

PAIN RELIEF AND PALLIATIVE CARE IN LEBANON PAIN MANAGEMENT IN CHILDREN WITH TERMINAL ILLNESSES

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ABSTRACT : Managing pain in children at the end of life is a complex area that requires an understanding of the unique challenges offered by this young population. The following article will assist the practitioner with the management of pain associated with terminal illnesses in children. Discussion will focus on concepts and principles that form the foundation of pediatric pain management. Prior to the presentation, an overview is presented to address the pharmacologic concerns in the younger patients and the assessment of pain in the different age groups.

INTRODUCTION

Patients with terminal illnesses including cancer, AIDS, neurodegenerative disorders and cystic fibrosis need approaches to palliative care that focus on optimal quality of life. In one study, 89% of parents whose children died of cancer reported that their child had at least one bothersome symptom in his/her last month of life, most commonly pain, and fatigue or dyspnea [1]. In the end of life, it is important to initiate a pain treatment plan even when the diagnosis may be unclear, the prognosis uncertain and the ability of the child to communicate limited. Presumptive therapy should be initiated promptly and treatment plans can be then modified based on the response. For the dying child in whom an accurate assessment of the cause of pain may be difficult because the child is unable to verbalize his/her pain, it is important to frequently reassess therapy knowing that it may take several doses and several medication adjustments in order to determine optimal analgesic requirements. The misconception about the patient becoming addicted to pain medications as well as desirability of saving stronger opioids for later has been overcome.

DEVELOPMENTAL PHARMACOLOGY

Several factors produce age-related differences in response to analgesics [2].

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PAINRELIEFAND PALLIATIVECAREGROUP

Bou Khalil MK. La prise en charge de la douleur chez l'enfant en fin de vie. *J Med Liban* 2008 ; 56 (2) : 93-99.

RÉSUMÉ : La prise en charge de la douleur chez l'enfant en fin de vie est un domaine complexe qui requiert la compréhension des caractéristiques propres à cette jeune population.

Le présent article procurera une aide au praticien dans le traitement de la douleur pédiatrique en fin de vie. La discussion portera sur les principes et les fondements de la prise en charge de la douleur. L'approche pharmacologique de même que l'évaluation de la douleur chez les différents groupes d'âge seront abordées en début d'article.

- Neonates and young infants have delayed maturation of hepatic enzyme system involved in drug metabolic inactivation. Analgesics metabolized in the liver, such as opioids and amino-amide local anesthetics have a prolonged elimination half-life in newborns. Rates of maturation of individual enzyme functions vary for most analgesics ; usually the metabolism has matured by the age of 6 months.
- Renal blood flow, glomerular filtration and tubular secretion increase dramatically in the first weeks and approach adult values by three to five months. Renal clearance of analgesics is often greater in toddlers and pre-school children than in adults, whereas premature infants tend to have reduced renal clearance of analgesics.
- Neonates and infants up to six months of age have decreased levels of albumin and 1 acid glycoproteins. This factors leads to the decreased plasma protein binding for many drugs such as local anesthetics.
- Children of all age are at an increased risk for local anesthetics toxicity due to their increased systemic absorption and rapid uptake. This risk occur secondary to the relatively higher cardiac output and regional blood flow in children [3].
- Infants have immature ventilatory reflexes in response to hypoxia and hypercarbia and have increased risk of hypoventilation in response to opioids.
- In the younger age nerves have a smaller fiber diameter, a thinner myelin sheath, and a shorter internodal distance, together these properties result in a decreased minimum concentration of local anesthetic required to block nerve [4].

Pain is the fifth vital signs now in many institutions. Pain is both a sensory and emotional experience. Assessment of pain is a greater challenge in children when compared with the adults, because of the communication barrier in the younger population, but children as young as three years of age can describe intensity, quality and duration as well. Self reporting is the gold standard for pain assessment in children three years and older [5]. For infants and preverbal children, parents, pediatricians, nurses and other caregivers are constantly challenged to interpret whether the distressed behavior of children represent pain, fear, hunger, or a range of other perceptions. A therapeutic trial of comfort measures (feeding, etc.), and analgesic medications may be helpful in clarifying the situation.

Self report by using a visual analog scale (VAS vertical 10 cm line, subject marks online between no pain and worst pain imaginable) is regarded as the most reliable estimate of pain. But only children who have attained a certain degree of cognitive ability (eight years and older) are able to provide information this way. Therefore face scale (either drawing or photographs representing increasing degrees of pain), color analogue scales (horizontal or vertical ruler on which increasing intensity of red signifies more pain) are designed for younger children (four years and older).

These scales are useful but there are concerns about the sensitivity and specificity of such tools particularly for younger children who may not report accurately or reproducibly and who may be influenced by how the scale is presented [2], furthermore the problems with these scales is that the happy face which is supposed to equal no pain may not always be chosen in the event of no pain secondary to the fact that the patient is probably not happy being in a hospitalized setting which is associated with distress, anxiety and boredom. Infants, preverbal children and individuals with communication difficulties may be among the most vulnerable to unrecognized pain and yet they are unable to describe or rate it.

Behavioral observation, change in physiologic characteristics or combinations of these indirect measures are used depending on the child context of pain and setting, number of pain related behavior has been identified, facial expressing being one of the most reproducible ; however this behavior is age related. Some physiologic measures such as heart rate, blood pressure, etc., can be used at all ages, and are useful for patients receiving mechanical ventilation, however they are non-specific, and can occur for issues unrelated to pain [6].

Overall there are numerous scales available for a variety of situations. The essential goal is to consider the context in which the pain is experienced and to thoroughly evaluate the child and his/her individual ability to report or display degrees of pain. Adequate training of observer is essential for the evaluation to be meaningful, and assessment should be frequent as pain is a dynamic process.

Acetaminophen has been shown to be safe even for newborns. The maximal daily doses of acetaminophen for infants and neonates are subject of controversy. Provisional recommendations are that daily dosing should not exceed 75 mg/kg/d for infants ; 60 mg/kg/d for term neonates and preterm neonates of more than 32 weeks of post-conceptual age, and 40 mg/kg/d for preterm neonates 28 to 32 weeks of post-conceptual age. Fever, dehydration, hepatic disease and lack of oral intake may all increase the risk of hepatotoxicity [2]. In children who are unable to take acetaminophen by mouth the rectal route is the next option, the intravenous route can also be used. The loading dose is 20 mg/kg PO or 40 mg/kg PR every 6 hrs and can be continued as long as drug is needed [7].

NSAIDs are effective for mild to moderate pain. They are more potent than acetaminophen but also they have a ceiling effect. **Ibuprofen, naproxen, diclofenac** and **ketorolac** are commonly used in pediatric population, the use of these medications [8], however is limited in the child with thrombocytopenia, gastritis and coagulopathy (See table I).

TABLE I
ORAL DOSAGE GUIDELINES
FOR COMMONLY USED NON OPIOID ANALGESICS

DRUG	Dose for patients < 60 kg mg/kg	Interval hr
Acetaminophen	10-15	4
Ibuprofen	6-10	6
Naproxen	5-6	12
Ketorolac	0.5	6-8

Ketamine is a NMDA-receptor antagonist. Pediatric experience has shown that ketamine is effective for the treatment of acute nociceptive pain, as well as for neuropathic pain, in low subanesthetic doses, both alone or in combination with opioids [9]. Ketamine is a dissociative anesthetic with rapid onset short duration of action and minimal hemodynamic side effects. It protects the airway reflexes within analgesic dosing and can be administered IV, IM, PO, PR or even intranasally [10].

Topical anesthetics : EMLA (Lidocaine-Prilocaine cream), and **AMETOP** (tetracaine) are effective topical anesthetics for children used to reduce pain from cutaneous procedures such as venipuncture, intravenous cannulation, portacath needle insertion. Because of their slow onset of action, they should be applied to the intact skin between 30 min (AMETOP) and 60 min (EMLA) before the procedure [11-12]. EMLA cream may cause methemoglobinemia with repeated uses, but it is used safely in children beyond neonatal age [13]. The topical anesthetics are known to be more effective in the face and scalp than in the extremities. Lidocaine patch 5% (**Lidoderm**)

TABLE II
ADJUVANT ANALGESICS FOR THE TREATMENT OF NEUROPATHIC PAIN

DRUG	Starting dose for patients < 50 kg
Amitriptyline	0.2 mg/kg PO once at night <i>titrated to a maximum of 1 mg/kg/d - 2 mg/kg/d over 2-3 weeks</i>
Gabapentin	2 mg/kg/dose - 5 mg/kg/dose PO qhs, then bid then tid, increase over 2-4 weeks <i>max. 10-20 mg/kg tid</i>
Ketamine low dose	0.04 mg/kg/h - 0.15 mg/kg/h IV/SC <i>titrated to effect : usually max. 0.3 mg/kg/h - 0.6 mg/kg/h</i>
Tramadol	1 mg/kg - 2 mg/kg q4-6h <i>max. of 8 mg/kg/d</i>

PO : oral qsh : everyday at bedtime bid : twice daily tid : three times daily IV : intravenous SC : subcutaneous

which is effective in the management of adult neuropathic pain, is also useful in selected children [7].

Tricyclic antidepressants are beneficial as coanalgesics in children with cancer pain; **Amitriptyline** is the first line tricyclic adjuvant analgesic for neuropathic pain. The analgesic effect may start to occur 3 to 7 days after initiation. **Gabapentin** is commonly used in pediatric neuropathic pain management (See table II).

Antispasmodics : used to treat muscle spasticity. One of the most common agents is **diazepam** 0.1-0.2 mg/kg rectally or orally. Chronic spasticity is often treated with **baclofen**, GABA agonist, can be given orally or intrathecally through an implanted infusion pump.

Glucocorticoids : A number of studies have documented the positive effects of corticosteroids on cancer related pain symptom.

Nitrous oxide : The poor response to opioids due to breakthrough pain observed near the end of life could potentially be addressed with nitrous oxide. It is an analgesic, anxiolytic, and sedative agent, with a rapid onset of action. Nitrous oxide is usually delivered in a 50% mixture with oxygen by a patient controlled mechanism. It was shown to be safe and effective when used by advanced cancer patients with breakthrough pain due to bone metastases. Environmental exposure to caregivers was minimal. Nitrous oxide should not be used in the presence of bowel distention [14].

Opioids : used for moderate to severe nociceptive pain, although they are sometimes used for neuropathic pain. Most commonly used opioids bind to Mu receptors. At equipotent doses all Mu agonists produce similar physiological effects and side effects, but they have different duration of action. **Morphine** is a standard opioid with which all other opioids are compared. It can be given through multiple routes (intravenous, oral, subcutaneous, intrathecal, epidural and intraarticular). **Methadone** is a synthetic opioid that is noted for its long elimination half-life and duration of action (12-36 hours). Traditionally used with opioid dependent patients, methadone is being increasingly used in cases of acute pain to provide stable levels of opioid analgesia. It has a high bioavailability 80% making it an attractive oral analgesic.

Fentanyl is a synthetic opioid that is 100 times more potent than morphine, it can be given in multiple routes (intravenous, epidural, spinal, transmucosal, and transdermal). Fentanyl is available in a candy matrix preparation for transmucosal administration. Transmucosal fentanyl has been used as a premedication for painful procedures and for breakthrough pain with an onset time of 20 min and duration of 2 hours. It provides good analgesia but the incidence of nausea with this modality is troublesome. Transdermal fentanyl is available in patches 12.5, 25, 50, 75, and 100 mcg/h for use lasting 2-3 days. It has a long onset time but also a long duration that persists after the patch is removed.

Meperidine is being used less frequently because it has the potential to cause seizures when used for an extended period. However it is still used in single doses for postoperative shivering.

Naloxone is an antagonist at all opioid receptors, it is used emergently for respiratory depression at a dosage of up to 10 mcg/kg IV. It is also used in smaller doses for pruritis (1-2 mcg/kg IV) (See table III).

MANAGEMENT STRATEGIES

Several concepts and principles form the foundation of pediatric pain management :

1. Follow a stepwise approach to the escalation of therapy, as codified by the World Health Organization [15], with an emphasis on drug selection based on the intensity of pain from acetaminophen and non steroidal anti-inflammatory drugs for mild pain to opioids for moderate to severe pain [16]. This approach can provide good and adequate pain relief with tolerable side effect profile.
2. At each stage, adjuvant analgesics appropriate to the nature of pain should be introduced [10].
 - Antidepressants or anticonvulsants for neuropathic pain.
 - Octreotide, anticholinergic for bowel spasm from obstruction.
 - Bisphosphonate, calcitonin, steroids, radiotherapy for bone pain secondary to tumor metastasis.

TABLE III
OPIOID DOSING REGIMENS

OPIOID	Route/Age group	Dose/Interval
■ MORPHINE	Oral immediate release : infants and children	0.3 mg/kg every 3-4 h
	Oral, sustained release : infants and children	0.25-0.5 mg/kg every 8-12 h
	IV bolus:	
	● Full term neonate	25-50 µg/kg/every 3-4h
	● Infants and children	50-100 µg/kg every 3 h
■ FENTANYL	IV infusion	
	● Full term neonate	5-10 mcg/kg/h
	● Infants and children	15-30 mcg/kg/hr
	Oral transmucosal	10-15 µg/kg (oralet)
	Intranasal	1-2 µg/kg
■ NALBUPHINE	Transdermal	12.5, 25, 50, 75, 100 µg/h patches
	IV bolus	0.5-1 µg/kg every 1-2h
	IV infusion	0.5 µg/kg/h
	IV bolus	
	● Full term neonate	25-50 µg/kg every 2-4h
■ MEPERIDINE	● Infants and children	50-100 µg/kg every 2-4h
	IV infusion	
	● Full term neonate	10-15 µg/kg/h
	● Infants and children	20 µg/kg/h
	IV bolus ● Infants and children	0.8 -1 mg/kg every 3-4h

- Benzodiazepine, botulinum toxin A, baclofen for muscle pain from neurodegenerative disease.
- Steroids for resistant pain.

3. Choose the least invasive route for medication : the oral route is preferred unless there are contraindications [17].

Not all patients are able to swallow tablets or capsules ; this is particularly true among children with neurodegenerative conditions. Oral dosing may fail for some patients with rapidly escalating pain and for children who are unable to tolerate oral opioids because of mucositis, vomiting or uleus. A range of alternative routes are available. IVinfusions or IVboluses or PCA can permit rapid titration for escalating pain. However, multiple peripheral cannulations for intravenous infusions is not always appropriate in the palliative care setting since the subcutaneous route is at least equally effective and much easier to set up and maintain at home or in a hospital. Transdermal route is another option : Fentanyl is available as a self adhesive patch – the usual interval between changes of patch is 72 hrs but a minority of patients may need it changed every 48 hrs. Portable syringes drivers which are battery operated are a convenient method for administering many drugs. Patient-controlled analgesia or nurse-controlled analgesia are effective means of delivering pain relief through IVor subcutaneous route. Some children will find rectal administration of medications unacceptable, for others it can provide rapid absorption and

avoids the need for injection. Relatively few strong opioids are available in rectal formulations. They include oxycodone, morphine and hydromorphone (not available in Lebanon) ; (tramadol is available in rectal formulation). Fentanyl oral tablets (not available in Lebanon) is a rapid acting drug usually used for breakthrough pain.

- 4. Determine the temporal characteristics of pain :** Pain that is limited to intermittent, brief episodes (breakthrough pain) may be controlled with as-needed doses, with an immediate acting opioid (Morphine immediate release every 4 hours), ongoing pain (constant pain) is an indication for an “around the clock” prescription with a long acting opioid (Morphine sustained release every 8 to 12 hours). For patients with severe pain, oral sustained release preparation of morphine is convenient for providing near constant basal analgesic effect with dosing three times daily. Often, a prolonged duration opioid is prescribed along with an immediate acting opioid with the former on a schedule and the later on as-needed basis : the initial treatment can start with morphine immediate release every 4 hours. Once patient is stabilized, conversion to a controlled release preparation should be made by calculating the total daily dose of immediate release morphine and dividing it by 2 or 3 equal doses of sustained release morphine. Immediate release morphine should be kept for breakthrough pain (one sixth of the total daily dose can be given as morphine immediate

release). The total dose should be reviewed every 48 hours with an increase in the regular dose being indicated if more than 2 breakthrough doses have been required in consecutive 24 hour-periods.

If immediate release tablet is not available, use IV or subcutaneous route. The slow release formulations of morphine seem to result in a less sustained serum concentration in children than in adults and it is common for children to require slow release oral morphine sulfate to be given at 8 hours interval rather than the recommended 12 hours interval [16].

Keep in mind that pain may be episodic for three reasons : the dose of regular medication may be too small, resulting in intermittent breakthrough pain for which the solution is to increase the regular medication. The cause of the pain may be episodic, for example movement (incident pain) can provoke pain from a pathologic fracture or from bony metastases. Identifying and avoiding the provoking factors are mainstays of treatment. Finally the pain may simply be of an episodic nature, for example, intestinal colic or

muscle spasm – this is a situation in which adjuvant therapy such as anticholinergics or muscle relaxants may be helpful [17].

5. Anticipate (prevent) or treat common side effects such as constipation, pruritis, nausea, dysphoria, and somnolence (See table IV). The adverse effect profile in children seems to be slightly different from that in adults. It is unusual for a child to become nauseated as a result of opioid therapy and prophylactic antiemetics are not usually indicated when starting opioid therapy in children. On the other hand constipation is very common and laxatives or a softener should always be started at time of prescribing a strong opioid.
6. Consider switching to a different opioid when limited by side effects (concept of opioid rotation). Sometimes, tolerance to strong opioids occurs even in a therapeutic range. The first step is usually to increase the dose of the opioid. If such increase leads to side effect, such as neuroexcitability, dysphoria, myoclonus and pruritus, switching to or rotating among different opioids may be the solution [18-19]. A patient who has developed

TABLE IV
COMMON OPIOID SIDE EFFECTS

SIDE EFFECT	Management	Notes
Constipation	Prophylactic stool softner (e.g. Lactulose) Stimulant laxative Low-dose naloxone	<i>Almost universal</i> <i>Should start prophylactically</i> <i>0.1-0.25 mcg/kg/hr</i>
Nausea Vomiting	Opioid rotation 5-HT3 receptor antagonist-Ondansetron Dexamethasone Metoclopramide Nalbuphine Naloxone Lorazepam	<i>Can decrease after 3-7 days</i> <i>0.1-0.2 mg/kg IV q 6h prn</i> <i>PO or IV : 0.1-0.2 mg/kg initially then up to 1-1.5 mg/kg/day divided into doses q 6h</i> <i>0.1-0.2 mg/kg dose IV q 6h</i> <i>10-20 mcg/kg/dose IV q 6h</i> <i>0.1-0.25 mcg/kg/h</i> <i>PO or IV : 0.03-0.2 mg/kg q 4-6h up to 2 mg/dose</i>
Pruritis	Diphenhydramine Hydroxyzine Opioid rotation Naloxone	<i>0.5-1 mg/kg q 6h</i> <i>IV continuous infusion 0.25 mcg/kg/h ; titrate up to 1 mcg/kg/h</i>
Fatigue	Opioid rotation, if unsuccessful : psychostimulant trial	<i>Can decrease after 3-7 days</i>
Confusion	Opioid rotation OR consider trial of dose reduction	<i>Increased with renal or hepatic impairment</i>
Myoclonus	Opioid rotation Muscle relaxant	<i>Usually occurs in patients on high dose opioids</i>
Urinary retention	Opioid rotation External bladder pressure Bethanacol	
Respiratory depression	Opioid rotation, if poor pain control Oxygen Naloxone	<i>Much less frequent than commonly thought</i> <i>Can be more common in neonates due to longer opioid half-life caused by immature enzyme systems</i>

IV : intravenous q : every h : hour prn : as needed PO : oral

tolerance to the analgesic effects of morphine may well be less tolerant to those of fentanyl. When substituting one opioid for another, the dose should be reduced because tolerance to the analgesic effect of the new opioid is incomplete, a corresponding reduction in toxicity will occur. The dose reduction is conventionally 25% thus a child who is toxic but not pain free on oral morphine 1000 mg/d can receive instead a fentanyl dose equivalent to only oral morphine 750 mg and get better analgesia and less toxicity. Given individual variability in conversion underestimating the initial fentanyl patch dose is appropriate, augmented with rescued doses of oral morphine if pain is not controlled. The dose 1.5 µg/h is equianalgesic to 1 mg morphine taken every 4 hrs. A dose of 25 µg/hr would be equianalgesic to 15 mg oral morphine taken every 4 hrs, patches take 18 to 24 hrs to achieve steady state serum levels of fentanyl and once removed have a half life of another 18 hrs [20].

7. Always include cognitive (guided imagery, distraction), physical (TENS, phyiotherapy, massage, acupuncture), behavioral techniques and others (prayer, music, art therapy) [21-22].
8. Consider invasive treatment modalities for pain that is difficult to treat (epidural and intrathecal catheters and neurolytics nerve blocks). There remains a small subgroup of children with cancer who require truly massive opioid dose escalation, who have intolerable side effects or who alternate between excessive sedation and inadequate analgesia. In selected cases, regional anesthetic approaches may be considered. The intrathecal route can provide better analgesia than the systemic route, with a favorable analgesia side effect profile. Techniques include external catheters for short term needs. Intrathecal pumps are usually placed if epidural infusion is no longer feasible secondary to local anesthetic toxicity or extend life expectancy. In pediatric population implantation is indicated if patient has more than two months life expectancy [13]. Intrathecal infusions of local anesthetics agents, opioids and clonidine can provide effective analgesia for patients with unremitting neuropathic pain, pain from tumor involvement of the spine, or refractory abdominal pelvic or limb pain [23].

Dying children have a multitude of symptoms in addition to pain for significant period before their death. Dyspnea is common because many children with chronic illnesses have difficulty swallowing and handling their airway secretions. Excessive airway secretion and salivation owing to poor swallowing may be treated with oral glycopyrolate. As death approaches a build-up of secretion may result in noisy respiration, that is often more distressing for others than for the child who is at this stage usually unconscious. Dyspnea can be relieved with the use of regularly scheduled plus as-needed doses of opioid. Opioids can be used without precipitating respiratory failure [24-25]. Nebulized fentanyl has been used successfully [26]. Seizures may increase in fre-

quency and severity toward the end of life. Anticonvulsants should be administered and parents can be taught to use rectal diazepam at home. Increased irritability may be particularly disruptive because of the resultant break in normal sleep-wake patterns. Judicious combination of sedatives in day time (e.g. benzodiazepines) and hypnotics at night (e.g. chloral hydrate) may achieve a balance that can dramatically improve the quality of life of the child.

In Lebanon intensive care units are the location where most children die. Improving the care of these hospitalized children and their families involves liberalizing visiting policies and respecting privacy as well as removing some of the obstacles inherent in intensive care setting such as routine testing and monitoring of vital signs.

CONCLUSION

In the end of life, pain management is a care priority and requires accurate pain assessment, frequent reevaluation, confident and rational use of opioids, flexibility in combining therapeutic modalities, prevention and aggressive management of opioid side effects.

Chronic pain and serious illness are rare in the pediatric population, however when they occur, their effects are devastating, not only to the children but also to their families and caregivers. Even though pain treatment in this population is challenging, it is however critically important to give the benefit of adequate analgesia to these vulnerable patients, and this may require the involvement of experts in developing safe and effective treatment regimens.

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