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Current practice and recent advances in pediatric pain management

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Abstract. – BACKGROUND: Differently from the adult patients, in pediatric age it is more difficult to assess and treat efficaciously the pain and often this symptom is undertreated or not treated. In children, selection of appropriate pain assessment tools should consider age, cognitive level and the presence of eventual disability, type of pain and the situation in which it is occurring. Improved understanding of developmental neurobiology and paediatric analgesic drugs pharmacokinetics should facilitate a better management of childhood pain.

AIM: The objective of this review is to discuss current practice and recent advances in pediatric pain management.

METHODS: Using PubMed we conducted an extensive literature review on pediatric pain assessment and commonly used analgesic agents from January 2000 to January 2012.

CONCLUSIONS: A multimodal analgesic regimen provides better pain control and functional outcome in children. Cooperation and communication between the anaesthesiologist, surgeon, and paediatrician are essential for successful anaesthesia and pain management.

Key Words:
Pain, Pain assessment, Analgesic drugs, Patient controlled analgesia, Childhood.

Introduction

Differently from the adult patients in paediatric age it is more difficult to assess and treat efficaciously the pain and often this symptom is 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[1].

Recent evidences have documented the deleterious physiologic effects of pain and the beneficial results of efficacious analgesia both in adult patients and in children[2,3]. 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[4].

Acute Pain Assessment in Pediatric Age

The pain experience includes physiological, sensory, affective, behavioural, cognitive and sociocultural components. While in adults is more easy to assess the pain symptoms, in children, selection of appropriate pain assessment tools should consider age, cognitive level and the presence of eventual disability, type of pain and the situation in which pain is occurring. There are some commonly used methods of measurement of pain that have been proved to be reliable[5]:

- Biological measures consider some physiologic parameters that may be modified by the presence of pain, such as heart and respiratory rates, blood pressure, etc.
- Observational and behavioural measures consider child's reaction to pain.
- Self-report measures rely on the child's description of his experience of pain.

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 parameters, even if non-specific, may be usefully associated to physiologic parameters such as heart rate, cardiac rate, arterial blood

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pressure, transcutaneous oxygenation and palmar sweating[8]. The Children's Hospital of Estern Ontario Pain Scale (CHEOPS) is one of the commonest scales used for pain management[9,10] (Figure 1).

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 (Figures 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[11]. The Comfort Scale is used to assess the level of sedation and distress in the paediatric intensive care unit (ICU), but recent studies have validated this measurement method also in procedural and postoperative pain[12].

Self-report measures of pain represent the gold standard in older children who can describe the subjective pain experience[10,13]. These 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. 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 Scale (VAS) and Facial Pain Scale are two of the commonest self rating scales to assess pain intensity in children (Figure 4A, B). 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[13]. 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. Faces scales represent another form of self reported measures: faces express different amounts of distress. The

ITEM	BEHAVIOR	SCORE	DEFINITION
Cry	*No Cry*	1	Child is not crying
	Moaning	2	Child is moaning or quietly vocalising; 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/without 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 in motion in a shifting or serpentine fashion
	Tense	2	Body is arched or rigide
	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 thigtly to body and kept there
	Standing	2	Standing, crouching, or kneeling
	Restrained	2	Child's legs are being held down

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

Figure 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.

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

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. Different versions exist, based anyway on the same measurement principle[14,15].

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.

Pain Management

Analgesic pharmacotherapy is the mainstay of 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. 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" (WHO: World Health Organization 1986) (Figure 5). Emphasizing that pain intensity should be the prime consideration in analgesic selection, the approach advocates three basic steps[16]:

Step 1: Patients with mild to moderate pain should be treated with a non-opioid analgesic, which should be combined with an adjuvant drug if a specific indication exists.

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.

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	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)	3	
Frequent elevations of 15% or more above baseline (more	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 muscles 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	

Figure 3. The comfort scale.

Analgesics Drugs

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

- The non-opioid analgesics;
- The opioid analgesics;
- The adjuvant analgesics

Non-opioids 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. 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[17-19].

Acetylsalicylic acid is a potent inhibitor of cyclo-oxygenases (COX) which is used frequently in medical care, but it 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.

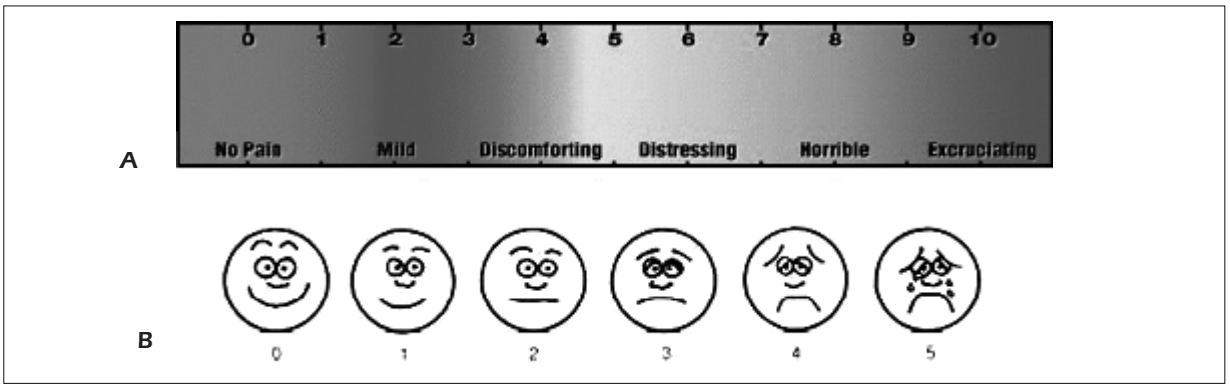

Figure 4. ***A,*** Visual analogue scale (VAS) This scale incorporates a visual analogue scale, a descriptive word scale and a colour scale all in one tool. ***B,*** Facial pain scale.

Paracetamol has analgesic and antipyretic properties and is devoid of the side effects typical of the NSAIDs[17]. The administration of paracetamol in children and infants is a well established and safe treatment option, if appropriately used. However, if paracetamol is dosed according to traditional recommendations (about 20 mg/kg body weight) frequently a sufficient analgesic effect cannot be achieved immediately after painful interventions[20]. Recently, a higher initial dose (40 mg/kg body weight) was suggested for effective postoperative pain control[21]. 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[21].

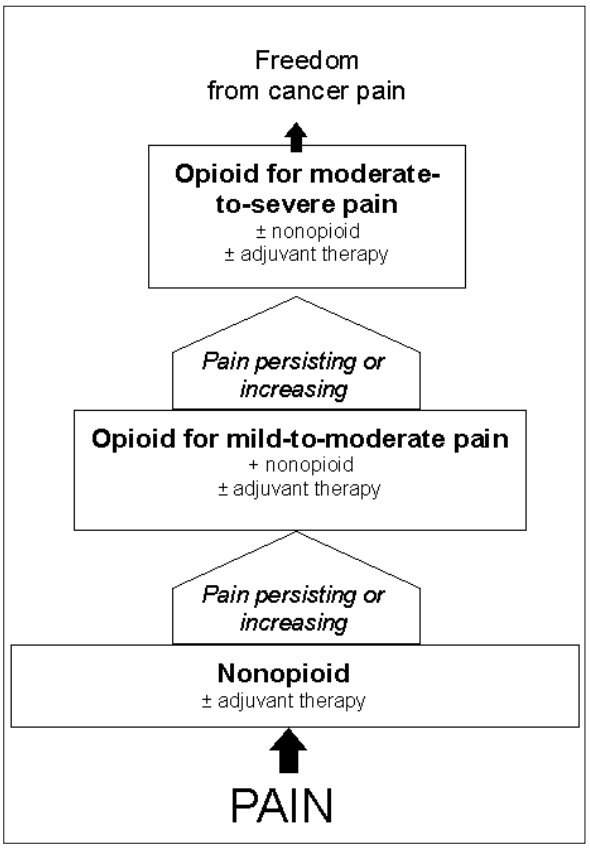

Figure 5. WHO guidelines for pain therapy.

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[22]. 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[23-25]. Less common adverse effects include confusion, precipitation of cardiac failure and exacerbation of hypertension[25].

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[26]. To date, none of the COX 2 inhibitors has been liberated for use in the pediatric age group. Only meloxicam and etoricoxib can be prescribed for adolescents (13 and 16 years, respectively)[27].

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. 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[28].

Table I shows the most commonly NSAIDs used in adults and in children for pain relief.

Opioid Analgesics

Pain of moderate or greater intensity should generally be treated with a systemically administered opioid analgesic[4]. Opioids should be used in a multimodal balanced analgesia approach that minimizes opioid requirement and the degree of their side effects[29]. 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[30] .

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. Analgesia

Table I. 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 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 g/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 g every 4-6 hr os	Reye's syndrome (children), gastroenteric or hematologic side effects

involves activation of *mu*$_1$ receptors in the brain and *kappa* receptors in the spinal cord. Humans that have become tolerant to activation of one receptor type are not necessarily tolerant to the others[31].

Based on their interactions with the various receptor subtypes, opioid compounds can be divided into agonist, partial agonist, and mixed agonist-antagonist drugs.

The pure agonist drugs (Table II) are most commonly used in clinical pain management, both in adult patients and in children (Table III). 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 function: dose increments on a logarithmic scale yield linear increases in analgesia. In practice, it is the appearance of adverse effects, 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.

The most frequent side effects of opioid drugs are represented by respiratory depression, nausea and vomiting, urinary retention, and physical dependence[32].

When respiratory depression occurs in patients on opioid therapy, administration of the specific opioid antagonist naloxone usually improves ventilation. An initial dose of naloxone 2-4 mg/kg should be given and repeated to a total of 10 mg/kg. Duration of action of naloxone is shorter than the most opioids and a continuous infusion may be required to mantein reversal[33].

Table II. 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 Multiple routes available	2-3	7.5	2-3	2-4	No known active metabolites.
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 Less histamine release	1	10 (p.r)	2-3	3-4	No oral formulation available.
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 g/h = 2-4 mg/h intravenous morphine			48-72	Patches available to deliver 25, 50, 75 and 100 g/h

Table III. Opioids commonly used for pain relief in children.

Drug	Iv/sc starting dose	Oral starting dose	Notes
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 1h Drip: 0.1-0.5 γ/kg/min	–	Respiratory depression, haemodynamic alterations

Opioids may produce nausea and vomiting through both central and peripheral mechanisms. 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. 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[34].

Urinary retention is an infrequent problem that is usually observed in elderly male patients[35].

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. 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[32].

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

The factors that influence opioid selection 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. 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[36].

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 cross-tolerance to various opioid ef-

fects (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 II)[36].

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[37].

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 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, hydro-morphone, 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 and buprenorphine are actually available as a transdermal preparation[38]. 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. 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 now available. Studies in cancer patients suggested that it is useful and that it can provide rapid and very effective relief of breakthrough pain[39].

In the paediatric population, results demonstrated some analgesic effect of intranasal (IN) fentanyl following myringotomy, no analgesic effect following voiding cystourethrography, and finally, no significant analgesic difference after long bone fractures, in burns patients, and in post-operative pain relief when compared to intravenous (IV morphine, oral morphine, or IV fentanyl, respectively. Significant analgesic effect of IN fentanyl was demonstrated in the treatment of breakthrough pain in cancer patients. However, the significant deficiencies in trials investigating acute and post-operative pain, and the paediatric population makes firm recommendations impossible[40,41].

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[42]. 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. 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:

To provide parenteral opioids to patients who already have venous access and are unable to tolerate oral opioids;

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[42,43].

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[44].

"Around the clock" dosing. Patients with severe pain generally benefit from scheduled "around the clock" dosing, which can provide the patient with continuous relief by preventing the pain from recurring. 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[45].

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[36,38]. 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[38].

"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[44,46].

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[47]. Use of a PCA device allows the patient to overcome variations in both pharmacokinetic and pharmacodynamic factors by carefully titrating the rate of opioid administration to meet individual analgesic needs. Althoug 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. 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[48].

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[49]. 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[50]. As continuous infusion, PCA allows a steady analgesic serum concentrations with safety and efficacy in pain control[51] (Figure 6).

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[49,52] (Table IV). 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 prevalence 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 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.

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[53]. These drugs may be combined with primary analgesics in any of

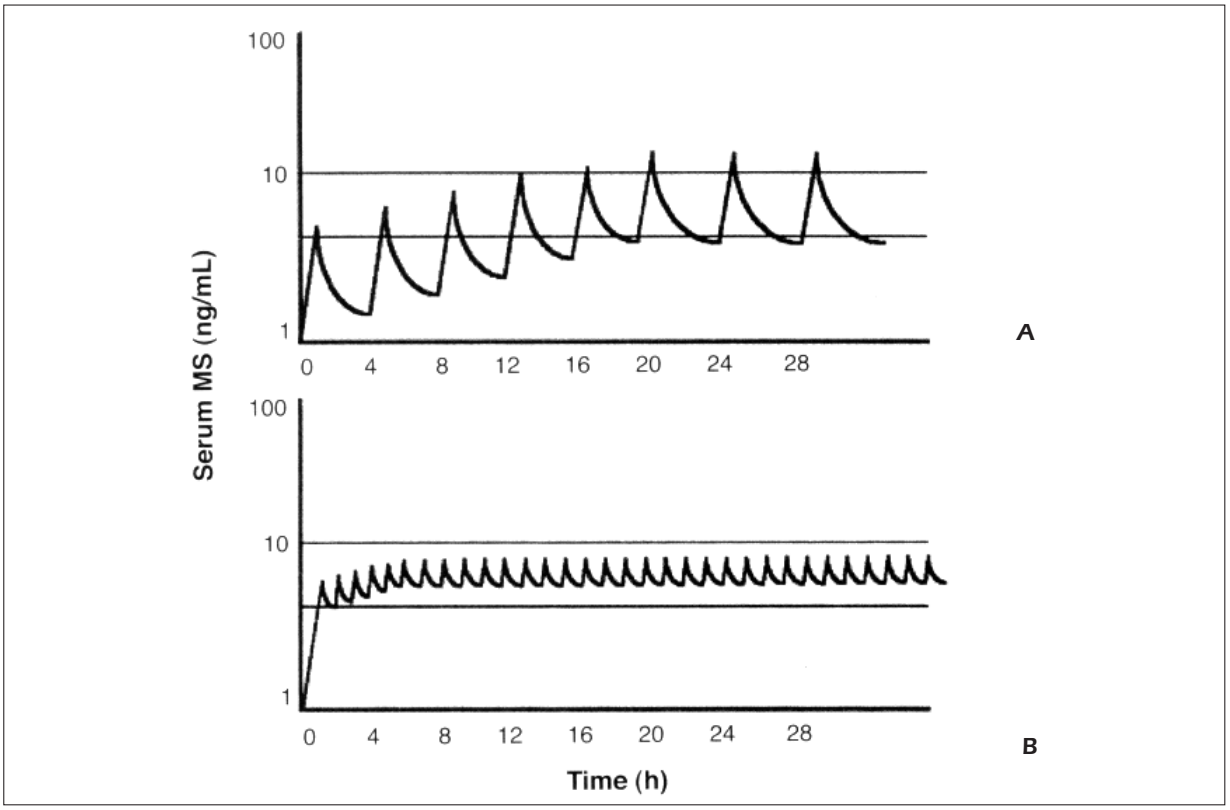

Figure 6. Opioids plasma concentration following bolus or PCA administration. ***A,*** Bolus infusion. ***B,*** PCA administration, PCA: patient-controlled analgesia.

Table IV. PCA protocol with morphine.

PCA protocol	Purpose (morphine)	Initial dose reccomandations
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 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 and 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.

The adjuvant drugs more frequently used are corticosteroids, topical and local anaesthetics, neuroleptics and benzodiazepines.

Corticosteroids. Corticosteroids are among the most widely used adjuvant analgesics[54]. 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.

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. 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 depression and rhythm anomalies[55].

Topical formulations are useful for needle procedures, including EMLA, a cream containing an **e**utecthic **m**ixture of 2 **l**ocal **a**naesthetics (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[56]. 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[56].

Neuroleptics. Methotrimeprazine is a proven analgesic and has been useful in bedridden patients with postoperative pain who experience pain associated with anxiety, restlessness or nausea[57]. 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[58].

Conclusions

Pediatric acute pain has emerged as an important issue because ethics aspects and associated morbidity and mortality. The diagnosis and treatment of the cause of acute pain must always have high priority. 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 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. However, more action is necessary. Firstly, more paediatric pain services are needed, to develop specific pain management programs. Such programs must involved clinicians who have pain management skills and are from a number of disciplines; they provide direct patient treatment and serve as practical and educational resources to others[59].

In specialised centres can now expect to benefit from up-to-date techniques of pain management, such as patient-controlled analgesia, nurse-controlled analgesia, and epidural infusions. They will be managed by ward nurses experienced and trained in paediatric pain relief, they will be attended by nurses whose special interest and training is the management of children's pain, and they will be provided with the techniques of analgesia by competent, trained anaesthetic staff[60]. Thus, the role and structure of pain treatment services should be more carefully examined and modified to help provide the high possible standard of pain care for all patients.

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 consider that the incidence of pain in children is similar to that of adults but that our knowledge of how to help children 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.

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