Prevention and Treatment of Pain in Hospitalized Infants, Children, and Teenagers: From Myths and Morphine to Multimodal Analgesia

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Educational Objectives

2. Evaluate assumptions about opioid use in children.
3. Discuss multimodal analgesia, explaining how multiple agents, interventions, rehabilitation, psychological modalities, and integrative (“non-pharmacological”) therapies act synergistically for more effective pediatric pain control with fewer side effects than a single analgesic or modality.

Introduction

The management of pain in infants and children has undergone dramatic changes in just one generation. In 1968 Swafford et al. [69] famously, and as we now know, erroneously proclaimed, “pediatric patients seldom need medication for the relief of pain. They tolerate discomfort well.” However, in 2016 it would be considered inappropriate to perform elective painful procedures in children without treatment to avoid or minimize pain, because poorly managed pain has serious short- and long-term consequences [66]. Analgesic treatment is mandatory for children when they undergo painful procedures, and no avoidable suffering is acceptable nowadays, even for so-called minor interventions [6,15].

Based on the 2012 World Health Organization (WHO) guidelines [78], this chapter will discuss evidence-based safe multimodal (i.e., opioid-sparing) analgesia, which may include one, several, or all of the following approaches in the effective treatment of an individual child: pharmacology (e.g., simple analgesia and/or opioids and/or adjuvant analgesia), anesthetic interventions (e.g., neuroaxial analgesia, nerve blocks), rehabilitation (e.g., physical therapy, occupational therapy, sleep hygiene), psychology (e.g., cognitive-behavioral therapy), and age-appropriate positioning and integrative (“nonpharmacological”) therapies, such as breathing techniques, self-hypnosis, and distraction.

Pain in Hospitalized Children

Data reveal that pain in children’s hospitals is common, underrecognized, and undertreated [35,68,73,80]. Children often suffer needless pain. Rosenfeld and colleagues, in their recent manuscript [60], describe using a “papoose board for restraint” while performing an exquisitely painful procedure (a myringotomy and tube insertion) without the benefit of topical or systemic analgesics. Bellini and Johnston recently reviewed 45 studies published between 2013 and 2015 that tested new analgesic treatments for procedural pain in neonates [6]. They found that despite international guidelines, neonates who were
included in control groups during painful procedures did not receive analgesia in the majority of cases. Compared to adults, pediatric patients generally receive fewer and/or incorrectly dosed analgesics during their daily routine [26], and the younger children are, the less likely they are to receive appropriate analgesia [8].

Why is it inappropriate in 2016 to deny evidence-based pain treatment or perform elective painful procedures in children without treatment to avoid or minimize pain? It is well documented that poorly managed pain has serious short- and long-term consequences [1,21,42,58,59,74]. Infants remember pain and suffer physiological consequences from untreated pain, with global consequences on sensory processing observed as long as 9–12 years later [66,74]. Each painful event causes immediate physiological and behavioral instability [42], and infants do remember pain. For example, pain ratings for the 4–6-month routine vaccination are higher in boys who have been circumcised without analgesia than in girls or uncircumcised boys [71,72]. Not surprisingly, appropriate analgesia after trauma significantly reduces the risk of developing post-traumatic stress disorder (PTSD) in infants and older children [54,55,61,62]. Inadequate analgesia and the memory of previous painful experiences during procedures in children diminishes the effects of adequate analgesia in subsequent procedures [77]. Up to 25% of adults have a fear of needles, with most fears developing in childhood, resulting in avoidance of health care, including nonadherence with vaccination schedules [70].

Multimodal (“opioid-sparing”) analgesia is an approach used to prevent and treat pain in children: multiple agents, interventions, rehabilitation, and psychological and integrative therapies often act synergistically for more effective pediatric pain control with fewer side effects than a single analgesic or modality [31] (Fig. 1). Multimodal analgesic therapy (versus opioids alone) reduces the length of hospitalization in patients undergoing surgery [52].

**World Health Organization Principles**

Clinical experiences suggest that applying the 2012 WHO “Guidelines on the pharmacological treatment of persisting pain in children with medical illness” results in good pain relief for the majority of children with acute somatic pain [78]. The WHO guidelines exclude acute trauma, perioperative and procedural pain, and chronic complex pain. Correct use of analgesic medicines will relieve pain in

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Fig. 1. Multimodal analgesia. CBT, cognitive-behavioral therapy; NSAIDs, nonsteroidal anti-inflammatory drugs; TCA, tricyclic antidepressants. Color reproduction available at http://ebooks.iasp-pain.org.
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most children with persisting pain due to medical illness and relies on the following key concepts: (1) using a two-step strategy, (2) dosing at regular intervals, (3) using the appropriate route of administration, and (4) adapting treatment to the individual child.

**Principle #1: Using a Two-Step Strategy: “By the Analgesic Ladder”**

**Principle:** It is recommended to use the analgesic treatment in two steps according to the child’s level of pain severity [78].

**Step 1: Mild Pain**

Paracetamol (also known as acetaminophen) and ibuprofen are the medicines of choice in the first step (mild pain) of the analgesic step ladder. No other nonsteroidal anti-inflammatory drug (NSAID) has been sufficiently studied for efficacy and safety in the pediatric population to be recommended as an alternative to ibuprofen. Although there is evidence for the superior analgesic properties of ibuprofen versus paracetamol (acetaminophen), it is considered to be of limited value because the studies were mostly performed in acute pain settings and lack long-term safety data. Both paracetamol (acetaminophen) and ibuprofen have potential toxicities. There are concerns about renal and gastrointestinal toxicity and bleeding with ibuprofen and other NSAIDs, and risks of hepatotoxicity and acute overdose are associated with paracetamol (acetaminophen) [78].

**Paracetamol (acetaminophen)** (10–15 mg/kg p.o./p.r./i.v. every 4–6 hours; dose limit: <2 years: 40 mg/kg/day; >2 years: 75 mg/kg/day) is generally well tolerated by children and lacks gastrointestinal and hematological side effects. Significant hepatotoxicity [41] is rare, but careful attention to dosing is paramount. Although approved by the Food and Drug Administration in the United States, we lack sufficient pediatric efficacy and safety data for the i.v. form of administration.

**Ibuprofen** (5–10 mg/kg p.o. every 6 hours; dose limit 2400 mg/day) has the least gastrointestinal side effects among NSAIDs that are nonselective for cyclooxygenase-2 (COX-2). It should be used with caution in individuals with hepatic or renal impairment, or a history of gastrointestinal bleeding or ulcers, and it inhibits platelet aggregation.

**Ketorolac** has the advantage of i.v. administration, but it should be rotated to oral ibuprofen, as soon as tolerated (<2 years: 0.25 mg/kg every 6 hours; >2 years: 0.5 mg/kg every 6 hours; max. 30 mg/dose; recommended dosing no longer than 3–5 days).

**Celecoxib** (a COX-2 inhibitor) might be considered if classical NSAIDs are contraindicated (e.g., owing to bleeding risks, or gastrointestinal side effects). It does not display less renal toxicity compared to classic NSAIDs. Safety and efficacy have been established only in children 2 years of age or older and for a maximum of 6 months of treatment in juvenile rheumatoid arthritis (1–2 mg/dose; max. 100 mg every 12–24 hours).

**Step 2: Medium to Severe Pain**

For medium to severe acute pain, the addition of morphine or other opioids is usually required (see below) [40]. Exceptions could include providing multimodal (“opioid-sparing”) analgesia (e.g., utilizing regional anesthesia or administering an α-agonist such as dexmedetomidine [43] or clonidine) (Fig. 1).

**Principle #2: Dosing at Regular Intervals: “By the Clock”**

**Principle:** When pain is constantly present, analgesics should be administered, while monitoring side effects, at regular intervals (“around-the-clock” and not on an “as needed” basis) [78].

Regular scheduling ensures a steady blood level, reducing the peaks and troughs of p.r.n. (“as needed”) dosing. The “p.r.n. only” method may take several hours and higher opioid doses to relieve pain and result in a vicious cycle of undermedication and pain, alternating with periods of overmedication and medication toxicity [2].

The “p.r.n. only” method might be appropriate if pain episodes are truly intermittent and unpredictable, such as in breakthrough pain. However, “p.r.n. only” (without scheduled dosing) may unfortunately translate into “Patient Receives Nothing” or “Give as little as possible” Pain in children is systematically undertreated: 69% of hospitalized pediatric patients for whom analgesics had been ordered did not receive a single dose in one study [44]. Commonly used opioid drug regimens include immediate-release oral morphine every 4 hours or controlled-release morphine twice daily, plus (for both strategies) a p.r.n. dose of 10% of the 24-hour morphine requirement as an hourly immediate-release breakthrough pain medication as needed [28,34] (Tables 1 and 11). For starting doses of opioid continuous infusions plus patient (or nurse)-controlled analgesia (PCA), see Table III.
Table I
Usual starting doses of opioid analgesics for children >6 months of age (capped at 50 kg body weight)

<table>
<thead>
<tr>
<th>Drug (Route)</th>
<th>Equianalgesic Dose (Parenteral)</th>
<th>Starting Dose (i.v.)</th>
<th>i.v.: p.o. Ratio</th>
<th>Starting Dose (p.o./Transdermal)</th>
<th>Starting Dose (Controlled Release)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (p.o., i.v., s.c., p.r.)</td>
<td>10 mg</td>
<td>Bolus dose: 50–100 µg/kg every 2–4 h; continuous infusion: 10–30 µg/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 h</td>
</tr>
<tr>
<td>Fentanyl (i.v., s.c., s.l., transdermal, buccal)</td>
<td>100–250 µg</td>
<td>Bolus dose: 1–3 µg/kg (slowly over 3–5 minutes; fast bolus may cause thorax rigidity); continuous infusion: 1–2 µg/kg/h</td>
<td>1:1 (i.v. to transdermal)</td>
<td>12 µg/h patch (must be on the equivalent of at least 30 mg oral morphine/24 hours, before switching to patch)</td>
<td>n/a</td>
</tr>
<tr>
<td>Hydromorphone (p.o., s.l., i.v., s.c., p.r.)</td>
<td>1.5 mg</td>
<td>Bolus dose: 15–20 µg/kg every 4 h; continuous infusion: 5 µg/kg/h</td>
<td>1:5</td>
<td>60 µg/kg every 3–4 h</td>
<td>180 µg/kg every 12 h; currently not available in United States</td>
</tr>
<tr>
<td>Oxycodeone (p.o., s.l., p.r.)</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>0.3–0.6 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 (p.o., p.r.)</td>
<td>100 mg</td>
<td>i.v. not available in United States (bolus dose: 1 mg/kg every 3–4 h; continuous infusion: 0.25 mg/kg/h)</td>
<td>1:1</td>
<td>1–2 mg/kg every 3–4 h, max. of 8 mg/kg/day (&gt;50 kg: max. of 400 mg/day)</td>
<td>2–4 mg/kg every 12 h</td>
</tr>
</tbody>
</table>

Abbreviations: i.v., intravenous; n/a, not applicable; p.o., by mouth; p.r., rectal; s.l., sublingual; s.c., subcutaneous.
Note: Calculated rescue (breakthrough) dose: 10–16% of 24-hour opioid dose to be given every 1–2 hours as needed.

Principle #3: Using the Appropriate Route of Administration: “By the Appropriate Route”

Principle: Medications should be administered to children by the simplest, most effective, and least painful route, making oral formulations the most convenient and least expensive route of administration [78].

If possible, the child should choose the route of administration. Painful intramuscular (i.m.) administration of pain medication is unnecessary and obsolete [30]. Novel routes usually make use of the high lipophility of certain opioids to cross the skin (e.g., transdermal fentanyl or buprenorphine) or the mucosa (rapid-onset fentanyl preparations).

The oral route (or the enteral route via nasogastric tube or percutaneous endoscopic gastrostomy tube) is convenient, noninvasive, and usually preferred by pediatric patients and their care providers. The titration of opioids by the enteral route can occasionally be challenging owing to the delayed onset of action compared to the i.v. route, which has a

Table II
Opioid analgesia for neonates and infants 0–6 months of age

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Dose</th>
<th>Route</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.075–0.15 mg (neonates 0–30 days)</td>
<td>p.o./p.r./s.l.</td>
<td>6 hours</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.08 – 0.2 mg (infants 1–12 months)</td>
<td></td>
<td>4–6 hours</td>
</tr>
<tr>
<td>Morphine*</td>
<td>0.025–0.05 mg/kg (neonates 0–30 days)</td>
<td>i.v./s.c.</td>
<td>6 hours</td>
</tr>
<tr>
<td>Morphine*</td>
<td>0.1 mg/kg (infants 1–6 months) Infusion (with PCA bolus of same dose): 0.005–0.01 mg/kg/h (neonates 0–30 days) 0.01–0.03 mg/kg/h (infants 1–6 months)</td>
<td></td>
<td>6 hours</td>
</tr>
<tr>
<td>Fentanyl*</td>
<td>1–2 µg/kg (neonates and infants 0–12 months) Infusion (with PCA bolus of same dose): 0.5–1 µg/kg/h (neonates and infants 9–6 months)</td>
<td>i.v./s.c.</td>
<td>2–4 hours</td>
</tr>
</tbody>
</table>

Abbreviations: i.v., intravenous; PCA, patient (nurse)-controlled analgesia; p.o., by mouth; p.r., rectal; s.l., sublingual; s.c., subcutaneous.
* The intravenous doses for neonates are based on acute pain management and sedation dosing information. Lower doses are required for nonventilated neonates.
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rapid and predictable onset of analgesia. Furthermore, absorption efficiency and kinetics are variable, being influenced by the type of diet taken by the patient, delayed gastric emptying, and first-pass metabolism.

The sublingual or buccal application of opioids (morphine, fentanyl, oxycodone, hydromorphone, and methadone) appears to be safe and well-liked by children and caregivers. In fact, these routes are often the preferred route of pediatric opioid application if oral administration is not feasible and there is no i.v. access.

The data for the absorption and bioavailability of sublingual opioid shows a wide variability, with morphine having a reported bioavailability ranging between 9% and 61% [51,76]. Although morphine has hydrophilic properties (and thus it would appear not to be ideal for the sublingual route), the bioavailability of sublingual and orally administered morphine is not meaningfully different from that of lipophilic medications [19,56]. The sublingual bioavailability of oxycodone is less than 20%, while that of hydromorphone is around 25% [76]. Methadone shows good bioavailability and rapid onset following sublingual administration, with adult doses ranging from 2 to 8 mg [39,76].

Intranasal application of opioids is usually well tolerated and appears safe [79]. Fentanyl may be applied via a nasal spray utilizing a mucosal atomization device. The pharmacokinetic profile of intranasal fentanyl seems to be similar to that of i.v. fentanyl [36]. Intranasal fentanyl does not irritate the nasal mucosa and has only minimal ciliotoxic properties [49,57]. Reported intranasal fentanyl doses in children (1–1.5 µg/kg) are equal to or only slightly higher than suggested intravenous doses [7,49].

Transdermal fentanyl patches are contraindicated for acute pain management owing to a long onset time (it may take more than 60 hours to reach peak concentrations in children), the inability to rapidly titrate drug delivery, and a long elimination half-life (up to 24 hours) [16,17]. Patches can be applied on intact, healthy skin every 48 to 72 hours. They must not be used for opioid-naive 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 µg/hour. Sufficient immediate-release breakthrough (rescue) opioid needs to be provided. Transdermal fentanyl has a role in stable acute pain or drug tolerance, when children require opioids for more than a week.

Rectal (p.r.) application is often unpopular and results in wide variability in therapeutic blood levels through variable absorption. However, experience shows that adequate analgesia can be achieved in children when suppositories (or liquid opioids via a small catheter rectally) are administered. In the United States, suppositories are available for hydromorphone (3 mg), oxymorphone (5 mg), and morphine (5 mg, 10 mg, 20 mg, and 30 mg). Adult data shows that controlled (extended/sustained) release morphine tablets may be administered p.r. at an oral : rectal conversion ratio of 1:1 [2,75].

The intravenous administration of opioids has the advantage of predictable bioavailability and rapid onset, and it is especially advantageous when there is already a central line in place (venous cannulation needle pain needs to be relieved by topical anesthetics). Opioids administered i.v. will typically have an onset of action within 4–6 minutes (faster for fentanyl) and are relatively easy to titrate (with the exception of i.v. methadone). Titration of strong opioids by parenteral administration allows for the adjustment of the medication to meet patients’ needs and minimizes the potential for toxicity by allowing patients to regulate administration. Patient (or nurse)-controlled analgesia (PCA) pumps with (as opposed to perioperative adult practice) a continuous background infusion and an as-needed bolus often provide excellent pain management [37]. Opioids in pediatric PCA pumps may include morphine, fentanyl, hydromorphone (also diamorphine, which is not available outside the United Kingdom), and occasionally under certain circumstances, methadone.

Alternatively, opioid analgesics may be administered subcutaneously in the same dose as for i.v. administration in a high-concentration, low-volume

<table>
<thead>
<tr>
<th>Drug</th>
<th>Continuous Infusion (µg/kg/hr)</th>
<th>PCA Bolus (µg)</th>
<th>Lockout Time (Minutes)</th>
<th>Maximum No. Boluses/ Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>20 (max. 1000)</td>
<td>20 (max. 1000)</td>
<td>5–10</td>
<td>4–6</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>3–5 (max. 250)</td>
<td>3–5 (max. 250)</td>
<td>5–10</td>
<td>4–6</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1 (max. 50)</td>
<td>1 (max. 50)</td>
<td>5</td>
<td>4–6</td>
</tr>
</tbody>
</table>

Note: Dose escalation is usually achieved in 50% increments, both for continuous and PCA bolus dose (Department of Pain Medicine, Palliative Care and Integrative Medicine, Children’s Hospitals and Clinics of Minnesota, USA).
preparation (less than 1–2 mL/hour). In palliative care, most children and their parents are comfortable with an i.v. (or occasionally s.c.) PCA pump to provide opioids for the management of pain and/or dyspnea in the home setting [23].

**WHO Principle #4: Adapting Treatment to the Individual Child: “With the Child”**

**Principle:** The treatment should be tailored to the individual child, and opioid analgesics should be titrated independently on an individual basis [78].

Analgesic treatment should be individualized according to the child's pain and response to treatment and frequently reassessed and modified as needed. Opioid dose titration for severe acute pain is usually performed at 50% increments of the current dose (not of the starting dose), if no oversedation or significant opioid-induced adverse effects are present. These increments could be higher or lower depending upon the circumstances. If there are no dose-limiting side effects such as oversedation or respiratory depression, the opioid can be titrated to effect and increased accordingly. Because of their increased risk of tolerance, some children may require extremely high doses of opioids (sometimes more than 10–100 times the starting dose) to control severe acute or chronic pain (usually in children with advanced cancer). Adjuvant analgesics (e.g., low-dose tricyclic antidepressants, gabapentinoids, low-dose ketamine, or α-agonists) may serve as valuable adjuncts, and they are usually given in addition to, not in lieu of, opioids [33,43] (Table IV).

At analgesic dosing one would not expect oversedation. Patients and their parents rarely have

| Table IV | Adjuvant analgesia in neuropathic pediatric pain management
| (Pain Medicine and Palliative Care, Children’s Hospitals and Clinics of Minnesota) |
|-----------|---------------------------------------------------------------|
| **Class** | **Medication** | **Dose** | **Route** | **Comments/Side Effects** |
| Tricyclic antidepressants | Amitriptyline | Starting dose 0.1 mg/kg q.h.s., usually slowly titrated up to 0.5 mg/kg (max 1–2 mg/kg) | p.o. | Tertiary amine TCA; stronger anticholinergic side effects (including sedation) than nortriptyline |
| | Nortriptyline | Starting dose 0.1 mg/kg q.h.s., usually slowly titrated up to 0.5 mg/kg (max 1 mg/kg) | p.o. | Secondary amine TCA; anticholinergic side effects |
| Gabapentinoids | Gabapentin | Starting dose 2.0 mg/kg q.h.s., usually slowly titrated up to initial target dose of 6 mg/kg/dose t.i.d. (max 300 mg/dose t.i.d.), Max. dose escalation to 24 mg/kg/dose t.i.d. (max. 1200 mg/dose t.i.d.) | p.o. | Slow dose increase required; side effects include ataxia, nystagmus, myalgia, hallucination, dizziness, somnolence, aggressive behaviors, hyperactivity, thought disorders, peripheral edema |
| | Pregabalin | Starting dose 0.3 mg/kg q.h.s., usually slowly titrated up to initial target dose of 1.5 mg/kg/dose b.i.d. (max 75 mg/dose b.i.d.), Max. dose escalation to 6 mg/kg/dose b.i.d. (max. 300 mg/dose b.i.d.) | p.o. | Switch from gabapentin, if distressing side effects or inadequate analgesia should occur; side effects include ataxia, nystagmus, myalgia, hallucinations, dizziness, somnolence, aggressive behaviors, hyperactivity, thought disorders, peripheral edema; associated with weight gain |
| Sodium channel blockers/local anesthetics | Lidocaine 5% | Max. of 4 patches (in patients >50 kg): 12 hours on/12 hours off Transdermal patch | Not with severe hepatic dysfunction |
| Glucocorticoids | Dexamethasone | 0.1–1.5 mg/kg [max. 10 mg] starting dose, then 0.1–0.25 mg/kg b.i.d. (for < 14 days); for malignant spinal cord compression (adult dose): dexamethasone 16–96 mg/day or equivalent | p.o., i.v. | Add gastroprotective agent |
| NMDA receptor antagonists | Ketamine (racemic mixture of S(+) / R(−) enantiomers) | i.v.: 0.06–0.3 mg/kg/hr; p.o.: 0.2–0.5 mg/kg t.i.d.–q.i.d. and p.r.n. | i.v., p.o., (s.c., s.l., intramuscular, p.r., spinal) | Typical side effects are rare at low doses, but would require benzodiazepine administration |
| Alpha-agonists | Dexmedetomidine | Infusion: 0.3 μg/kg/hr; titrate to max. 2 μg/kg/hr | i.v. |
| Clonidine | 1–3 μg/kg every 4–6 hours | p.o. |

*Abbreviations:* b.i.d., twice a day; i.v., intravenous; p.o., by mouth; p.r., by rectum; p.r.n., as needed; q.i.d., four times a day; q.h.s., every night at bedtime; s.c., subcutaneous; s.l., sublingual; TCA, tricyclic antidepressant; t.i.d., three times a day;
Opioids

Opioids can be categorized into separate families: phenanthrene derivatives (such as morphine, hydro- morphine, oxycodone, and hydrocodone), phenylpiperidine derivatives (such as fentanyl and meperidine), and diphenylethylamine derivatives (such as methadone and propoxyphene). Opioid rotation may be necessary, if tolerance develops or dose-limiting opioid toxicity occurs. In our experience opioid rotation is necessary in at least 10% of children provided with opioids by the Pain and Palliative Care Team at the Children’s Hospitals and Clinics of Minnesota in Minneapolis/St. Paul [32]. A switch from one opioid to another is often accompanied by a change in the balance between analgesia and side effects [24]. A favorable change in opioid side-effect profile may be experienced if there is less cross-tolerance at the opioid receptors mediating analgesia than at those mediating adverse effects. When rotating opioids because of decreasing effectiveness or limiting side effects (i.e., because of incomplete cross-tolerance), it is best to begin at around 50% of the equianalgesic dose and titrate to effect. However, the required decrease for incomplete cross-tolerance may be higher or lower, depending on the clinical context of the individual patient [32].

Morphine

Analgesic Properties

The most frequently used opioid and the gold standard in pediatrics for moderate to severe pain remains morphine. Opioid-associated side effects (e.g., constipation, pruritus, and nausea) should be anticipated and treated accordingly. For recommended starting doses, see Tables I and II. Morphine undergoes strong first-pass metabolism (hence the oral : i.v. conversion rate 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 (40–100 times stronger) and elicits adverse effects including nausea, vomiting, sedation, and respiratory depression. M3G is not an analgesic but is a μ-opioid antidote with unique adverse effects, especially hyperexcitability and neurotoxicity. The ratio of M6G/M3G thereby defines the analgesia to adverse-effect profile in individual children. Both metabolites need to be excreted by the kidney, and children in renal failure have a higher risk of unwanted side effects. Fentanyl or methadone, neither of which is excreted renally, are likely to be a better choice in this scenario.

Morphine is considered the gold standard for analgesia with which all other opioids are compared. It was introduced into clinical practice over 200 years ago and is derived from a species of poppy. Routes of administration include oral, sublingual, intravenous, intramuscular, subcutaneous, intrathecal, and epidural. Morphine is also effective topically in open wounds [45]. In standard practice, morphine is most commonly administered via the oral or i.v. routes. The currently accepted oral : i.v. potency ratio for morphine is 1:3. Therefore the usual practice when converting oral morphine to i.v. morphine is to divide the oral dose by 3 (3 mg oral morphine equals 1 mg i.v. morphine). Morphine is available orally as a concentrated solution, immediate-release tablets, and sustained-release tablets and sachets (the latter not available in the United States).

Associated Risks

Renal impairment: M3G does not possess analgesic properties, but is instead nociceptive, does not bind to opioid receptors, and may be responsible for some of the adverse central nervous system effects such as myoclonus. M3G and M6G are excreted by the kidneys, and their elimination is directly related to creatinine clearance. In patients with renal compromise, M3G and M6G may accumulate in the blood and cerebrospinal fluid, leading to unwanted toxicity (M6G: oversedation, pruritus, nausea, etc., M3G: increased nociception, hyperexcitability). Morphine should therefore be administered with caution to patients with renal impairment.

Liver impairment: Only with severe liver failure (e.g., as shown by increased prothrombin time) does morphine’s half-life substantially increase, making opioid-induced side effects more likely.

Morphine in Neonates

Morphine appears to be safe and efficacious in full-term neonates; however, starting doses are usually lower compared to those used in older children.

Starting doses (titrated to effect): p.o./s.i.: 0.07–0.15 mg/kg every 4–6 hours i.v./s.c.: 0.025–0.05 mg/kg every 4–6 hours.
Infusion: 7–10 μg/kg/hr plus 7–10 μg/kg clinician-administered PCA bolus (2–4 boluses/hour)

Long-term neurodevelopmental outcome years after former preterm or full-term babies are exposed to continuous morphine or fentanyl infusion display no adverse effects of the opioids on intelligence, motor function, or behavior [20,48,50,67].

Opioid pharmacokinetics and pharmacodynamics in neonates and young infants (up to 6 months of life) require one to administer lower starting doses than in older children. This principle is based on the following: (1) Infants display delayed maturation of hepatic enzyme systems involved in metabolic drug inactivation. For most opioid analgesics, metabolism matures at approximately 6 months of age. (2) Decreased glomerular filtration and renal tubular secretion result in decreased elimination of opioids and their active metabolites. (3) Decrease levels of α1-acid glycoprotein and albumin translate into decreased plasma protein binding for many drugs and can thus lead to increased concentrations of pharmacologically active unbound drug. (4) As a result of the above facts, the morphine elimination half-life in children older than 6 months is 3–4 hours. In full-term infants, the half-life is 7 hours, and in preterm infants 9–10 hours. (This information helps explain why we might schedule morphine every 4 hours in a 1-year-old, but every 6–8 hours in a 1-day-old full-term infant.) (5) Infants have immature ventilatory reflexes in response to hypoxia and hypercarbia and are at increased risk of hypoventilation in response to opioids; they therefore require closer observation than older children. (6) However, morphine may not provide adequate analgesia for acute procedural pain among preterm neonates, which is one reason why fentanyl might be a better opioid to manage acute pain in this age group (although it may result in faster development of opioid tolerance) [9]. The liver of neonates and young infants (biliary excretion results in small-intestine absorption) preferentially produces M3G, with little if any M6G detected.

Other Opioids Commonly Used in Pediatric Analgesia

Oxycodone is a selective μ-opioid receptor agonist, although some animal studies suggest κ-receptor agonist activity as well [53]. The oral potency ratio of oral oxycodone to morphine is between 1:1 and 2:1 [47]. One advantage of oxycodone over morphine is the slightly longer half-life, which may enable less frequent dosing (i.e. every 6 hours as opposed to every 4 hours with morphine). Renal and hepatic impairment increase oxycodone serum levels [46].

Hydromorphone is another selective μ-opioid receptor agonist. Unlike morphine metabolism, there is no hydromorphone-6-glucuronide (H6G), but metabolism of the parent compound does result in hydromorphone-3-glucuronide (H3G). Opioid hyperexcitability has been reported in patients with renal failure taking hydromorphone [4,18]. The normal H3G to hydromorphone plasma ratio is 27:1, but in renal failure it is 100:1 [5].

Fentanyl is a popular opioid for analgesia prior to painful procedures owing to its rapid onset (about 1 minute) and its brief duration of action (30–45 minutes). It is also used to manage pain in children with cancer, for intravein and postoperative analgesia, in pediatric palliative care, and for sedation-analgesia in ventilated children in the intensive care unit. Fentanyl provides a good alternative to morphine when tolerance or dose-limiting side effects mandate opioid rotation [14,38].

Methadone is an excellent opioid choice in advanced pediatric analgesia and pediatric palliative care, but it remains underutilized [27,29]. It is a μ (δ, κ)-opiod receptor agonist, an NMDA-channel blocker, and a presynaptic blocker of serotonin and norepinephrine reuptake. Advantages include methadone’s long half-life (allowing every 8–12 hour dosing), high effectiveness in complex pain conditions, including the management of neuropathic pain, decreased incidence of constipation, lack of active metabolites, and safe usage in renal failure and in stable liver disease.

There are several disadvantages, however, including wide dosing variation, a long half-life (which may lead to accumulation, making quick titration difficult), and a more complex equianalgesic conversion, which requires longer and closer patient observation than with other opioids. The incidence of fatal overdose with methadone, as well as with other opioids, has risen over the past several years, and the drug should not be prescribed by those unfamiliar with its use. Safe use requires that the effects of methadone should be closely monitored for several days, particularly when it is first started and after any dosing change.

The recently published 2016 Guidelines for Prescribing Opioids for Chronic Pain by the Center for Disease Control and Prevention [22] does not apply to children and teenagers [64]. Its scope encompasses only “patients aged ≥18 years with chronic pain outside of palliative and end-of-life care.” The
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guidelines state further that the “recommendations do not address the use of opioid pain medication in children or adolescents aged <18 years.”

Opioids should not be administered to pediatric patients with primary pain disorders [63], i.e., chronic pain defined that extends beyond the expected time of healing and hence lacks the acute warning function of physiological nociception. Opioids may be more likely to cause more harm than benefit in the treatment of “primary pain disorders,” which include conditions such as tension headaches/migraines, chronic musculoskeletal pain/fibromyalgia, “chronic sickle cell pain” (pain that extends beyond the expected time of acute vasoocclusive crisis), and functional abdominal pain/centrally mediated abdominal pain syndrome. In our clinical practice we do not prescribe opioids for primary pain disorders in children or teenagers, and we consider them contraindicated.

We are among the pediatric specialists who believe that opioids administered for primary pain disorders have low long-term efficacy, a poor safety profile, and commonly a worse clinical outcome [3,10–13,25,65]. On the other hand, in persistent pain conditions (i.e., long-lasting and/or repetitive nociceptive pain caused by tissue injury, such as in children with junctional epidermolysis bullosa, osteogenesis imperfecta, or advanced metastasized bone tumors (e.g., Ewing sarcoma), opioids usually do play an important role in long-term analgesic management.

**Conclusions**

Withholding evidence-based analgesia to hospitalized infants and children in pain not only is unethical, but may cause immediate and long-term harm. Analgesic treatment is mandatory for children when they undergo painful procedures, and no avoidable suffering is acceptable nowadays, even for so-called minor interventions. The potential risks associated with the administration of analgesics are real, but manageable. The best practice involves using multimodal (opioid-sparing) analgesia, which may include polypharmacy, procedural interventions, rehabilitation, and psychological and integrative therapies that act synergistically for more effective pediatric pain control with fewer side effects than any single analgesic or modality. In the treatment of primary pain disorders (including headaches/migraines, functional abdominal pain, and musculoskeletal pain/fibromyalgia), i.e., chronic pain that persists beyond the expected time of healing, opioids are not indicated for children and teenagers. For persistent pain due to longstanding and repetitive tissue injury, opioids should be provided very cautiously, and only after proper screening and continuous monitoring, which must include a practical exit strategy.

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**References**


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