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Strong Opioids in Pediatric Palliative Medicine

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Abstract

The management of pain in the palliative care of children is somewhat different from that in adults. It also differs in approach from the management of other types of acute and chronic pain in childhood. Whereas once opioids were thought to be highly dangerous drugs, unsuitable for use in children, they have now taken their place as the mainstay for provision of good analgesia to manage moderate-to-severe pain in both malignant and non-malignant life-limiting conditions.

There are relatively little clinical or laboratory data regarding opioids specifically in children. However, much of what has been published regarding the management of pain in palliative medicine in adults can be extrapolated. On saying that, early research in children does suggest some significant differences in opioid pharmacokinetics, particularly with respect to morphine clearance, which seems to be faster in adults.

Thus, the use of opioids in pediatric palliative care presents some unique challenges. Confident and rational use of opioids by pediatricians, illustrated by the WHO guidelines, is essential for the adequate management of pain complicating the palliative phase in children with life-limiting conditions.

The verb 'to palliate' means to relieve without curing. Palliative medicine was first recognized as a medical specialty in the UK in 1987. It has been defined as "the study and management of patients with active progressive, far advanced disease for whom the prognosis is limited and the focus of care is on the quality of life".[1] The WHO further elaborated on the multi-dimensional care inherent in this ideal, summarizing palliative care as "the active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms and of psychological, social and spiritual problems is paramount. The goal of palliative care is the achievement of the best quality of life for patients and their families".[2]

Palliative medicine in children was initially defined in 1997 by the Royal College of Paediatrics and Child Health working with the Association of Children with Life-Limiting or Life-Threatening Conditions and their Families.[3] The basic principle remains the same as for adults; palliative care for children and young people with life-limiting conditions is described as "an active and total approach to care embracing physical, emotional, social and spiritual elements. It focuses on enhancement of quality of life for the child and support for the family, and includes the management of distressing symptoms, provision of respite care through death and bereavement". Life-limiting conditions are those for which there is no hope of cure and from which children will eventually die, though often years or even decades after diagnosis. For many, the progress of the disease is such that they become increasingly dependent on others. Because an end to life is imminent or anticipated in the foreseeable future, care and interventions may sometimes differ from those chosen in acute care, where therapy is aimed at reversing a disease process. They may even differ from chronic care, where optimal management of long-term conditions is the goal.

Opioids often play a central role in analgesic management in palliative care. They are commonly divided into weak and strong opioids. They have no 'ceiling effect'. The dose can be escalated as required to achieve adequate analgesia. Occasionally this can be limited by increasing toxicity, in which case an alternative may be equally effective with fewer adverse effects. Such a limitation is more likely with weak opioids.

Strong opioids are the predominant analgesics used in palliative care, and this review examines aspects of their use for the treatment of pain in children with life-limiting conditions. They are also used in neonates in the treatment of conditions such as sickle cell anemia. The pharmacokinetics, role, and use of opioids in these situations is very different from their use in palliative care and are therefore outside the scope of this article.

Historically, the approach taken by physicians to using major opioids in their patients has been an illustration of the human tendency to place more faith in myth than in evidence. We are particularly prone to believe myths that appear to carry the authority of scientific research. For decades it was believed that opioids were highly addictive drugs whose therapeutic potential was trivial compared with their threat to society. The fear of prescribing morphine, now often termed 'morphophobia', has been and perhaps remains the single greatest threat to the comfort of patients with moderate-to-severe pain.

Children are especially vulnerable to under-treatment of their pain. In caring for a child, the instinct of adults may be to adopt a precautionary approach. The belief that morphine is a highly dangerous drug, however ill supported by evidence, is enough to cause many pediatricians to hesitate before prescribing it. Other myths have developed to justify such an approach. These include the traditional notion that children are physiologically less capable of feeling pain,[4] or that they can and should 'tolerate discomfort well'.[5]

Provided that basic prescribing principles are observed throughout, morphine and other strong opioids are very safe in the management of moderate-to-severe pain. The risks of adverse effects and addiction in adult palliative care are small[6] and there is no evidence that children differ in this regard.[7]

1. Major Opioids in Palliative Medicine in Children

1.1 Measuring Pain in Children

Pain is one of the most prevalent and distressing symptoms experienced by children with life-limiting conditions, and is rightly given high priority by the WHO.[8] For the dying child, accurate assessment of pain is often difficult and it is frequently necessary to review the effectiveness of therapy. Furthermore, many children with life-limiting illnesses are unable to verbalize their symptoms and will instead communicate their discomfort nonverbally. A great deal of work has been published in developing age-appropriate scales for measuring pain.[9,10] Choosing a pain assessment scale suitable for day-to-day clinical use is important. However, it can be problematic. There are multiple tools available and this reflects the fact that none is ideal. Also, the measurement of pain in cognitively impaired children remains a challenge.[11] Whatever tool is chosen, it must remain part of the cycle of assessment, intervention, and review or re-assessment.

1.2 The Place of Morphine in Pain Control

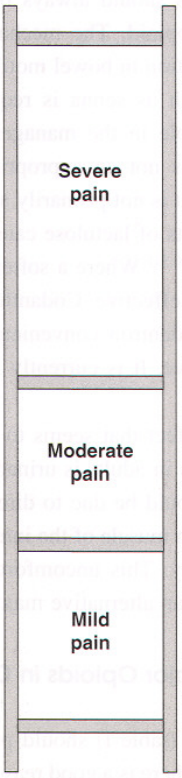
In attempting to address misunderstandings about opioids, the WHO developed an analgesic ladder[2,8,12] (figure 1). This provides a rational, simple, stepwise approach to pain, in which simple analgesics comprise the first rung, weak opioids such as codeine the second, and strong opioids such as morphine the third. Analgesia on a higher rung of the ladder is introduced only if the previous one becomes ineffective.

This three-step approach has to be taken in conjunction with a number of other principles. Firstly, at each stage, adjuvant analgesics appropriate to the nature of pain should be introduced. It is particularly important to identify features of neuropathic or bone pain. Secondly, there is no place for strong opioids to be given only *pro re nata*; if a strong opioid is required it should always be given on a regular schedule, by the clock. The prescription of a regular dose of a strong opioid should always be accompanied by a breakthrough dose that should be a fixed fraction of the total daily requirements. The total dose should be reviewed every 48 hours, with increases in the regular dose being indicated if more than two breakthrough doses have been required in consecutive 24-hour periods. Thirdly, the oral route is always preferred unless there is a contraindication (e.g. cytotoxic-induced mucositis).

Notwithstanding these general principles, a child suddenly presenting with severe pain may need a strong opioid from the outset, often parenterally and in frequent doses, until pain control is achieved.

1.3 Pharmacokinetics of Morphine in Children

Morphine remains the most frequently prescribed strong opioid in children and is the one about which most is known. Among strong opioids, it is the archetype. It is best to consider opioids in children by examining the characteristics of morphine first, and then other strong opioids insofar as they differ in indication or in pharmacology from morphine itself.



Strong opioid + laxative
Initial treatment
- Use morphine liquid or immediate-release morphine tablet
- Dose: <1 year = 100 µg/kg 4 hourly
  1–12 years = 100 µg/kg 4 hourly
  >12 years = 10mg every 4 hours

Breakthrough pain
- Give one-sixth of the TDD of opioid as immediate-release preparation every 2–4 hours as needed orally

Maintenance treatment
- Review need for breakthrough after 48 hours. Add total breakthrough required to TDD and calculate new breakthrough dose
- Once patient is stabilized convert to a controlled-release preparation (MST) and give twice daily. Divide TDD by two and give in equal doses every 12 hours. Give the first dose of slow-release preparation with the last dose of Oramorph®[1] or immediate-release tablet preparation

Weak opioid + laxative
Dihydrocodeine
Age 1–4 years = 500 µg/kg every 4–5 hours
Age 4–12 years = 500µg – 1 mg/kg every 4–6 hours
Maximum single dose = 30mg
Maximum TDD = 6 mg/kg/day

Simple analgesic
Paracetamol
Age 3–12 months = 60–120mg every 4–6 hours
Age 1–5 years = 120–240mg every 4–6 hours
Age 6–12 years = 250–500mg every 4–6 hours

Fig. 1. An example of the WHO pain ladder approach to pain relief. At each 'rung', appropriate adjuvants should be considered (e.g. radiation for metastatic bone pain, NSAIDs for musculoskeletal pain, antidepressants or anticonvulsants for neuropathic pain). **MST** = slow-release oral morphine sulfate; **TDD** = total daily dose; * indicates starting doses only (note there is no ceiling dose). **1** The use of trade names is for product identification purposes only and does not imply endorsement.

Morphine appears to be well absorbed from the child's gastrointestinal tract.[13,14] The oral to parenteral potency is approximately 50%; in other words, to achieve the same effect, an oral dose of morphine should be twice that given intravenously or subcutaneously. There is extensive biotransformation in the liver to a number of compounds, of which the two most important are morphine 3-glucuronide (M3G) and morphine 6-glucuronide (M6G).[14,15] Both are more soluble in water than the parent compound. M3G is quantitatively the most important but has little or no affinity for the mu-opioid receptor, and no analgesic activity.[16,17] There is some evidence to suggest that it may contribute to some of the adverse effects of morphine, particularly neuroexcitability,[17] though this is hard to explain. M6G on the other hand, has a high affinity for mu-opioid receptors[18] and is a powerful analgesic[19,20] with an effectiveness that exceeds that of morphine. The capacity to form both glucuronides is present from an early stage in fetal development[21] and there is some evidence that it increases over the first 12 months of life.[22,23]

The distribution of morphine and M6G seems to be similar in children and adults.[14,15] Clearance of the glucuronides is almost entirely renal and much of the parent compound is also excreted in the urine. The clearance of morphine and M6G in children appears to exceed that in adults.[14,15,22,24] This may be both due to better renal clearance and faster glucuronidation in children.

In order to have a therapeutic effect, morphine and M6G must cross the blood brain barrier to have access to receptors in the brain. Both morphine and M6G can penetrate into the cerebrospinal fluid of children. There is no evidence to suggest that outside infancy this happens more easily in children than in adults,[15] making it unlikely that children are any more sensitive to centrally mediated effects of opioids, such as respiratory depression.[25,26]

Morphine is the only major opioid whose pharmacokinetics have been extensively studied in children. The results have often been inconsistent but the most reliable seem to suggest that the volume of distribution per kilogram in children is much the same as adults but that clearance and half-life are rather shorter.[14,15] The ratio of glucuronides to morphine may be higher in children than in adults.[14] The kinetics in a child under 12 months of age are very different, with rather lower clearance particularly in children under 2 weeks old.[27-29] One study that concluded that clearance appeared to reach adult levels by 2 years of age[24] did not address the likelihood that it then improves further before declining to adult levels at puberty.

There is anecdotal evidence to support the use in children of a smaller opioid dosage interval than in adults, particularly in the use of slow-release morphine and fentanyl patches. 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-hour intervals rather than the recommended 12-hour interval. Such a difference has not been shown in immediate-release preparations of morphine, but this may be because when the appropriate breakthrough-dose interval of 2–4 hours is used the difference does not have time to manifest.

1.4 Clinical Use and Adverse Effects of Morphine in Children

Typical guidelines for the management of pediatric pain are shown in figure 1. The adverse-effect profile in children seems to be slightly different from that in adults. It is distinctly 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 should always be started at the time of prescribing a strong opioid. The mechanism of opioid-induced constipation is a reduction in bowel motility. To overcome this, a stimulant laxative such as senna is required. Lactulose, which enjoys a prominent role in the management of constipation in children in the UK, is not an appropriate laxative for opioid-induced constipation. It is not primarily a stimulant. Furthermore, the breakdown products of lactulose cause flatulence, abdominal distension, and colic.[30,31] Where a softener is required, magnesium hydroxide is very effective. Codanthrusate, a combination of sodium docusate and dantron conveniently combines a softener and a stimulant laxative. It is currently licensed only for use in palliative care.[30,31]

Another adverse effect that seems to occur much more commonly in children than in adults is urinary retention. The mechanism is not clear; it could be due to direct stimulation of opioid receptors in the smooth muscle of the internal sphincter, or due to anti-muscarinic activity. This uncomfortable complication is an indication to consider an alternative major opioid.

2. Alternative Major Opioids in Children

Alternative opioids (table I) should probably only be considered in children when there is a good reason to abandon morphine. There are several potential reasons, and it is helpful to consider the alternative opioids that are available in terms of the advantages they confer over morphine.

Table I. Dose equivalents of major opioids commonly used in children and their potential advantages over morphine

Opioid	Advantages over morphine	Relative potency compared with oral morphine (approximately)
Diamorphine (oral)	More soluble (when given parenterally)	1.5
Fentanyl (patch)	Patch formulation	100
	Less constipation[32]	
	Less itch[a]	
	Less urinary retention[a]	
Methadone (oral)	Anti-neuropathic activity[33]	Variable
Hydromorphone (oral)	None	5
Pethidine (oral)	None	0.125
Tramadol (oral)	None	0.25
Oxycodone (oral)	None	1.5–2

a Anecdotal information not based on clinical trial data.

Of all the steps in the WHO pain ladder, the final major opioid step offers the greatest variety to choose from. Large numbers of opiates and synthetic or semi-synthetic opioids are available. Many offer dubious advantage over morphine itself and do not have the benefit of its long track record and predictable clinical effectiveness. Others, however, offer real benefits to the individual patient experiencing a specific difficulty using morphine.

2.1 Diamorphine

Diamorphine is currently thought to act in precisely the same way as morphine itself. Its major difference is simply that it is more easily soluble in water. It has a role where a child requires a parenteral dose of morphine that cannot be dissolved in a convenient volume of fluid. Many palliative medicine units make diamorphine their standard parenteral opioid while retaining morphine as their standard oral opioid. Diamorphine is slightly more potent than morphine, needing approximately two-thirds of the dose to give the same effect. To have the same effect as an oral dose of morphine, a parenteral dose of diamorphine should therefore be one-third of the dose.

2.2 Fentanyl

Fentanyl is a synthetic opioid that may offer a number of advantages over morphine for some children.[34,35] It does not appear to accumulate to the same degree when renal clearance is impaired,[36,37] it may cause less constipation than morphine,[32] and it does not seem to cause urinary retention. Perhaps most importantly from the child's perspective, it is available as a transdermal patch, which can avoid the need for a subcutaneous or an intravenous syringe driver in children needing prolonged major opioid therapy at home. The smallest patch size currently available, which delivers fentanyl 25 µg/hour, is too high a starting dose for many children. Fentanyl, being a completely different molecule from morphine, may also be effective when tolerance has developed to morphine or diamorphine. Fentanyl is often used in children as a second-line strong opioid after morphine or diamorphine.[38]

2.3 Hydromorphone

In adults, hydromorphone is approximately five times more potent than morphine,[39,40] and can therefore offer an alternative solution to the problem of solubility of large parenteral doses of opioid where diamorphine is not yet available. It is metabolized in a similar way to morphine,[41] and probably confers little or no advantage over diamorphine where the latter is available. Its main role is in countries where diamorphine is not yet freely available for prescription because of unfounded fears of heroin addiction.

2.4 Methadone

Despite anecdotal reports of its safe use even in outpatients, there is little published experience of methadone in children.[42,43] This is a pity; potentially methadone has an important role in the management of pediatric pain. Methadone combines the effects of an opioid with those of an NMDA antagonist.[33] This gives it a potentially major role in the management of neuropathic pains, such as those following thoracotomy, amputation, or nerve damage due to compression by a tumor.[44-48] More research is required into the use of methadone in children before it can be recommended; it has an unusual distribution curve that can result in toxicity many hours or even days after the drug is commenced.[49,50]

3. Other Opioids

3.1 Pethidine

Nowadays, pethidine has little role in pediatric pain relief. It is considerably less potent than morphine (table I). Enteral absorption is erratic.[51,52] The major toxicities of pethidine are on the brain, where accumulation of its metabolites causes convulsions.[53-56] Its one advantage over morphine is that it causes less constriction of the sphincter of Oddi, and proven biliary colic is perhaps its only, very rare, indication in children.

3.2 Oxycodone

Although oxycodone is a kappa as well as a mu agonist, its properties are very similar to those of morphine.[57,58] Its oral bioavailability is about 75% and like morphine it is biotransformed in the liver to a potent analgesic metabolite (oxymorphone). Again, like morphine, the onset of action for oral oxycodone is 20–30 minutes and its duration of action is around 4–6 hours. Its clearance is impaired in renal failure.

There is little experience of the use of oxycodone in palliative medicine, but it appears safe and effective in acute pain.[59] The risk of ventilatory depression may be higher than with morphine.[60] In general, there is no evidence that oxycodone offers any advantage over morphine in adults or in children. Its role in pediatric palliative care, if any, remains unclear. It seems little different from morphine.

3.3 Tramadol

Tramadol is a weak opioid but its analgesic strength is augmented by an additional effect in inhibiting monoamine neurotransmitter reuptake.[61] Nevertheless its potency is only one-fifth to one-tenth that of morphine and it is probably best considered a weak or intermediate opioid.

Its bioavailability is about 75%. Its onset and duration of action are similar to morphine. Its clearance is significantly impaired in liver dysfunction.

Tramadol has a potency intermediate between codeine and morphine. It is more nauseating than oxycodone[62] and, like pethidine, can induce seizures.[63,64] Most research in children has been in the peri- or post-operative context rather than the palliative. Like morphine, any effects on respiratory depression appear clinically insignificant.[65]

4. Episodic and Breakthrough Pain

Breakthrough pain has been defined as "a transitory exacerbation of pain superimposed on a background of persistent but usually well controlled pain".[66] The difficulty in managing episodic pain is that a dose of analgesic adequate for pain at its worst is often toxic when pain is at its least. Extra doses of morphine may be ineffective for severe episodic pain, since the time taken for it to reach effective serum levels means the pain has often subsided before it can work.

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 review 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 some bony metastases. Identifying, anticipating, and where possible avoiding the provoking factors are the 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.

Because these causes for breakthrough pain are closely related, the definitions are often confused and the incidence is therefore difficult to estimate.[67] The prevalence and characteristics of episodic and breakthrough pain have been evaluated. Patients report a wide variety of types of pain that can break through their regular analgesia, and similarly variable events that could precipitate it.[68]

5. Choosing the Most Appropriate Route

The oral route is usually best for children. However, not all patients are able to swallow tablets or capsules. This is particularly true among children with neurodegenerative conditions, though many may have alternative enteral routes such as gastrostomy. Patients who are experiencing nausea and vomiting may simply be unable to tolerate oral medication. A range of alternative routes is available.

Fentanyl is available as a self-adhesive patch.[34,35] The usual interval between changes of patch is 72 hours but a significant minority of patients may need it changed every 48 hours. It is important that adequate breakthrough medication continues to be made available, usually as immediate-release oral morphine, or transmucosal fentanyl.[69]

The subcutaneous route is often overlooked in the management of children. Portable syringe drivers, which are battery operated, are a convenient method for administering many drugs through

Table II. Using opioids effectively: principles of good pain management in children

Do not be afraid of strong opioids in children – the risks of serious toxicity or addiction are extremely small when they are used therapeutically and rationally
Always:
use rational approach to diagnose pain and its cause
use rational approach to manage pain (use pain ladder)
balance benefit of any diagnostic or therapeutic approach with burden to patient or family
use simplest approach that is effective (e.g. oral route where possible)
use appropriate adjuvants at each 'rung'
prescribe stimulant laxatives when major opioid is started
Avoid:
intramuscular route
strong opioids 'prn' except as breakthrough
novel opioids unless they are a genuine improvement on morphine

prn = as required.

subcutaneous infusion. This approach combines the advantages of intravenous infusion (consistent delivery, easy titration, and potential for simultaneous administration of multiple drugs) with simplicity. Subcutaneous syringe drivers can be sited by nurses and can be managed at home with little medical or nursing input. Adverse effects can include local irritation at the site but this is usually easily managed by rotation through different sites.

Patient-controlled analgesia is an effective means of delivering post-operative pain relief. A modification of patient-controlled analgesia in children is nurse-controlled analgesia. This approach requires interpretation by an adult of a child's pain experience and can result in delays to drug administration or even over-ruling of a child's reports of pain.

Where a child already has an indwelling central line, the intravenous route may be preferred.[70] This again permits constant plasma concentration, although this advantage is sometimes offset by difficulties maintaining the line. Multiple peripheral cannulation for intravenous infusion is not usually appropriate in the palliative phase since the subcutaneous route is at least equally effective and much easier to set up and maintain at home or in a hospice.

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,[71] and hydromorphone.

Many strong opioids can be absorbed directly from the nasal or oral mucosa and can therefore be given via the buccal or intranasal route. This approach is particularly widespread among those working in children's hospices, where facilities for immediate intravenous or subcutaneous infusion may not be immediately available. The transmucosal route avoids first pass metabolism, which may influence the effectiveness of opioids that are extensively metabolized in the liver.

6. Opioid Rotation or Substitution

It is likely that in some children tolerance to strong opioid analgesia can occur even in a therapeutic setting. The solution to this is usually to simply increase the dose of the major opioid. Rarely, such increases are constrained by dose-limiting toxicity such as neuroexcitability. One solution is to change to an alternative strong opioid of a different class.[38,72] A patient who has developed tolerance to the analgesic effects of morphine may well be less tolerant to those of fentanyl, for example. This phenomenon is termed 'incomplete cross-tolerance'. When substituting one opioid for another the dose should be reduced because tolerance to the analgesic effect of the new opioid will be 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/day can receive instead a fentanyl dose equivalent to only oral morphine 750mg, and yet enjoy better analgesia and less toxicity. This is further helped by the fact that tolerance to the adverse effects of opioids often occurs more rapidly than tolerance to the beneficial effects. It is probable that there is little advantage in changing drugs within a class, for example, substituting diamorphine for morphine, since cross-tolerance is not likely to be incomplete.

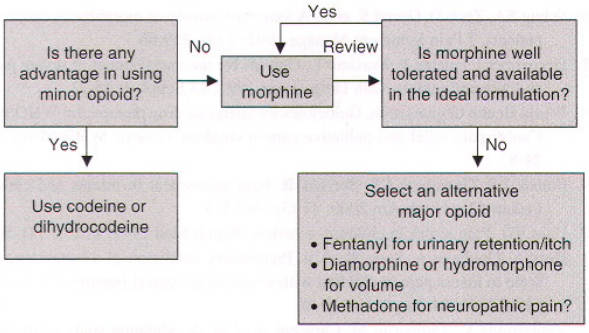


Fig. 2. A logical approach to the use of opioids in children. Until and unless evidence accumulates to suggest that another major opioid is more effective, less toxic, or cheaper (or ideally all of these), oral morphine should usually remain the first line of treatment.

7. Conclusion

The clinical evidence is accumulating that strong opioids can be used safely and effectively in children with moderate-to-severe pain. They should be used as part of a rational approach to the diagnosis, assessment, and management of pain (table II, figure 2). The WHO pain ladder provides a straightforward structure to such an approach and is recommended to all professionals who deal with pain in children suffering from a life-limiting condition.

The evolution of clinical expertise and experience has been paralleled and supported by an expansion of the research evidence base. This seems to show that, where children differ from adults in their handling of morphine, the result is morphine is cleared more rapidly. It is plausible that this may make children more resilient to its effects than adults. More research is needed, as in so many other areas of pediatric clinical pharmacology. Important research areas include the clinical use of methadone in children and the CNS pharmacokinetics of morphine outside adulthood.

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