Bisphosphonate Infusion Therapy

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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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