Clinical Pearls

From Coke to Pepsi to Mountain Dew? Rotating Opioids in Advanced Pediatric Palliative Care

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If children with serious illnesses being treated for pain or dyspnea experience good symptom control but display opioid-induced side effects, such as oversedation, an experienced clinician usually reduces the opioid dose. However, if both poor analgesia and dose-limiting side effects occur, opioid rotation has been shown to be very effective for improving analgesia and dyspnea management and lessening side effects in children. Differences between opioids in the balance between analgesic cross-tolerance level and the level of cross-tolerance to adverse effects can be exploited to clinical advantage. Switching opioids can achieve a more favorable
balance between analgesia and adverse effects, hence the rationale for trial of a different opioid in the event of toxicity or inadequate analgesia.  

Children differ in their response to opioid analgesics. Even in well designed, successful clinical trials, up to 40% of patients do not respond well to the analgesic being studied. Not surprisingly, children—like adults —may require trials of several opioids to find effective analgesia with acceptable tolerability. Individuals display a variety of combinations of different μ-opioid receptor (MOR) subtypes generated through alternative splicing, which is known to enhance protein diversity. The binding profiles and resulting pharmacologic effects of opioid receptor subtypes vary among μ-opioids and contribute to individual variance in therapeutic response and incomplete cross-tolerance (Figure 1).  

Problems with Equi-Analgesic Tables

There are significant problems with adult-based conversion tables used in pediatrics, especially with the conversion rate of fentanyl (Figure 2). Problems may include

- tremendous inter-individual variability in relative potency estimates
- tolerance development with repetitive dosing: dose reduction 25%-75% (or more) for incomplete cross-tolerance often inadequately portrayed
- assumption that relative potency ratios remain irrespective of level of opioid
- no account for unidirectional cross-tolerance
- no account for possibility of active metabolite accumulation.
For instance, the intravenous conversion rate from hydromorphone to morphine is 1:7 for single doses (i.e., 1 mg hydromorphone = 7 mg morphine), but once it reaches the initial steady-state the ratio is 1:5, and for a long-term continuous infusion the ratio is only 1:3.5. For fentanyl, an intravenous conversion rate of 1:100 is commonly cited (10 mcg fentanyl = 1000 mcg or 1 mg morphine). However, clinical experience in pediatrics with continuous infusion (not single doses) has shown that in children older than 6 months the rate is 1:40 (i.e., 50 mcg fentanyl/hour = 1 mg IV morphine/hour). In infants, who become tolerant faster (the flip-side of brain plasticity is rapid development of tolerance), the conversion rate is closer to 1:13-20. Using the standard adult 1:100 conversion may result in significant oversedation (if rotated from fentanyl to another opioid) or underdosing (if rotated from another opioid to fentanyl).
**Conclusion**

If medium to severe opioid-induced side effects occur, opioid rotation at equi-analgesic doses (minus reduction for incomplete cross-tolerance) is often effective in pediatric palliative care (PPC).

Of note, the opioid rotation to methadone is often highly effective in PPC. However, due to methadone’s long half-life and wide dosing variation, the equi-analgesic conversion is far more complex and beyond the scope of this article.

**References**

4. Argo CE. Clinical implications of opioid...


Case Example Part 1:

Andrea is a 10-year-old girl in severe pain (VAS 8/10) due to metastasized osteosarcoma; weight: 20 kg.

- She is now on morphine continuous infusion of with a PCA Dose of the same (1.3 mg, lockout 10 minutes).
- She was appropriately titrated to effect in 50% increment steps over the last week.
- The last dose escalation from 0.9 mg/hr plus 0.9 mg PCA bolus to current dose occurred yesterday.
- She self-administered 7 boluses over the last 24 hours. However, she now complains about severe nausea following PCA boluses and poor analgesia.

**Question 1: Why, unlike adult medicine, does pain medicine in pediatrics nearly always consist of a continuous opioid infusion plus patient-controlled/nurse-controlled analgesia and not PCA bolus only?** In children, according to the World Health Organization, analgesics are scheduled around-the-clock and not “as-needed” (In fact, “PRN” usually translates into “patient receives nothing”). Also, a meta-analysis could show that the addition of continuous (or background) infusion to the PCA bolus (or demand) dose for IV-PCA is not associated with a
higher incidence of respiratory events than PCA bolus alone in pediatric patients (in contrast to adults).²

**Question 2: When undertaking an opioid rotation, do all PCA boluses count for calculation?** It depends on the clinical scenario. If continuous infusion equals the PCA bolus dose, then consider these rules of thumb.

- 1-12 boluses/24 hours: might not count towards conversion [as in our case example]
- 13-24: depend on clinical scenario
- >24 PCA bolus: count towards opioid conversion

**Question 3: Once I calculate the equianalgesic dose, how much must I decrease the new opioid by for incomplete cross-tolerance?** Again, it depends! In any given clinical scenario, the answer may be anywhere from 0%-90%.

- If a child has escalating pain, one would usually be inclined to increase the current dose by 50%. However, if an opioid rotation occurs in this scenario due to side effects such as pruritus, then the decrease of the final opioid may be much less than 50%.
- If a child is on astronomical doses of morphine (eg, a 1 year old on 15 mg IV morphine/hour), ineffective analgesia and increased neuro-excitability might be due to accumulation of the “bad” nociceptive metabolite morphine-3-glucorinide, ie, the “dose doesn't reach the patient,” in which case a decrease of 90% might be appropriate.
- In standard clinical pediatric situations, a decrease of 50% might be appropriate.

**Question 4: How do I calculate a “rescue” or “breakthrough” or “PRN” opioid dose in children?** It is usually (not for fentanyl infusion)
10% of the total daily dose once every 1-2 hours. It is recommended to inform the prescribing clinician for re-evaluation if the patient uses more than 3 PRN doses in less than 24 hours (i.e., patients are usually not invited to take 12-24 additional PRN doses per day).

**Case Example [Conversion IV:IV]**

**Morphine PCA**  
Continuous Infusion (Basal Rate): 1.3 mg/hr (= 1300 mcg/hr)

**Fentanyl [M:F = 40:1]**

1300 mcg/hr Morphine  
65 mcg/kg/hr

\[ \frac{1}{40} \]

32 mcg/hr Fentanyl  
1.6 mcg/kg/hr

\[ \downarrow \text{50% Dose reduction} \]

21 mcg/hr Fentanyl  
1 mcg/kg/hr

\[ \rightarrow \text{32 mcg PCA Bolus} \]

Lockout 5 min, max 6 hr

\[ \rightarrow \text{21 mcg PCA Bolus} \]

Lockout 5 min, max 6 hr

**Case Example [Conversion IV:IV]**

**Morphine PCA**  
Continuous Infusion (Basal Rate): 1.3 mg/hr (= 1300 mcg/hr)

**Hydromorphone [M:H = 7:1]**

1.3 mg/hr Morphine  
65 mcg/kg/hr

\[ \frac{1}{7} \]

0.19 mg/hr Hydromorphone  
9 mcg/kg/hr

\[ \downarrow \text{50% Dose reduction} \]

0.1 mg/hr Hydromorphone  
4.5 mcg/kg/hr

\[ \rightarrow \text{0.19 mg PCA Bolus} \]

Lockout 7 min, max 6 hr

\[ \rightarrow \text{0.1 mg PCA Bolus} \]

Lockout 7 min, max 6 hr
Case Example Part 2:
One week later, Andrea is comfortable (VAS 1/10) on her PCA and would like to go home without being hooked up to an infusion pump.

Current settings Hydromorphone PCA

<table>
<thead>
<tr>
<th>Basal Rate: 0.45 mg/hr</th>
<th>[22 mcg/kg/hr]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCA bolus: 0.45 mg</td>
<td>[18 boluses in last 24 hours]</td>
</tr>
<tr>
<td>Total drug use: 0.45 mg/hr x 24 hr</td>
<td>= 10.8 mg/day</td>
</tr>
<tr>
<td></td>
<td>0.45 mg x 18 boluses</td>
</tr>
<tr>
<td>TOTAL:</td>
<td>= 18.9 mg/day</td>
</tr>
</tbody>
</table>
References

   [http://whqlibdoc.who.int/publications/2012/97](http://whqlibdoc.who.int/publications/2012/97)


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