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Prevention and Treatment of Postoperative Pain with Particular Reference to Children

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With 7 Figures

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Abstract

Pain therapy is an important aspect of medical practice for patients of all ages, to optimize care, to obtain an adequate quality of life and to improve their general conditions. Pain is among the most prevalent symptoms experienced by patients undergoing surgery. The success of postoperative pain therapy depends on the ability of the clinician to assess the presenting problems, identify and evaluate pain syndromes and formulate a plan for comprehensive continuing care. The prevalence of acute pain has led to the need to develop techniques for the assessment and management of this symptom in order to focus the attention on an interdisciplinary therapeutic approach (including pharmacologic, cognitive-behavioral, psychologic and physical treatment) and on the timing of different interventions (pre and postoperative). In this chapter we describe the principal therapeutic approaches to control pain in post-operative patients, such as non-opioid, opioid and adjuvant analgesics with particular attention in paediatric age. Moreover we report the principal scales to assess the pain intensity in the post-operative period. The need of a multidisciplinatory team and of a pre and postoperative pain management program represents an important goal in order to obtain effective pain relief and optimize pediatric care and rapid recovery. The introduction of a perioperative team service will improve the approach to pain management programs and it is considered the most important challenge for future.

Keywords: Pain; pain assessment; analgesics drugs; patient controlled analgesia; childhood.

Introduction

Pain is among the most prevalent symptoms experienced by patients undergoing surgery. The success of postoperative pain therapy depends on the ability of the clinician to assess the presenting problems, identify and

evaluate pain syndromes and formulate a plan for comprehensive continuing care. This requires familiarity with a range of therapeutic options and an approach to optimise medical care that is responsive to the changing needs of the patient. The formulation of an effective therapeutic strategy for the management of post-operative pain is predicated on a comprehensive assessment of the patient. The assessment should clarify the characteristics of the pain and its impact on function and psychological well-being, identify the pain syndrome and infer the putative mechanisms that may underlie the pain. In addition, the assessment should evaluate both the nature and extent of the underlying disease and identify concurrent problems that are contributing, or may soon contribute, to patient or family distress. The particular therapeutic strategy that evolves from this information depends on the goals of care. These goals are diverse, but can generally be grouped into two broad categories:

1. optimizing comfort
2. maximising function

The relative priority of these goals provides an essential context for therapeutic decision making. The therapeutic strategy should address a prioritized problem list that best serves both the current goals of the patient and the anticipated problems that would benefit from advanced planning. Most postoperative patients can attain satisfactory relief of pain through an approach that incorporates primary treatments, systemic analgesic therapy and, at times, other non-invasive techniques (such as psychological or rehabilitative interventions). Some patients whose pain is refractory to this approach benefit from invasive anaesthetic or other treatments. Such patients should have access to specialists in pain management, who can provide additional expertise in addressing these complex problems. Differently from the adult patients in paediatric age it is more difficult to assess and treat efficaciously the pain and postoperative pain in childhood have been undertreated or not treated. In some areas this practice still exists and is a likely reflection of persistence of myths related to the infant's ability to perceive pain. Such myths include the lack of ability to perceive pain, remember painful experiences and other reasons (Box 1). Recent evidences have documented the deleterious physiologic effects of pain and the beneficial results of efficacious postoperative analgesia both in adult patients and in children. Due to the increasing prevalence of both acute and chronic pain in the paediatric age new techniques for pain management have been developed. In 2001, the American Academy of Paediatrics and the American Pain Society issued a statement to ensure human and competent treatment of pain and suffering in all children and adolescents in order to focus the attention on an interdisciplinary therapeutic approach, including pharmacologic, cognitive-behavioural, psychologic and physical treatments (Box 2) [1]. There is a growing awareness of the effects of unrelieved pain

Box 1. *Reasons for the inadequate management of acute pain in children*

- Idea that pain is merely asymptom and not harmful in itself
- Mistaken impression that analgesia makes accurate diagnosis difficult or impossible
- Fear of the potential for addiction to opioids
- Concerns about respiratory depression and other opioid-related side effects
- Lack of understanding of the pharmacokinetic of analgesic drugs
- Prescriptions for opioids which include the use of inappropriate doses
- Thinking that opioids must not be given more often than 4 hourly
- Patient's difficulties in communicating their need for analgesia

Box 2. *Clinical practice and acute pain: guidelines and major goals*

Guidelines

- A collaborative, interdisciplinary approach to pain control, including all members of the healthcare team
- Assessment and frequent reassessment of the patient's pain
- Use both drug and non-drug therapies to control and/or prevent pain

Major goals

- Reduce the incidence and severity of patient's postoperative pain
- Educate patients about the need to communicate regarding unrelieved pain, so they can receive prompt evaluation and effective treatment
- Enhance patient comfort and satisfaction
- Contribute to fewer postoperative complications and shorter stays after surgical procedures

in children and the need to provide effective pain relief, especially with regard to acute pain. Some principles can be extended to all forms of acute pain, but some of them are particularly decisive in postoperative pain management both in adults and in children (Box 3) [2]. Several studies documented that in children undertreatment after surgery is more common than in adults leading to unnecessary distress and suffering for children and their families [3]. The need of a multidisciplinary team and of a pre and post-operative pain management program represent an important goal in order to obtain effective pain relief and optimize medical care and rapid recovery after post-operative procedures. The introduction of a perioperative team service and the utilization of pain management programs will represent an important challenge for the future.

Box 3. *Priciples of safe and effective acute post-operative pain management*

- Adverse physiological and psychological effects result from unrelieved severe pain
- Proper assessment and pain control require patient involvement
- Pain is best treated early, because established, severe pain is more difficult to treat
- While it is not possible to completely alleviate all pain in the postoperative period, it should be possible to reduce pain to a tolerable or comfortable level
- Postoperative analgesia should be planned preoperatively, with consideration given to the type of surgery, perioperative use of analgesics and regional anaesthetic techniques
- Frequent assessment of pain intensity and charting of analgesia
- Adequate education of all involved in pain management, including the patient
- Formal programmes, protocols and guidelines covering acute pain management

Acute Pain Assessment in Paediatric Age

The pain experience includes physiological, sensory, affective, behavioural, cognitive and sociocultural components. While in adults is more easy to assess the pain simptoms, in children pain assessment should consider age, cognitive level and the presence of eventual disability, type of pain and the situation in which pain is occurring. McGrath on the subject of assessment of pain in children states: ''Measurement of pain should be distinguished from the assessment of pain. Measurement refers to the application of a specific metric to a specific element of pain, usually the intensity of pain. Assessment is a much broader endeavor that includes the measurement of various elements that impact on the pain experience'' [4]. Despite this consideration, there are some commonly used methods of measurement of pain that have been proved to be reliable. Observational and behavioural measures consider child's reaction to pain. Self-report measures rely on the child's description of his experience of pain. Biological measures consider some physiologic parameters that may be modified by the presence of pain, such as heart and respiratory rates, blood pressure, etc. [5]. In infants and non-verbal children, self-report measures are unavailable, but behavioural indices (motor responses, vocalization, facial expressions, crying and complex behavioural responses such as the sleep-wake patterns) can be easily evaluated to assess pain. Different behavioural scales have been validated by several studies that enrolled infants and neonates [6, 7]. Behavioural

ITEM	BEHAVIOR	SCORE	DEFINITION
Cry	*No cry*	1	Child is not crying
	Moaning	2	Child is moaning or quietly vocalizing;silent cry
	Crying	2	Child is crying, but the cry is gentle or whimpering
	Scream	3	Child is in a full-lunged cry;sobbing;may be scored with/whitout complaint
Facial	*Composed*	1	Neutral facial expression
	Grimace	2	Score only if negative facial expression
	Smiling	0	Score only if definite positive facial expression
Child verbal	*None*	1	Child not talking
	Other complaints	1	Child complaints, but not about pain
	Pain complaints	2	Child complaints about pain
	Both complaints	2	Child complaints about pain and about other things
	Positive	0	Child makes any positive statement or talks about other things without complaint
Body	*Neutral*	1	Body (not limbs) is at rest; torso is inactive
	Shifting	2	Body is is in motion in a shifting or serpentine fashion
	Tense	2	Body is arched or rigid
	Shivering	2	Body is shuddering or shaking involuntarily
	Upright	2	Child is in a vertical or upright position
	Restrained	2	Body is restrained
Touch	*Not touching*	1	Child is not touching or grabbing at wound
	Reach	2	Child is reaching for but not touching wound
	Touch	2	Child is gently touching wound or wound area
	Grab	2	Child is grabbing vigorously at wound
	Restrained	2	Child's arms are restrained
Legs	*Neutral*	1	Legs may be in any position but are relaxed
	Squirming/ kicking	2	Definitive uneasy or restless movements in the legs or striking out with feets
	Drawn up/tensed	2	Legs tensed and/or pulled up tightly to body and kept there
	Standing	2	Standing, crouching, or kneeling
	Restrained	2	Child's legs are being held down

Fig. 1. CHEOPS Score. CHEOPS pain score: SUM (points for all 6 parameters), Minimum score: 4 (min pain); Maximum score: 13 (max pain)

parameters, even if non-specific, may be usefully associated to physiologic parameters such as heart rate, cardiac rate, arterial blood pressure, transcutaneous oxygenation and palmar sweating [8–10]. The Children's Hospital of Estern Ontario Pain Scale (CHEOPS) is one of the commonest scales used for postoperative pain management (Fig. 1) [11]. Parents who are able to assess behavioural changes related to discomfort or pain may help differentiate pain from anxiety or stress due to other causes [12, 13]. Children aged 3 to 7 years are increasingly able to describe pain characteristics. Observational scales as well as self-report scales represent useful tools to assess pain in this period of life. Composite measures of pain have been developed combining behavioural and biological items, such as the Objective Pain Scale and the Comfort Scale (Figs. 2, 3). The Objective Pain Scale is used to assess both physiologic parameters and behavioural changes in children that may be modified by the presence of pain or discomfort after procedures and/or postoperative interventions [14, 15]. The Comfort Scale is used to assess the level of sedation and distress in the paediatric intensive care unit, but recent studies have validated this measurement method also in procedural and postoperative pain [16, 17]. Self-

Parameter	Finding	Points
Systolic blood pressure	increase < 20% of preoperative blood pressure	0
	increase 20-30% of preoperative blood pressure	1
	increase > 30% of preoperative blood pressure	2
Crying	not crying	0
	responds to age appropriate nurturing (tender loving care)	1
	does not respond to nurturing	2
Movements	no movements relaxed	0
	restless moving about in bed constantly	1
	thrashing (moving wildly)	2
	rigid (stiff)	2
Agitation	asleep or calm	0
	can be comforted to lessent the agitation (mild)	1
	Cannot be comforted (hysterical)	2
Complains of pain	Asleep	0
	states no pain	0
	Cannot localize	1
	localizes pain	2

Fig. 2. Objective Pain Scale (*OPS*). Minimum score: 0; Maximum score: 10, Maximum score if too young to complain of pain: 8, The higher the score the greater the degree of pain

report measures of pain represent the gold standard in older children who can describe the subjective pain experience [18, 19]. These methods include different strategies such as routine and direct questioning, verbal and non verbal methods (i.e. pictorial scales) and self rating scales. Visual Analogue

ALLERTNESS	Time						
Deeply asleep	1						
Lightly asleep	2						
Drowsy	3						
Fully Awake and alert	4						
Hyper-alert	5						
CALMNESS/AGITATION							
Calm	1						
Slightly anxious	2						
Anxious	3						
Very anxious	4						
Panicky	5						
RESPIRATORY RESPONSE							
No coughing and no spontaneous respiration	1						
Spontaneous respiration with little or no response to ventilation	2						
Occasional cough or resistance to ventilator	3						
Actively breathes against ventilator or coughs regularly	4						
Fights ventilator; coughing or choking	5						
PHYSICAL MOVEMENT							
No movement	1						
Occasional, Slight movement	2						
Frequent, Slight movement	3						
Vigorous movement limited to extremities	4						
Vigorous movement including torso and head	5						
BLOOD PRESSURE (MAP) BASELINE							
Blood pressure below baseline	1						
Blood pressure consistently at baseline	2						
Infrequent elevations of 15% or more (1-3)	3						
Frequent elevations of 15% or more (more than 3)	4						
Sustained elevation ≥ 15%	5						
HEART RATE BASELINE							
Heart rate below baseline	1						
Heart rate consistently at baseline	2						
Infrequent elevations of 15% or more above baseline (1-3) during observation period	3						
Frequent elevations of 15% or more above baseline (more than 3)	4						
Sustained elevation ≥ 15%	5						
MUSCLE TONE							
Muscles totally relaxed; no muscle tone	1						
Reduced muscle tone	2						
Normal muscle tone	3						
Increased muscle tone and flexion of fingers and toes	4						
Extreme muscle rigidity and flexion of fingers and toes	5						
FACIAL TENSION							
Facial muscles totally relaxed	1						
Facial muscle tone normal; no facial muscle tension evident	2						
Tension evident in some Facial muscles	3						
Tension evident throughout Facial muscles	4						
Facial muscles contorted and grimacing	5						

Fig. 3. The Comfort Scale

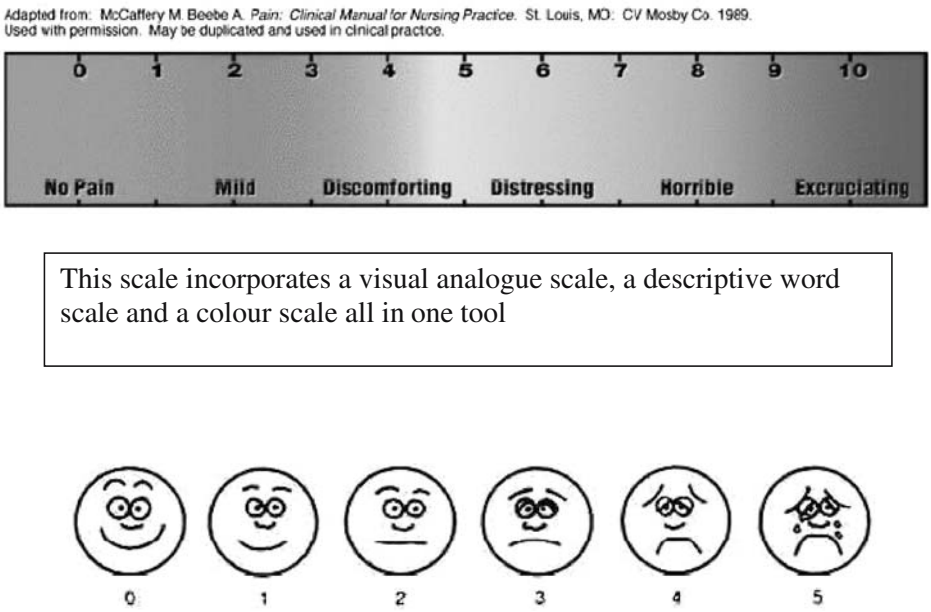

Fig. 4. Visual Analogue Scale (VAS) and Facial Pain Scale

Scale (VAS) and Facial Pain Scale are two of the commonest self rating scales to assess pain intensity in children (Fig. 4) [20, 21]. In the VAS children rate the intensity of pain on a 10 cm line anchored at one end by a label such as ''no pain'' and at the other end ''severe pain''. The scores are obtained by measuring the distance between the ''no pain'' and the patient's mark, usually in millimetres. The VAS has many advantages: it is simple and quick to score, avoids imprecise descriptive terms and provides many measuring points. Disadvantages are represented by the need of concentration and coordination, which can be difficult post-operatively or in children with neurological disorders. Self reported measures require a cognitive and linguistic development related to the capacity to answer to different questions. They are reliable to monitor pain relief in every single patient, while are less specific and effective if utilized to compare different patients. Self reported measures include categorical scales that use words (from four to five) to describe the magnitude of pain. However, in specific categories of patients, they are not useful. Faces scales represent another form of self reported measures: faces express different amounts of distress. The Facial Pain Scale is the commonest used in young children who may have difficulty with more cognitively demanding instruments. The original scale was composed by seven faces without an absolute meaning, but related to children's experience [20]. Different versions exist, based anyway on the same measurement principle [21, 22]. In figure 4 we report one

of them more used in the clinical practice. The Oucher Scale is a variant of the faces scale and is designed to measure pain intensity in children aged 3–12 years [23]. Adequate paediatric pain assessment can improve comfort in ill children and avoids pain undertreatment in several cases. Pain should be measured routinely with appropriated tools related to age and disease. Simple pain measurement methods would improve not only pain relief in children, but would also decrease nurses and health professional workload and create a common language and an adequate communication among the medical and nurse staffs [24].

Specific Aspects of Post-Operative Pain

The perception of acute and post-operative pain is a complex interaction that involves sensory, emotional, and behavioural factors. The role of psychological factors must always be considered to be an important component in the perception and expression of post-operative pain. The biological processes involved in our perception of acute pain are no longer viewed as a simple ''hard-wired'' system with a pure stimulus-response relationship. Trauma to any part of the body, and nerve damage in particular, can lead to changes within other regions of the nervous system, which influence subsequent responses to sensory input. There is increasing recognition that long-term changes occur within the peripheral and central nervous system following noxious input. This plasticity of the nervous system then alters the body's response to further peripheral sensory input. Based on these mechanisms pain relief in postoperative patients represents an important therapeutical aspect, leading to significant physiological benefit. Surgical trauma are associated with an injury response or ''inflammatory response''. Part of the inflammatory response is the release of intracellular contents from damaged cells and inflammatory cells such as macrophages, lymphocytes and mast cells. Nociceptive stimulation also results in a neurogenic inflammatory response with the release of substance P, neurokinin A and calcitonin gene-related peptide (CGRP) from the peripheral terminals of nociceptive afferent fibres. Release of these peptides results in a changed excitability of sensory and sympathetic nerve fibers, vasodilatation, and extravasation of plasma proteins. These interactions result in the release of several inflammatory mediators such as potassium, serotonin, bradykinin, substance P, histamine, cytokines, nitric oxide and products from the cyclooxygenase and lipooxygenase pathways of arachidonic acid. These chemicals then act to sensitize high-threshold nociceptors which results in the phenomenon of peripheral sensitisation [5]. Following sensitization, low-intensity mechanical and thermal stimuli which would not normally cause pain are now perceived as painful. This zone of ''primary hyperalgesia'' surrounding the site of injury is caused by

peripheral changes and is a feature that is commonly observed following surgery and other forms of trauma. Following injury, there is an increased responsiveness to normally innocuous mechanichal stimuli (allodynia) in a zone of ''secondary hyperalgesia'' in uninjured tissue surronding the site of injury. These changes are believed to be a result of processes that occur in the dorsal horn of the spinal cord following injury. This is the phenomenon of central sensitisation [5]. Several changes have been noted to occur in the dorsal horn with central sensitisation. Firstly, there is an expansion in receptive field size so that a spinal neuron will respond to stimuli that would normally be outside the region that respond to nociceptive stimuli. Secondly, there is an increase in the magnitude and duration of the response to stimuli that are above threshold in strength. Lastly, there is a reduction in threshold so that stimuli that are not normally noxious activate neurons that normally transmit nociceptive informations. These changes may be important both in acute pain states such as post-operative pain and in the development of chronic pain syndromes. Transmission of nociceptive information is subject to modulation at several levels of the neuraxis including the dorsal horn. Afferent impulses arriving in the dorsal horn initiate inhibitory mechanisms which limit the effect of subsequent impulses. Inhibition occurs through the effect of local inhibitory interneurons and descending pathways from the brain. In the dorsal horn incoming nociceptive messages are modulated by endogenous and exogenous agents that act on opiod, alpha-adreno-, GABA, and glycine receptors located at pre- and post-synaptic sites. Opioids are widely used and generally efficacious in the management of post-operative pain. Opioid receptors are found both pre- and postsynaptically in the dorsal horn, although the majority are located presynaptically. Activation of presynaptic opioid receptors results in a reduction in the release of neurotransmitters from the nociceptive primary afferent. Activation of alpha-adrenoceptors in the spinal cord has an analgesic effect either by endogenous release of noradrenaline by descending pathways from the brain stem or by exogenous spinal administration of agents such as clonidine. There are a number of alpha-adrenoceptor subtypes and the development of selective alpha-adrenoceptor subtype agonists has the potential to provide effective new analgesic agents with reduced side effects. Both GABA and glycine are involved in inhibition of nociceptive input, and loss of their inhibitory action can result in features of neuropathic pain. Descending inhibition involves the action of endogenous opiod peptides as well as other neurotransmitters, including serotonin, noradrenaline and GABA. Many of the traditional strategies available in acute and post-operative pain management such as the use of opioids and non-opiod drug administration, such as NSAIDs, act via these inhibitory mechanisms. Opioids have traditionally been viewed as centrally acting drugs. However, there is now evidence for

the action of endogenous opioids on peripheral sites following tissue damage. Opioid receptors are transported toward the central terminal in the dorsal horn and toward the periphery. These peripheral receptors then become active following local tissue damage. This occurs with unmasking of opioid receptors and the arrival of immunocompetent cells that possess opioid receptors and have the ability to synthesize opioid peptides. This has led to an interest in the peripheral administration of opioids following surgery or topical administration of morphine. NSAIDs are commonly used for peripheral analgesia and one of their actions is a reduction in the inflammatory response. Agents such as aspirin and other NSAIDs provide their anti-inflammatory action by blocking the cyclooxigenase pathway. Cyclooxigenase exists in two forms, COX1 and COX2. While COX1 is always present in tissues, including the gastric mucosa, COX2 is induced by inflammation. This presents an opportunity for the development of agents that have a selective anti-inflammatory effect without gastric side effects. Selective COX2 inhibitor drugs (e.g. rofecoxib, celecoxib) that may offer analgesia with less gastrointestinal toxicity than NSAIDs have been developed. Besides the peripheral action of NSAIDs, there is increasing evidence that they exert their analgesic effect through central mechanisms [5]. The discovery of the changes associated with the phenomenon of peripheral and central sensitization has led to attempts to prevent these changes occurring. It was hoped that steps which would reduce or abolish noxious imput to the spinal cord during a painful event such as surgery would reduce or minimize spinal cord changes and thereby lead to reduced pain postoperatively. This concept has led to an increasing interest in the use of pre-emptive analgesia. Preemptive analgesia is based on the administration of an analgesic such as opioids and NSAIDs before a painful stimulus generates, so as to prevent the subsequent rebound mechanism [26]. Opioids and NSAIDs have been used alone or in combination and have been administered locally, epidurally, intrathecally or sistemically. Several studies have purported to show that pre-emptive analgesia results in reduced pain, decreased analgesic requirements, improved morbidity and decreased hospital stay [27–30]. However, pre-emptive analgesia may also be important in reducing the incidence and prevention of chronic pain states but further studies are necessary to address this important question. Improvement of post-operative pain control can be achieved by better education for all staff concerned postoperative pain relief and by making the assessment and recording of pain levels part of the routine management of each patient. The best strategy is to reduce or eliminate pain and discomfort with a minimum of side effects. A multidisciplinary acute pain service can ensure an adequate pain assessment and relief using different tools in order to reduce post-operative course with earlier discharge from hospital (Box 4) [31, 32].

Box 4. *Organizational aspects of an anaesthesiology-based postoperative pain programme*

1. Education
- Anaesthetists
- Surgeons
- Nurses
- Patients and families

2. Areas of regular administrative activity
- Mainteinance of clear lines of communication
- Evaluation of equipment (e.g. pumps)
- Economic issues
- Continuous quality improvement
- Pain management-related research

3. Collaboration with nursing services
- Nursing policies and procedures
- Nurses in-service and continuing education
- Definition of roles in patient care
- Continuous quality improvement
- Research activities

4. Elements of documentation
- Preprinted orders
- Procedures
- Protocols
- Bedside pain management flow sheets
- Daily consultation notes
- Educational packages

Post-Operative Pain Management

There is evidence that patients benefit from the use of multimodal, or balanced, analgesia after surgery. NSAIDs, paracetamol, local anaesthetics, adjuvant drugs, and opioids are employed in combination to improve pain relief (Table 1). Multimodal analgesia employs a variety of drugs, given by different routes, to achieve analgesia, with a reduction in the incidence and severity of side effects. NSAIDs contribute significantly to multimodal analgesia and postoperative recovery of the patient by minimizing opioid side effects including the inevitable opioid-induced gastrointestinal stasis that delays the resumption of normal enteral nutrition after surgery. However, the effect on morbidity and mortality has been disappointing in some studies, demonstrating that very good pain control is not automatically associated with an improvement in outcome. Recent studies have suggested

Table 1. *Scientific Evidence for Pharmacological Interventions to Manage Post-operative Pain in Adult Patients*

Intervention	Level of evidence	Comments
NSAIDs		
Oral (alone)	I	Effective for mild to moderate pain. Relatively contraindicated in patients with renal disease and risk or actual coagulopathy. Risk of coagulopathy, gastrointestinal bleeding and other risk factors should be carefully sought
Oral (adjunct to opioid)	I	Potentiating effect resulting in opioid sparing. Caution as above
Parenteral (Ketorolac)	I	Effective for moderate to severe pain. Useful where opioids contraindicated or to produce "opioid sparing", especially to minimize respiratory depression, sedation, and gastrointestinal stasis. Best used as part of a multimodal analgesia regimen
Opioids		
Oral	IV	As effective as parenteral in appropriate doses. Use as soon as oral medication tolerated.
Route of choice		
Intramuscular	I	Has been the standard parenteral route, but injections painful and absorption unreliable. Hence, avoid this route when possible.
Subcutaneous	I	Preferable to intramuscular because of patient comfort and a reduced risk of needlestick injury
Intravenous	I	Parenteral route of choice after major surgery. Suitable for titrated bolus or continuous administration. Significant risk of respiratory depression with inappropriate dosing
PCA (systemic)	I	Intravenous or subcutaneous routes recommended. Good steady level of analgesia. Popular with patients but requires special infusion pumps and staff education.
Epidural and intrathecal		When suitable, provides good analgesia. Risk of respiratory depression (as with opioids by other routes), but (as with opioids by other routes), but sometimes delayed in onset. Requires careful monitoring. Use of infusion pumps requires additional equipment and staff education. Expensive if infusion pumps are employed

Table 1. (*Continued*)

Intervention	Level of evidence	Comments
Local anaesthetics		
Epidural and intrathecal	I	Indications in particular settings. Effective regional analgesia. May blunt "stress response" and aid recovery. Opioid sparing. Addition of opioid to local anaesthetic may improve analgesia. Risks of hypotension, weakness, numbness. Requires careful monitoring. Use of infusion pumps requires additional equipment and staff education. Expensive if infusion pumps are employed
Peripheral nerve block	I	Plexus block, peripheral nerve block and infiltration. Effective regional analgesia. Opioid sparing

that the use of multimodal analgesia after major surgery may improve recovery and thus reduce costs of hospital stay. Several authors have proposed that the "pain-free state" should be employed as a fundamental component of an aggressive regimen of postoperative mobilization and early oral feeding in a process of acute rehabilitation after surgery. Multimodal analgesia employing NSAIDs to minimize opioid requirements has the particular advantage over unimodal systemic opioid administration. In addition, by using non-opioid drugs as part of a balanced analgesic plan, the patient can return to normal enteral nutrition much more quickly by avoiding the undesiderable opioid problems of gastrointestinal stasis, nausea and vomiting. The best approach to post-operative pain therapy is based on pharmacologic protocols, using all drugs involved in post-operative pain relief (Table 1). In fact, a correct use of drugs for pain should control symptoms and achieve a good outcome. As the World Health Organization guidelines support there are two main goals to consider [25]: Pain therapy must be assessed "By the Patient" and "By the Ladder".

By the Patient

Different factors may alter the amount of pain suffered by the individual patient. The general conditions, the patient himself, his disease and psychological factors are important factors to consider in order to start an adequate pain management (Box 5a, 5b). Severe pain can cause a number of changes in an individual behaviour, including increased self absorption

Box 5.

a. Psychological factors affecting pain response
- Cultural differences
- Cognitive appraisal
- Fear and anxiety
- Neuroticism and extroversion
- Perceived control of events
- Coping style
- Attention/distraction

b. Psychological methods for reducing pain
- Placebo and expectation
- Psychological support
- Sensory information
- Relaxation training
- Cognitive coping strategies

and withdrawal from interpersonal contact. Fear and anxiety are the major emotional concomitants of acute pain and are especially pronounced when associated with fear of death. Severe acute pain that remains unrelieved for days may lead to depression and helplessness as a result of patients experiencing a loss of control over their environment. It is now generally agreed that unrelieved severe acute pain exacerbates premorbid tendencies for anxiety, hostility, depression, or preoccupation with health. In a few cases, the inability to cope with pain may create an acute psychotic reaction. However, acute pain is one of the important factors contributing to the development of delirium in intensive care units. For all these reasons psychological approaches are an integral part of the medical care of the patient with pain (Box 5b). All patients can benefit from psychological assessment and support and some are good candidates for specific psychological therapy. Cognitive-behavioural interventions can help some patients decrease the perception of distress engendered by the pain through the development of new coping skills and the modification of thoughts, feelings and behaviours. Relaxation methods may be able to reduce muscular tension and emotional arousal or enhance pain tolerance. Other approaches reduce anticipatory anxiety that may lead to avoidant behaviours or lessen the distress associated with the pain. Approaches that give patients more control are likely to be successful in reducing anxiety and decreasing the requirement for pain and medication. Patient-controlled analgesia (PCA) is a highly successful example (see below). Successful implementation of these approaches in the postoperative patients requires a cognitively intact patient and a dedicated, well-trained clinician.

By the Ladder

Analgesic pharmacotherapy is the mainstay of postoperative pain management. Although concurrent use of other interventions is valuable in many patients and essential in some, analgesic drugs are needed in almost every case. The guiding principle of analgesic management is the individualization of therapy. Through a process of repeated evaluations, drug selection and administration is individualized so that a favourable balance between pain relief and adverse pharmacological effects is achieved and maintained (Table 1). An expert committee convened by the World Health Organization (WHO) has proposed a useful approach to drug selection for acute and chronic pain states, which has become known as the 'analgesic ladder' (World Health Organization 1986) (Fig. 5). The World Federation of Societies of Anaesthesiologist (WFSA) has been developed to treat acute and post-operative pain. Initially, pain can be expected to be severe and may need strong analgesics in combination with local anaesthetic blocks and peripherally acting drugs to be controlled (Fig. 6). When combined with appropriate dosing guidelines, this approach is capable of providing adequate pain relief to patients. Emphasizing that pain intensity

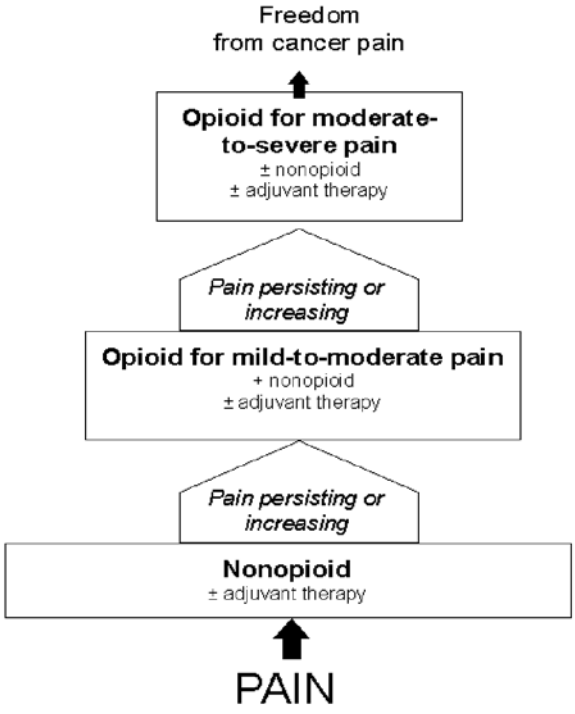

Fig. 5. WHO guidelines for pain therapy

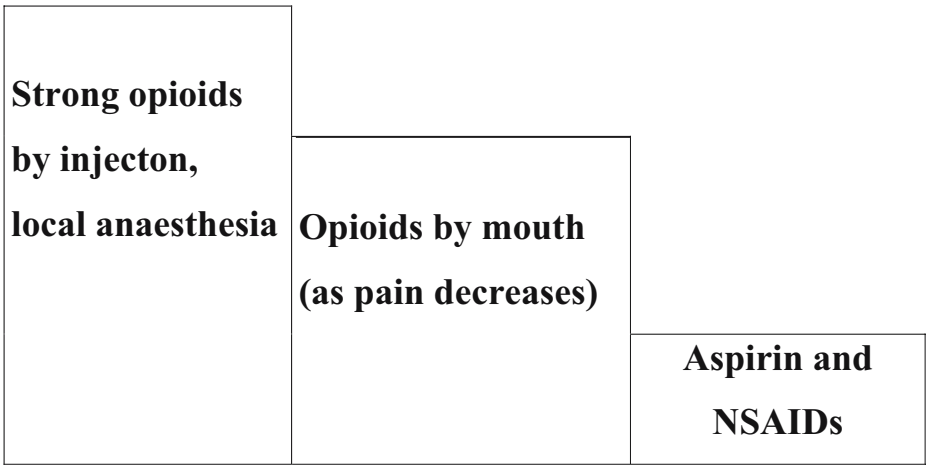

Fig. 6. WFSA analgesic ladder

should be the prime consideration in analgesic selection, the approach advocates three basic steps:

Step 1

Patients with mild to moderate post-operative-related pain should be treated with a non-opioid analgesic, which should becombined with an adjuvant drug if a specific indication exists. For example, a patient with mild to moderate arm pain caused by fracture may benefit when a tricyclic antidepressant is added to acetaminophen.

Step 2

Patients who are relatively opioid naive and present with moderate to severe pain, or who fail to achieve adequate relief after a trial of a non-opioid analgesic, should be treated with an opioid conventionally used to treat pain of this intensity. This treatment is typically accomplished by using a combination product containing a non-opioid (e.g. aspirin or acetaminophen) and an opioid (such as codeine, oxycodone or propoxyphene). This drug can also be co-administered with an adjuvant analgesic.

Step 3

Patients who present with severe pain or fail to achieve adequate relief following appropriate administration of drugs on the second rung of the 'analgesic ladder' should receive an opioid agonist conventionally used for

pain of this intensity. This drug may also be combined with a non-opioid analgesic or an adjuvant drug. Recently, the evidence of the long-term efficacy of this approach has been the subject of criticism. Nonetheless, the approach remains widely used and has been strongly endorsed.

Based on clinical convention, analgesic drugs can be divided into three groups:

1. the non-opioid analgesics
2. the opioid analgesics
3. the adjuvant analgesics (which are drugs with other primary indications that can be effective analgesics in specific circumstances).

Non-Opioid Analgesics

The non-opioid analgesics acetylsalicylic acid, acetaminophen and the nonsteroidal anti-inflammatory drugs (NSAIDs) constitute a heterogeneous group of compounds that differ in chemical structure but share many pharmacological actions (Table 2). These drugs are useful alone for mild to moderate pain (step 1 of the analgesic ladder) and provide additive analgesia when combined with opioid drugs in the treatment of more severe pain [33–42]. Acetylsalicylic acid is a potent inhibitor of cyclooxygenases which is used frequently in medical care. Acetylsalicylic acid may be used as solution or as salt for very fast absorption, distribution, and pain relief. The inevitable irritation of the gastric mucosa may be acceptable in otherwise healthy patients. Acetylsalicylic acid should not be used in pregnant women (bleeding, closure of ductus arteriosus) or children before puberty (Reye's syndrome). Acetaminophen (or paracetamol) is a specific drug with characteristics similar to NSAIDs. Paracetamol has analgesic and antipyretic properties and is devoid of the side effects typical of the NSAIDs [33, 34]. The administration of paracetamol in children and infants for postoperative pain after minor surgery is a well established and safe treatment option, if appropriately used. However, if paracetamol is dosed according to traditional recommendations (about 2 mg/kg body weight) frequently a sufficient analgesic effect cannot be achieved immediately after painful interventions [38]. Recently, a higher initial dose (40 mg/kg body weight) was suggested for effective postoperative pain control [44]. Current recommendations also involve appropriate timing and route of administration of paracetamol to be most effective under different clinical circumstances. The rectal route of administration is unreliable for eliciting an analgesic effect and the oral route is to be prefer. The risk for liver toxicity appears to be very low if the daily paracetamol dose does not exceed 90 mg/kg body weight in healthy children and if specific risk factors of the individual patient are always considered [44]. The NSAIDs can be categorized into four different groups:

Table 2. *Non-Opioid Analgesics*

Chemical class	Generic name
Non-acidic	Acetaminophen
	Nabumetone
	Nemuselide
	Meloxicam
Acidic	
Salicylates	Aspirin
	Diflunisal
	Choline magnesium trisalycilate
	Salsalate
Proprionic acids	Ibuprofen
	Naproxen
	Fenoprofen
	Ketoprofen
	Flurbiprofen
	Oxaprosin
Acetic acids	Indomethacin
	Tolmetin
	Sulindac
	Diclofenac
	Ketorolac
Oxicams	Piroxicam
Fenamates	Mefenamic acid
	Mecolofenamic acid

a. NSAIDs with low potency and short elimination halflife
b. NSAIDs with high potency and short elimination halflife
c. NSAIDs with intermediate potency and elimination halflife
d. NSAIDs with high potency and long elimination halflife

a. NSAIDs With Low Potency and Short Elimination Halflife

The prototype of this group is ibuprofen. The bioavailability of ibuprofen is complete; the elimination is always fast even in patients with severe impairment of the liver or kidney function. Ibuprofen is used in single doses between 200 mg and 0.8 g. Ibuprofen (at low doses) appears particularly useful for treatment of acute and post-operative pain. It may also be used in chronic rheumatic diseases. Ibuprofen is also used as a pure S-enantiomer and this enantiomer is a direct COX-inhibitor. It has not been proven whether the use of the pure S-enantiomer offers any benefit.

b. NSAIDs With High Potency and Short Elimination Halflife

The drugs of this group are standard in the therapy of rheumatic pain. The most widely used compound is diclofenac, which is less active on COX1 than on COX2. This is taken as a reason for the low incidence of gastrointestinal side effects. The limitations of diclofenac result from the usual galenic formulation consisting of a monolythic acid-resistant encapsulation. This may cause retarded absorption of the active ingredient. Moreover, diclofenac encounters first-pass metabolism, which limits oral bioavailability (about 50%). The higher incidents of liver toxicity with diclofenac may result from first-pass metabolization. This group contains important drugs such as indometacin and ketoprofen. All of them show high oral bioavailability and good effectiveness in post-operative pain relief.

c. NSAIDs With Intermediate Potency and Elimination Halflife

This group of drugs is intermediate in potency and speed of elimination. Some forms of migraine and post-operative pain appear as adequate indications for diflunisal and naproxen.

d. NSAIDs With High Potency and Long Elimination Halflife

The fourth group consists of the oxicam drugs (meloxicam, piroxicam, and tenoxicam). These compounds owe their slow elimination to slow metabolization together with a high degree of enterohepatic circulation. The long half-life (days) does not make these oxicam drugs of first choice for acute and post-operative pain. Their main indications is inflammatory pain likely to persist for days (i.e. bone metastases). The high potency and long persistence in the body may be the reason for the higher incidence of serious adverse effects in the gastrointestinal tract and the kidney.

Unlike opioid analgesics, the non-opioid analgesics have a ‘ceiling’ effect for analgesia and produce neither tolerance nor physical dependence. Some of these agents, like acetylsalicylic acid and the NSAIDs, inhibit the enzyme cyclo-oxygenase and consequently block the biosynthesis of prostaglandins, inflammatory mediators known to sensitize peripheral nociceptors [43–45]. A central mechanism is also likely and appears to predominate in acetaminophen analgesia, because its action on PGE2 synthesis. The safe administration of the non-opioid analgesics requires familiarity with their potential adverse effects. Acetylsalicylic acid and the other NSAIDs have a broad spectrum of potential toxicity. Bleeding diathesis due to inhibition of platelet aggregation, gastroduodenopathy (including peptic ulcer disease) and renal impairment are the most common [46–50]. Less common adverse effects include confusion, precipitation of cardiac failure

and exacerbation of hypertension. Particular caution is required in the administration of these agents to patients at increased risk of adverse effects, including the elderly and those with blood clotting disorders, predilection to peptic ulceration, impaired renal function and concurrent corticosteroid therapy [51–55]. Of the NSAIDs, the drugs that are relatively selective cyclo-oxygenase-2 inhibitors (e.g. nabumetone, nemuselide and meloxicam) and those that are non-acetylated salicylates (choline magnesium trisalicylate and salsalate) are preferred in patients who have a predilection to peptic ulceration or bleeding; these drugs have less effect on platelet aggregation and no effect on bleeding time at the usual clinical doses. The development of NSAIDs that are fully selective cyclo-oxygenase-2 inhibitors may provide additional agents with favourable safety profiles that may be preferred in the treatment of the medically frail. Acetaminophen rarely produces gastrointestinal toxicity and there are no adverse effects on platelet function; hepatic toxicity is possible, however, and patients with chronic alcoholism and liver disease can develop severe hepatotoxicity at the usual therapeutic doses. The optimal administration of non-opioid analgesics requires an understanding of their clinical pharmacology. There is no certain knowledge of the minimal effective analgesic dose, ceiling dose or toxic dose for any individual patient with post-operative pain. These doses may be higher or lower than the usual dose ranges recommended for the drug involved. These observations support an approach to the administration of NSAIDs that incorporates both low initial doses and dose titration. Through a process of gradual dose escalation, it may be possible to identify the ceiling dose and reduce the risk of significant toxicity [56]. Several days are needed to evaluate the efficacy of a dose when NSAIDs are used in the treatment of grossly inflammatory lesions, such as arthritis. Since failure with one NSAID can be followed by success with another, sequential trials of several NSAIDs may be useful to identify a drug with a favourable balance between analgesia and side effects [57–60]. Table 3 shows the most commonly NSAIDs used in adults and in children for postoperative pain relief.

Opioid Analgesics

Postoperative pain of moderate or greater intensity should generally be treated with a systemically administered opioid analgesic [1, 5]. The need for analgesia largely depends on the magnitude of the surgical trauma. Generally, the greater the magnitude of surgery, the greater the postoperative discomfort. Major surgery typically requires more aggressive and complex pain management techniques to achieve optimal analgesia. Major surgery usually requires postoperative pain therapy with opioids associated with other drugs, such as oral or parenteral NSAIDs and local anaes-

Table 3. *NSAIDs Commonly Used for Postoperative Pain Relief in Adult and Pediatric Patients*

Drug	Pediatric dosage	Adult dosage	Notes
Acetaminophen or Paracetamol	10–15 mg/kg every 4–5 hr os 20–40 mg/kg every 6 hr rectally or Bolus 20 mg/kg + 15 mg/kg every 4 hr os Bolus 40 mg/kg + 20 mg/kg every 6 hr	325–650 mg every 4–6 hr (max 4 gr/day) os	No gastroenteric or hematologic side effects, No antinflogistic effect
Ibuprofen	5–10 mg/kg every 6–8 hr	200 mg every 3–4 hr os	gastroenteric or hematologic side effects, antinflogistic effect
Naproxen	5 mg/kg every 8–12 hr	0,5–1 gr/day	gastroenteric or hematologic side effects, antinflogistic effect
Ketorolac	Bolus: 1–3 mg/kg every 8 hr Drip: 0.20 mg/kg/hr	10 mg every 4–6 hr os (max 40 mg/day) 10–30 mg every 4–6 hr im or iv (max 90 mg/day)	Renal and hepatic toxicity
Acetylsalicylic acid	10–15 mg/kg every 6–8 hr	0,5–1 gr every 4–6 hr os	Reye's syndrome (children), gastroenteric or hematologic side effects

thetics, administered by different ways (wound infiltration, peripheral nerve block, epidural or iv). Opioids should be used in a multimodal balanced analgesia approach that minimizes opioid requirement and the degree of their side effects [70, 71]. Optimal use of opioid analgesics requires a sound understanding of the general principles of opioid pharmacology, the pharmacological characteristics of each of the commonly used drugs and principles of administration. Fear of potential side effects has limited their use in many countries; this cultural phenomenon seems now to be overcame by the effective opioid titration with the use of incremental doses and a careful monitoring of side effects: this has largely increased their use both in adult patients and especially in children [68, 72]. The mechanism of action of opioid analgesics depends on the interaction of these molecules with specific receptors to which they bind and their intrinsic activity at that receptor [5]. The receptors have a pharmacologic nomenclature: μ (1 and 2), δ, κ. All opioids exert their effects by activating one or more of these receptors. Analgesia involves activation of mu_1 receptors in the brain and *kappa* receptors in the spinal cord. Mu_2 receptors are involved in respiratory depression and intestinal constipation. The contribution of *delta* receptors to analgesia in unclear, and may be more closely related to euphoria. The actions of opioids on receptors can vary depending on the location within the body. For example, a particular opioid may act as an antagonist at the *kappa* receptors in the brain, but as an agonist at the same type of receptors in the large intestines. Activation of Mu_1, Mu_2, and *delta* receptors close potassium channels, while *kappa* receptors are linked to calcium channels. Humans that have become tolerant to activation of one receptor type are not necessarily tolerant to the others.

Opioid Classification

Based on their interactions with the various receptor subtypes, opioid compounds can be divided into agonist, partial agonist, and mixed agonist-antagonist drugs (Table 4). The pure agonist drugs (Table 5) are most commonly used in clinical pain management, both in adult patients and in children (Table 6). The mixed agonist-antagonist opioids (pentazocine, nalbuphine, butorphanol and dezocine) and the partial agonist opioids (buprenorphine) play a minor role in the management of post-operative pain because of the existence of a ceiling effect for analgesia, the potential for precipitation of withdrawal in patients physically dependent to opioid agonists and, in some cases, the problem of dose-dependent psychotomimetic side effects that exceed those of pure agonist drugs. The pure agonist opioid drugs appear to have no ceiling effect for analgesia. As the dose is raised, analgesic effects increase until either analgesia is achieved or the patient loses consciousness. This increase in effect occurs as a log-linear

Table 4. *Opioid Classification*

Agonists	Partial agonists	Mixed agonist/antagonists
Morphine	Buprenorphine	Pentazocine
Codeine		Butorphanol
Oxycodone		Nalbuphine
Hydrocodone		Dezocine
Dihydrocodeine		
Heroin		
Oxymorphone		
Meperidine		
Levorphanol		
Hydromorphone		
Methadone		
Fentanyl		
Sufentanil		
Alfentanil		
Propoxyphene		

function: dose increments on a logarithmic scale yield linear increases in analgesia. In practice, it is the appearance of adverse effects, including confusion, sedation, nausea, vomiting or respiratory depression, that imposes a limit on the useful dose. The overall efficacy of any drug in a specific patient will be determined by the balance between analgesia and side effects that occurs during dose escalation.

'Weak' Versus 'Strong' Opioids

The division of opioid agonists into 'weak' versus 'strong' opioids was incorporated into the original 'analgesic ladder' proposed by the WHO. This distinction was not based on a fundamental difference in the pharmacology of the pure agonist opioids, but rather reflected the customary manner in which these drugs were used. This explains the observation that some opioids that were customarily used for moderate pain (step 2 of the analgesic ladder), such as oxycodone, are also used for severe pain in selected patients. Indeed, the controlled-release formulation of oxycodone is now widely used in the management of severe pain. Conversely, low-dose formulations of controlled-release morphine are suitable for the management of pain of moderate severity. Weak opioids are indicated in mild to moderate pain, usually associated to other drugs such as paracetamol. A weak opioid should be added to, not substituted for, a non opioid and it's important not to "kangaroo" from weak opioid to weak opioid. If a weak

Table 5. *Opioid Agonist Drugs*

Drug	Dose (mg) equianalgesic to 10 mg morphine IM	P.O.	Half-life (hrs)	Duration of action (hrs)	Comments
Codeine	130	200	2–3	2–4	Usually combined with a non-opioids
Oxycodone	15	30	2–3	2–4	Usually combined with a non-opioids
Propoxyphene	100	50	2–3	2–4	Usually combined with a non-opioids. Norpropoxyphene toxicity may cause seizures
Morphine	10	30	2–3	3–4	Multiple routes of administration available. Controlled release available. M6G accumulation in renal failure
Hydromorphone	2–3	7.5	2–3	2–4	No known active metabolites. Multiple routes available
Methadone	10	3–5	15–190	4–8	Plasma accumulation may lead to delayed toxicity. Dosing should be initiated on a p.r.n. basis. When switching to Methadone from another opioid, potency may be much greater than expected; the dose of Methadone should be lowered by 75–90% to account for this
Meperidine	75	300	2–3	2–4	Low oral bioavailability. Normeperidine toxicity limits utility. Containdicated in patients with renal failure and those receiving MAO inhibitors
Oxymorphone	1	10 (p.r)	2–3	3–4	No oral formulation available. Less histamine release
Heroin	5	60	0.5	3–4	High-solubility morphine prodrug
Levorphanol	2	4	12–15	4–8	Plasma accumulation may lead to delayed toxicity
Fentanyl transdermal	Empirically, transdermal fentanyl 100 μg/h = 2–4 mg/h intravenous morphine			48–72	Patches available to deliver 25, 50, 75 and 100 μg/h

Table 6. *Opioids Commonly Used for Postoperative Pain Relief in Children*

Drug	Iv/sc starting dose	Oral starting dose	Notes
Codeine	—	0.5–1 mg/kg every 3–4 hr	Nausea, vomiting
Idromorphone	Bolus: 0.015 mg/kg every 2–4 hr Drip: 0.006 mg/kg/hr	0.06 mg/kg every 3–4 hr	Nausea, vomiting, urinary retention
Morphine	Bolus: 0.05–0.1 mg/kg every 2–4 hr Drip: 0.03 mg/kg/hr	0.15–0.3 mg/kg every 4 hr	Nausea, vomiting, urinary retention, pruritus
Fentanyl	Bolus: 0.5–1 γ/kg every 1–2 hr Drip: 0.5–3.0 γ/kg/hr	—	Nausea, vomiting, urinary retention, pruritus, respiratory depression
Remifentanyl	Bolus: 0.1–0.5 γ/kg every 1 h Drip: 0.1–0.25 γ/kg/min	—	Nausea, vomiting, urinary retention, pruritus, respiratory depression
Sufentanyl	Bolus: 0.2 γ/kg every 1 h Drip: 0.1–0.5 γ/kg/min	—	Respiratory depression, haemodynamic alterations

opioid is inadequate when given regularly, the right step is to change to strong opioids.

Factors in Opioid Selection

The factors that influence opioid selection in post-operative pain states include pain intensity and the presence of co-existing disease.

Pain Intensity

Patients with moderate pain are conventionally treated with a combination product containing acetaminophen or aspirin plus codeine, dihydrocodeine, hydrocodone, oxycodone and propoxyphene. The doses of these combination products can be increased until the customary maximum dose of the non-opioid co-analgesic is attained (e.g. 4000 mg acetaminophen). Beyond this dose, the opioid contained in the combination product could be increased as a single agent or the patient could be switched to an opioid conventionally used for severe pain. New opioid formulations may improve the convenience of drug administration for patients with moderate pain.

These include controlled-release formulations of codeine, dihydrocodeine, oxycodone and tramadol. In some countries controlled-release morphine is available as a 10 mg tablet, which may also be used to treat moderate pain in the opioid-naive patient. The opioid drugs available to treat severe pain vary from country to country. Many countries provide clinicians with numerous options. In the United States, for example, patients who present with severe pain can be treated with morphine, hydromorphone, oxycodone, oxymorphone, fentanyl, methadone or levorphanol. As discussed previously, the agonist-antagonist opioids (e.g. pentazocine) are not preferred in the management of post-operative pain. Similarly the pharmacological characteristics of meperidine limit its role in the postoperative patients because its important side effects as tremulousness, multifocal myoclonus and, occasionally, seizures. Selective toxicity of meperidine can also occur following administration to patients receiving monoamine oxidase inhibitors. This combination may produce a syndrome characterized by hyperpyrexia, muscle rigidity and seizures, which may occasionally be fatal. The pathophysiology of this syndrome is related to excess availability of serotonin at the 5HT^ receptor in the central nervous system. Some patients will require sequential trials of several different opioids before a drug which is effective and well tolerated is identified. The frequency with which this strategy is needed is unknown, but it is estimated to be in the range of 15–30% of patients. The existence of different degrees of incomplete crosstolerance to various opioid effects (analgesia and side effects) may explain the utility of these sequential trials. To date, there are no data to suggest a specific order for opioid rotation. It is strongly recommended that clinicians be familiar with at least three opioid drugs used in the management of severe pain and have the ability to calculate appropriate starting doses using equianalgesic dosing data (Table 5).

Co-Existing Disease

Pharmacokinetic studies of meperidine, pentazocine and propoxyphene have revealed that liver disease may decrease the clearance and increase the bioavailability and half-lives of these drugs. These changes may eventuate in plasma concentrations higher than normal. Although mild or moderate hepatic impairment has only minor impact on morphine clearance, advanced disease may be associated with reduced elimination. Patients with renal impairment may accumulate the active metabolites of propoxyphene (norpropoxyphene), meperidine (normeperidine) and morphine (morphine-6-glucuronide). In the setting of renal failure or unstable renal function, titration of these drugs requires caution and close monitoring. If adverse effects appear, a switch to an alternative opioid is often recommended.

Selecting the Appropriate Route of Systemic Opioid Administration

Opioids should be administered by the least invasive and safest route capable of providing adequate analgesia.

Non-Invasive Routes

The oral route of opioid administration is the preferred approach in routine practice. Alternative routes are necessary for patients who have impaired swallowing or gastrointestinal dysfunction, those who require a very rapid onset of analgesia and those who are unable to manage either the logistics or side effects associated with the oral route. For highly tolerant patients, the inability to prescribe a manageable oral opioid programme due to an excessive number of tablets or volume of oral solution may be an indication for the use of a non-oral route. For patients who do not require very high opioid doses, non-invasive alternatives to the oral route of opioid administration include the rectal, transdermal and sublingual routes. Rectal suppositories containing oxycodone, hydromorphone, oxymorphone and morphine have been formulated and controlled-release morphine tablets can also be administered per rectum. The potency of opioids administered rectally is believed to approximate oral administration. Fentanyl is the only opioid available as a transdermal preparation. The fentanyl transdermal system consists of a drug reservoir that is separated from the skin by a copolymer membrane that controls the rate of drug delivery to the skin surface such that the drug is released into the skin at a nearly constant amount per unit time. There is some interindividual variability in fentanyl bioavailability by this route and this phenomenon, combined with large differences in elimination pharmacokinetics, necessitates dose titration in most cases. Transdermal patches capable of delivering 25, 50, 75 and 100 μg/h are available. Multiple patches may be used simultaneously for patients who require higher doses. At the present time, the limitations of the transdermal delivery system include its cost and the requirement for an alternative short-acting opioid for breakthrough pain. Sublingual absorption of any opioid could potentially yield clinical benefit, but bioavailability is very poor with drugs that are not highly lipophilic and the likelihood of an adequate response is consequently low. Sublingual buprenorphine, a relatively lipophilic partial agonist, can provide adequate relief of mild to moderate postoperative pain. Both fentanyl and methadone are relatively well absorbed through the buccal mucosa and sublingual administration of an injectable formulation is occasionally performed in the relatively opioid-naive patient who transiently loses the option of oral dosing. Overall, however, the sublingual route has limited value due to the lack of formulations, poor absorption of most drugs and the inability to

deliver high doses or prevent swallowing of the dose. An oral transmucosal formulation of fentanyl, which incorporates the drug into a candy base, is under evaluation. Studies in cancer patients suggested that it is useful and that it can provide rapid and very effective relief of breakthrough pain.

Invasive Routes

For patients undergoing a trial of systemic drug administration, a parenteral route must be considered when the oral route is precluded or there is need for rapid onset of analgesia, or a more convenient regimen. Repeated parenteral bolus injections, which may be administered by the intravenous (IV), intramuscular (IM) or subcutaneous (SC) routes, may be useful in some patients but are often compromised by the occurrence of prominent 'bolus' effects (toxicity at peak concentration and/or pain breakthrough at the trough). Repetitive IM injections are a common practice, but they are painful and offer no pharmacokinetic advantage; their use is not recommended. Repeated bolus doses without repeated skin punctures can be accomplished through the use of an indwelling IV or SC infusion device. To deliver repeated SC injections, a 27-gauge infusion device (a 'butterfly') can be left under the skin for up to a week. Intravenous bolus administration provides the most rapid onset and shortest duration of action. Time to peak effect correlates with the lipid solubility of the opioid and ranges from 2–5 minutes for methadone to 15–30 minutes for morphine and hydromorphone. This approach is commonly applied in two settings:

1. to provide parenteral opioids to patients who already have venous access and are unable to tolerate oral opioids;
2. to treat very severe pain, for which IV doses can be repeated at an interval as brief as that determined by the time to peak effect, if necessary, until adequate relief is achieved.

Continuous parenteral infusions are useful for many patients who cannot be maintained on oral opioids. Long-term infusions may be administered IV or SC. In practice, the major indication for continuous infusion occurs among patients who are unable to swallow or absorb opioids. Continuous infusion is also used in some patients whose high opioid requirement renders oral treatment impractical. Continuous SC infusion is often used for ambulatory postoperative patients. A range of pumps is available, which vary in complexity, cost and ability to provide patient-controlled 'rescue doses' as an adjunct to a continuous basal infusion. Opioids suitable for continuous SC infusion must be soluble, well absorbed and non-irritant. Experience has been reported with heroin, hydromorphone, oxymorphone, morphine and fentanyl. Methadone appears to be relatively irritating and is not recommended. To maintain the comfort of an infusion site, the SC infusion rate should not exceed 5 cc/hr. Patients who require high doses

may benefit from the use of concentrated solutions. In selected cases, concentrated opioid solutions can be compounded specifically for continuous SC infusion. Subcutaneous infusion, like repeated SC bolus injections, can usually be administered using a 27-gauge 'butter-fly' needle. The infraclavicular and anterior chest sites provide the greatest freedom of movement for patients, but other sites may be used. A single infusion site can usually be maintained for 5–7 days. Occasional patients develop focal erythematous swelling at the site of injection; this appears to be a common complication with methadone and has also been described with morphine and hydromorphone. Continuous SC delivery of drug combinations may be indicated when nausea, anxiety or agitation accompanies pain. An antiemetic, neuroleptic or anxiolytic may be combined with an opioid, provided that it is non-irritant, miscible and stable in combined solution. Experience has been reported with metoclopromide, haloperidol, scopolamine, cyclizine, methotrimeprazine, chlorpromazine and midazolam. In some circumstances, continuous IV infusion may be the most appropriate way of delivering an opioid. The need for very large doses, or treatment with methadone, may suggest the utility of this approach. If continuous IV infusion is to be continued on a long-term basis, a permanent central venous port is recommended.

Scheduling of Opioid Administration

The schedule of opioid administration should be individualized to optimize the balance between patient comfort and convenience. 'Around the clock' dosing and 'as needed' s dosing both have a place in clinical practice.

'Around the Clock' Dosing

Patients with severe post-operative pain generally benefit from scheduled 'around the clock' dosing, which can provide the patient with continuous relief by preventing the pain from recurring. Clinical vigilance is required, however, when this approach is used in patients with no previous opioid exposure and when administering drugs that have long half-lives (methadone or levorphanol) or produce metabolites with long half-lives (e.g. morphine-6-glucuronide and norpropoxyphene). In the latter situations, delayed toxicity may develop as plasma drug (or metabolite) concentrations rise toward steady state levels. Most patients who receive an 'around the clock' opioid regimen should also be provided a so-called 'rescue dose', which is a supplemental dose offered on an 'as needed' basis to treat pain that breaks through the regular schedule. The frequency with which the rescue dose can be offered depends on the route of administration and the time to peak effect for the particular drug. Oral rescue doses are usually

offered up to every 1–2 hours and parenteral doses can be offered as frequently as every 15–30 minutes. The integration of 'around the clock' dosing with 'rescue doses' provides a method for safe and rational stepwise dose escalation, which is applicable to all routes of opioid administration. Patients who require more than 4–6 rescue doses per day should generally undergo escalation of the baseline dose. The quantity of the rescue medication consumed can be used to guide the dose increment. Controlled-release preparations of opioids can lessen the inconvenience associated with the use of 'around the clock' administration of drugs with a short duration of action. Currently, controlled-release formulations are available for administration by the oral, transdermal and rectal routes. The largest experience has been reported with oral controlled-release morphine preparations with 8–12 hours' duration of effect. Other controlled-release formulations include once-daily morphine preparations, controlled-release morphine suppositories and liquid suspension, transdermal fentanyl, and controlled-release tablets of oxycodone, hydromorphone, codeine and dihydrocodeine. Clinical experience suggests that controlled-release formulations should not be used to rapidly titrate the dose in patients with severe pain. The time required to approach steady-state plasma concentration after dosing is initiated or changed (at least 24 hours) may complicate efforts to rapidly identify the appropriate dose. Repeat-dose adjustments for patients with severe pain are performed more efficiently with short-acting preparations, which may be changed to a controlled-release preparation when the effective 'around the clock' dose is identified.

'As Needed' Dosing

In some situations, opioid administration on an 'as needed' basis, without an 'around the clock' dosing regimen, may be beneficial. In the opioid-naive patient, 'as needed' dosing may provide additional safety during the initiation of opioid therapy, particularly when rapid dose escalation is needed or therapy with a long half-life opioid such as methadone or levorphanol is begun. 'As needed' dosing may also be appropriate for patients who have rapidly decreasing analgesic requirement or intermittent pain separated by pain-free intervals.

Patient-Controlled Analgesia

Patient-controlled analgesia (PCA) generally refers to a technique of parenteral drug administration in which the patient controls an infusion device that delivers a bolus of analgesic drug 'on demand' according to parameters set by the physician. Use of a PCA device allows the patient to overcome variations in both pharmacokinetic and pharmacodynamic fac-

tors by carefully titrating the rate of opioid administration to meet individual analgesic needs. Although is should be recognized that the use of oral 'rescue doses' is, in fact, a form of PCA, the term is not commonly applied to this situation. Long-term PCA in postoperative patients is most commonly accomplished via the intravenous route using an ambulatory infusion device. In most cases, PCA is added to a basal infusion rate and acts essentially as a rescue dose. Rare patients have benefited from PCA alone to manage episodic pain characterized by an onset so rapid that an oral dose could not provide sufficiently prompt relief. Long-term intravenous PCA can be used for patients who require doses that cannot be comfortably tolerated via the subcutaneous route or in those who develop local reactions to subcutaneous infusion. PCA has also been applied to spinally administered opioids and non-opioid approaches such as nitrous oxide. In pediatric age PCA is recommended for children of 8 years or more, without disabilities, in whom moderate to severe pain is anticipated for 24 hours or more. Most children over the age of 7 years understand the PCA concept, and sometimes even younger children can learn to use PCA, but some may not have the cognitive or emotional resources to use it. In children as young as 5 or 6 years PCA has also been used, however pain relief is not always satisfactory because of poor patient understanding. In these patients Nurse or Parent Controlled Analgesia (NCA/PCA) represent a more suitable modality of drug administration. As continuous infusion, PCA allows a steady analgesic serum concentrations with safety and efficacy in pain control (Fig. 7) [90]. The use of a background infusion of opioids in PCA therapy is controversial. It might provide better analgesic during sleep but this is not strongly supported by literature. However it may increase the occurrence of adverse effects such as nausea and respiratory depression [87, 88]. Morphine is the most common drug used in PCA, followed by Fentanyl and Hydromorphone [88–91]. The selection of opioid used in PCA is perhaps critical than the appropriate selection of parameters such as bolus dose, lockout and background infusion rate (Table 7) [91]. PCA dosage regimens must be individualized on the basis of pain intensity and monitoring pain parameters must be age appropriate. Monitoring involves measurements of respiratory rate, level of sedation and oxygen saturation. Efficacy of PCA therapy is assessed by self-reporting, visual analogue scales, faces pain scales and usage pattern. The effectiveness of analgesic techniques may be limited by the incidence and severity of adverse effects; potential adverse effects of PCA therapy, including respiratory depression, nausea, vomiting, and pruritus, can be prevented or controlled by the use of adjuvant drugs and by careful titration. The patient should be instructed in the use of PCA prior to coming to operating room or even in the anaesthetic room before induction. Clinicians must become aware on age-related and developmental differences in

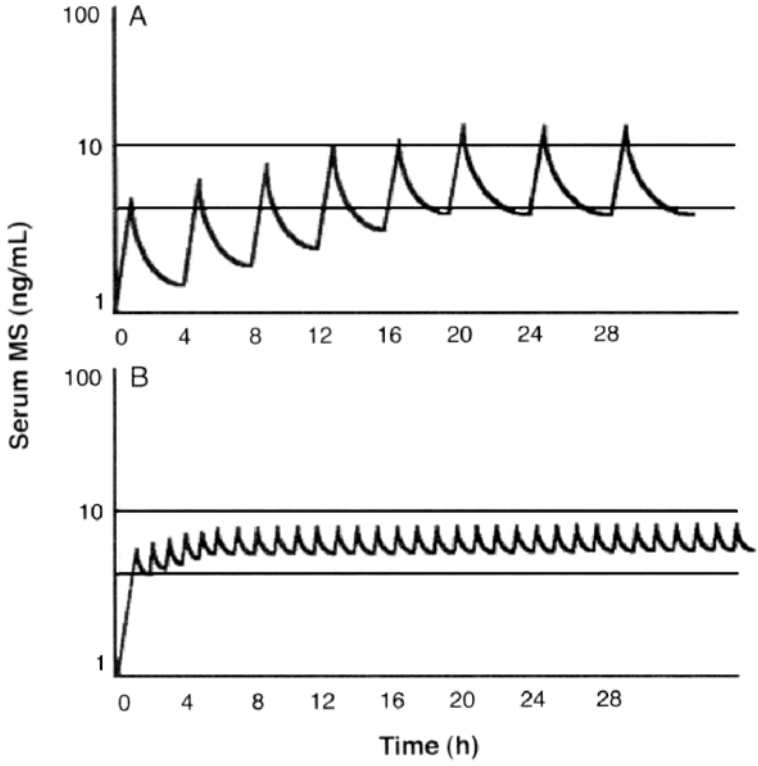

Fig. 7. Opioids plasma concentration following bolus or PCA administration. (A) bolus infusion; (B) PCA administration

Table 7. *PCA protocol with morphine*

PCA protocol	Purpose	Initial dose recomandations (Morphine)
Loading dose	Obtain immediate pain control	0.05 to 0.1 mg/kg max 10 mg
Background infusion (basal rate)	To mantain pain control	0.01 to 0.02 mg/kg/hr
Interval dose (PCA dose)	A bolus interval dose to tritate pain control by the patient himself	0.01 to 0.02 mg/kg
Lockout	To prevent overdose	6–15 minutes
4 hours maximum	To prevent overdose	0.25 to 0.35 mg/kg

the pharmacokinetic, pharmacodynamic and monitoring parameters for the patients with PCA therapy. To date, safety and efficacy of PCA also in paediatric patients has been established and a role of this procedure has been proposed in postoperative pain management as well as burns, oncology and palliative care.

Management of Opioid Adverse Effects

Successful opioid therapy requires that the benefits of analgesia clearly outweigh treatment-related adverse effects. This implies that a detailed understanding of adverse opioid effects and the strategies used to prevent and manage them are essential skills for all involved in postoperative pain management. The pathophysiological mechanisms contributing to adverse opioid effects are incompletely understood. The appearance of these effects depends on a number of factors, including patient age, extent of disease, concurrent organ dysfunction, prior opioid exposure, the route of drug administration, and the adverse drug interactions. The potential for additive side effects and serious toxicity from drug combinations must be recognized. The sedative effect of an opioid may add to that produced by numerous other centrally acting drugs, such as anxiolytics, neuroleptics and antidepressants. Likewise, drugs with anticholinergic effects probably worsen the constipatory effects of opioids. As noted previously, a severe adverse reaction, including excitation, hyperpyrexia, convulsions and death, has been reported after the administration of meperidine to patients treated with a monoamine oxidase inhibitor. The most frequent side effects of opioid drugs are represented by respiratory depression, nausea and vomiting, urinary retention, and physical dependence.

Respiratory Depression

Respiratory depression is potentially the most serious adverse effect of opioid therapy. Although these drugs may impair all phases of respiratory activity (rate, minute volume and tidal exchange), a compensatory increase in respiratory rate may obscure the degree of respiratory effect. This phenomenon explains the observation that patients who appear to have normal respiration during opioid therapy may be predisposed to respiratory compromise if any pulmonary insult occurs. Clinically significant respiratory depression is always accompanied by other signs of central nervous system depression, including somnolence and mental clouding. Respiratory compromise accompanied by tachypnoea and anxiety is never a primary opioid event. With repeated opioid administration, tolerance appears to develop rapidly to the respiratory depressant effects of the opioid drugs. As a result, opioid analgesics can be used in the management of post-

operative pain without significant risk of respiratory depression. Indeed, clinically important respiratory depression is a very rare event in the postoperative patient whose opioid dose has been titrated against pain. When respiratory depression occurs in such patients, alternative explanations (e.g. pneumonia or pulmonary embolism) should be sought. Opioid-induced respiratory depression can occur, however, if pain is suddenly eliminated (such as may occur following neurolytic procedures) and the opioid dose is not reduced. This latter observation suggests that patients whose respiratory function is well compensated following repeated opioid administration do not entirely lack opioid effect on respiration, but rather have respiratory function that reflects a balance between ongoing opioid effects and factors that increase the respiratory drive, including pain, anxiety and alertness. When respiratory depression occurs in patients on opioid therapy, administration of the specific opioid antagonist naloxone usually improves ventilation. Naloxone is a potent pure semisynthetic opioid antagonist and it is used to reduce the effects of opioids and treat opioid overdoses. It has a high affinity for morphine receptors sites and reverses the effect of opioid analgesics by displacement. The degree of displacement is dose related [5]. When respiratory depression is observed, an initial dose of naloxone 2–4 μg/kg should be given and repeated to a total of 10 μg/kg. Duration of action of naloxone is shorter than the most opioids and a continuous infusion may be required to mantein reversal. Naloxone can precipitate a severe abstinence syndrome and should be administered only if strongly indicated. If the patient is bradypnoeic but readily arousable and the peak plasma level of the last opioid dose has already been reached, the opioid should be withheld and the patient monitored until improved. If severe hypoventilation occurs (regardless of the associated factors that may be contributing to respiratory compromise) or the patient is bradypnoeic and unarousable, naloxone should be administered. In the comatose patient, it may be prudent to place an endotracheal tube to prevent aspiration following administration of naloxone.

Nausea and Vomiting

Opioids may produce nausea and vomiting through both central and peripheral mechanisms. These drugs stimulate the medullary chemoreceptor trigger zone, increase vestibular sensitivity and have effects on the gastrointestinal tract (including increased gastric antral tone, diminished motility and delayed gastric emptying). In ambulatory patients, the incidence of nausea and vomiting has been estimated to be 10–40% and 15–40%, respectively. The likelihood of these effects is greatest at the start of opioid therapy. With the initiation of opioid therapy, patients should be informed that nausea can occur and that it is usually transitory and controllable.

Routine prophylactic administration of an antiemetic is not necessary, except in patients with a history of severe opioid-induced nausea and vomiting, but patients should have access to an antiemetic at the start of therapy if the need for one arises. Anecdotally, the use of prochlorperazine and metoclopramide has usually been sufficient. In patients with more severe or persistent symptoms, the most appropriate antiemetic treatment may be suggested by the clinical features. For nausea associated with early satiety, bloating or postprandial vomiting, all of which are features of delayed gastric emptying, metoclopramide is the most reasonable initial treatment. Patients with vertigo or prominent movement-induced nausea may benefit from the use of an antivertiginous drug such as scopolamine or meclizine. If signs of neither gastroparesis nor vestibular dysfunction are prominent, treatment is usually began with a neuroleptic, such as prochlorperazine or metoclopramide. Drug combinations are sometimes used and, in all cases, doses are escalated if initial treatment is unsuccessful. If these drugs are ineffective at relatively high doses, other options include trials of alternative opioids or treatment with antihistamines (e.g. hydroxyzine), other neuroleptics (e.g. haloperidol, chlorpromazine or droperidol), benzodiazepines (e.g. lorazepam) or steroids (e.g. dexamethasone) or the new serotonin antagonists (e.g. ondansetron).

Urinary Retention

Opioid analgesics increase smooth muscle tone and can occasionally cause bladder spasm or urinary retention (due to an increase in sphincter tone). This is an infrequent problem that is usually observed in elderly male patients. Tolerance can develop rapidly but catheterization may be necessary to manage transient problems. Rare patients appear to benefit from co-administration of either a cholinomimetic drug (e.g. bethanecol) or an a-adrenergic antagonist (e.g. terazocin).

Physical Dependence

Physical dependence is a pharmacological property of opioid drugs defined by the development of an abstinence (withdrawal) syndrome following either abrupt dose reduction or administration of an antagonist. Despite the observation that physical dependence is most commonly observed in patients taking large doses for a prolonged period of time, withdrawal has also been observed in patients after low doses or short duration of treatment. Occasionally, patients who are switched from a pure agonist opioid to transdermal fentanyl will develop an abstinence syndrome within the first 24 hours, presumably as a result of a delay in establishing blood levels after the transdermal system is placed. Physical dependence rarely becomes

a clinical problem if patients are warned to avoid abrupt discontinuation of the drug; a tapering schedule is used if treatment cessation is indicated and opioid antagonist drugs (including agonist-antagonist analgesics) are avoided.

Adjuvant Analgesics

The term 'adjuvant analgesic' describes a drug that has a primary indication other than pain but is analgesic in some conditions. A large group of such drugs, which are derived from diverse pharmacological classes, is now used to manage non-malignant pain. In the post-operative patients, these drugs may be combined with primary analgesics in any of the three steps of the 'analgesic ladder' to improve the outcome for patients who cannot otherwise attain an acceptable balance between relief and side effects. The potential utility of an adjuvant analgesic is usually suggested by the characteristics of the pain or by the existence of another symptom that may be amenable to a non-analgesic effect of the drug. Whenever an adjuvant analgesic is selected, differences between the use of the drug for its primary indication and its use as an analgesic must be appreciated. Because the nature of dose-dependent analgesic effects has not been characterized for most of these drugs, dose titration is reasonable with virtually all. Low initial doses are appropriate given the desire to avoid early side effects. The use of low initial doses and dose titration may delay the onset of analgesia, however, and patients must be forewarned of this possibility to improve compliance with the therapy. There is great interindividual variability in the response to all adjuvant analgesics. Although patient characteristics, such as advanced age or coexistent major organ failure, may increase the likelihood of some (usually adverse) responses, neither favourable effects nor specific side effects can be reliably predicted in the individual patient. Furthermore, there is remarkable intraindividual variability in the response to different drugs, including those within the same class. These observations suggest the potential utility of sequential trials of adjuvant analgesics. The process of sequential drug trials, like the use of low initial doses and dose titration, should be explained to the patient at the start of therapy to enhance compliance and reduce the distress that may occur if treatments fail. In the management of postoperative pain, adjuvant analgesics can be broadly classified based on conventional use. The adjuvant drugs more frequently used in post-operative pain are corticosteroids, topical and local anaesthetics, neuroleptics and benzodiazepines.

Corticosteroids

Corticosteroids are among the most widely used adjuvant analgesics. They have been demonstrated to have analgesic effects in different conditions to

significantly improve quality of life and to have beneficial effects on appetite, nausea, mood and malaise. The mechanism of analgesia produced by these drugs may involve anti-oedema effects, anti-inflammatory effects and a direct influence on the electrical activity in damaged nerves. The relative risks and benefits of the various corticosteroids are unknown and dosing is largely empirical. In the United States, the most commonly used drug is dexamethasone, a choice that gains theoretical support from the relatively low mineralocorticoid effect of this agent. Dexamethasone has also been conventionally used for raised intracranial pressure and spinal cord compression. Prednisone, methylprednisolone and prednisolone have also been widely used for other indications. Patients who experience pain and other symptoms may respond favourably to a relatively small dose of corticosteroid (e.g. dexamethasone 1–2 mg twice daily). In some settings, however, a high-dose regimen may be appropriate. Although high steroid doses are more likely to lead to adverse effects, clinical experience with this approach has been favourable. Although the effects produced by corticosteroids in patients with postoperative pain are often very gratifying, side effects are potentially serious and increase with prolonged usage. The varying constellations of adverse effects associated with brief or prolonged administration or with the withdrawal of these drugs following long-term use are widely appreciated. The risk of peptic ulcer is approximately doubled in patients chronically treated with corticosteroids. Several risk factors for peptic ulceration have been identified: relatively high dose, previous history of peptic ulceration, and concurrent administration of an NSAID. In general, the combined administration of a corticosteroid and an NSAID should be avoided. Patients who are predisposed to peptic ulcer disease can be considered for ulcer prophylaxis. Active peptic ulcer disease and systemic infection are relative contraindications to the use of corticosteroids as adjuvant analgesics.

Topical and Local Anaesthetics

Local anaesthetics are amazing drugs now commonly used in prevention and management of post-operative pain. Injected into tissue, around a nerve or for a regional block, they produce reversible block. For some operations, as inguinal hernia repair, there is proven advantage of regional over general anaesthesia. The use of local anaesthetics can produce reduced blood loss, faster surgery, reduced morbidity and faster rehabilitation. Local infiltration, blockade of peripheral nerves and plexuses, epidural blockade and regional analgesia represent the most frequent techniques adopted. Lidocaine and Bupivacaine are the most common local anaesthetics used in clinical practice. Particular attention to maximum drug dosing is required; excessive doses can cause seizures, cardiac depres-

sion and rhythm anomalies [5, 92]. Often local anaesthetic are combinated with epidural opioids to provide reliable analgesia in several pain contexts and extradural infusions of these drugs are used widely now for post-operative analgesia. Epidural local anaesthetics and opioids have been used for many years in the management of acute post-operative pain, and trauma. Several studies have confirmed synergism between local anaesthetics and opioids and support what has been observed clinically; that low doses of local anaesthetic and opioid can produce good analgesia. The mechanism of the synergy is not know. It may be that the local anaesthetic, by reducing the afferent input, is moving the opioid dose-respone to the right. Clinical observations suggest that chronic infusion of these two drugs can produce selective blockade, blocking pain fibers while leaving other sensory input intact. The adverse effects of these two drug classes are different. Epidural local anaesthetics can produce hypotension because of sympathetic blockade. Epidural opioids can produce delayed respiratory depression, urinary retention, priritus, nausea and vomiting. The epidural combination of these two drugs can produce pain relief, and the synergism between the drug classes offers the potential of effective analgesia at low doses of the components, minimizing the adverse effects of both. A clear demonstration of the advantage of the combination of local anaesthetic and opioid was seen in a comparison of 0.125% bupivacaine in saline, diamorphine 0.5 mg in 15 ml and diamorphine mixed with 0.125% bupivacaine infused for pain after major gynaecological surgery. The combination produced significantly superior analgesia to either of its component alone, without major side effects. Giving the diamorphine intravenously with epidural bupivacaine was significantly less effective than giving the same dose epidurally in combination with epidural bupivacaine. Three strategies in dosage of combination of these drugs are discernible: the low, the intermediate, and the high. High doses (bupivacaine 0.5% 25 mg/h and morphine 0.5 mg/h) were used to produce analgesia immediately after upper abdominal surgery but a some risk. Lower doses (bupivacaine 0.1% 4 mg/h and morphine 0.4 mg/h) did not provide total pian relief after major surgery, as thoracotomy. The issue of the minimum effective dose is of great importance, and unfortunately may have to be defined for particular circumstances. Topical formulations are useful for needle procedures, including EMLA, a cream containing an eutecthic mixture of 2 local anaesthetics (lidocaine 2.5% and prilocaine 2.5%). It is very effective in numbing the skin and the tissues just underneath the skin. Topical local anaesthetics can be used in the management of painful cutaneous and mucosal lesions and as a premedication prior to skin puncture. However, the depth of the skin which becomes numb is dependent upon how long the cream is left on. The maximum depth is about six to seven millimeters, after the cream has been left on the skin for two hours. This medication has

been successfully used for a number of painful procedures, as bone marrow aspiration and lumbar puncture; the cream should be applied from 30 min to 1 hour before the shot or needle procedure [93]. Satisfactory numbing of the skin occurs 1 hour after application, reaches a maximum at 2 to 3 hours (1 hour for children less than 3 months), and lasts 1 hours after removal. EMLA has beeen proven to be safe, with low plasma local anaesthetic concentration. Mild side effects generally disappear spontaneously within 1 or 2 hours (skin paleness, redness, a changed ability to feel hot or cold, swelling, itching, and rash). It should not be used in children affected by a rare condition of congenital or idiopathic methaemoglobinemia, or in infants under the age of 12 months who are receiving treatment with methaemoglobin-inducing agents [93].

Neuroleptics

The role of neuroleptic drugs in the management of postoperative pain is limited. Methotrimeprazine is a proven analgesic and has been useful in bedridden patients with postoperative pain who experience pain associated with anxiety, restlessness or nausea. In this setting, the sedative, anxiolytic and antiemetic effects of this drug can be highly favourable and side effects, such as orthostatic hypotension, are less of an issue. Methotrimeprazine may be given by continuous SC administration, SC bolus injection or brief IV infusion (administration over 20–30 minutes). A prudent dosing schedule begins with 5–10 mg every 6 hours or a comparable dose delivered by infusion, which is gradually increased as needed. Most patients will not require more than 20–50 mg every 6 hours to gain the desired effects. Given their potential for serious toxicity and the limited evidence in support of analgesic efficacy, other neuroleptics should be used only for the treatment of delirium and nausea.

Benzodiazepines

There is little evidence that benzodiazepines have meaningful analgesic properties in most clinical circumstances and, indeed, there is some evidence that they may, in some circumstances, antagonize opioid analgesia. These drugs may play a role in the management of anxiety and muscle spasm.

Conclusions

Acute and post-operative pain has emerged as an important issue because ethics aspects and associated morbidity and mortality. Substantial progress in understanding peripheral, spinal cord and brain mechanisms involved

in acute post-operative pain continues to be made with important consequences for treatment. The diagnosis and treatment of the cause of acute pain must always have high priority and post-operative pain management is an important goal in order to optimise medical care. Improved understanding of the pharmacology of the analgesics and the development of new techniques for analgesic administration have greatly enhanced the ability of medical doctors to success manage patients in pain. For some post-operative conditions the success of pharmacological strategies is remarkable, especially in adult patients. Even for children and adolescent with the most severe pain early evidence shows that it may be possible to reduce the impact of pain on the lives of the patients and their families. More action is necessary. Firstly, more paediatric centres are needed, to develop specific post-operative pain programmes. Secondly, collaboration between centres will be necessary to provide large enough samples of patients with the various pain conditions, considering the lack of data on this field. Finally, we must considerer that the incidence of post-operative pain in children is similar to that of adults but that our knowledge of how to help children cope with acute pain is underdeveloped. The psychological and physiologic uniqueness of children must not be forgotten. Cooperation and communication between the anaesthesiologist, surgeon, and paediatrician are essential for successful anaesthesia and pain management. The introduction of acute pain services has been shown to improve post-operative pain relief, but it is foreseeable that their role should expand and integrate into general perioperative care (Box 4). For these reasons the alleviation of pain and anxiety in post-operative patients is actually a high priority of all post-operative services and all persons involved in perioperative management of these patients are very much a part of ''continuity of care'' concept to obtain effective pain relief.

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