PHARMACOLOGICAL PAIN RELIEF IN PEDIATRIC PATIENTS

MEENU CHADHA*

Introduction

Pain has been defined by the International Association for the Study of Pain Subcommittee on Taxonomy[1] as 'an unpleasant sensory and emotional experience connected with actual or potential tissue damage, or described in terms of such damage". It is suggested that pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. Thus in the definition of pain are two components – a neurophysiologically determined sensory component and an emotional one based on the affective state. Pain has afflicted, affected and fascinated generations of human beings over the ages. There have been many misconceptions about its meaning and many different approaches. Thomas Jefferson in 1786 wrote, 'The art of life is the avoiding of pain'. Perhaps no age group is more ill equipped to avoid pain than infants and children.

Over the past 15 years, there has been considerable progress in studies of neonatal and pediatric analgesia. Until recently it was widely held that infants did not have the cortical maturation to experience pain. Progress in perinatal care has improved neonatal prognosis and survival rates. As a result, increasing number of very young and physiologically immature infants experience pain in the newborn periods, especially those who spend time in intensive care units or undergo surgery. Newborn infants respond differently to pain compared to older children but are unable to communicate the location and severity of pain. Until 25 years ago, it

* Dr. Chief Anesthetist & OT Superintendent Vishesh Hospital & Diagnostic Solutions Indore. Mailing Address: A-103 Kanchan Residency, 70 Paliwal Nagar, Near Saket, Indore, Madhya Pradesh, 452018. Phone: 07312593080, Mobile: 9977161035,
E-mail: chadha.meenu@gmail.com chadha54@rediffmail.com

was considered that neonates felt little or no pain even during significant tissue damaging events. This misconception was reinforced by reports that infants often suffered adverse consequences from analgesia, thus potent analgesics were sparingly prescribed. It appears that children's pain is undertreated for a number of complex and interacting reasons, which have allowed the status quo to continue. The explanation may be divided into four categories (Table 1).

Table 1

Explanations for undertreatment

A – Incorrect Assumptions
- a) There is correct amount of pain for a given injury.
- b) Children's nervous systems are too immature to experience pain.
- c) Children metabolize opioids differently.
- d) Children have no memory of pain.
- e) Children become easily addicted to narcotics.

B – Attitudes
- a) Pain is necessary because of its religious implications.
- b) Pain is necessary because it is character building.
- c) The use of analgesics is evidence of weak character.
- d) Some families have attitudes, which deny the open discussion of pain and its treatment.
- e) Physicians and nurses tend to have attitudes about pain in children minimizing their role as causers of pain.

C – Complexity of pain assessment
- a) Pain is difficult to assess in children because they often cannot tell or will not tell us in the ways adults can.
- b) There is no single universally accepted, well standardized measure of pain assessment in children.
- c) Inadequate assessment techniques foster under treatment, because PRN dosing is based on patient's report of need for analgesics.
- d) Inadequate assessment techniques complicate research on pain and its management.

D – Research and training adequacy
- a) Research is limited by inadequate assessment techniques.
- b) Research is complicated by ethical constraints.
- c) There are few sources of information regarding pain management in children.
- d) Faculty discomfort with pain management transmits lack of concern for this problem to trainers.
- e) There is limited information on pain management in medical school curriculum.

In the late 1980's it was observed that even premature neonates mount a substantial hormonal and metabolic stress-response to painful inputs and this is attenuated by analgesia. Thus infant pain management became the focus of considerable research interest.

Before pain in pediatric patients can be treated, its existence must be accepted, its severity assessed and relevant clinical decisions made by anesthesiologists in consultation with the parents, surgeon and the nursing staff.

Pain Assessment

Pain measurement is essential for good management. The severity of pain during procedures or in situations of continued pain, for example post operative, should be measured routinely to assess the need for analgesia and response to treatment. Infants are unable to report their pain, therefore measurement tools use observations of physiological measures and/or behaviors to estimate and quantify pain. Several scales have been devised. It is important to select one that is valid for both gestational age and setting.

Methods for measuring pain in children can be divided into three categories:

a) Self reported measures of pain-this includes routine questions, verbal scales, numeric scales and pictorial scales.

b) Behavioral measures of pain – this includes motor responses, facial expressions, crying and complex behavioral responses such as the sleep wake patterns. These scales permit the observer to assess pain based on the presence or absence of those actions believed to be associated with pain.

c) Physiologic measures of pain – they include changes of pulse rate and blood pressure as well as measure of palmer sweating. Thus, they rely on various parameters that can be measured directly at the bedside or other physical, chemical or hormonal measurements from the laboratory.

Scales and Techniques

To assess pain in children who lack a sophisticated vocabulary, investigators have turned to analogies that even young children can grasp.

Szyfelbein[2] and Osgood[3] have described a thermometer like pain scale with range from 0 to 10, labeled from' no pain' to' pain as bad as it could be" which is presented as white numbers on a crimson background This is especially helpful in children who undergo burn dressing changes. Hester's Poker Chip Tool[4] attempts to help children between 4-8 years of age to quantitate their pain by offering four white poker chips as symbols of the amount of hurt a child experiences. Bayer's Oucher[5] consists of two vertical scales with the label 'Oucher' across the top. One scale is a 0 to 100 vertical scale in increments of 10 without labels as to any pain or worst pain. The second scale is a selection of 6 photographs showing a young white child in various degrees of distress. It was developed for 3-8 years of age. Hannallah and coworkers[6] developed a pain/discomfort scale with scores ranging from 0 to 12 developed by adding 0, 1 or 2 patients for assessment of specific criteria in each of these six areas including blood pressure, crying, movement, agitation, posture and complaints of pain where appropriate.

The Abu-Saad pediatric pain assessment tool[7] is a pediatric version of the McGill Questionnaire[8] developed for Dutch school children. Disadvantage is that it requires a well trained individual and fair degree of verbal fluency in the patient.

Pain Physiology

Safe and effective pain management requires an understanding of the neurodevelopmental changes taking place during the period of treatment.

Development of Nociception

The anatomical nociceptive apparatus is in place by 24-28 weeks of gestation and even the youngest and smallest infant is able to mount a considerable, measurable, physiological response to painful inputs. The

mechanism, however, is different from adults[9]. The developing sensory system in infancy is more sensitive to noxious and non noxious inputs. The immediate pain response is characterized by reflex withdrawal from the stimulus. The threshold of withdrawal is lower in the very young and the flexion withdrawal reflex is more exaggerated and accompanied by synchronous contra lateral movement and sometimes by movement of the whole body. This response compares with a more localized and coordinated response later in the development, reflecting important difference between the immature and mature nervous system. In adults, high threshold unmyelinated C fibers normally conduct nociceptive inputs, but they are not fully functional during early development. Instead low threshold, myelinated, Aβ fibers, which are not usually nociceptive, form the afferent arc of the neonate's withdrawal reflex. Furthermore, in the neonate, the receptive fields of individual nerves are relatively larger and more overlapping, which may reduce spatial discrimination, but also leads to an increased probability of activation of individual nerve. In the spinal cord of the neonate, the A fibers terminate in the substantia gelationosa of the superficial dorsal horn, a nociceptive area in close association with the C-fiber terminals.

Later they withdraw to deeper laminae where they sub serve non-painful pain sensation, such as touch. In addition, descending modulatory systems from the brain, particularly descending inhibition, are not fully functional until some after time birth, probably contributing to these enlarged receptive fields and exaggerated responses.

Tissue damage leads to local inflammatory response and sensitization of nociceptors. In addition changes taking place in the spinal cord lead to lower thresholds and augmented transmission of nociceptive inputs via projection neurons to the brain. A well known component of this sensitizing process is known as 'wind up' and is mediated by N-methyl-D-aspartate (NMDA) receptors. The extent and degree of this sensitization is related to the magnitude and type of injury. These processes also change in the post natal period. The distribution and function of key molecules, channels and receptors (including opioid receptors and NMDA receptors) change with

developmental age and this has important consequences for pain signaling in the CNS. This affects the pain management strategies.

Long Term Consequences of Pain

Maturation of CNS is an activity dependent process. Normal development depends on inputs or events occurring at specific times during developmental period. There is some evidence to suggest that abnormal, severe or excessive pain related inputs may lead to adverse effects in nociception or pain perception in the long term. Children who spend long periods in the ICU as neonates appear to show different characteristics regarding pain and may have different pain thresholds compared to their peers.

Pharmacological Considerations

In order to understand the pharmacological management in children the following points should be kept in mind:

a) Neonates have delayed maturation of liver enzyme systems which is involved in drug metabolism.

b) Children have a higher percentage of body weight as water and less as fat. Dosages of water soluble drugs vs. fat soluble drugs should be adjusted.

c) Children have reduced plasma albumin. This results in greater availability of active drugs and increased risk of toxicity.

d) Neonates have immature blood brain barriers. This means that there is increased medication passage into the brain. Neonates have diminished ventilatory responses to decreased oxygen content in the blood.

A recent study evaluating perioperative outcome has stressed the advantage of administering potent opioids to pediatric patients undergoing extensive surgical procedures[7]. These advantages are greater

hemodynamic stability and decrease in catecholamine and neuroendocrine response. Severe postoperative pain can exacerbate emergence delirium and precipitate tachycardia, hypertension and increasing anxiety[10-13]. In severely ill children, the combination of hemodynamic instability and agitation may lead to increased bleeding from the surgical site, cardiac decompensation and pulmonary compromise[11-14].

Analgesic Dosing Options for Pediatric Patients

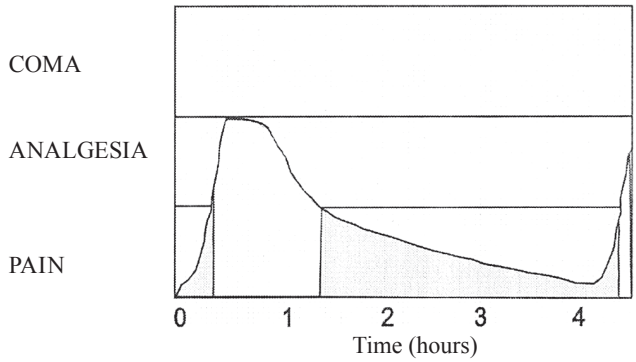
Intermittent Analgesic Dosing

Oral analgesics is the route of choice in children tolerating fluids and food, but this route becomes unreliable after surgery because of increased incidence of nausea, vomiting and ileus in the immediate post operative period[16,17]. Most opioid analgesics are subject to extensive metabolism if given by mouth. Rectal route is a useful alternative, especially if pain is accompanied with nausea and vomiting. Opioids can be given by a suppository but are not ideal for acute pain because of slow and erratic absorption, though they are ideal for maintenance of analgesia. Further, there is an argument that there is no role of intramuscular injections in children as they are slowly effective and poorly controlled. It is possible to effectively titrate rapidly and painlessly an i/v bolus of analgesic medication[15,16,17], as these patients generally have an i/v catheter in place immediate post operatively. I/V boluses of analgesics are generally associated with higher peak plasma levels, a more profound but short lasting peak effect and a short duration of activity than that observed when comparable doses are administered I/M (Fig. 1).

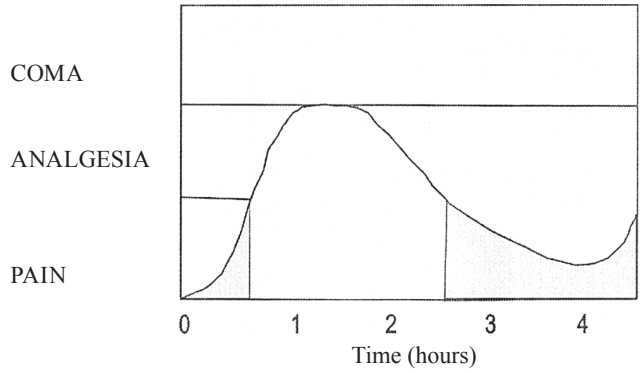
Fig. 1

Typical course of analgesia in patients treated with different forms of opioid administration. A, Intravenous boluses of intermediate-duration opioids (morphine, meperidine) result in dramatic fluctuations in plasma levels and clinical effect when given at 4-hour intervals. B, Intramuscular administration is associated with less dramatic fluctuations in plasma levels and effect. C, Continuous infusion can provide more uniform plasma concentrations and a clinical effect that remains between the extremes of inadequate analgesia and sedation. A slow rise in plasma concentration should be anticipated; however skilled assessment and dose adjustments can prevent progressive increases in sedation and respiratory depression. D, Intravenous administration of methadone by initial loading followed by small supplemental boluses every 4 to 8 hours can also provide relatively constant plasma concentrations and uniform levels of analgesia. E, Administration of opioids by patient-controlled analgesia accommodates for interpatient variability's in analgesic requirement and offers effective pain relief and high patient satisfaction.
(From Berde CB: Pediatric Clin North Am 36:921-940, 1989).

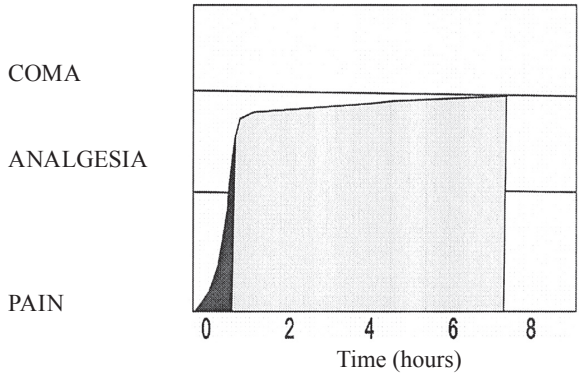
A - *Opioid administration by intravenous boluses*



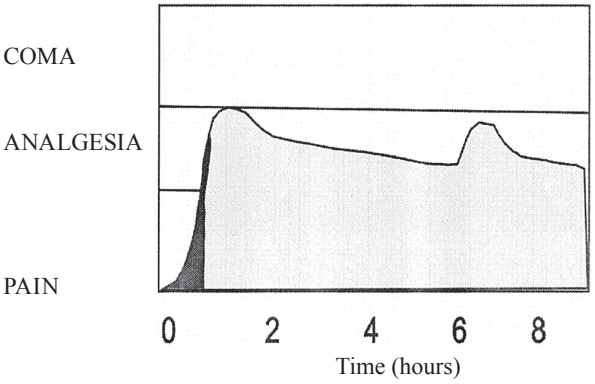
B - *Intramuscular administration of opioids*



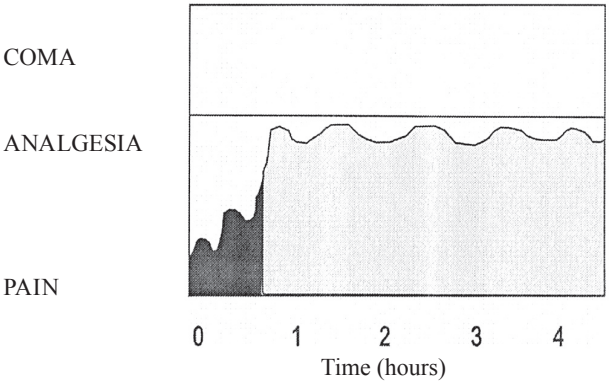
C - *Opioid administration by continuous infusion*



D - *Intravenous administration of methadone by loading dose and small supplemental boluses.*



E – *Patient controlled analgesia*



Thus the doses should be at more frequent intervals and infused slowly to avoid periods of discomfort and acute episodes of over narcosis (Table 2).

Table 2

Oral and parenteral analgesics-dosing guidelines in children

Agent	**Potency**	**Dosage**	**Route**	**Duration (Hrs.)**	**Age GP**
Opiods					
Morphine	1	0.05- 0.1 mgm/kg 0.3-0.6 mg/kg 50-100 µg/kg	IV/IM Oral IV	2-3 2-3 4-12	2+ months 2 months Neonates
MS-Contin	1	0.3 mgm/kg	Oral	8-12	4+ Years
Meperidine	0.1	0.3-1.5 mgm/kg 0.4-2 mgm/kg	IV/IM Oral	2-3 3	3+ months 3 months
Hydromorphone	6-8	10-40 µg/kg	IV	2-3	3+ months
Methadone	1	0.05-0.2 mg/kg	IV/IM Oral	6-12	3+ months
Fentanyl	80	0.5-5 µ/kg	IV	1-3	Neonates
Oxycodone	1	0.05-0.15 mg/kg	Oral	3-4	1+ Year
Codeine	0.8	0.5-1.0 mg/kg	Oral	3-4	1+ month
Nonsteroidal anti-inflammatory drugs					
Acetaminophen	-	10-20 mg/kg	Oral/ Rectal	4	All
Ibuprofen	-	4-10 mg/kg	Oral	6-8	2+ Years
Naprosyn	-	2.5-7 mg/kg	Oral	8-12	2+ Years
Ketorolac	-	1 mg/kg load, Then 0.5 mg/kg	IV	6	1+ Years

The dosing should be by the clock, but nowadays this has been superseded by the greater convenience and uniformity of analgesic effect offered by continuous IV infusions and PCA.

Continuous Opioid Infusion

Parentally administered opioids are more effective when continuously infused by an infusion pump[17,12,13]. Continuous infusion avoids the troughs and peaks of narcosis observed with intermittent I/V boluses or I/M injection,

and provide a more uniform level of analgesia. Though the technique has a high degree of safety, expertise skill is required to prevent severe pain or development of excessive sedation or respiratory depression[15,12]. Lyn and colleagues have evaluated plasma morphine concentration in pediatric patients treated with continuous infusion in an effort to determine what level of drug consistently provided adequate post operative analgesia. They reported that morphine plasma levels of 8-12 ng/ml offered effective and safe pain relief. When administered by continuous infusion, morphine steady state plasma concentration are not attained for 9-11 hours (4-5 half lives)[18]. The addition of morphine "loading dose" (0.05 to 0.1 mg/kg) decreases the time required to achieve steady state with a 10-20 μg/kg/hr continuous infusion to only 4 hours[18,13,19]. Dosing guidelines of continuous infusions are given in Table 3.

Table 3

Continuous opioid infusion and intermittent intravenous methadone dosing guidelines

CONTINUOUS INTRAVENOUS OPIOID INFUSION

INTIAL LOADING DOSES

Morphine 0.05 to 0.15 mg/kg I/V (children)
Morphine 25-50 μg/kg I/V (neonates)
Fentanyl 1-2 μg/kg I/V
Hydromorphone 0.015 mg (15 μg/kg) I/V (children)
Loading doses are administered intravenously by butretol over a 10-20 minute period while under constant supervision.

MAINTENANCE DOSING

Morphine 0.02-0.04 mg/kg/hr (children)
Morphine 5-15 μg/kg/hr (neonates)
Fentanyl 0.5 to 4 μg/kg/hr
Hydromorphone 4 to 8 μg/kg/hour (children)

INDICATIONS – For relief of severe pain resulting from surgery, trauma, vaso-occlusive crisis, pancreatitis, other acutely painful medical conditions, and agitation secondary to mechanical ventilation. These techniques are relatively contraindicated in non intubated infants less

than 4-6 months of age and others with evolving neurological conditions and altered ventilatory control. Extreme caution should be applied in patients presenting with hepato renal disease. Safe administration requires continuous assessment of ventilatory status, appropriate in servicing of the nursing staff, and immediate availability of nalaxone and resuscitative equipment.

Hendrickson and colleagues[20] compared the safety and quality of post operative analgesia provided by intermittent I/M injections and continuous I/V infusion of morphine in children between 1-16 years of age. They noted that children in I/V group did require greater amount of drug, but were more comfortable with less side effects.

Other advantages associated with opioid infusion therapy were:

a) Improved pain relief during activity.

b) Less time spent on drug administration.

Barrier to widespread use of continuous infusion is:

a) Lack of familiarity with technique.

b) Requirement of an infusion pump.

c) Need for I/V access.

Patient Controlled Analgesia (PCA)

Goal of analgesia in pediatric age group is to provide high level of patient comfort with acceptable side effects.

PCA is a therapeutic modality that allows patients to administer pain medication in amount proportional to a perceived pain stimulus. Optimal PCA requires the patient to be responsible for the analgesic dosing. Patient and nurse assisted PCA has been advocated in younger children. At what age children can effectively utilize PCA is open to question. Research has shown that children 9 years and older can make competent decision regarding analgesic self-administration[21]. Raven and Ho[22] evaluated the safety and suitability of PCA in children recovering from extensive spinal fusion surgery. Based on respiratory rate, level of consciousness and behavior scores, PCA was found to be safe, effective and well accepted

by children and adolescents. This therapy eliminated the emotional trauma associated with anticipating and receiving I/M injections while promoting control and independence. The only drawback was increase in pain scores in the evening hours. This was because children often fell asleep and awoke during the night in significant pain. A low dose continuous infusion on first and second post operative day may solve this problem[22]. Brown and Broadman[23] in a series of 150 children noted that only 3 of 150 children recovering from major surgery and treated with PCA required an alternative pain management program. Tyler and Krane[24] suggest that PCA can be routinely offered to children 12 years of age and older provided they are of average intelligence (Table 4 & 5).

Table 4

Patient controlled analgesia

ADVANTAGES

1. Painless administration (intravenous or subcutaneous clysis).
2. Accommodates for inter individual analgesic requirements.
3. Patient participation in therapy helps diminish feelings of helplessness and improves psychological control.
4. Avoids peaks, troughs and delays in analgesia.
5. May be associated with fewer side effects.
6. Nursing staff spends less time dosing drugs and has more time for pain assessment and other aspects of patient care.

DISAVANTAGES

1. Requires specialized equipment and monitoring.
2. Requires emotional maturity, patient self awareness and cooperation.
3. Potential for operator or mechanical errors.
4. Children may experience increased pain after periods of sleep.

Table 5

PCA guidelines for children and adolescents

Opioid	**Route**	**Conc**	**Loading Dose (mg)**	**Cont Infu**	**PCA dose (mg)**	**Dosing interval**	**4-hour limit**
Morphine	IV	1 mg/ml	0.03 mg/kg 2 or 3 doses	0.015 mg/kg/hr	0.02 mg/kg	6-10 mins.	0.25 mg/kg
Meperidine	IV	10 mg/ml	0.3 mg/kg 2 or 3 doses	Not recommended	0.15-0.2 mg/kg	6-10 mins.	0.25 mg/kg

Analgesics for Oral and Parenteral Administration

Opioids

The term opioid is used to describe this group of drugs whose action is "morphine like". Opiate refers to phenanthrence alkaloids such as morphine and codeine, which are derived from opium, an extract of poppy seeds[25]. Other synthetic opioid drugs such as meperidine, methadone and phenylpiperidines (fentanyl and its analogues) are structurally different from morphine though acting in similar ways. The term narcotic is commonly used to refer to opioid analgesics. Opioids are generally thought to produce analgesia by binding to opioid receptors in the brain, brainstem and spinal cord mimicking effects of endogenous opioid peptides. Although action on mu receptors is generally correlated with analgesia, some of the differences in the action and side effects of different opioids may relate to differences in their receptor speicifities[25,26].

The experience of pain involves both sensation of noxious stimulation (nociception) and the emotional component of subjective distress (suffering). Opioids appear to exert effects on both aspects of pain experience. They diminish the distress component to a great degree, patients often state, "The pain is still there but it bothers me less". In addition opioids suppress the autonomic responses to noxious stimulation such as sweating, tachycardia and hypertension.

Opioids can be administered by a number of routes, including oral, intravenous, subcutaneous, intramuscular, transdermal and transmucosal, epidural and subarachnoid[27]. For patients who can ingest and absorb tablets or elixirs, the oral route is preferred. Even in cases of severe pain oral administration can be quite effective if adequate doses are given. The intravenous route is preferable especially in the postoperative phase, because nausea and transient ileus are common and most patients have an intravenous line in place.

Opioids are mainstay for treatment for moderate to severe post surgical, trauma or malignant pain. They are associated with dose dependent increase in pain tolerance and drug related side effects. They

depress respiration decreasing the sensitivity of brainstem respiratory nuclei to elevations in carbon dioxide concentrations[35]. Thus, the doses should be titrated to clinical effect or as limited by dose related side effects. Unlike many classes of drugs, opioids should not be administered like a cookbook, but rather a stepwise administration and constant assessment of efficacy should be done.

Other side effects especially in pediatric population are increased sedation, bradycardia, nausea and vomiting, inhibition of intestinal motility, biliary spasm and urinary retention.

Opioids are metabolized in liver[28] and the metabolites are excreted in the urine. Patients with hepatic and renal dysfunction may have exaggerated responses to opioids. Newborns have variable and unpredictable reductions in their metabolism of opioids[29-33] and a portion of the sensitivity of newborns to opioids reflects their diminished clearance as well as pharmacodynamic factors. Beyond the newborn period, the commonly used opioids have elimination half life in the range of 2-3 hours. Thus, in most settings associated with severe pain, it is apparent that dosing at intervals of 4-6 hours will create fluctuations in plasma levels and alteration of pain with discomfort.

Morphine

Morphine is the gold standard against which all other opioids are compared. It is most widely used for the management of acute pain in children and adults. It is hydrophilic and does not cross the blood brain barrier well. It also has poor bioavailability (20-30%), which necessitates a larger PO dose when converting from parenteral to enteral routes of drug administration. Despite these limitations it is probably the best studied opiate in children[34]. In addition to the PO, I/V, I/M and SC routes, morphine can be administered in nebulized, epidural and intrathecal formulations. Morphine is metabolized in the liver by microsomal mixed function oxygenases that require the P-450 system. Two metabolites of morphine are morphine 6-glucoronide (which is active and more potent than morphine) and morphine 3-glucoronide (which is inactive but competes competitively

with morphine at binding sites). These metabolites are excreted renally, so morphine (and opioids that are metabolized into morphine e.g. codeine and methadone) must be used with caution in patients with renal failure because the active metabolite accumulates in the blood. Morphine induces histamine release and must be used carefully in patients with asthma or atopy. It also leads to vasodilatation and so may produce hypotension in hypovolemic patients.

Opioid of choice in pediatric patients. Has the advantage of:

a) Extensive clinical experience.

b) Economy.

c) Fairly predictable blood levels.

d) Reliable and effective control of pain and excitement[19,24].

Intravenously, it should be avoided in babies less than 1 month of age and premature infants less than 60 weeks after conception[36,37]. If the infant displays behavior consistent with severe pain, intermittent boluses of morphine should be restricted to 100 μgm/kg I/V every 4-6 hours in infants and less frequently in premature infants[38].

The patient should be carefully monitored with apnea monitor and pulse oximetry and acetaminophen given when intensity of pain has decreased. Morphine infusions are safer than intermittent doses[36].

Morphine may be safely given to older babies and younger children suffering from acute or chronic pain. In children 1-15 years of age morphine's elimination half life is approximately 133 minutes and minimum effective plasma concentration ranges from 12-30 ng/ml depending upon the surgical procedure[39,40,41].

I/V dose of 0.05-0.2 mg/kg is well tolerated by healthy normovolemic children. Larger doses can be given to ventilated patients but careful titration is needed in patients with renal or hepatic dysfunction and central nervous system diseases.

Hydromorphone has a similar pharmacokinetic profile as morphine but greater potency 6-8 times and less likely to release histamine.

Side effects of morphine (and all other opioids at equipotent doses) include decreased mental alertness, respiratory depression, hypotension, bradycardia, nausea, vomiting, pruritis, urinary retention and at high doses myoclonus and seizures.

Meperidine

Meperidine (Demerol) has one tenth the analgesic potency of morphine. It offers no advantage over morphine in terms of sphincter of Oddi or bowel motility or respiratory depression. Compared to morphine it provides lower intensity of pain relief but has a lower incidence of nausea, pruritis and excessive sedation[24,35]. It can be given orally or parenterally. Orally 5-70% bioavailability is there.

Meperidine is most effective in post surgical pain[35,41]. Since it causes less release of histamine or increased biliary pressure, it can be given in patients with acute asthma, biliary colic or pancreatitis.

Meperidine's major metabolite, normeperidine is slowly eliminated by the kidneys and excessive plasma concentration is associated with CNS excitability, hence infusion is not recommended and it is avoided in children with renal failure and epilepsy.

Meperidine interacts catastrophically in patients taking monoamine oxidase inhibitors for depression. In these patients meperidine may cause neuroleptic malignant syndrome, a life threatening condition manifested by hyperpyrexia, acidosis, shock and death.

Fentanyl

Fentanyl is highly lipid soluble, equilibrates rapidly at the effect or site, and has no active metabolite. It can be administered by I/V, I/M, SC, transmucosal and transdermal route. It is most commonly used for short painful procedures but can also be used for post surgical and burn patients.

Advantageous over morphine because of its rapid onset of analgesia,

negligible release of histamine and greater hemodynamic stability[35,42,43]. Continuous infusion of fentanyl effectively saturates its volume of distribution and results in more uniform plasma concentration and long lasting analgesia.

Singleton and coworkers[44] noted that 4 hours after administration of fentanyl 20-30 μgm/kg plasma concentration were low in infants, medium in children and high in adults.

Fentanyl offers therapeutic advantages in preterm infants and children with cardiovascular dysfunction who cannot tolerate excessive catecholamine response and perioperative hemodynamic instability[45,42]. Large bolus doses of 30-50 μgm/kg and continuous infusion of fentanyl is capable of abolishing stress response and improves clinical stability in babies recovering from PDA ligation[45,46]. In ventilator dependent patients, fentanyl abolishes the hemodynamic and pulmonary vasoconstrictive responses associated with endotracheal suctioning[47].

Large bolus doses 35-40 μgm/kg and continuous infusions of 2 μgm/kg/hr of sufentanil also provides effective post operative analgesia in ventilated neonates after cardiac surgery[45].

Methadone

This is a lipophilic opioid analgesic that has a large volume of distribution and prolonged elimination with a half life of approximately 19 hours in children[12,24,48]. It is associated with less sedation and euphoria than morphine[24,35].

Children undergoing extensive surgery are given 0.1 mg/kg loading dose intraoperatively and 0.05 mg/kg incremental doses in the recovery room.

Another advantage of methadone is its relative resistance to first pass metabolism and high bioavailability after oral administration[14,35]. Methadone elixir can be administered earlier in the post operative period and is more reliably absorbed than morphine and meperidine. Mixed with small amount of grape juice it is highly acceptable orally.

Side Effects of Opioids

To ensure safety and efficacy of therapy, steps should be taken to reduce the incidence of side effects and treatment protocols are developed to minimize severity.

Respiratory Depression

Most feared side effect with opioids. Premature infants and children with history of upper airway obstruction and sleep apnea are at a higher risk for respiratory depression.

Respiratory depression is more common in:

a) Children treated with continuous infusion where improper attention is paid to the total dose administration.
b) Within minutes of IV loading dose or maintenance bolus of methadone or fentanyl.
c) After administration of inappropriate dose of barbiturate or benzodiazepines to patients being treated with continuous opioid infusion or intermittent methadone bolus.
d) When excessive dose in continuous infusion is added to the PCA.

The following protocol should be adhered to with continuous opioids infusion, initial dose of methadone or PCA. Vital signs should be monitored every 15 minutes for the first hour, every 30 minutes for the second hour and every hour for the first 4 hours and then every 2-4 hours after. Nalaxone should always be available and oxygen, ambu bag, mask and suction should always be available at bedside.

Opioid induced respiratory depression is less problematic in infants receiving mechanical ventilation but requires continuous monitoring in non intubated infants.

Nausea and Vomiting

Most common side effect with opioids. This is as distressing as untreated pain, as it is frightening to young children and embarrassing to adolescents.

One of the simplest things that can be done to decrease nausea is to decrease the size of the PCA bolus. Switching from one opioid to another can also be tried. Small doses of droperidol or metoclopramide can be used to decrease nausea and vomiting. Metoclopramide is effective in blunting cramping spasmodic pain associated with nausea and vomiting in children recovering from abdominal or genitourinary procedures[14].

In children using PCA, small doses of metoclopramide (5-10 mgm) and phenergan (2-5 mgm) may be added to each 30 mgm morphine PCA syringe so that small amount of drug is self administered with each dose of opioid.

Physical Dependence

Although acute tolerance and physical dependence is seen, risk of addiction in children is very low and should not be considered as a deterrent to the use of opioids. Children treated with opioid analgesics for extended periods of time may display physiologic signs of withdrawal if such therapy is abruptly discontinued. Therefore, opioid analgesics should be slowly tapered in all children who have been treated for a period of 10 days or more.

Pruritis and Urinary Retention

Pruritis is a common side effect associated with I/V morphine and meperidine and usually reflects non-specific histamine release from subcutaneous mast cells and macrophages. Mild pruritis is treated by decreasing the size of opioid bolus and cold compresses. Moderate pruritis is treated with small doses of diphenhydramine and switching to a different opioid. Severe pruritis is associated with generalized rash and may indicate a topic hypersensitivity or acute anaphylaxis. For this, treatment consists of diphenhydramine, oxygen, corticosteroids, epinephrine and airway support.

Urinary retention reflects the effects of the opioid analgesic on detrusor muscle. In children who are not catheterized it can lead to severe

discomfort and UTI. Treatment includes reduction in opioid dose and administration of small amount of nalaxone and bethanecol (Table 6).

Table 6
Treatment of opioid induced side effects

Adverse Event	Incidence	Agent	Dose	Route
Nausea/Vomiting	10%	Droperidol	10-20 μg/kg	IV
		Metoclopramide	0.1-0.2 mg/kg	IV
		Prochlorperazine	0.1-0.15 mg/kg	IM
			1.25-10 mg	PR
Pruritis	5%	Diphenhydramine	1.25 mg/kg	IV/Oral
		Naloxone	1-3 μg.kg/hr	IV
Sedation	5-10%	Naloxone	1-3 μg/kg	IV
		Dextroamphetamine	0.2 mg/kg	Oral
Urinary	3-5%	Naloxone	2-4 μg/kg/hr	IV
Retention		Bethanecol	0.05 mg/kg	SC
Respiratory	1%	Naloxone	5-10 μg/kg	IV
Depression			3-5 μg/kg/hr	IV

Weak Opioids

When analgesia is insufficient with acetaminophen, salicylates or an NSAID alone, a weak opioid (e.g.codeine, oxycodone or hydrocodone) can be added to the analgesic regimen. All of these agents provide analgesia through interaction with the mu opioid receptor in the CNS, a mechanism similar to other opioids. When combined with a PSI, these agents may provide analgesia for moderate pain when NSAID or acetaminophen is ineffective. Tobia et al[49] compared the efficacy of acetaminophen 15 mgm/kg versus acetaminophen with codeine 10 mgm/kg + 1 mgm/kg administered preoperatively to children undergoing myringotomy and placement of pressure equalization tubes. Children who received acetaminophen with codeine had lower pain scores during the first two post operative hours, decreased need for codeine in the recovery room and faster time to discharge home than children who received acetaminophen.

Codeine

The analgesic effect of codeine results from its direct agonistic properties at the mu opioid receptor. When used in equipotent doses, its analgesic and respiratory depressant effects are similar to those of morphine, and other opioids.

Opiate alkaloid which can be administered orally or parenterally and provides effective control of mild to moderate pain and also has a potent antitussive activity. Codeine's bioavailability after oral ingestion approaches 60%[50]. In children oral codeine 0.5-1 mgm/kg is combined with acetaminophen 10 mg/kg. This potentates codeine's analgesic action thus decreasing the overall dose requirement and may limit dose dependent side effects. I/V may be associated with higher incidence of nausea and histamine release so it is generally not recommended.

Compared with other opioids including morphine, codeine undergoes less first pass hepatic metabolism, accounting for its greater PO availability. Approximately 10% of codeine undergoes hepatic demethylation to morphine, which may account for a significant proportion of its analgesic efficacy. A major issue with codeine is that as much as 10% of the population lacks the enzymes required for codeine demethylation, thereby making it a less effective analgesic in this group.

Oycodone and Hydrocodone

Oxycodone and hydrocodone are semi synthetic opioids that like codeine provide analgesia through interactions with the mu opioid receptor. Both are similar to codeine in that they retain a PO bioavailability of 50%-60%: reach peak concentrations within 1-2 hours, and exhibit half lives of 2.5-4 hours. As with codeine these compounds typically are prescribed in combination with acetaminophen or acetylsalycilic acid. These agents are available in liquid and tablet formulations. Dosing is based on oxycodone or hydrocodone component starting at 0.1 mgm/kg every 3-4 hours. Another combination which can occur is hydrocodone 7.5 mgm with ibuprofen 200 mgm in a tablet, thereby providing the advantage of the anti-inflammatory

effects of the NSAID in addition to the analgesia of the opioid hydrocodone. Oxycodone is also available nowadays in a sustained release preparation.

Tramadol

Another option to control mild to moderate pain in the inpatient and outpatient setting is tramadol, an analgesic that includes agonistic effects at the mu opioid receptor and inhibition of the reuptake of the neurotransmitters, norepinephrine and serotonin in the CNS. These two mechanisms interact synergistically to produce analgesia. It has potency roughly equivalent to that of codeine and an oral bioavailability of 75%. Tramadol undergoes hepatic metabolism partially by the P-450 system, to an active metabolite (M1 or an O-desmethyltramadol). The latter has potency six times that of the parent compound. Because of the metabolism by P-450 system, potential interactions; with other medications may increase or inhibit the metabolism of the parent compound, thereby altering the therapeutic response. M_1 is dependent on subsequent renal excretion and may accumulate in the presence of renal insufficiency or failure. The adverse effect profile of tramadol is similar to that of other weak opioids although CNS symptoms seem to be more common with tramadol. Reports of the use of tramadol in the pediatric age group are limited.

Dezocine

Synthetic opioid agonist that has ceiling effect in terms of its ability to activate mu receptors. Clinically equipotent to morphine, provides effective analgesia and is associated with mild to moderate respiratory depression[51]. Low dose 0.05 to 0.1 mgm/kg are equipotent to morphine, whereas higher doses become progressively less effective than equipotent doses of morphine. Not very useful in children.

Adverse Effects

Like any opioid that demonstrates mu agonist activity, the weak opioids can cause excessive sedation and respiratory depression. The latter

are uncommon except with excessive dosing or the following underlying medical conditions that may increase the patient's sensitivity to the central respiratory depressant effects of opioids.

Additional side effects include sedation, constipation, pruritis, nausea and vomiting.

Non Opioids

Non opioid analgesics, including acetaminophen and non-steroidal anti-inflammatory drugs act at peripheral sites of injury by inhibiting prostaglandin synthesis and blocking the activation or primary afferent nerve endings[52,53]. In children, acute pain may result from musculoskeletal strain or bony fracture, outpatient surgery or an acute medical illness such as pneumonia or pleuritis, headache or otitis media. Regardless of the cause, acute pain that requires outpatient treatment primarily relies on the use of oral agents such as NSAIDs or acetaminophen, alone or in combination with weak opioids. Recommendations from the World Health Organization (WHO) for the control of pain suggest a graded approach using a three step ladder[54]. According to the WHO ladder, mild pain can be controlled with a non opioid analgesic agent such as a prostaglandin-synthesis inhibitor (PSI) e.g. acetaminophen or acetylsalycic acid or an NSAID as ibuprofen. The initial approach to the control of moderate pain includes a combination of drugs.

Prostaglandin Synthesis Inhibitors

PSIs share a similar mechanism in that they interfere with the function of the enzyme cyclooxygenase and thereby prevent the conversion of arachidonic acid to prostaglandin. The prostaglandins are potent vasodilators and proinflammatory compounds that account for hyperemia, erythema and pain associated with peripheral tissue damage. The end products of arachidonic acid metabolism (i.e. prostaglandins and thromboxanes), in conjunction with other inflammatory mediators, stimulate

free nerve endings, resulting in nociceptive input to the CNS. In addition the proinflammatory actions, prostaglandins and thromboxanes govern several other peripheral and physiologic actions including hyperalgesia, vasodilatation, gastrointestinal tract mucin production, platelet aggregation, smooth muscle relaxation, increased renal blood flow, increased capillary permeability, increased inflammatory response and pyrexia.

The salicylates and NSAIDs block the peripheral and central production of prostaglandins and thromboxanes, providing analgesic and anti-inflammatory effects. Although the mechanism of action of acetaminophen is the same, its effects are primarily central, providing analgesia with limited peripheral anti-inflammatory action. Because of its lack of effect on peripheral cycloxygenase acetaminophen does not produce the adverse effect profile as the salicylates and the NSAIDs. The PSIs can be can be classified as follows:

1. PARA-AMINOPHENOL DERIVATIVES
   - Acetaminophen
   - Phenacetin
2. SALICYLATES
   - Acetylsalicylic acid
   - Choline magnesium trisalicylate
3. NSAIDs
   - Ibuprofen
   - Naproxen
   - Tolmetin
   - Ketorolac
   - Indomethacin

Acetaminophen

This is the most commonly prescribed analgesic in the treatment of mild to moderate pain. Its mechanism of action involves the inhibition of central cyclo oxygenase, with little effect on peripheral prostaglandin formation, thereby accounting for its lack of anti-inflammatory properties.

The latter also accounts for its lack of adverse effects on renal, GI and platelet function. Additional mechanism of action has also been suggested for acetaminophen, including the inhibition of nitric oxide formation, which results from activation of substance P and N-methyl D-aspartate receptor stimulation[55]. Acetaminophen is available in various formulations like drops, liquids, tablets, sustained release tablets, and suppositories. It can be used alone for mild pain, combined with weak opioid and administered orally for the control of mild to moderate pain, or used as an adjunct to I/V opioids for the control of severe pain. It is effective for mild to moderate pain and can be given as oral suspension in the dose of 15 mgm/kg to a maximum dose of 60 mgm/kg in 2 hours. Slightly higher dose of 20 mgm/kg are needed if the drug is used rectally.

Salicylates and NSAIDs

The first NSAID, acetylsalicylic acid, has been in clinical use since the second half of the nineteenth century, however because of the association with the Reye's syndrome its pediatric use has decreased dramatically over the past 15 years.

The NSAIDs and the salicylates are weak organic acids that are rapidly and completely absorbed following oral administration. Metabolism occurs by the cytochrome P-450 system of the liver, with renal excretion of 5% to 10% of unmetabolized drug. Peak plasma concentrations typically are achieved within 2-3 hours but may be delayed by the alterations of GI motility or gastric emptying time, timed release preparations and enteric coatings. Plasma half lives vary greatly (2-45 hrs) depending on individual agent[56]. These agents have a high degree of protein binding resulting in a low volume of distribution. The NSAIDs are classified according to their chemical structure such as acetic acid, propionic acid, fenamic acid, enolic acid and non acidic compounds[57].

Combination of opioids and local anesthetics with the NSAIDs and or paracetamol is particularly useful in children undergoing surgery. In patients who are somnolent at rest but have pain on moving, NSAIDs

are useful because they do not cause respiratory depression and limited CNS depression. NSAIDs are effective in postoperative pain management because surgery causes both pain and inflammation and they have analgesic, anti-inflammatory, antiplatelet and antipyretic action. However, they have a ceiling effect on their analgesic effectiveness. Dosing beyond the ceiling provides little or no analgesia but may be associated with increase in side effects.

Few studies have compared different doses of NSAIDs in children. Ketorolac 0.5 mgm/kg is as effective as morphine 0.1 mgm/kg but at a dose of 0.2 mg/kg it does not provide adequate analgesia[38]. Higher doses of ketoralac are no more effective. Ketoprofen is an effective analgesic at 0.3 mg/kg. While at higher doses of 3 mgm/kg better analgesia is achieved without any increase in side effects[59].

The safety of NSAIDs in infants has not been established, although both indomethacin and ibuprofen are commonly used for treatment of PDA in preterm infants[60]. In children over 6 months some of the older NSAIDs may be used safely. The evidence of propionic acid derivatives and diclofenac is extensive and these days seem to be useful in younger children[61]. Data of using COX2 inhibitors is however limited[62].

Ibuprofen, diclofenac, ketoprofen and ketorolac are most extensively evaluated NSAIDs in children. Concurrent use of two NSAIDs is not recommended but pain relief is assumed to be improved by addition of paracetamol.

Post operative fever is common in children after surgery, but NSAIDs treatment for children may have reduced duration of pyrexia because of its antipyretic action[63]. However the use of NSAIDs is associated with certain side effects, they prevent platelet aggregation and thus may increase bleeding[64]. So it should be used with care in children with thrombocytopenia or coagulopathies. They should also be used with caution in children with bronchial asthma, liver dysfunction, impaired renal function, hypotension or hypovolemia[61].

The first dose of NSAID should be given after surgery before pain occurs. The route preferred is I/V, if the IV is in place, otherwise they can

be given I/M, orally or rectally. Nimuselide is a new non-steroidal anti-inflammatory drug of sulphonalide class. It has a unique pharmacological profile within the currently available NSAIDs as it is highly selective cyclo oxygenase 2 inhibitor not interfering with the physiological production of prostaglandins in the stomach and kidney (regulated reaching peak concentrations within two hours). Clinical studies have established the analgesic, anti-inflammatory and antipyretic by cyclo oxygenase and as a consequence it causes less local gastrointestinal toxicity[65]. It is administered orally and is rapidly absorbed reaching peak plasma concentration within two hours. Clinical studies have established the analgesic, anti-inflammatory and antipyretic effectiveness of nimuselide. However, there are limited studies on the therapeutic efficacy of nimuselide in children (Table 7).

Table 7
Doses of Different NSAIDs

Drug Dose	Loading Dose (mg/kg)	Maint Dose (mg/kg)	Interval (hrs.)	Daily Max (mg/kg)
Ketoprofen	2	1	6-8	5
Ibuprofen	10	10	6-8	40
Naproxen	10	5	8-12	15
Diclofenac	2	1	6-8	3
Ketorolac	0.5	0.25	6-8	2

Adverse Effects of Salicylates and The NSAIDs

Even when used in therapeutic doses with careful patient selection and monitoring, adverse effects can occur with the salicylates and NSAIDs. They are headache, dizziness, drowsiness, personality changes and blurred vision, nausea, vomiting, photo toxicity, pruritis, rash, erythema multiforme, peptic ulcer formation, GI bleeding, decreased GFR, renal dysfunction, hepatic dysfunction, platelet dysfunction, bronchospasm, bone marrow suppression, sodium and water retention, inhibition of fibroblast proliferation and interactions with other medications. Absolute and relative contraindications to its use include-true allergy, peptic ulcer disease, renal failure, uncorrected hypovolemia, bleeding dyscrasia, platelet dysfunction,

significant risk of surgical bleeding, asthma and proven influenza or varicella infection.

Adjuvant Medication

Children recovering from extensive surgical procedures or suffering from chronic pain may be treated with several non analgesic drugs that can either potentate pain relief or modify the opioid side effects. Tricyclic antidepressants can improve the opioid analgesia by stimulating central and descending pain inhibitory systems[12,52].

These drugs can improve sleep cycles and mood. Tricyclic antidepressants are administered two hours before bedtime[12], The efficacy of therapy can be assessed in the morning. Stimulants such as dextroamphetamine and methyl phenidate may be used to decrease opioid induced sedation and improve mood[53]. These should be given in the morning so that insomnia is avoided. Neuroleptics such as droperidol may increase opioid analgesia and may improve patient cooperation for short painful procedures. Small doses of ketamine may be used for the same. Benzodiazepines may decrease anxiety in a frightened child and may provide amnesia during short surgical procedures. They produce muscle relaxation and potentate opioid induced respiratory depression.

Anticonvulsants and corticosteroids may relieve neuropathic pain and pain syndromes associated with swelling and inflammation.

Tricyclic Antidepressants

The tricyclics are[66-71] are useful analgesics in several forms of chronic and neuropathic pain. They are thought to act centrally on monoaminergic pain inhibitory systems. Although patients with chronic pain are frequently depressed[72,73] and these agents are effective antidepressants, evidence suggests that the pain relieving actions of tricyclics are at least in part analgesic per se and not solely mediated through their antidepressant effects[74]. Patients with chronic pain often have disturbed sleep, and many of them catnap during day time due to drowsiness. In these patients nightly

administration of small doses of tricyclic antidepressants is the most appropriate agent for long term use to normalize sleep. The major side effects are morning somnolence and dry mouth. Amitryptiline is widely used in pediatrics, can be started as low as 0.1 mgm/kg advancing as tolerated over 2-3 weeks to 0.5-2 mgm/kg. Imipramine and desipramine have also been used in pediatrics. Tricyclics are used with extreme caution in patients with cardiac conduction disturbances.

Stimulants

Methylphenidate and Dextroamphetamine have both shown to enhance analgesia and oppose sedation produced by opioid analgesics. These drugs are especially helpful in cancer pain; its use in other pains should be judicious and restricted to short term.

Membrane Stabilizing Drugs

This refers to those drugs that are thought to relieve pain by altering neuronal excitability via direct or indirect actions on ion channels. They are commonly employed for neuropathic pain and for migraine. Anticonvulsants, local anesthetics and calcium channel blockers are widely used class of these agents.

Anticonvulsants

They are often[75,76,77] used in patients with migraine or neuropathic pain.

Local Anesthetics

They are thought to block[78,79] the axonal impulse conduction by reversible blockade of sodium channels, but they may have other actions as well.

Calcium Channel Blockers

They have been employed in the treatment of migraine and other vasomotor abnormalities[80].

Beta Blockers

Propranolol and other beta blockers have been widely used for treatment of migraine in children.

Corticosteroids

They can relieve pain associated with swelling and inflammation and also used for refractory nausea in cancer patients.

Sedatives and Hypnotics

These agents are mentioned mainly to discourage the widespread practice of administering sedatives to children in pain in place of opioid analgesics. In most circumstances our aim should be to provide analgesia not simply render the child too sleepy to complain or resist.

Antihistaminics

They are used to treat opioid induced side effects.

Barbiturates

These agents produce little or no analgesia in fact may be antianalgesic.

Benzodiazepines

Are useful premedicants for surgery or procedures.

Neuroleptics

Phenothiazines and butyrophenones are used in the treatment of nausea and vomiting particularly associated with cancer chemotherapy.

Future

The past decade has brought about an explosion of knowledge about the physiology of nociception and many new techniques for pain relief, new analgesic drugs and new applications of old analgesic drugs. These techniques include methods of opioid administration by transdermal and transmucosal absorption and the use of neuraxial analgesia for management of pain in children. Perhaps the greatest advance has been the paradigm shift in the recognition that pain not only exists in infants and children but also is a significant cause of morbidity and mortality. With the recognition that children deserve effective analgesic therapy, the evolution of pediatric pain specialists and the continued growth and development of pediatric pain services, the future of pain relief in this patient population is promising. 'As in any new movement, political or philosophical, diverse ideas prevail. But to ignore the tide of change is to be swept away in the current'.

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