison of commonly available catheter sizes with their estimated flow rates is shown in Table 16.2.

Mechanism of Action

The mechanism by which IVH alleviates pain, in particular headache syndrome pain, is not well understood and controversial. With regards to headaches resulting from dehydrated states, it is understood that correction of the headache's etiology has the expected result of resolution of their symptoms. In the case of low cerebrospinal fluid (CSF) pressure and postdural puncture headaches, it was proposed that the administration of fluid would promote increased rate of CSF by the choronic villi and lead to a decrease in gravitational pull exerted on the meninges. This theory, however, was not supported by several studies which failed to demonstrate an impact on CSF production secondary to hydration [9]. The mechanism underlying effects on migraine headache are even less well understood, with further research required.

Indications

Water-Deprivation Headache

Headache from dehydration has been reported from conditions that may lead to decreased water intake, such as fluid deprivation, or increased water loss, such as hemodialysis and the consumption of alcohol [10]. Though lacking substantive support in the literature, it is hypothesized that meningeal traction during these states of relative hypovolemia may act as a pain generator. This proposed mechanism would be analogous to that believed to underlie low cerebral spinal fluid (CSF) pressure headaches.

Small, uncontrolled studies suggest that oral rehydration may help in the treatment of these types of headaches, and therefore it is rational to expect IVH may offer benefit. Evidence in support of this theory, however, remains limited.

Despite unclear efficacy, empiric IVH remains a common therapy for patients presenting to the emergency department with symptoms of severe headaches [11]. Prior to consideration of IVH for the treatment of headache, a thorough history and physical examination should be performed to asses for symptoms and signs of dehydration, including an assessment of daily water intake. If present, an underlying cause of dehydration should be established to ensure that the patient does not have an undiagnosed, serious medical conditions, such as those that promote diuresis as seen in uncontrolled diabetes mellitus and diabetes insipidus. Any underlying conditions should be addressed, and laboratory results of serum electrolytes should be obtained, prior to infusion treatment.

Low Cerebrospinal Fluid Pressure and Postdural Puncture Headaches

Postdural puncture headaches (PDPH) occur as a consequence of dural perforation or tear. Typically, the cause is iatrogenic following spinal procedures such as neuraxial anesthesia and spine surgery. Once the dura is violated, cerebrospinal fluid (CSF) may persistently leak from the site of the tear into the epidural space. In most cases, the dura will spontaneously close, sealing the tear and resolving the headache. In a minority of cases, however, the leak will continue, and the patient will develop a severe headache. After 7 days post-puncture, approximately 80% of patients will still achieve resolution of their symptoms without intervention [12]. The incidence of PDPH has been studied most thoroughly in the obstetric literature, with recent data suggesting an incidence of PDPH in 0.5–5% of neuraxial anesthetics [13].

In addition to PDPH, other causes of low CSF headaches have been reported, notably spontaneous intracranial hypotension (SIH). This condition is often idiopathic, but the proposed etiology involves acute interruption of CSF drainage followed by a brief elevation of CSF pressure. The resultant increased stress on the dura causes a rupture at a vulnerable site, leading to leak of CSF into the epidural space and consequent headache similar to that seen in PDPH.

In both PDPH and SIH, leaking CSF enters the circulatory system through the epidural venous plexus, where it is often absorbed at a faster rate than CSF is produced; the net effect of this imbalance is a decrease in CSF pressure. In extreme cases, this result can lead to cranial nerve traction and dysfunction, dysphagia, and even evidence of intracranial sagging visible on imaging. Low CSF headaches are also believed to involve reflect meningeal vasodilation and traction upon the upper cervical nerve roots, particularly C1, C2, and C3, as well as the fifth, ninth, and tenth cranial nerves [14]. In addition to contributing to the pain of low CSF headaches, these effects have been reported to act as a trigger in patients predisposed to migraine headaches [15].

The prototypical feature of this headache is dynamic changes to symptoms associated with position. Generally, assuming an upright position results in severe, sometimes debilitating, pain, while changing to a supine position is accompanied by rapid improvement or even resolution the headache. Concomitant photophobia,

nausea, vomiting, and posterior cervical spine muscle tension have also been reported. If left untreated, ongoing pain may become sub-acute or, in rare cases, may convert to a chronic pain state. In these cases, the positional nature of the headache converts to more constant pain.

Traditionally, conservative treatment for PDPH includes aggressive intake of oral fluids and caffeine, usually given as 300–500 mg by mouth or IV twice daily. These approaches, however, do not appear to increase CSF production as had been initially postulated [16]. IVH is therefore most rational as part of a treatment plan for patients with PDPH and concomitant dehydration, as seen in profuse emesis or diarrhea. As an aside, IVH is often used as prophylaxis for post-operative nausea and vomiting in high-risk patients during the perioperative period [17].

It is this author's experience, corroborated by absence of support from high quality literature, that IVH does not substantially alter the course of PDPH symptoms nor the likelihood that the patient may require a procedure to assist in sealing the leak. Such an intervention is an epidural blood patches (EBP), in which approximately 20 mL of the patient's blood is aspirated and injected into the epidural space at a level near that of the suspected tear. The evidence in support of EBP for the treatment of PDPH is strong, with an estimated 75% of patients achieving complete resolution of their pain after one treatment, and after 2 treatments there is a reported 95% resolution rate. Though EBP is employed to treat cases of SIH, there is sparse data regarding its success.

Migraine (Acute or Intractable)

Migraine headaches are occasionally unremitting and severe enough for patients to present to the hospital for treatment. IVH is a commonly used as an initial treatment for severe migraine in the emergency department. Though routinely employed, the efficacy of this treatment lacks support from high quality, controlled studies. A comparative efficacy trial of IVF (n = 112) versus metoclopramide (n = 458) failed to demonstrate any difference in pain reduction or headache freedom [12]. In light of the paucity of evidence supporting its use as sole migraine therapy, IVH likely doesn't convey any unique benefits and may best act as the carrier for better-supported intravenous migraine treatments.

Recommendations

In light of a long history of use as initial therapy in the treatment of acute presentations of headaches despite sparse supporting evidence, this author proposes a more appropriate role for IVH in the treatment algorithm. In the urgent care or emergency department setting, first-line treatments should take precedence. If, however, the patient requires further evaluation such as imaging studies, laboratory assays, and consultations, initiation of IVH is appropriate as a means to provide a potential adjunct to ongoing therapy. In the chronic pain setting, IVH may be most

appropriate for patients whose condition remains refractory to first-line treatments, and who are further unwilling or unable to pursue more invasive modalities.

Contraindications

While the administration of IVH is generally well-tolerated in the ambulatory setting, caution should be taken when deciding on treatment in specific patient groups. Regardless of fluid selection, patients with decompensated congestive heart failure are at particular risk of fluid overload and the administration of exogenous fluids is relatively contraindicated if their condition is poorly controlled. These patients warrant further optimization of their condition prior to the administration of elective IVH therapy.

For patients with end-stage renal disease (ESRD), even potassium-containing balanced salt solutions should be considered safe when administered in limited doses. In these patients, infusion volumes exceeding 100 mL for a typically sized adult would be relatively contraindicated in the absence of further medical optimization and risk/benefit analysis.

In patients with underlying electrolyte abnormalities, the selection of an appropriate IV fluid is of particular concern. In particular, the presence of hyperkalemia should warrant further workup to identify the cause of the imbalance and treat it accordingly prior to initiation of IVH for pain. The use of balanced salt solutions carries the risk of contributing further to total body potassium in the case of patients who are incapable of potassium excretion; this, however, is only an issue in cases of complete renal failure which, given the added risk of volume overload from IVH, should be considered a contraindication to proceeding with the therapy. Administration of NS, given the associated risk of secondary hyperkalemia that could further increase potassium levels, should be done so only under close supervision. Attention should be paid to the volume and rate of administration as well as electrocardiogram (EKG) changes, in particular the development of peaked T-waves, that may indicate worsening hyperkalemia.

Side Effects

Access-Related Adverse Events

Patients under consideration for intravenous therapies should be evaluated to predict difficulty in obtaining intravenous access. A history of multiple hospitalizations, intravenous drug use, or placement of a central venous catheter during an elective procedure should all prompt further scrutiny. In some cases, absent clues from the history, intravenous access may still prove difficult to obtain and require specialized tools such as ultrasonography or light-assisted vein location devices. In extreme cases, the patient may even require more invasive access in the form of midline venous catheters or peripherally inserted central catheters, so-called PICC

lines; lastly, there is the option for central venous catheterization. Given the elective nature of most pain procedures, however, pursuing this degree of intervention is highly unlikely.

Complications from intravenous cannulation are generally rare. Typically, intravenous placement causes only brief procedural pain which is well tolerated. Some patients may experience significant stress and anxiety during cannulation, which may precipitate a vasovagal response. Should the patient report nausea, become faint, or become unresponsive, the needle should be immediately removed, and the patient placed in the supine position. If symptoms do not resolve, the patient's legs should then be elevated to increase preload to the heart and improve perfusion to the brain. Though cardiac arrest is a rare consequence of vasovagal reactions, providers should be trained in CPR and ready to initiate rapid response should the patient become unresponsive and a pulse undetectable.

Bruising from catheter placement is another possible complication, as is infiltration of the vein. Providers should vigilantly monitor for signs of infiltration by checking the intravenous site periodically throughout treatment. If left untreated, large-scale infiltration may lead to tissue damage. Patients may be unaware of the infiltration due to minimal discomfort or their state of sedation. The management of infiltration begins with immediate removal of the catheter. Application of gentle, cool compression to the affected area as well as elevation of the extremity will help facilitate the reduction of interstitial fluid. If any active pharmacologic agents was infiltrated during the infusion, the provider should consider that portion of medication to behave with intramuscular pharmacodynamics. Similarly, unrecognized dislodgment of the intravenous catheter results in wasted time, medication, and supplies. These events will also raise doubt regarding the delivery of effective therapy.

Metabolic Disturbances

When infused liberally at rates exceeding 30 mL/kg/h, as seen in massive resuscitation efforts, NS may contribute to hyperchloremic metabolic acidosis. Additionally, secondary hyperkalemia may develop due to compensatory shift of intracellular potassium to balance the sudden and dramatic excess of negatively charged chloride ions in the extracellular space. Severe metabolic effects are unlikely to be clinically detectable or problematic in commonly administered ambulatory doses of 2–20 ml/kg or less. As such, normal saline remains one of the most commonly utilized fluids in medical practice.

In large quantities, balanced salt solutions are not without their own potential for harm, particularly in states of impaired end-organ function, as seen in renal or hepatic failure. Each of these fluids contain a small amount of potassium which was previously believed to be detrimental to patients with impaired renal function given the potential of developing dangerous hyperkalemia. Recent evidence, however, suggests that NS may actually result in a more profound hyperkalemia than balanced salt solutions, likely a result of secondary hyperkalemia [18]. Since their

potassium concentrations approximate normal physiology, moderate volumes of balanced salt solutions may even assist in normalizing hyperkalemia for all but the most severe cases of end-stage renal disease (ESRD) wherein the patient remains completely incapable of eliminating potassium. In the vast majority of cases, a single fluid bolus of 2–20 mL/kg administered over approximately 1–2 h is unlikely to result in any noticeable alterations to serum potassium levels.

For patients with poorly controlled or brittle diabetes, the use of dextrose-containing solutions may lead to hyperglycemia given the sudden increased load of exogenous glucose. Conversely, in cases where a patient becomes hypoglycemic, these same solutions may be clinically beneficial and used for this exact effect.

High-Risk Comorbidities

Conditions that require special consideration for any intravenous fluid infusion include decompensated congestive heart failure (CHF), end-stage renal disease (ESRD) requiring hemodialysis (HD), and poorly controlled hypertension (HTN).

Hypervolemia

Rapid fluid administration in patients with CHF or ESRD may precipitate an acutely hypervolemic state. This state of fluid overload may further predispose the patient severe adverse effects including pulmonary edema and right heart strain, or it may increase the risk that the patient may develop delayed complications in the perioperative period.

Dialysis Complications

For dialysis-dependent patients, total body electrolytes such as serum sodium and potassium, may rise following administration of IVH. The increased burden to correct these imbalances during subsequent HD treatment may predispose the patient to experiencing increased severity of HD-related side effects. These including fluid shifts, nausea, and orthostatic hypotension. In the ambulatory setting, such patients should be considered having an ASA Physical Status Classification Score of 4 and managed accordingly. With regard to fluid administration, total volume of the infusion should be limited to 100 mL.

Severe Hypertension

Preload will rise during IVH as the increased plasma volume fills compliant vascular compartments. In healthy ambulatory adults, fluid rates of 2–20 ml/kg will not likely lead to adverse hypervolemia. On the contrary, this range may provide unique benefits by mitigating the orthostatic hypotension experienced by fasting patients as well as preventing post-operative nausea and vomiting (PONV).

Patients with poorly-controlled HTN, on the other hand, could experience severe hypertensive episodes as a consequence of increased intravascular volume from IVH. Depending on the severity of elevation to blood pressure, a patient's hypertensive episode could lead to dangerous sequelae such as myocardial ischemia or hemorrhagic stroke.

Neurological Injury

When deliberately employed to modify the body's sodium levels, the administration of hypertonic and hypotonic saline requires close regulation. When 3% sodium chloride is used to reduce interstitial cerebral edema, ongoing assessment of the patient through frequent laboratory assays and neurological examinations are critically important to ensure that the patient does not develop devastating complications. A severe consequence of overzealous sodium correction, osmotic demyelination syndrome (ODS; previously referred to as central pontine myelinolysis or CPM) leads to irreversible injury within the pons and other deep brain structures. ODS is a life-threatening condition with the potential to cause long-term neurological injury [19]. Current guidelines recommend that serum sodium be corrected no more rapidly than 8 mmol/L/day.

Increased Urine Production

Natriuresis and increased urine production are expected during and after IVH. Adults receiving as little as 250 cc of isotonic fluid over 1 h may feel the need to void. This normally should not present a problem for the ambulatory patient, except in the cases when anesthetic agents are used, such as during ketamine infusion. Patients who receive hypnotic agents are at increased risk of falls and should be supervised during and after receiving infusions. If there is potential for unsteadiness, a bedside commode or urinal is the safest alternative to ambulation in order to access a distant restroom. The need for bladder catheterization is highly unlikely. Exceptions include patients with an etiology that prevents reliable urination as seen in benign prostate hypertrophy (BPH) or preexisting neurological impairment such as spinal cord injury (SCI).

Hypothermia

Rapid administration of room temperature fluid can contribute to relative hypothermia. This effect is most commonly seen in the setting of massive resuscitation efforts, but healthy ambulatory patients are unlikely to have any adverse clinical effect. Pre-warming intravenous fluid is one method for increasing patient comfort while avoiding temperature changes from the infusion fluid.

Monitoring

In clinical practice, ambulatory patients receiving IVH for pain would most benefit from non-invasive blood pressure monitoring (NIBP). In particular, patients with HTN or peripheral vascular disease (PVD) may develop elevated BP in cases of rapid fluid administration, and use of NIBP may guide adjustments to fluid rate and volume to mitigate associated complications. Additionally, NIBP monitoring of

patients receiving ketamine infusions would alert the provider to the undesired sympathomimetic activity of this medication and inform modifications to the treatment.

The use of pulse oximetry provides multiple valuable data points, including audible pulse rate and a measure of adequate oxygenation. Tachycardia during infusion of ketamine may indicate excessive administration and stimulation of the sympathetic nervous system, signaling the need for modification to infusion rate and dose. Patients with pre-existing pulmonary disease or obstructive sleep apnea (OSA) may be at increased risk of hypoxia when infusions contain sedating medications; in the setting of CHF, pulmonary edema may manifest as decreased oxygenation. Routine use of pulse oximetry in these patients is therefore prudent.

Continuous electrocardiography (EKG) may be considered for patients with known cardiac disease or baseline electrolyte abnormalities. Signs of demand ischemia may be appreciated as depressions of the ST-segment, in particular the precordial leads V3–5 [20]. These leads best evaluate the conduction of the left ventricle, where ischemia is most likely to occur. The best lead for monitoring changes to the P wave, and thus detecting dysrhythmias, is lead II. Standard anesthesia practice involves continuously monitoring leads II and V5, the combination of which is 80% sensitive for the detection of ischemic events. Elevations of serum potassium may be detected by the appearance of peaked T-waves. Such a finding provides an opportunity to correct this imbalance and prevent further complications.

If patients are suspected to be dehydrated, then monitoring urine output (UOP) may be considered. The accuracy of UOP as a surrogate for correcting hypovolemia in these patients is debatable, however, since oliguria from dehydration often continues despite adequate resuscitation in the acute stage. The result of ongoing activity of the renin-angiotensin-aldosterone system (RAAS), this persistent oliguria, therefore, limits the specificity of UOP monitoring to evaluate successful resuscitation. As such, the provider will need to include additional clinical indicators when determining the patient's volume status. In ambulatory patients, measurement of UOP may be accomplished by use of graduated collection basins and urinals.

Diabetic patients may benefit from point-of-care (POC) finger-stick glucometer testing. These patients are at increased risk of hypoglycemia due to pre-infusion fasting, which often precedes treatment using sedating pharmacologic agents.

Algorithm for Intravenous Hydration Regimens

The following algorithm table highlights recommendations for the administration of IVH with particular attention to high-risk patient groups and their potential complications (Table 16.3). While the exact volume and rate of administration of IVH must be tailored to the patient, general recommendations include limiting total volume to 20 mL/kg and continuing the infusion for 1–2 h.

Table 16.3 Algorithm for the management of intravenous hydration

Consideration	Recommendation
Recommended rate of infusion	Volume of infusion: 2–20 mL/kg; Duration of infusion: 1–2 h
History of multiple hospitalizations	Anticipate difficult venous access
History of intravenous drug abuse	Anticipate difficult venous access
History of central venous catheterization for elective procedures	Anticipate difficult venous access
Poorly-controlled diabetes mellitus (DM)	Avoid dextrose-containing solutions
Poorly-controlled hypertension (HTN)	Avoid infusion rates >30 mL/kg/h; Monitor blood pressure closely
Decompensated congestive heart failure (CHF)	Avoid infusion rates >30 mL/kg/h
End-stage renal disease (ESRD)	Avoid infusion rates >30 mL/kg/h; Limit volume ≤ 100 mL
Patients receiving sedating infusions (e.g. Propofol, ketamine)	Avoid ambulation to void by providing bedside urinal; Monitor closely for signs of infiltration

Summary

Intravenous hydration (IVH) may provide relief for headaches due to water restriction or dehydration, though further research is needed to demonstrate efficacy. Despite the lack of high-quality evidence, IVH continues to be a common therapy in the acute setting for low cerebrospinal fluid pressure headaches, such as postdural puncture headache, as well as intractable migraine. IVH is unlikely cause harm except in patients with severe medical comorbidities, where its judicious administration is of paramount importance. Despite a relatively high safety profile, IVH is not a completely benign therapy, and should be approached with the same caution as any intravenous medication. The provider should be vigilant to anticipate and manage complications including those related to placement or failure of the intravenous catheter as well as the physiologic alterations caused by the administered fluid. IVH may have other useful effects in the peri-procedural setting, including prophylaxis for post-operative nausea and vomiting in high-risk patients. IVH will invariably accompany any infusion therapy as the carrier for the active pharmacological agent, thus familiarity with the physiological interplay between the fluid and the patient's body is important regardless of the infusion therapy. As such, parameters including fluid volume and rate of administration should be considered in the development of the patient's treatment plan.

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