Learning Objectives

• Case Example [“hook”]
• Discuss indications for and misconceptions about opioid conversion [“attitude”]
• Review cross-tolerance and rationale for opioid rotation and combining Opioids [“knowledge”]
• Practice examples for opioid conversion [“skill”]

Case Example

• Andrea is a 10-year-old girl in severe acute pain (VAS 8/10) due to metastasized osteosarcoma; weight: 20 kgs
• Andrea has been started on morphine 3 days ago - now the nurse calls you that she is poorly arousable, respiratory rate 9/min, oxygen saturation 82% when eyes closed
• What might be your next questions & steps?
  • Over sedation => good analgesia?
  • Over sedation => poor analgesia?
Management of Opioid Adverse Effect “Over Sedation”

- **Dose reduction**
  - If good analgesia
- **Opioid rotation**
  - If poor analgesia and/or medium-severe side effects
- **Adverse effect targeted therapy**
  - If mild side effects or opioid rotation not possible

- What arguments might you hear from parents, patients or colleagues/care team NOT to rotate the opioid?

Analgesic Response

- Patients differ in their response to opioid analgesics
- Even in well designed, successful clinical trials, as much as 40% of patients do not respond well to analgesic being studied

Argoff CE, Yanni LM. Pharmacogenetics and pain. Prim Care Q 2010;1-8

- Unsurprising, patients may require trials of several opioids to find effective analgesia with acceptable tolerability

μ-Receptor Subtypes

- Individuals display variety of combinations of different mu-receptor subtypes
- Generated through “alternative splicing”, known to enhance protein diversity
- Binding profiles & resulting pharmacologic effects of opioid receptor subtypes vary among μ-opioids
- Contributing to individual variance in therapeutic response & incomplete cross-tolerance

Cross-tolerance

- **Tolerance**: Decrease in drug effect as result to prior exposure to the drug (for analgesia and/or adverse effect)

- **Cross-tolerance** (between two opioids): Phenomenon whereby tolerance to a particular opioid effect from an existing opioid is conferred to a newly substituted opioid
  - Effect: complete or incomplete
  - Symmetric, asymmetric or unidirectional


Opioid tolerance: Non-pharmacodynamic factors

- **Pain related**
  - Disease progression or infection at tumor site
  - Impact of other therapies and adjuvant drugs

- **Pharmacokinetic**
  - Absorption of opioid - change of route of administration
  - Drug interactions
  - Drug biotransformation and metabolism
  - Antinociceptive metabolites (e.g. morphine-6-glucoronide)
  - Nociceptive metabolites (e.g. morphine-3-glucoronide)
  - Renal function
  - Pharmacogenetics

- **Behavior/psychological state**
  - Somatization, psychological distress
  - Cognitive Status; delirium

Switching Opioids

*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 possibly 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.*

Adding and Mixing Opioids

**Perceived Efficacy of Analgesic Drug Regimens Used for Koalas (Phascolarctos cinereus) in Australia**
De Kauwe T, Kimble B, Govendir M

‘Analgesic drug combinations were generally thought efficacious’

Morphine [Structural formula]
Heroin [Structural formula]
Fentanyl [Structural formula]
Morphine 6-Glucuronide [Structural formula]
Methadone [Structural formula]
Comparison of sustained-release morphine with sustained-release oxycodone in advanced cancer patients

Addition of a second opioid may improve opioid response in cancer pain: preliminary data

Analgesic Efficacy and Tolerability of Intravenous Morphine Versus Combined Intravenous Morphine and Oxycodone in a 2-Center, Randomized, Double-Blind, Pilot Trial of Patients With Moderate to Severe Pain After Total Hip Replacement
Analgesic and adverse effects of a fixed-ratio morphine-oxycodone combination (MoxDuo®) in the treatment of postoperative pain

Patricia Richards, MD, PhD; Dennis Riff, MD; Robin Kelen, RN; Warren Stern, PhD;
for the MoxDuo Study Team

Journal of Opioid Management 7:3 © May/June 2011
Take Home Messages
Combining Opioids

• May cause analgesic synergy
• Unlikely to increase side effects
• Useful manoeuvre to employ as part of a multi-modal therapy

Opioid Rotation (at equianalgesic doses!)
..."eminence", not evidence based...

“Gold Standard”: Morphine

Route of administration:
Oral (sublingual, rectal)

Oxycodone

Hydromorphone

Methadone

Route of administration:
Intravenous (subcutaneous)

Fentanyl

Hydromorphone

Methadone

Problems with Equianalgesic Tables?

Opioid Conversion

<table>
<thead>
<tr>
<th>Opioid Agent</th>
<th>Equianalgesic Dose (ED)</th>
<th>IV to PO Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td>NA</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 to 5</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 to 3</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>NA</td>
<td>20</td>
</tr>
</tbody>
</table>

(Real life example)

• 10 mg IV Morphine = 1.5 mg Hydromorphone?
• 1.5 mg Hydromorphone = 10 mg IV Morphine?
• 50 mcg/hour [0.05mg] IV Fentanyl = 5 mg IV/hour Morphine????
Relative Potency


  - Morphine:Hydromorphone 5:1 or 7:1
    - M:HM => (median) 5.0 - 5.3
    - HM:M => (median) 3.6 - 3.7

  - ...And what is the difference between 1:7 and 7:1....????

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Relative Potency

**Published experience: Hydromorphone : Morphine** (Davis MP, McPherson ML. Tabling hydromorphone: do we have it right?J Palliat Med. 2010 Apr;13(4):365-6.

- Single dose: 1:7
- Initial steady-state (PO/IV): 1:5
- Long-term infusion: 1:3.5

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Problems with Equianalgesic Tables

- Tremendous **inter-individual variability** in relative potency estimates
- **Tolerance development** with repetitive dosing; Dose reduction 25-75% for incomplete cross-tolerance often inadequately portrayed
- Assumption that relative potency ratios remains irrespective of level of opioid

- No account for **unidirectional cross-tolerance**
- No account for possibility of **active metabolite accumulation**
Case Example [Conversion IV:IV]

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

- **Continuous Infusion (Basal Rate):** 0.4 mg/hr -> 0.6 mg/hr -> 0.9 mg/hr -> 1.3 mg/hr

- **PCA Dose:** 0.4 mg -> 0.6 mg -> 0.9 mg -> 1.3 mg

- (Lock out: 10 min; 4 Boluses/hr)

- Received 7 Boluses/24 hr [count or not count...?]

- Over sedation => good analgesia!
- Over sedation => poor analgesia!
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
32 mcg/hr
Fentanyl
1.6 mcg/kg/hr
32 mcg
PCA Bolus
Lockout 5-10 min, max 4-6/hr
21 mcg/hr
Fentanyl
1 mcg/kg/hr
21 mcg
PCA Bolus
Lockout 5-10 min, max 4-6/hr

...Dose reduction...?

Clinical Context
Incomplete Cross Tolerance:
Decrease dose by
(0 - 33% -) 50% (or more?)

...it depends...

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
0.19 mg/hr
Hydromorphone
9 mcg/kg/hr
0.19 mg
PCA Bolus
Lockout 7 min, max 6/hr
0.1 mg/hr
Hydromorphone
4.5 mcg/kg/hr
0.1 mg
PCA Bolus
Lockout 7 min, max 6/hr
Case Example [Conversion IV:PO]

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
Basal Rate: 0.45 mg/hr [22 mcg/kg/hr]
PCA bolus: 0.45 mg [18 boluses in last 24 hours]

Total drug use: 0.45mg/hr x 24 hr = 10.8 mg/day
0.45mg x 18 boluses = 8.1 mg/day
= 18.9 mg/day

Case Example [Conversion IV:PO]

19 mg/day IV Hydromorphone
=> PO Hydromorphone

Hydromorphone [IV:PO = 1:3.5]

19 mg/day IV Hydromorphone
x 3.5
66.5 mg/day PO Hydromorphone

50% Dose Reduction?

33 mg/day PO Hydromorphone (not including PCA doses?)

11 mg PO Q4h
6.6 mg PO Q1-2qh PRN

Case Example [Conversion IV:PO]

19 mg/day IV Hydromorphone
=> PO Oxycodone

19 mg/day IV Hydromorphone
x 5
95 mg/day IV Morphine
x 3
285 mg/day PO Morphine

190 mg/day PO Oxycodone

95 mg/day PO Oxycodone

22.5 mg PO Q6h Oxycodon [or 50 mg Q12h extended-release]
10 mg PO Q1-2h PRN Oxycodon immediate release
Case Example [Conversion IV:Transmucosal]

19 mg/day IV Hydromorphone

=> Fentanyl Patch

19 mg/day IV Hydromorphone

× 5

95 mg/day IV Morphine

/ 40

2375 mcg/day IV Fentanyl

50 mcg/hr IV Fentanyl

50 mcg/hr transdermal Fentanyl Q48-72h

Hydromorphone 6.5 mg PO Q1-2h PRN or Fentanyl lozenge?

50 % Dose reduction

Rescue Dose = 10%

99 mcg/hr IV Fentanyl

/ 24

Spinal Opioids

Epidural: IV Opioid Ratios:
Morphine 1:10 [0.1 mg/hr epidural = 1 mg/hr IV]
Fentanyl 1:3 [10 mcg/hr epidural = 30 mcg/hr IV]
Hydromorphone 1:3 [0.1 mg/hr epidural = 0.3 mg/hr IV]

Intrathecal: IV Opioid Ratios:
Morphine 1:100 [0.01 mg/hr intrathecal = 1 mg/hr IV]
Fentanyl 1:30 [1 mcg/hr intrathecal = 30 mcg/hr IV]
Hydromorphone 1:30 [0.01 mg/hr intrathecal = 0.3 mg/hr IV]

Andrea would like to thank you for your excellent opioid analgesia management.

Well done, old chap!
Conclusions

- Children usually sleep well... once pain is finally well controlled – prepare parents & bed-side nurses (but rule out over sedation)

- If medium-severe opioid-induced side effects: Opioid rotation at equianalgesic doses [minus reduction for incomplete cross-tolerance]

- Don’t manage severe opioid-induced side effects with medications – rather rotate the opioid instead (if feasible)

- IV opioid administration is usually not better than oral administration (only faster) – switch to oral administration once pain well controlled and child is eating and drinking
Further Training:
CIPPC@ChildrensMN.org

9th Annual Pediatric Pain Master Class
• Minneapolis, MN | June 11-17, 2016

Education in Palliative & End-of-life Care [EPEC]: Become an EPEC-Pediatrics Trainer
• 8th Conference: Montevideo, Uruguay | Sept 5, 2015
• 9th Conference: Chicago, IL | March 12-13, 2016