The Distinct Pharmacology of Opioid Analgesics

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Prescription Opioid Misuse Academy: The Dark Side of Prescription Opioids

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“Not All Opioids are Created Equally”

- Compare the potency, duration of action, and equianalgesic doses of fentanyl, hydrocodone, hydromorphone, morphine, and oxycodone
- Explain the clinical implications of these properties
- Discuss the unique characteristics of special formulations (e.g. Duragesic, Oxycontin)
- Highlight unique characteristics that produce relevant clinical effects
Case

- 24 yo man with recurrent shoulder dislocations presents to ED. While preparing for conscious sedation and reduction, morphine 4 mg IV is given. RN returns stating morphine did nothing for his pain and he is demanding an alternative agent. Hydromorphone 2mg IV is given.

- A code is called to the patient’s room when he becomes obtunded, apneic and hypoxic
What happened?

- Iatrogenic opioid overdose
- Was it a lack of understanding of the equianalgesic dose compared to morphine?
- Did the clinician fail to account for variation in potency for the route of administration?
Knowledge Deficits Regarding Opioids Include:

- Drug choice/specific agents
- Appropriate routes of administration
- Calculation of equianalgesic doses
- Titration of doses
- Management of side effects
- Risk of tolerance and addiction
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Definitions

- **Potency**: intensity of analgesic effect for a given dose. This is based on access to and binding affinity for the receptor site.
  - Amount of pain relief per mg
- **Equianalgesia**: two doses that provide approximately the same amount of pain relief.
  - Relative to one opioid to compared to another
  - Or relative to a change in route of the same opioid
Hydromorphone (HM)

- Frequently associated with error and patient harm
  - misunderstanding equianalgesic dosing
  - Look-alike packaging
  - Name similarity

- Numerous reports in the medical literature
Similar Packaging Contributes to Errors Related to Hydromorphone

A COMPARISON OF MAJOR ANALGESICS WITH RESPECT TO DOSAGE, AND DURATION; BASED ON SINGLE-DOSE STUDIES - DOSES REQUIRED MAY BE LOWER WITH REPEATED ADMINISTRATION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equianalgesic Doses (mg)</th>
<th>Duration of Action in (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>(IV/IM/subQ) 10</td>
<td>4 to 6</td>
</tr>
<tr>
<td></td>
<td>(Oral IR) 30 to 40</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>(Oral CR) * 30 to 40</td>
<td>8 to 12</td>
</tr>
<tr>
<td></td>
<td>(Oral SR) ** 20 to 60</td>
<td>12 to 24</td>
</tr>
<tr>
<td></td>
<td>(Rectal) 10</td>
<td>4 to 24 ***</td>
</tr>
<tr>
<td>Codeine</td>
<td>(IM/subQ) 120 to 130</td>
<td>4 to 6</td>
</tr>
<tr>
<td></td>
<td>(Oral) 180 to 200</td>
<td>4 to 6</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>(IV) 0.1</td>
<td>1 to 2</td>
</tr>
<tr>
<td></td>
<td>(Oral transmucosal) 0.2 to 0.4</td>
<td>less than 1</td>
</tr>
<tr>
<td></td>
<td>(Transdermal) See Table 2</td>
<td>48 to 72</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>(Oral) 30</td>
<td>4 to 6</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>(IM, subQ) 1.5 to 2</td>
<td>4 to 5</td>
</tr>
<tr>
<td></td>
<td>(Rectal) --</td>
<td>6 to 8</td>
</tr>
<tr>
<td></td>
<td>(Oral) 6 to 7.5</td>
<td>4 to 6</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>(IM, subQ) 2</td>
<td>4 to 6</td>
</tr>
<tr>
<td></td>
<td>(Oral) 4</td>
<td>6 to 8</td>
</tr>
<tr>
<td>Meperidine****</td>
<td>(IM, subQ) 75 to 100</td>
<td>2 to 4</td>
</tr>
<tr>
<td></td>
<td>(Oral) 300</td>
<td>3 to 4</td>
</tr>
<tr>
<td>Methadone</td>
<td>(IM, subQ) 5 to 10</td>
<td>3 to 8</td>
</tr>
<tr>
<td></td>
<td>(Oral) 2.5 to 15 +</td>
<td>2 to 10 ++</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>(Oral) 20 to 30</td>
<td>4 to 6</td>
</tr>
<tr>
<td></td>
<td>(Oral CR) --</td>
<td>12</td>
</tr>
</tbody>
</table>
Things to Keep in Mind Regarding Equianalgesic Conversion Tables

- Derived from older single-dose studies
  - Repetitive dosing and accumulation not accounted for
  - Some emerged based on clinical observation
  - Data not substantiated by methodologically sound studies
- Can not anticipate variability of patient response
- Concept of incomplete cross tolerance
Problems and Pitfalls of Equianalgesic Tables

- Incomplete cross-tolerance
  - Tolerance to the analgesic and side effects of a given opioid but may not have the same degree of tolerance for another agent

- Must emphasize that they do not provide recommended initiation doses
  - Doses are standardized to the equivalent of 10 mg of parenteral (IM) morphine
Other factors not taken into account

- Half-life
- Bioavailability
- Hepatic and renal clearance
- Drug interactions (CYP 3A4)
- Type of pain
- Genetic polymorphism (CYP 2D6)
- Prior opioid exposure
Hydromorphone

- Discrepancies between equianalgesic table info and clinical experience prompted further investigation
- A retrospective analysis of oral MS and HM ratios found a directional influence
  - 5.33:1 in going from MS to HM and 3.8:1 in going from HM to MS
- Another study looked at parenteral dosing and found it changed over time (50 days)
  - Changed from 7:1 ~day 7 to 3:1 by day 13
  - Highlighting limitation of single dose studies
What about Oxycodone?

- Available in IR and CR formulations as well as in combination with APAP or ASA
- Hepatically metabolized to noroxycodone and oxymorphone
- Duration of Action: IR 3-6 hrs, CR ~12 hrs
- Elimination half-life: IR 2-4 hrs, CR ~5 hrs
  - Prolonged in cirrhosis ~14 hours
Oxycodone: Equianalgesia and Potency

- Potency of Parenteral Oxy ~ 70% of MS
  - Confirmed by double blind randomized cross-over study, 30% more Oxy to produce = analgesia to MS

- Determining relative potency of oral Oxy and MS is more problematic
  - Variability in oral bioavailability MS 15-46% while Oxy is 60-87%
  - Incomplete cross tolerance
  - Debatable bidirectional difference

- MS:Oxy ratios ranged from 1:1 to 2.3:1
Oxycodone Has Bigger Problems

- Abuse has reached epidemic proportions
- Tremendous efforts to try to control drug diversion
- Naively, thought CR preparations would be less appealing to abusers
  - Biphasic absorption minor initial peak at ~ 40 min. and later major peak at ~ 6 hrs
Formulations to Deter Abuse

• Abusers will crush or pulverize the CR pills releasing large concentrations of Oxy that can be swallowed, snorted, smoked, injected

• Innovative formulations to make extraction more difficult
  – Abuse-deterrent vs. abuse-resistant
Building a Better Mouse Trap

- One reformulation already introduced that increased tamper resistance
- Attempts to dissolve the tablets results in a gummy substance that can’t be drawn into a syringe
- Abusers persevere
Even a Better Mouse Trap

- Extended release Oxy in a high viscosity, hard gelatin (insoluble) matrix capsule
  - Resists chewing and crushing
  - Deters injection (high viscosity)
  - Snorting (gel cap)
  - Thermal extraction

- Immediate release Oxy with sub-therapeutic niacin (Acurox® 7.5/30 mg)
Hydrocodone

- C-III controlled substance used as an analgesic and antitussive
- Hepatically metabolized to hydromorphone (2D6) and norhydrocodone (3A4)
- Onset of action 10-20 min
- Duration 4-8 hours
- Elimination half-life 3.3-4.4 hours
- What about its potency?
Potency of Hydrocodone

• Many equianalgesic tables and studies indicate it is equal in potency to oxycodone
• Others suggest Oxycodone is more potent
• One DBRCT of chronic cancer pain concluded hydrocodone/APAP was not superior in analgesic efficacy to tramadol
## Equianalgesic Conversion

<table>
<thead>
<tr>
<th>Opioid Agonist</th>
<th>Oral</th>
<th>Parenteral</th>
<th>Dosing Interval</th>
<th>Forms Available</th>
<th>PO</th>
<th>Transdermal</th>
<th>IV</th>
<th>SQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30 mg</td>
<td>10 mg</td>
<td>q 3 - 4 h</td>
<td>Tabs, Liquid, Sustained release</td>
<td>--</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid)</td>
<td>7.5 mg</td>
<td>1.5 mg</td>
<td>q 3 - 4 h</td>
<td>Tabs</td>
<td>--</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Meperidine (Demerol)</td>
<td>300 mg</td>
<td>100 mg</td>
<td>q 2 -3 h</td>
<td>Tabs</td>
<td>--</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Methadone</td>
<td>20 mg</td>
<td>10 mg</td>
<td>q 6 - 8 h, quite variable</td>
<td>Tabs, Liquid</td>
<td>--</td>
<td>(+)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Fentanyl (Duragesic)</td>
<td>variable</td>
<td>--</td>
<td>transdermal patches: q 3 days</td>
<td>--</td>
<td>--</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Oxycodone (Oxycontin)</td>
<td>20 mg</td>
<td>N/A</td>
<td>q 3 - 4 h</td>
<td>Tabs, Sustained release</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Codeine</td>
<td>180 -200 mg</td>
<td>N/A</td>
<td>q 3 - 4 h</td>
<td>Tabs, Liquid</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30 mg</td>
<td>N/A</td>
<td>q 3 - 4 h</td>
<td>Tabs, Liquid</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
Hydrocodone’s Abuse Potential

• Despite Class III status several studies indicate risk of abuse is similar to Oxycodone and Morphine

New Vicodin draws activist fire amid opioid abuse epidemic

Posted on January 27, 2012 by Erin Marie Daly

San Diego-based Zogenix Inc.’s bid for FDA approval to begin marketing Zohydro – a new version of pure, extended-release hydrocodone that is said to be 10 times more powerful than Vicodin – has prompted some activists to appeal to the agency not to rubber-stamp more opioid drugs in the midst of an out-of-control epidemic. Proponents of extended-release versions of opioids – such as Purdue Pharma’s recently reformulated OxyContin, OP – claim the drugs are safer because they are “abuse-resistant,” but others point out that many opioid-addicted people simply swallow the pills whole. (Addicts are also already finding their way around allegedly tamper-proof versions.)
Case

- 58 yo woman admitted for uncontrolled severe burning, dysesthetic left shoulder pain
- Taking fentanyl TTS, carbamazepine, amitriptyline
- Fentanyl gradually increased over time
How Many Patches?

- Husband diligently changed 34 patches every 72 hours
- Despite 3400 mcg/hr patient had no respiratory insufficiency
- Plasma fentanyl level was 178 ng/ml
Did Someone Say “Potent” Fentanyl

- Highly potent mu agonist
- High lipophilicity and undergoes extensive first pass metabolism
- Onset of action is almost immediate with IV administration
- Duration of action is 0.5-1 hr due to redistribution, elimination half-life is 2-4 hrs
- Analgesia achieved with plasma concentrations of 0.6-1.5 ng/ml
Delivery Systems

• Transdermal therapeutic systems (TTS)
• Iontophoretic Transdermal systems (ITS)
• Oral transmucosal fentanyl citrate (OTFC)
• Fentanyl buccal tablets (FBT)
• Sublingual/buccal film formulations
• Intranasal fentanyl (INF)
• Transpulmonary administration
Transdermal Therapeutic Systems

- Two different systems marketed
  - Reservoir and matrix
- Reservoir is made of 4 layers
  - Outer impermeable layer
  - Second layer is the drug reservoir
  - Rate control membrane
  - Peel strip is removed to reveal an adhesive layer that delivers and initial bolus
- Patches contain 2.5, 5, 7.5 or 10 mg
- ~50% of the drug remains after 72 hrs of use
Matrix Systems

- Largely superseded reservoir patch
- Fentanyl containing dipropylene glycol droplets incorporated in the polyacrylate adhesive
- Pharmacokinetic profiles and bioequivalence are similar
- Initial bolus occurs due to the large concentration in the adhesive
TTS

- Depot forms in the stratum corneum
- Skin permeation is the rate limiting step
  - Therapeutic concentration are achieved in ~17-24 hours
- Bioavailability is nearly 100%
- Serum concentrations are similar to IV
- Takes ~48 hrs to determine if dose is adequate
Considerations

• ~30% of the dose remains in the skin after patch removal
  – explains the terminal $t_{1/2}$ of 22-25 hrs
  – 2-3 X longer than IV
• Effects may worsen or persist after removal
• Absorption can be increased by ~33% with a rise in body temperature $>40^\circ$ C
Equianalgesic Dosing of Transdermal Fentanyl

- Conservative conversion for oral MS to TD fentanyl is 100:1
Patient Controlled Fentanyl Iontophoretic Transdermal System

- Electronic controller and a reservoir with fentanyl gel
  - releases 40 mcg when the button is pressed twice
- Imperceptible electric current initiates delivery
- Pharmacokinetics are similar to IV
ITS

• Several large studies found it safe and achieved equivalent analgesia compared to MS PCA pumps
• Approved in US and Europe for short-term severe post-op pain in hospitalized patients
• Marketing suspended due to corrosion of a component
• Cost analysis has not been performed
OTFC

- Lozenge with an applicator
  - 200-1600 mcg in a dissolvable sugar based matrix
- ~25% absorbed through the buccal mucosa with rapid onset and early peak
- Remaining 75% swallowed with slow intestinal absorption
- Onset of effect 5-10 min duration ~2 hrs
- Overall bioavailability 50%
Fentanyl Buccal Tablet

- Approved for use for breakthrough pain in opioid tolerant cancer patients
- Effervescent reaction and change in pH facilitate dissolving and enhanced absorption across buccal mucosa
- Bioavailability ~65% (higher than OTFC)
- Serum concentrations rise faster and are higher than OTFC
  - 30% dose reduction required
FDA Warning

- Issued after reports of deaths and adverse effects regarding FBTs
- All occurred after improper patient selection or dosing

Figure 1. Mean Plasma Concentration Versus Time Profiles Following Single Doses of FENTORA and Actiq in Healthy Subjects

Actiq data was dose adjusted (800 mcg to 400 mcg).
Case

• 68 yo with DM, CAD, CKD patient treated with morphine 4 mg q 3-4 hrs prn pain following ventral hernia repair
• HD #2 patient somnolent and delirious
• Lab studies unremarkable other than glucose of 247 and BUN/Cr of 38/3.3
• What is the likely explanation?
Morphine

- Hepatically metabolized to normorphine, M3G and M6G
- Clearance of parent compound in renal failure is not significantly different than in normal subjects
- Glucuronide metabolites do accumulate
- M6G is an analgesic and CNS depressant that crosses the BBB and exerts prolonged CNS effects
- Appears dialyzable but rebound may occur
Other Opioids in Renal Failure

- **Codeine**
  - Several reports of severe AE
  - Renal clearance of metabolites significantly reduced (M6G)

- **Hydromorphone**
  - Many metabolites all excreted renally
  - Variability among studies some suggest accumulation of 3-glucuronide metabolite which may be neurotoxic
  - Clinical use in patients with RF without toxicity
Other Opioids in Renal Failure

• Oxycodone
  – Data limited, t1/2 prolonged in uremic patients
  – Oxymorphone present in very small amounts
    significance of impaired excretion in RF
    unknown

• Fentanyl
  – No adverse effects in renal failure noted,
    appears safe. Not readily dialyzable

• Methadone
  – Likely safe but not dialyzable
# Opioids in Renal Failure: Bottomline

<table>
<thead>
<tr>
<th>Safe</th>
<th>Use with caution</th>
<th>Unsafe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Dilaudid</td>
<td>Morphine</td>
</tr>
<tr>
<td>Methadone</td>
<td>Oxycodone</td>
<td>Codeine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meperidine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tramadol</td>
</tr>
</tbody>
</table>
Case

- 45 yo man with chronic recurrent abdominal pain and frequent ED visits presents complaining of worsening pain and is requesting something to help until he can see his pain specialist in the a.m.
- Unable to obtain an IV, you give a dose of analgesic IM.
- Patient develops N/V, diarrhea, yawning, piloerection, dysphoria, diaphoresis….

You gave Nalbuphine 10 mg of IM
Agonist-Antagonists or Partial Agonists

- Nalbuphine, butorphanol, pentazocine, buprenorphine
- Kappa receptor agonists while acting as antagonists or partial agonists at mu receptors
- Must be aware that in opioid tolerant individuals acute withdrawal can be precipitated
References


References


