Sustained Release Opioids or Continuous Infusions + PCA Is Safe in the Opioid Naïve Post-Operative Patient

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Very Special Thanks

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Thank you

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  – Rimena Natanson, Lisa Redekop
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Thank you
Conflict of Interest Disclosure

• Authors Conflicts of Interest;
  – Jason Sawyer – No Conflicts

• A 63-year-old, 109 kg, opioid-naïve female
• admitted to a hospital with fractures sustained in a fall.
• two doses of morphine 4 mg and one dose of HYDROMorphine (Dilaudid®) 1 mg in the ED
• Upon arrival to the inpatient unit, she was started on HYDROMorphine PCA
  – continuous infusion of 0.5 mg per hour
  – dose of 0.2 mg
  – lockout interval of 10 minutes
  – 4 hour limit of 6 mg

• Continuous pulse oximetry was not used
• Five hours later, the patient was found unresponsive. RR 6/min, and her nail beds were beginning to turn blue.
• Oxygen saturation 44%.
• BMI 38.6, sleep apnea,
• did not have a CPAP machine
Introduction

- Opioids continue to be a mainstay of postoperative pain control

- Controversy regarding efficacy and safety of using:
  - PCA and oral sustained release opioids
  - PCA and intravenous continuous infusions of opioids

- Can this approach be safe? YES  Effective? Unclear

Objectives

- Evaluate the safety of our local standard of care for patients receiving opioid based analgesia and cared for by an Acute Pain Service (APS)

- Briefly review the relevant pharmacokinetics of Hydromorphone by the oral and IV route

- Describe how human factors engineering can improve the safety of opioid prescribing and administration

- Retrospective chart review of 1500 PCA patients
- Adults (orthopedic/general surgery
- 2 standard preparations
  - Morphine 2mg/ml & Meperidine (Demerol®) 20mg/ml
- 11 cases of severe respiratory depression (undefined) all recovered
- (3 excluded as PCA had not been initiated)
• Prospective RCT, 230 women for abdominal hysterectomy
• 4 groups – all received Morphine PCA
  – GROUP 1 Control group 2mg dose, minimum 10 min. lockout
  – GROUP 2 0.5mg/hr 2mg dose, minimum 10 min. lockout
  – GROUP 3 1mg/hr 1mg dose, minimum 10 min. lockout
  – GROUP 4 2mg/hr 1mg dose minimum 10 minute lockout
• Infusions started in Recovery Room, continued until the morning of POD #1 and then at night POD #2,3
Key Outcomes

• PCA use was not different between groups
• Infusion did not improve pain scores
• No subjective improvement in sleep
• Patients ≥ 70 had higher incidence of excessive sedation despite less analgesia than those ≤ 40 years

Prospective RCT of 96 people for abdominal surgery
• 83 completed Morphine 3 days duration
• Group 1 Morphine PCA 1mg lockout 5 minutes
• Group 2 Morphine 1mg/ml continuous infusion or placebo, + PCA 1mg lockout 5 minutes

Key Outcomes

• Patients with continuous infusions had lower pain scores in first 24 hours
• No difference in demand/delivery ratio
• Total morphine delivery > in PCA+Continuous Infusion group
• Use caution when using continuous infusions
• Had value into the 2nd but not 3rd postoperative day
• PCA only group had more PCA use on postoperative days 1&2

72 elective CABG surgery patients
• Randomized non blinded 72 hours
• Group 1 HYDROMorphone 0.1mg/hr + PCA 0.2mg lockout 5 minutes (max of 6 doses/hour)
• Group 2 morphine 2.5mg IV q 1h prn to extubation and then meperidine 1mg/kg q 4h prn +
• Tylenol #3® 1-2 tabs q 4h prn

Outcomes
• Better pain control in PCA group, despite similar analgesic use over course of the study
• No difference in side effects
Synopsis

- Morphine
  - Continuous infusions 0.5-1mg/hr have demonstrated benefit
  - Continuous infusions of >1mg/hr have not demonstrated benefit, and lead to increased side effects/harm

- HYDROMorphone
  - Continuous infusion of 0.1-0.2 mg/hr has demonstrated benefit
  - Continuous infusions of 0.5mg/hr have demonstrated harm

- Meperidine
  - 20mg/hr + PCA provided best balance of pain relief without undesired sedation


Study Design

- Prospective, observational

- Sample population from surgical units
  - All patients consulted to Acute Pain Service (APS) were eligible: postoperative*, post-trauma
– Receiving oral sustained release OR intravenous basal infusion of opioids in addition to patient controlled analgesia (PCA)
– Varying degrees of multimodal analgesia (acetaminophen ± anti-inflammatory ± gabapentinoid
• This was/is our standard of care for patients unable to receive neuraxial or peripheral blocks

Methods
• Surgical units and Step Down ICUs

• Data collected daily using a standardized form
  – Follow-up until patients transitioned off the PCA to oral analgesics only

• Naloxone administration tracking sheet
  – ALL cases on surgical units were captured and included (i.e. both APS and non-APS patients)
  – Detailed chart review of circumstances and patient outcome

Table 1: Expected incidence of respiratory depression as mediated by naloxone

<table>
<thead>
<tr>
<th>Analysis technique</th>
<th>Number of units</th>
<th>Total number of patients</th>
<th>Respiratory depression (in %)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEXUS</td>
<td>11</td>
<td>35.46</td>
<td>0.2</td>
<td>0.8-1.70</td>
</tr>
<tr>
<td>LIFE R</td>
<td>13</td>
<td>35.46</td>
<td>0.4</td>
<td>0.0-2.15</td>
</tr>
<tr>
<td>UCS/RLCA</td>
<td>1</td>
<td>35.46</td>
<td>0.8</td>
<td>0.0-2.00</td>
</tr>
<tr>
<td>Combined</td>
<td>24</td>
<td>35.46</td>
<td>0.3</td>
<td>0.0-2.00</td>
</tr>
</tbody>
</table>

(Cashman and Dolin 2004)
Data Collection

- Type of data
  - Demographics (age, gender, BMI and/or weight)
  - Relevant health history (e.g. sleep apnea)
  - Surgical procedure (general, gynecological, orthopaedic surgery)
  - Nausea and vomiting (e.g. risk factors, time, treatment, dose)
  - Pruritis (e.g. time, treatment, dose)
  - Pain scores (at rest and with movement)
  - Use of naloxone (e.g. risk factors, time, dose, patient outcome)

Study Recruitment

Figure 1: Study recruitment exclusion and inclusion
Total n= 404, (24% opioid tolerant n=96)

Demographics

- Sample size, n= 404
- Age (Avg±SD) 55.4±17.7 years; Age >70, 24.5%
Usual Opioid Standard of Care

- HYDROMorphone-PCA
  - Dose: 0.2mg (Dose range 0.1-0.3mg)
  - Continuous Infusion 0.2mg/hr (range 0.1-0.2mg/hr)

- Oral Sustained release opioids
  - HYDROMorphone (Contin®) 3mg of 6mg TID
  - OXYcodone (OXYcontin®) 10mg or 15 mg TID

Incidence of respiratory depression defined as administration of naloxone,

<table>
<thead>
<tr>
<th>Naloxone administration</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases captured during study period</td>
<td>22</td>
</tr>
<tr>
<td>APS at time of naloxone administration</td>
<td>11</td>
</tr>
<tr>
<td>PCA and oral sustained release contin</td>
<td>2</td>
</tr>
<tr>
<td>PCA and continuous rate</td>
<td>1</td>
</tr>
<tr>
<td>Opioid likely primary cause of resp. issue</td>
<td>2</td>
</tr>
</tbody>
</table>

Respiratory depression
3/404 patients overall 0.74%
2/308 in opioid naïve 0.65%

PCA Monitoring

Table 6: APS flow sheet used to monitor pain scores at rest and with movement, respiratory rate, and sedation scores for patients who are receiving PCA

<table>
<thead>
<tr>
<th>PCA Monitoring</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not monitored Q1H for first 4 hours</td>
<td>248 (61.4)</td>
</tr>
<tr>
<td>Completed monitoring for first hour (28%)</td>
<td>72 (17.3)</td>
</tr>
<tr>
<td>Completed monitoring for first 2 hours (50%)</td>
<td>29 (7.2)</td>
</tr>
<tr>
<td>Completed monitoring for first 3 hours (70%)</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>Completed monitoring for first 4 hours (100%)</td>
<td>8 (2.4)</td>
</tr>
</tbody>
</table>
Conclusion

• Administration of sustained release or basal infusions of opioids in additions to PCA CAN be safe
• Unclear what the demonstrated benefits are

About Continuous Infusions

• How do you know what continuous infusion to use?
• Depends on the goal….

Focus on HYDROmorphine (HM)

• How do we know what doses are beneficial? Harmful?
1985-2003  Hydromorphone (HM) detected in 251 coroner death investigations

<table>
<thead>
<tr>
<th>Drugs Implicated</th>
<th>HM Blood Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>HM sole drug detected (N=4)</td>
<td>77-2684ng/ml</td>
</tr>
<tr>
<td>HM &amp; Ethanol (N=6)</td>
<td>50-163ng/ml</td>
</tr>
<tr>
<td>HM &amp; multiple drugs that in isolation be considered therapeutic or incidental (N= 28)</td>
<td>51-411 ng/ml</td>
</tr>
<tr>
<td>Natural causes (N=5)</td>
<td>75-423ng/ml</td>
</tr>
</tbody>
</table>

- Fatalities due to HM occur at 51ng/ml and greater
- Concentrations can be much higher than this when cause of death is natural

- 43 patients with chronic severe pain
  - 37 advanced cancer
  - 3 unclear origin
  - 1 pancreatitis
  - 1 crush injuries
  - 1 sickle cell

(Wallage and Palmentier 2006)
Serum level < 4ng/ml
• 0/15 had pain control

Serum level > 4ng/ml
• 7/17 had pain control (bone/soft tissue pain)
• 0/11 patients with nerve pain had good pain control regardless of serum level

Those reporting good pain control
– (bone and soft tissue pain)
– HM 24-96mg/day median 48

Those without good pain control
– HM 8-280 mg/day median 36 mg (NS)

Those with nerve pain (N=11)
– HM 16-202 mg/day
– Serum levels up 29ng/ml and 9/11 > 4ng/ml

Mean daily HM dose of 48 ±11 mg (range 6-216 mg) to provide optimal analgesia
Inturrisi (1998) found half maximal pain relief was produced at approximately 20ng/ml. About 2x this for sedation to occur.

- 50 patients undergoing cardiac surgery
- 40-80 years of age
- Quite healthy (other than needing cardiac surgery)
- Opioid naïve (at least 14 days)
- Pain naïve

During Anesthesia

- Group 1 - target sufentanil 0.4ng/ml
- Group 2 target sufentanil 0.8ng/ml
- At the end of sufentanil infusion all patients given 1mg of HYDROMorphone intravenous push
Details from this study

- 12 healthy volunteers (6 male)
- 27 years of age (21-34)
- Experimental pain model
- 5 different study sessions, at least 5 days apart
- Double blind design
- 8mg IR in first session, then randomized to placebo
  8mg, 16 mg and 32 mg of SR Hydromorphone in subsequent sessions

(Angst, Drover et al. 2001)
Equilibration delay with IRH formulation between plasma and effect site. The effect site concentration is 2.24 ± 1.19 ng/ml similar to 32 mg of SRH.

### Table 1. Pharmacokinetic Indices after Administration of Immediate- and Extended-release Hydrodorphone

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Peak Plasma Concentration (ng/ml)</th>
<th>Time to Peak Cmax (h)</th>
<th>Fmax Cmax &gt; 50% Peak (h)</th>
<th>Lactmax Cmax &gt; 50% peak (h)</th>
<th>Duration Cmax &gt; 50% Peak (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1.74 ± 1.70</td>
<td>0.8 (0.6-1.0)</td>
<td>0.4 ± 0.2</td>
<td>1.6 ± 0.6</td>
<td>1.1 ± 0.7</td>
</tr>
<tr>
<td>9</td>
<td>2.07 ± 3.30</td>
<td>12.0 (9.9-13.6)</td>
<td>5.4 ± 1.7</td>
<td>20.9 ± 12.6</td>
<td>24.2 ± 16.0</td>
</tr>
<tr>
<td>12</td>
<td>2.41 ± 0.85</td>
<td>16.5 (17.2-21.1)</td>
<td>5.5 ± 1.8</td>
<td>35.8 ± 9.9</td>
<td>20.5 ± 7.5</td>
</tr>
</tbody>
</table>

- High degree of intra and inter individual variance of dosing and plasma concentration to achieve analgesia
- Short acting oral and intravenous push doses can cause rapid escalation of plasma concentrations
- In the cardiac surgical population:
  - HM of 0.26mg/hr (0.07-0.93/hr) results in a maximum plasma target concentration of 2.4ng/ml (0.9-7ng/ml)
  - Age and weight can impact this by approximately 30%
Summary

- A minimum of 4ng/ml is required to achieve analgesia
- A plasma concentration of 51ng/ml has been implicated in a HM death
- Documented safety above 51ng/ml in opioid naïve and tolerant patients

Human Factors Engineering (HFE)

- Uses scientific methods to improve system performance and prevent accidental harm
- Goals
  - Support the cognitive and physical work of healthcare professionals
  - Promote high quality safe care for patients

- About designing systems that are resilient to unanticipated events
- Addresses problems by modifying the design of the system
- Applies to the individual and organizational level
- Focus on redesigning systems, tools and techniques rather than training to yield sustainable improvement
- Healthcare providers and HFE specialists can form a powerful synergistic relationship.
HFE and Infusion Pumps

- HFE is becoming integrated in infusion pump procurement decisions
- Health Canada recommends that hospitals ensure pump manufacturers meet human factors standards

### Purchasing a Pump

- Evaluated to a failure mode and effects analysis (Human Factors Evaluations)
- Limited to a single model

#### Before PCA is Prescribed or Dispensed

- Standard ordersets designed to guide drug selection, doses, lockout period, monitoring and precautions
- Pumps programming sequence should be used to test ordersets
- Training for the pumps should happen as close to implementation as possible
- Use simulations to run intentionally incorrect orders to evaluate safety options (independent double checks, monitoring, etc.)

#### Establish Patient Criteria

### Prescribing PCA

- Standard ordersets are required, and all sections must be completed
- Minimize verbal orders
- Always writing in "mg" or "mcg"
- Home analgesics should be taken into consideration

### Dispensing PCA

- 1 standardized concentration for each opiate
- Stock only standard concentrations on wards
- Max dose limits should be programmed into the pump
- "Tall Man" lettering for HYDROMORPHONE

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Health Canada 2004 (Ginsburg 2005)

Grissinger 2008
2 Methodology

The Human Factors evaluation consisted of three main phases:

1. Shadowing of end users at Sunnybrook Hospital and the Holland Centre
2. Heuristic evaluation of the candidate pumps
3. Usability testing with end users from Sunnybrook Hospital and the Holland Centre
Conclusion

• Our study, and pharmacokinetic data indicate that a HYDROMORPHONE infusion (or oral equivalent) of 0.1-0.2mg/hr is safe

• Human factors and multimodal analgesia further enhance the safety of opioid prescribing