Pain Management in Pediatric Palliative Care

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Abstract
The majority of the more than 14,000 children dying from life-limiting diseases in the USA each year suffer from pain during their last weeks of life. Data suggest that applying the World Health Organization principles of pain management results in good pain relief for the majority of children with advanced cancer, however less has been reported on the effectiveness of the WHO approach for non-malignant pediatric life-limiting conditions. The management of children with intractable pain remains challenging and requires an interdisciplinary approach. State of the art pain management in the 21st century requires that pharmacological management must be combined with integrative, non-pharmacological therapies to manage a child's pain and suffering effectively.

Introduction
Only a few generations ago it was common in many families that infants and children died during their first years of life. Nowadays the death of a child is a rare and catastrophic incidence in industrialized countries and modern societies are often not prepared to deal with it. Palliative care for children and young people with life-limiting conditions is 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 management of distressing symptoms, provision of respite and care through disease, death and bereavement. [1] Among the many domains of pediatric palliative care, the management of distressing symptoms, especially pain, is one of the most important – but can only be seen in the global picture of a holistic, multidisciplinary approach to the child, siblings and parents and cannot be limited to the application of drugs during the last days of life.

1. Broad-band analgesia
Robert Twycross [51] introduced the term “broad-band analgesia” to manage pain in palliative care. In the management of intractable pain in children it may be necessary to combine non-opioids, opioids, integrative therapies, adjuvant analgesia and anesthetic or neurosurgical interventions.
2. Pain Assessment
The majority of children dying from a life-limiting (both cancer and non-malignant diseases) experience pain during their last week of life. [2, 3, 4, 5] Regular pain assessment followed by appropriate analgesia is necessary to adequately relief the children's suffering. Using one-dimensional self-report measures (e.g. visual analogue scales with the anchor points 0=no pain, 10=worst possible pain or faces scale, Figure 2) [6, 7, 8] provide easy pain assessment of alert and responsive children communicating with the caregiver or provider. For infants and children younger than 4 years of age several pain assessment tools have been validated, requiring independent observers recording the physical behaviors, as well as the frequency of their occurrence. [9] Behavioral observation measures to assess pain in cognitively impaired children are increasingly used. [10, 11] As children may suffer from different pains, such as nociceptive, neuropathic, visceral, or spiritual, to name a few, a single pain rating may not be sufficient to assess the whole dimension of pain. A provider may have to become creative and more detailed-focused to evaluate the different pain aspects of the child. An example could be: "How would you rate your constant achy pain, and how would you rate the occasional shooting pain. "Do you have pain anywhere else, in your heart or soul?"
3. Integrative Pain Management

State of the art pain management in the 21st century demands that pharmacological management is no longer the sole approach to the management of a child's pain and suffering. [12] Integrative therapies, used on its own or together with pharmacology, include cognitive behavioral techniques (such as guided imagery, hypnosis, abdominal breathing, distraction) and physical methods (such as cuddle/hug, massage, Transcutaneous Electrical Nerve Stimulation [TENS], comfort positioning, heat, cold, aromatherapy). Children cope better with pain and other distressing symptoms, when they understand what is happening and when they are encouraged fully in the process to attain relief from their pain. [13] Comprehensive pain control at the end of life requires tailoring to the needs of the individual child and integrating methods of pain management.

4. Pharmacological Pain Management

4.1. WHO-Principles

Data suggest that applying the World Health Organization (WHO) principles of pain management [14] results in good pain relief for the majority of children with advanced cancer, however less has been reported on the effectiveness of the WHO approach for non-malignant pediatric life-limiting conditions. In our experience, those four principles usually prove to be equally effective in managing children with non-malignant conditions:

- “By the Analgesic Ladder”
- “By the Clock”
- “By the appropriate route”
- “With the Child”
4.1.1. “By the Analgesic Ladder”
The choice of analgesic drugs should be based on the WHO analgesic ladder.

Figure 3: The WHO three-step analgesic ladder [14]

An assessment of pain severity dictates the choice of analgesic. Severe pain requires strong pain medication, i.e. opioids. A child with severe pain should not slowly step up the ladder commencing with acetaminophen, than later adding codeine before eventually changing to morphine. In this scenario WHO step III (strong opioids) should have been commenced immediately. There is considerable discussion in the field regarding the usefulness of a step 2, especially as codeine often proves to be a rather unfavorable choice (see below). Some authorities argue to discontinue step 2, using lower doses of “strong” opioids of step 3 instead.
4.1.2. “By the Clock”
Regular scheduling ensures a steady blood level, reducing the peaks and troughs of PRN (“as needed”) dosing. Commonly used opioid drug regimes include immediate release oral morphine every 4 hours or controlled-release morphine twice daily plus (for both strategies) 1/10-1/6 of the 24-hours morphine requirement as a hourly fast-release breakthrough pain medication as needed. (Table 1)

4.1.3. “By the appropriate route”
The least invasive route of administration, chosen by the child, has to be chosen, making painful intramuscular pain medication unnecessary and obsolete. Novel Routes usually make use of high liphophilicity of certain opioids to cross skin or mucosa.

The oral route (or via nasogastric-tube/PEG-tube) is convenient, non-invasive and usually preferred by the children and their care providers.

The sublingual application of opioids (morphine, fentanyl, oxycodone, hydromorphone, and methadone) appears safe and well liked by children and caregivers. In fact, this is our preferred route of pediatric opioid application, if oral administration is not feasible and there is no intravenous access (usually in children with nonmalignant conditions). The data for sublingual opioid is somewhat confusing, for morphine suggesting a bioavailability between 9% - 61% [31, 32]. Although morphine has hydrophilic properties, hence is not ideal for the sublingual route, the
bioavailability of sublingual and oral administered morphine is interestingly not statistically different. [33, 34]

Oxycodone has a sublingual bioavailability of less than 20% and hydromorphone of 25% [31]. Methadone shows a good bioavailability via sublingual administration [35] and very rapid onset of relief of breakthrough pain in seven adult patients in a dose 2-8 mg [36].

Case reports suggest good analgesia with sublingual liquid Fentanyl [37], and a commercial sublingual fentanyl application (Fentora™) is now available, demonstrating a bioavailability of 65%.

**Intranasal application** of opioids is pain free and safe. [15] Fentanyl can be diluted in normal saline solution (0.9%) and may be applied as a nasal spray or in drops. The pharmacokinetic profile of intranasal fentanyl seems to be similar to intravenous fentanyl. [16] Intranasal fentanyl does not irritate the nasal mucous membrane and has only minimal ciliotoxic properties. [17, 18] Reported intranasal fentanyl doses in children (1-1.5 mcg/kg) are equal to or only slightly above suggested intravenous doses [17, 19] (table 1).

**Oral transmucosal fentanyl:** The fentanyl lozenge is a solid drug matrix with berry flavour providing oral transmucosal fentanyl citrate (OTFC). Due to fentanyl’s high lipophilicity absorption across the oral mucosa directly into the systemic blood is rapid. OTFC has been used for children 3 years of age and above. Recent studies in opioid-naïve children showed typical opioid side effects of OTFC including respiratory depression. Earlier pediatric trials, which reported higher rates of respiratory depression, either used high doses of OTFC (>20 mg/kg) and/or treated cardiosurgical patients, including children with cyanotic heart defects. [22] Some pediatric trials reported nausea and vomiting commonly, others rarely or not at all. Due to these adverse effects, the indications for OTFC have been changed. Currently, OTFC in indicated exclusively for the treatment of breakthrough pain in cancer patients and is no longer used for sedation or pre-medication. If used for this purpose, certain guidelines should be followed. [23] An FDA approval for late 2008 is expected for an oral adhesive disc technology (BEMA™ Fentanyl): A small, dissolvable, polymer film for application to the buccal membranes, with the smallest fentanyl dose of 200 mcg. Studies on adult subjects have shown a bioavailability of 70% (50% absorbed through mucosa), similar to sublingual fentanyl (Fentora™: 65% [48%]), higher than OTFC (Actiq™: 47% [22%]). [52]

**Transdermal fentanyl** patches are contraindicated for acute pain management due to a long onset time (it may take more than 60 hours to reach peak concentrations in children) [20, 21], inability to rapidly titrate drug delivery and long elimination half-life (up to 24 hours). Patches can be applied on intact, healthy skin every (48-) 72 hours. They cannot be used for opioid naïve children – patients need to be on the equivalent of 30-60 mg oral morphine/24 hours to safely rotate to a fentanyl patch. The smallest patch delivers 12.5 mcg/hour. Sufficient immediate release breakthrough (rescue) opioid needs to be provided.

The Duragesic™ patch contains a selective semipermeable membrane with a fentanyl reservoir, hence it cannot be divided or cut as this would result in “dose dumping” with potential overdosing. However, a generic fentanyl patch (Mylan Pharmaceuticals) contains fentanyl in a different matrix system. Although the company clearly states “Do not cut or damage fentanyl transdermal system” the matrix formulation makes dividing the patch theoretically possible, and pediatric experience suggest that cutting these generic matrix may be feasible. Transdermal fentanyl has its role in chronic, stable pain.

**Rectal application** is often unpopular and may deliver a wide variability in therapeutic
blood levels through variable absorption, however experience shows good analgesia can be achieved in children when suppositories (or liquid opioids via a small catheter rectally) are administered.

The intravenous administration of opioid may be feasible, especially when there is a central line in place. Patient-controlled-analgesia/nurse-controlled-analgesia (PCA/NCA) pumps (e.g. morphine, fentanyl, hydromorphone, methadone) with a continuous background and an as-needed bolus often provides excellent pain management. Alternatively the opioid analgesics can be applied subcutaneously in the same dose as i.v. Many children and their parents we cared for were comfortable in terminal care with a s.c or i.v. PCA/NCA pump providing opioids for the management of pain and dyspnea in the home settings.

4.1.4. "With the Child"
The analgesic treatment should be individualized according to the child’s pain, response to treatment, frequently reassessed and modified as required. Some children may require extremely high doses of opioids (sometimes more than 500 times the starting dose) to control severe pain. Adjuvant drugs (e.g. amitriptyline, gabapentin, low-dose ketamine, benzodiazepines, bisphosphonates) may be appropriate in the pain management of the individual child.

4.2. Non-Opioids
The most frequently used non-opioids are acetaminophen and ibuprofen (alternative via intravenous administration: ketorolac).

**Acetaminophen** (10-15 mg/kg PO/PR Q4-6h; dose limit: <2 years: 60mg/kg/day, >2 years: 90mg/kg/day) is generally well tolerated by children and lacks gastrointestinal and hematological side-effects. Significant hepatotoxicity [24] is rare, but careful attention to dosing is paramount.

**Ibuprofen** (10mg/kg PO TDS-QID; dose limit 2400mg/day) has the least gastrointestinal side effects among the NSAIDs. It should be used with caution with hepatic or renal impairment, history of GI bleeding or ulcers and it may inhibit platelet aggregation.

**Ketorolac** has the advantage of IV administration, but should be rotated to oral ibuprofen, as soon as tolerated (< 2 years= 0.25mg/kg TID; > 2 years: 0.5 mg/kg q6h; max. 30 mg/dose; recommended dosing no longer than five days).

4.3 "Weak" Opioids
Codeine and tramadol are frequently used for mild-moderate pain and are so called "weak opioids" due to their ceiling effect (increasing above recommended dosing does increase adverse effects, but does not increase analgesia).

Codeine cannot be recommended in pediatric analgesia: Not only has codeine a variable bioavailability (15-80 %), but also produces its analgesic effect only through its metabolite morphine. This pathway depends on the activity of the enzyme cytochrome P450 2D6 (CYP 2D6). Slow metabolizers (in white Caucasians 10%, in Chinese 30%) therefore do not achieve analgesia by codeine. On the other hand, around 5% of the general population have multiple copies of CYP 2D6 and are ultra rapid metabolizers [38], and therefore metabolize unusually high doses of morphine. The author recently cared for a 10-year old girl who after receiving an appropriate dose of 1mg/kg codeine for post surgical pain displayed significant respiratory depression (rate 6/minute) and required several doses of the opioid-antagonist
naloxone (with immediate response).

A better pediatric choice of a “weak” opioid is tramadol (Ultram™), which has been used in pediatrics since the 1970’s in Europe. It been trialed in neonates and children (mainly postoperative) and shown to be safe and effective. [39, 40]. The analgesic strength of tramadol (a weak mu-receptor agonist - even weaker for delta and kappa) is augmented by an additional effect in inhibiting monoamine neurotransmitter (norepinephrine-serotonin) reuptake and it has a potency intermediate between codeine and morphine [25]. Although tramadol is metabolized by CYP 2D6 (and to a lesser degree by CYP 3A4) into the more potent O-desmethytramadol, tramadol itself is a potent analgesic. For slow CYP 2D6 metabolizers the parent compound (tramadol) remains active, hence those individuals experience no decrease or only a slightly diminished effect on their analgesia. [41] Common adverse effects include nausea, vomiting, dizziness, constipation, and sedation. A rare, but severe side effect is the serotonergic syndrome. Tramadol appears not to increase the risk of ideopathic seizures; but patients with seizure tendency or medication that lower seizure treshold (tricyclic antidepressents, SSRI, MAOI, antipsychotics) may be at increased risk. Tramadol appears fairly safe regarding respiratory depression with overdose: No symptoms noted in children < 6 years who ingested 10/mg/kg or less, and in 87 adult patients with overdose only two demonstrated respiratory depression. In the USA tramadol is available in tablets only, however it’s easy to compound in a stable liquid, so both our inpatient and many outpatient pharmacies in our region now compound the liquid tramadol.

“Weak” and “strong” opioids should not be combined due to an unfavorable side effect profile.

4.4. “Strong” Opioids

The most frequently used opioid in pediatrics for moderate to severe pain remains morphine. Opioid-associated side effects (e.g. constipation, pruritus, nausea) have to be expected and treated accordingly. For recommended starting doses see Table 1. Morphine undergoes a strong first-pass metabolism (hence oral:intravenous conversion of 3:1), and is metabolized by liver glucuronyl transferase into Morphine-6 glucuronide (M6G) and Morphine-3 glucuronide (M3G). M6G is a much stronger analgesic (x40-100) and displays adverse effects including nausea, vomiting, sedation, and respiratory depression. M3G is not an analgesic and rather a mu-antidote with unique adverse effects, especially hyperexcitability / neurotoxicity. The ratio of M6G/M3G thereby defines in parts its analgesia to adverse effect profile in individuals. Both metabolites need to be excreted by the kidney, and children in kidney failure have a higher risk of unwanted side effects. Fentanyl or methadone, both not excreted renally, are likely to be a better choice in this scenario.
Table 1
Opioid analgesics: usual starting doses [9,15]

<table>
<thead>
<tr>
<th>Drug (Route of administration)</th>
<th>Equianalgesic dose (parenteral)</th>
<th>Starting dose IV</th>
<th>IV:PO ratio</th>
<th>Starting dose PO (transdermal)</th>
<th>Starting dose controlled release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (PO, SL, IV, SC, PR)</td>
<td>10 mg</td>
<td>Bolus dose: 50-100 mcg/kg every 2-4 h Continuous Infusion: 10-30 mcg/kg/h</td>
<td>1:3</td>
<td>0.15-0.3 mg/kg every 4 h</td>
<td>0.45-0.9 mg every 12 hours</td>
</tr>
<tr>
<td>Fentanyl (IV, SC, SL, transdermal, buccal)</td>
<td>100-250 mcg</td>
<td>Bolus dose: 1-3 mcg/kg (slowly over 3-5 minutes - fast bolus may cause thorax rigidity) Continuous Infusion: 1-2 mcg/kg/h</td>
<td>1:1 (IV to Transdermal)</td>
<td>12 mcg/h patch (must be on the equivalent of at least 30 mg oral morphine/24 hours, before switched to patch)</td>
<td>n/a</td>
</tr>
<tr>
<td>Hydromorphone (PO, SL, IV, SC, PR)</td>
<td>1.5 mg</td>
<td>Bolus dose: 15-20mcg/kg every 4 h Continuous Infusion: 5 mcg/kg/h</td>
<td>1:5</td>
<td>60 mcg/kg every 3-4 h</td>
<td>180mcg/kg every 12 h – currently not available in USA</td>
</tr>
<tr>
<td>Oxycodone (PO, SL, PR)</td>
<td>5-10 mg</td>
<td>n/a</td>
<td>n/a</td>
<td>0.1-0.2 mg/kg every 4-6 h</td>
<td>0.3-0.9 mg/kg every 12 h</td>
</tr>
<tr>
<td>Codeine (not recommended)</td>
<td>120 mg</td>
<td>n/a</td>
<td>n/a</td>
<td>0.5-1 mg/kg every 3-4 h</td>
<td>n/a</td>
</tr>
<tr>
<td>Tramadol (PO, PR)</td>
<td>100 mg</td>
<td>IV not available in USA [Bolus dose: 1 mg/kg every 3-4 h Continuous Infusion: 0.25 mcg/kg/h]</td>
<td>1:1</td>
<td>1-2 mg/kg every 3-4 h, max. of 8 mg/kg/day (&gt; 50kg: max. of 400 mg/day)</td>
<td>2-4 mg/kg every 12 hours</td>
</tr>
</tbody>
</table>

Calculated rescue (breakthrough) dose: 10-16 % of 24-hour opioid dose to be given every 1-2 hours as needed

IV = intravenous
PO = by mouth
SL = sublingual
SC = subcutaneous
PR = rectal
n/a = not applicable
Opioids can be categorized into separate families: Phenanthrene derivatives (Morphine, Hydromorphone, Oxycodone, Hydrocodone), phenylpiperidine derivatives (Fentanyl, Meperidine) and diphenylheptane derivatives (Methadone, Propoxyphene). An opioid rotation may be necessary, if dose limiting opioid toxicity occurs. [26] This is necessary in about 10 per cent of the children provided with opioids by the “Pain & Palliative Care Team” at the Children’s Hospitals and Clinics of Minnesota in Minneapolis/St. Paul. An observation is that a switch from one opioid to another is often accompanied by change in the balance between analgesia and side effects. [27] A favorable change in opioid analgesia to side-effect profile to side-effect profile will be experienced if there is less cross-tolerance at the opioid receptors mediating analgesia than at those mediating adverse effects. [28] If changing between opioids with short duration of action, start new opioid—because of incomplete cross-tolerance—at 50% of equianalgesic dose and titrate to effect. Even when a child may become unconscious during the last days of life due to the underlying disease (and not as a opioid toxicity), ceasing regular opioid analgesic drugs may provoke unpleasant withdrawal.

Oxycodone is a selective mu-opioid receptor agonist, although some animal studies suggest a kappa receptor agonist activity. [42] The oral potency of oral Oxycodone to Morphine is between 1:1 to 2:1 [43]. One advantage of oxycodone over morphine is the slightly longer half-life, frequently allowing a Q6h dosing (as oppose to Q4h in morphine). Renal and hepatic impairment increases the oxycodone serum level. [44]

Hydromorphone is another selective mu-opioid receptor agonist. Unlike morphine metabolism, there is no hydromorphone-6-glucuronide (H6G), but similar to the morphine metabolism there is hydromorphone-3-glucuronide (H3G). Opioid hyperexcitability has been reported in patients with renal failure taking hydromorphone [45, 46] Normal H3G to hydromorphone plasma ratio is 27:1 but in renal failure it is 100:1 [47]

Fentanyl is a popular opioid for analgesia prior to painful procedures due to its rapid onset (about 1 minute) and its brief duration of action (30-45 minutes). It is also used in the pain management of children with cancer, for intra- and postoperative analgesia, in pediatric palliative care, and in sedation analgesia for ventilated children on the intensive care unit. Fentanyl provides a good alternative to morphine when dose-limiting side effects of the latter mandate a rotation of opioid drug. [48, 49, 50]

Methadone is an excellent opioid choice in pediatric palliative care and remains underutilized. It is a mu (delta, kappa)- opioid receptor agonist, a NMDA-receptor antagonist, and presynaptic blocker of serotonin and norepinephrine re-uptake. Advantages include Methadone’s long half-life (allowing BID or TID dosing), high effectiveness in chronic pain relief as well as in the management of neuropathic pain, NMDA receptor antagonist mechanism (helps preventing tolerance), lower incidence of constipation, absent active metabolites, safe usage in renal failure and in stable liver disease, and its inexpensiveness. There are some disadvantages though, including wide dosing variation, long half-life (may lead to accumulation; making quick titration difficult), and more complex equianalgesic conversion, which requires a much longer and closer patient observation than other opioids.

We are using an equianalgesic conversion chart (Table 2) when switching to oral (or sublingual) methadone in our pediatric patients. When switching from the oral to intravenous route of administration (either TID, or continuous infusion via a PCA-pump with additional boluses) we use 50-80% of the oral daily methadone dose.
Table 2
Equianalgesic Methadone Chart

<table>
<thead>
<tr>
<th>Total Daily Oral Morphine Dose</th>
<th>Estimated Daily Oral Methadone Requirement</th>
</tr>
</thead>
</table>
|                               | Gazelle G (2002):  
  www.epcr.gscw.edu | ROXANE LABORATORIES, INC.  
  Columbus, OH 43215 | Toombs JD (2005) American Family Physician  
  71(7):1355-6 |
| < 100 mg                      | 3:1 | 20% - 30% | 33% |
| 101mg - 300mg                 | 5:1 | 10% - 20% | 20% |
| 301mg - 600mg                 | 10:1 | 8% - 12% | 10% |
| 601mg - 800mg                 | 12:1 | 5% - 10% | 8% |
| 801mg - 1000mg                | 15:1 | 5% - 10% | 7% |
| > 1000mg                      | 20:1 | < 5% | 5% |

4.5 Combination Analgesia

Fixed combination analgesia, usually acetaminophen plus an opioid should not be used in pediatric analgesia. Examples include Acetaminophen/Hydrocodone (e.g. Vicodine™), Acetaminophen/Oxycodone (e.g. Percocet™, Roxicet™) or Acetaminophen/Codeine (e.g. Tylenol No3™). The fixed ratio of acetaminophen to the opioid leaves dangerous choices: Either using suboptimal opioid doses or, when using adequate opioid doses administering a liver-toxic dose of acetaminophen. Also it is unclear, if a child takes a scheduled combination formulation, what to choose for a rescue (breakthrough) dose – can we be certain, that caregivers will not administer additional doses of the drug, if their child remains in pain (and thereby grossly increasing the risk of an acetaminophen overdose)? How to increase/titrate the opioid to effect?

State of the art pediatric analgesia therefore requires the individual titration of stand-alone acetaminophen with a single opioid, the latter titrated to effect.

5. Obstacles

Many myths still remain and may be responsible for the inadequate pain management of many children in palliative care. Especially infants and very young children as well as severely impaired children and teens often do not receive sufficient analgesia, because their discomfort is different from that of adult. It is fallacious to believe, that children's nervous systems are immature and therefore unable to perceive experience pain. All available data suggests, that those theories are wrong. [29] The application of an opioid to treat pain or dyspnea does not hasten a child’s death, if titrated by effect. The correct provision of opioids for symptom management not only improves the quality of life of a dying child significantly, but often prolongs the end-of-life period due to the improved quality of life.

6. Conclusions

Children in severe pain quite often need strong pain medication, i.e. morphine or other strong opioids. A dose limiting side effect may require an opioid rotation. Pediatric evidence and experience also supports novel routes of opioid application: transmucosal, transdermal and intranasal opioid applications are well tolerated by
children, effective and safe. But neither transdermal nor transmucosal opioids must be used in opioid-naive children and transdermal opioids are contraindicated in acute pediatric pain management. Providing a good pain management for a dying child usually requires a holistic, multidisciplinary approach and the knowledge to apply appropriate analgesic drugs in combination with integrative non-drug therapies.

Managing intractable pain in children at the end-of-life will usually require the integration of pharmacology (non-opioids plus opioids - following the WHO-principles) with non-pharmacological, integrative therapies. (Figure 4). Not uncommonly children may require the addition of adjuvant analgesia or invasive approaches. Only if all six circles of Figure 4 have been exhausted, and not earlier, would it be necessary to consider sedation to unconsciousness, hence making the latter a very rarely needed intervention (estimated less than once per year in large pediatric palliative care programs).

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