Hydromorphone versus Morphine

A Retrospective Chart Review to Evaluate the Effectiveness of Post-Operative Analgesia in Elective Surgical Patients

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Background

• Morphine (M) and hydromorphone (HM) are commonly prescribed post-operative analgesics

• Historically, M has been the most commonly used medication but HM use is increasing\(^1\)

• Chemical structure of HM makes it 5-10 x more potent and enhances distribution in brain allowing for easier titration\(^1\)

• Unlike morphine, HM has no active metabolite\(^1\)
Table 1: Key pharmacological properties of hydromorphone and morphine. *K_i values specifying the concentration of competing ligand which would occupy 50% of the receptor if no radio-ligand was present (calculated according to the Cheng–Prusoff equation)

<table>
<thead>
<tr>
<th>Physicochemistry</th>
<th>Hydromorphone</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>285.388 g mol(^{-1})</td>
<td>285.34 g mol(^{-1})</td>
</tr>
<tr>
<td>(pK_a)</td>
<td>8.2(^{43})</td>
<td>8.21(^{43})</td>
</tr>
<tr>
<td>Octanol water partition coefficient</td>
<td>1.28(^{43})</td>
<td>0.7(^{43})</td>
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<thead>
<tr>
<th>Pharmacokinetics</th>
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<tbody>
<tr>
<td>Plasma elimination half-life</td>
<td>2 – 3 h(^{4})</td>
<td>2 – 3.5 h(^{4})</td>
</tr>
<tr>
<td>Transfer half-life plasma effect site, (t_{1/2,ke0})</td>
<td>18 – 38 min(^{40})</td>
<td>1.6 – 4.8 h(^{37})</td>
</tr>
<tr>
<td>Volume of distribution, (V_d)</td>
<td>1.22 litre kg(^{-1}) (^{44})</td>
<td>1.0 litre kg(^{-1}) (^{44})</td>
</tr>
<tr>
<td>Oral bioavailability (immediate-release formulation)</td>
<td>50%(^{45})</td>
<td>30%(^{46})</td>
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<thead>
<tr>
<th>Pharmaceutical formulations</th>
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<tbody>
<tr>
<td>Oral administration in solutions, capsules, or tablets with either immediate or sustained release</td>
<td>Sustained-release hydromorphone is used once daily</td>
<td>Sustained-release morphine is used every 12 h</td>
</tr>
<tr>
<td>I.V.</td>
<td></td>
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<tr>
<td>Suppositories</td>
<td>Available in Canada</td>
<td>Available in Canada and Germany</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Possible (no commercial brands available)</td>
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<thead>
<tr>
<th>Pharmacodynamics</th>
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<tbody>
<tr>
<td>[^{3}H] DAMGO replacement ((\mu)-opioid receptor affinity)*</td>
<td>0.6 nM(^{67})</td>
<td>1.2 nM(^{67})</td>
</tr>
<tr>
<td>[^{3}H] DPDPE replacement ((\delta)-opioid receptor affinity)*</td>
<td>—</td>
<td>68.5 nM(^{68})</td>
</tr>
<tr>
<td>[^{3}H] U69,593 replacement ((\kappa)-opioid receptor affinity)*</td>
<td>55 nM</td>
<td>26 nM(^{49})</td>
</tr>
<tr>
<td>[^{3}H] N/OFQ replacement (orphan-opioid receptor affinity)*</td>
<td>—</td>
<td>(&gt;10\ 000) nM(^{50})</td>
</tr>
<tr>
<td>(\mu)-opioid receptor cAMP inhibition</td>
<td>67%(^{48}) (^{49}) (^{51})</td>
<td>48%(^{48}) (^{49}) (^{51})</td>
</tr>
<tr>
<td>(\delta)-opioid receptor cAMP inhibition</td>
<td>65%(^{48}) (^{49}) (^{51})</td>
<td>39%(^{48}) (^{49}) (^{51})</td>
</tr>
<tr>
<td>(\kappa)-opioid receptor cAMP inhibition</td>
<td>55%(^{48}) (^{49}) (^{51})</td>
<td>26%(^{48}) (^{49}) (^{51})</td>
</tr>
<tr>
<td>Orphan receptor [^{35}S]GTP(\gamma)S binding</td>
<td>—</td>
<td>0%(^{50})</td>
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Background

- RCT (2006) in ED population compared IV HM 0.015mg/kg to M 0.1mg/kg for treatment of acute pain
  - IV HM produced greater decrease in pain scores
  - Similar adverse effects, except pruritis which only occurred with M

- Cohort analysis investigating acute pain management in the ED
  - Similar pain score changes in patients receiving 2 mg of morphine and 2 mg hydromorphone with increase sedation in the HM population

- Only RCT directly comparing analgesic properties and potency of HM and M in postoperative patients published in 1975
  - HM was more potent than previously believed
  - Similar or greater incidence of “sleepiness” than M

- Meta-analysis of 11 studies (2011) suggested a slight advantage of HM over M for analgesia with similar side effects
  - Small effect size
  - Based on few, heterogeneous studies
  - Lack of comparative studies in surgical setting
Rationale

• Lack of studies comparing HM to M in postoperative patients

• Ongoing RCT at HHS and SJH investigating morphine versus hydromorphone
  • Most effective opioid analgesia in ambulatory surgeries

• Retrospective chart review will provide further information on prescribing practices, analgesia and side effects in the same population
Research Question

- **P**: 500 elective, adult surgical patients within HHS
- **I**: Intravenous (IV) hydromorphone as post-op analgesia in the PACU
- **C**: IV morphine as post-op analgesia in the PACU
- **O**: Satisfactory analgesia as determined by subjective pain scores, as well as total equipotent opioid dose, opioid side effects and length of PACU stay
- **T**: First 500 cases that meet inclusion criteria from January 2014
Methods

- Multi-site retrospective chart review of elective surgical patients at HHS
- 12 months of data- January 2014 – January 2015
- Sample size of 500 patients chosen
- HHS operating room record and Perioperative Flow Sheet
Inclusion Criteria

• ≥ 18 years of age

• Elective surgical patient
  • General surgery, ENT, Plastics, Gyne, Ortho
  • Same day admission, same day home, same day overnight
  • Excluded if admitted prior to the OR

• General Anesthesia
  • Extubated prior to arrival in PACU

• IV morphine or hydromorphone ordered as PACU analgesia
  • Single opioid agent only
  • Excluded if PCA, epidural, regional analgesia
  • Excluded if chronic pain patient
Further Methodological Considerations

• **Sampling**
  • Plan is to use convenience sampling

• **Data Abstraction**
  • Principle investigators will participate in data abstraction along with additional help from abstractors who will need to be trained
    • Abstractors will not be blinded to objective of the study
    • Increase in reviewer bias

• **Pilot Test**
  • ~50 charts
  • Evaluate study design, feasibility, methodology and procedures of the investigation

• **Inter-rater reliability**
  • Chart audits
Outcomes

• Primary Outcome:
  • Effective analgesia
    • Numerical Analogue Scale at 2h or on readiness to discharge from PACU, if occurs before 2h

• Secondary Outcomes:
  1. Total equipotent opioid dose in morphine equivalents
    • Potency ratio 1:5 (M:HM)
  2. Opioid side effects
    • Nausea/Vomiting
      • 0-3
    • Sedation
      • 0-3, S
    • Pruritus
      • 0-3
  3. Length of PACU stay
### Respiratory Control
- **Spontaneous (SIMV)**
- **Assisted (AC)**

### Pain Scale
- 0 = No pain
- 10 = Worst pain

### Sedation Scale
- 0 = Alert
- 1 = Occasionally drowsy, easy to arouse
- 2 = Frequently drowsy, easy to arouse
- 3 = Somnolent, difficult to arouse
- 4 = Normal, sleep, easy to arouse

### Motor Scale
- 0 = No motor block, able to flex hips, extend knees, flex ankles
- 1 = Inability to raise the leg (flex hip)
- 2 = Inability to flex hip and extend knee
- 3 = Inability to flex hip, extend knee, flex ankle = Complete motor block

### Sensory Scale
- 0 = Full sensation
- 1 = Sympathetic withdrawal
- 2 = Parasympathetic withdrawal
- 3 = Full sensory block

### Nausea/Vomiting/Pruritus Scale
- 0 = None
- 1 = Mild, no prescription needed
- 2 = Moderate, prescription effective
- 3 = Severe, prescription ineffective

### Pupils
- 0 = Absent
- 1 = Weak
- 2 = Normal

### Skin Temperatures
- CD = Cold
- CL = Cool
- WM = Warm
- H = Hot
- M = Mottled
- B = Blanched
- P = Pink
- BK = Black
<table>
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<th>INIT.</th>
<th>IV-PCA: DRUG</th>
<th>DOSE</th>
<th>LOCKOUT</th>
<th>4 h LIMIT</th>
<th>CONTINUOUS</th>
<th>TOTAL AMOUNT AT DISCHARGE:</th>
<th>PCA TEACHING BY:</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- mg/ml</td>
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<td>min</td>
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<th>TOTAL AMOUNT AT DISCHARGE:</th>
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<tr>
<td></td>
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<td>RATE: mL/hr</td>
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<th>INITIALS</th>
<th>TIME</th>
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<th>DOSE</th>
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Additional Information

- Multimodal analgesia
  - Most patients will have received multimodal analgesia in the PACU
    - Tylenol, Ketoralac + opioids

- Other variables to include
  - Surgical type and duration, day surgery vs admission, patient demographics
Conclusion

- Retrospective studies have an inferior level of evidence to prospective studies
  - Prone to bias and confounding
  - Can still be a valid and reliable research method

- Goals of this study are to provide valuable information on patient analgesia in the PACU as well as aid in the ongoing prospective RCT
References


