Updates in the Management of Pain, Sedation, and Delirium in the ICU

Thursday, December 8, 2011
9:00 AM – 12:00 PM

Disclosures

The program chair and presenters for this continuing pharmacy education activity report no relevant financial relationships except:

Joseph Dasta
Consultant: Hospira; Pacira, Cadence; Speaker's Bureau: Cadence

John Devlin
Research Grant Recipient and Consultant: Hospira

Management of Pain in the Intensive Care Unit

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University of Arizona

Overview of Presentation

- Case presentation
- General principles of pain management ED to ICU
- Analgo-sedation versus sedato-analgesia
- Opioids
  - General comparisons
  - Adverse effects
  - Conversions
- Non-opioid analgesics/adjuncts

Case Presentation

- 33 y/o obese man with MVA leg injury 2 days PTA
- PMH: not significant but difficult to elicit due to pain
- FH/SH/DH: not able to assess
- Afebrile but tachycardia with severe pain
- Initial BP 170/70 mm Hg
- Swollen leg with subcutaneous emphysema and two bullae
- WBC 18.1 x 10^9/L with 29% bands

Case Continued…
Question
Which of the following statements about the use of opioids in the ED is true?
A. Morphine should be dosed using a weight-based approach (i.e., mg/kg)
B. Patients should be given single IV doses of morphine of at least 0.1 mg/kg
C. Hydromorphone causes less nausea and vomiting than morphine
D. Appropriate use of protocols have been shown to improve pain relief

Opioids in the ED
- Research: no important differences between opioids in terms of efficacy/adverse effects
- Patients commonly under-dosed
- Single doses < 0.1 mg/kg of IV morphine (or equivalent) unlikely to be effective
- Titrate- don’t try estimate one large effective dose
- No evidence for weight-based dosing
- Use of protocols has demonstrated more timely administration and effective pain relief

Patanwala et al. Ann Pharmacother published online 10/26/10

Case Continued…
- Started on broad spectrum antibiotics – taken to OR
- Extensive debridement for necrotizing fasciitis
- Recovery room: respiratory distress requiring reintubation, bradycardia, hypotension
- All cultures grew Group A Streptococcus
- Prolonged ICU and hospital stay with multiple trips to OR for further debridements
- Postop course also complicated by severe pain and renal dysfunction

Pain Management in the ICU
- Lack of high-level evidence for clinical decision making
- Data typically extrapolated from studies in other settings
- Substantial intra/inter-patient variability in response
- Difficult to distinguish ADEs from other medical problems
- Rapid titration of pain meds so risk of increased ADEs
- Bioavailability concerns with non-IV routes
- Unique considerations with specialized analgesia
- Challenges with pain assessment

Question
The trauma resident caring for the patient is talking to you about postop pain management and makes several questionable statements. Which of his following statements regarding fentanyl is true?
A. It offsets beneficial effects of dexmedetomidine on delirium
B. It is only opioid that has been associated with chest rigidity
C. Its duration of action is short regardless of dosing regimen
D. It is preferred over morphine in patients with renal failure

Analgo-Sedation vs. Sedato-Analgesia-Dexmedetomidine
- Efficacy versus effectiveness (your hospital vs. studies)
  - Best evidence is for use from admit on
  - Often no mandated daily sedative interruptions
  - How might results change?
  - Usually on continuous infusions of benzodiazepines to match infusions of dexmedetomidine in ICU trials
  - What about bolus dose benzodiazepines?
  - Benefits beyond propofol (no ↑ patient satisfaction)?
  - Fentanyl boluses for pain (sedato-analgesia)
  - 4-fold ↑ in requirements with dex in MENDS but still had benefits for delirium; clinical importance of opioid-sparing?
Analgo-Sedation ICU Trial

- Ventilated ICU patients (n=428) randomized to no sedation vs. sedation with daily interruption
  - No sedation group given morphine 2.5-5 mg boluses (no validated pain scale) with:
    - Haloperidol for delirium (DSM IV), propofol prn (subjective)
  - Sedation group given morphine boluses plus:
    - Titrated propofol infusion changed to midazolam at 48 h
  - Both ICU and hospital LOS ↓ in no sedation group (p=0.0316 and p=0.0039, respectively), but ↑ delirium (p=0.0400) and ↑ healthcare personnel (p=0.0247)

Strom et al. Lancet 2010;375:475

Analgo-Sedation vs. Sedato-Analgesia

- Open-label (randomized) involving 105 mixed ICU patients expected to receive mechanical ventilation > 72 hours (protocol change after 30 patients)
- Remifentanil (midazolam added) vs. midazolam-based (fentanyl or morphine added) regimen
- Significant differences in favor of remifentanil for time to extubation (94 h vs. 147.5 h, p=0.033) and weaning time to extubation (0.9 h vs. 27.5 h, p<0.001)
- No significant differences in time from study drug to start of weaning or until ICU discharge
- No significant differences in ADEs (no bolus remifentanil)


Analgo-Sedation vs. Analgo-Sedation

- Remifentanil compared to fentanyl-based analgesia
- Double-blind RCT involving 152 mixed ICU patients on mechanical ventilation; opioids by infusion
- Mean percent of hours in optimal sedation (SAS score of 4) was 88.3% and 89.3% (ns)
- No significant difference in primary endpoint of ratio of between-patient variability (unless 1 patient excluded from remifentanil group who failed to reach SAS of 4)
- No significant differences in hemodynamic parameters or LOS from drug start to ICU discharge

Muellejans et al. Crit Care 2004;8:R1-R11

Sedation +/- Opioid

- Adverse events of opioids must be considered in light of consequences of untreated pain
- Example is RCT comparing IV infusions of midazolam vs. midazolam + fentanyl (co-sedation)
- Patients enrolled if respiratory failure, expected mechanical ventilation > 48 h, and receiving a sedative but no opioid
- Investigators cited surveys in Europe and US that found opioids routinely used ≈ 50% of time

Richman et al. Crit Care Med 2006;34:1395

Midazolam vs. Midazolam/Fentanyl

Question

The trauma resident is considering a sedation-only approach. He states that with enough sedation, he could knock out a horse so pain is not a major concern. In the only RCT that compared IV infusions of midazolam to IV infusions of combined midazolam + fentanyl, what was the result?

A. Fewer daily dose adjustments in the midazolam only group
B. Drug costs significantly less in the midazolam only group
C. Significantly less ventilator asynchrony in combined group
D. Significantly less time to sedation in combined group

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Midazolam vs. Midazolam/Fentanyl

PTSD if Inadequate Analgesia

- Retrospective study of morphine use by military in Iraq
  - Diagnosis by DSM-IV (credentialed providers)
  - Assessed PTSD 1 – 24 months post-injury
  - Excluded patients with severe TBI
  - Two groups with/without PTSD had similar characteristics other than morphine use
  - Morphine use was lower in PTSD (60%) vs. non-PTSD (76%) group, p<0.001
  - Limited information on dosing regimen or response
  
  Holbrook et al. NEJM 2010;362:110

Question

Using a numeric rating scale, the patient’s pain associated with line placements has increased during hospitalization with no obvious explanation. The trauma resident has heard of such a condition that might be responsive to an opioid tapering strategy. Your response is:

A. Opioid tolerance
B. Subtherapeutic opioid doses
C. Opioid-induced hyperalgesia
D. Inadequate pain control

SNPs Altering Morphine Analgesia

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Frequency in Population</th>
<th>Direction and Magnitude of Needed Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPRM1 ( μ receptor)</td>
<td>118A→G exon 1</td>
<td>12%</td>
<td>Increase by 2.2</td>
</tr>
<tr>
<td></td>
<td>C→T intron 1</td>
<td>6%</td>
<td>Increase by unknown factor</td>
</tr>
<tr>
<td>COMT</td>
<td>472G→A exon 4</td>
<td>46%</td>
<td>Decrease by 0.67</td>
</tr>
<tr>
<td>UGT2B7</td>
<td>211G→T exon 1</td>
<td>15</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>802C→T exon 2</td>
<td>54</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Question

Which of the following statements regarding morphine metabolites is true:

A. 3-glucuronide is likely responsible for neurotoxicity
B. 3-glucuronide is of most concern in renal failure
C. 6-glucuronide half-life is 6 hours in renal failure
D. 3- and 6-glucuronide are removed by hemodialysis

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## Opioid Comparisons

<table>
<thead>
<tr>
<th>Opioid</th>
<th>t½ (h)</th>
<th>Cl (mL/kg/min)</th>
<th>Vc/Vdss (L)</th>
<th>logPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphineb</td>
<td>1.5-5</td>
<td>14</td>
<td>25/225</td>
<td>1.2</td>
</tr>
<tr>
<td>metabolite</td>
<td>25-50</td>
<td>(6-glucuronide-slow CNS transfer but will accumulate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphoneb</td>
<td>3</td>
<td>20</td>
<td>25/300</td>
<td>1.2</td>
</tr>
<tr>
<td>Fentanylc</td>
<td>1.3-3</td>
<td>13</td>
<td>15/325</td>
<td>4.1</td>
</tr>
</tbody>
</table>
| Remifen
d | 0.05   | 50             | 10/30       | 1.8   |

* a log of octanol/water partition coefficient
* b glucuronidation
* c CYP3A4
* d degraded by plasma esterases so context sensitive half-time

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### Morphine in Renal Failure - Dialysis

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### Opioids - Metabolite Issues Complicating Study Interpretation

- **RCT comparison of intermittent lorazepam vs. continuous propofol**
- **Patients in both groups given ≥ 2 mg morphine “or equivalent opioid” every 4 hours (or by infusion)**
- **Mean ventilator free days (primary endpoint) were lower with propofol (5.8 vs. 8.4, p=0.04)**
- **However, 20% of patients in lorazepam group had renal failure vs. 10% in propofol group**
- **Only 3 patients received opioid other than morphine (2 fentanyl, 1 hydromorphone)**

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### Case Presentation

- 50 y/o obese woman post-pancreatectomy, post-auto-islet cell transplantation
  - PMH: chronic pancreatitis, fibromyalgia, depression
  - FHSHVD: not significant; morphine SR 100 mg every 8 h; fentanyl patches 200 mcg/h (every 72 h); hydromorphone 2-4 mg every 4 h pm pain, clonazepam 40 mg daily, pregabalin 150 mg twice daily, tramadol 100 mg h.s.
  - **Current labs:** stable, no renal or hepatic dysfunction
  - **Current complaint:** constant, severe pain ranging from 10/10 prior to IV bolus opioid to 8/10 after IV bolus
  - **Current meds:** hydromorphone IV infusion 6 mg/h plus hydromorphone-PCA 0.3 mg every 6 minutes pm (PCA available in standard 0.2 mg/mL in 25 mL, unless palliative care that is 5 mg/mL in 55 mL size), fentanyl patches 200 mcg/h

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### Many Urban Myths Related to Opioid Comparisons

- **Anecdotal information often suggests differences in efficacy or adverse effect profiles of opioids**
- **Some differences are legitimate with sound biological basis (e.g., normeperidine causing seizures)**
- **Other noted differences often idiosyncratic**
- **RCTs that have been performed typically do not show differences in efficacy or common toxicities**
  - **RCT comparing morphine to hydromorphone PCA**
  - **No differences in efficacy or a number of adverse effects including N/V, pruritus**

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Question

The intensivists want to transfer this patient to the floor. The patient has a surgically-placed jejunostomy and is receiving enteral feedings with attempted transition to oral diet. What is your suggested conversion plan to optimize analgesia while reducing the risk of medication errors and adverse events?

A. My shift is over and it’s time to go home
B. Quote Sponge Bob: “Well, good luck with that!”
C. Recommend 1 to 2 acetaminophen tabs every 6 hours
D. Recommend 900 mg of morphine SR every 8 hours

Opioid Adverse Drug Events (ADEs)

- Allergy
- Arrhythmias
- Bowel dysfunction
- CNS/respiratory depression
- Cough
- Drug Interactions
- Dry mouth
- Endocrinopathy
- Hearing loss
- Histamine release
- Immunomodulation
- Increased intracranial pressure
- Myoclonus
- Nausea/vomiting
- Neurotoxicity
- Pruritus
- Rigidity
- Serotonin syndrome
- Urinary retention
- Withdrawal

Medications Involved in Actual, Preventable ADEs in ICU Studies

<table>
<thead>
<tr>
<th></th>
<th>Adult Observation n=22</th>
<th>Pediatrics Observation n=7</th>
<th>Cullen SICU</th>
<th>Sedation/analgesia n=115</th>
<th>Antibiotics n=97</th>
<th>Cardiovascular n=88</th>
<th>GI agents n=82</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>32%</td>
<td>28%</td>
<td>32%</td>
<td>28%</td>
<td>28%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>GI agents</td>
<td>18%</td>
<td>14%</td>
<td>18%</td>
<td>14%</td>
<td>14%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>14%</td>
<td>14%</td>
<td>14%</td>
<td>14%</td>
<td>14%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>MEDMARX</td>
<td>Insulin 10.2%</td>
<td>Heparin 6.3%</td>
<td>Morphine 5%</td>
<td>Dopamine 3.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Opioid Near-Miss Prescribing Errors

- Retrospective analysis of errors detected and prevented by pharmacists at teaching hospital
  - Handwritten or pre-printed orders at time of study
  - 714,290 orders; 2.87 errors/1000 orders; 22% rated serious (0.63/1000 orders); dosing errors accounted for \( \approx 50\% \) of errors in adults and \( \approx 75\% \) in children
  - Proximal causes: lack of drug knowledge and pt info
  - Highest error rates with infrequently prescribed meds
  - Of common meds, highest error rates with ketorolac and long-acting forms of morphine and oxycodone

- General characteristics of major errors
  - Sound-alike names (e.g., oxycodone vs. Oxycontin®)
  - Meds that should be scheduled given as needed
  - Availability of multiple routes (as per Scrubs it’s an “analgesic, not analgesic”)
  - Atypical dosing regimens (e.g., lidocaine patches on 12 hours, then off 12 hours; fentanyl patches q 72 h)
  - Atypical dosing forms (e.g., transdermal)

Fentanyl patch

“ I need a fentanyl patch, Stat!!”

- Not useful for acute pain (lack of rapid titration)
- Peak blood levels > 15 hr (usual range 1-3 days)
- Levels not constant- heat may increase absorption rate; effect of substantial edema?
- Duration of action variable- may switch every 2 days
- Recommended conversion to patch from oral morphine is conservative (not vice-versa!)
### Conversion Example

<table>
<thead>
<tr>
<th>Conversion Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine (M)</strong></td>
</tr>
<tr>
<td>Morphine: M iv ↔ M po = 1 : 2-3</td>
</tr>
<tr>
<td>Hydromorphone: M iv → HM iv = 4 : 7 : 1</td>
</tr>
<tr>
<td>Hydromorphone: M po → HM po = 5-8 : 1</td>
</tr>
<tr>
<td>Fentanyl: M iv → F iv = 50-100 : 1</td>
</tr>
<tr>
<td>Fentanyl: M po → F transd = 70-150 : 1</td>
</tr>
<tr>
<td>Methadone: ~90 mg/day M po → ME po = 4-9 : 1</td>
</tr>
<tr>
<td>Methadone: 90-300 mg/day M po → ME po = 8-10 : 1</td>
</tr>
<tr>
<td>Methadone: &gt;300 mg/day M po → ME po = 12-14 : 1</td>
</tr>
</tbody>
</table>

### Non-Opioid Analgesics/Adjuvants
- NSAIDs/acetaminophen (IV forms becoming available)
- Muscle relaxants
- Anticonvulsants- neuropathic pain
- Antidepressants- neuropathic pain
- Calcitonin- bone pain (vertebral fx)
- Lidocaine (various routes)- neuropathic pain
- Ketamine- NMDA antagonist; opioid sparing
- Adenosine (regulates pain transmission through neuromodulation)- opioid sparing
- Corticosteroids- prolonged antihyperalgesic effects even when given in single doses with opioids

### Ketamine
- Little high-level evidence for use outside of ED and OR, particularly when given by continuous infusion in adults
- Has been investigated for opioid-sparing actions but nursing issues with it being anesthetic
  - Dissociative doses (IV > 1.5 mg/kg or IM > 3-4 mg/kg → dissociation) for procedures, sub-dissociative doses (= 0.4 to 1 mg/kg/h IV infusion) studied for sedato-analgesia in ICU
- Small RCTs of morphine-ketamine combination (e.g., 1 mg of morphine + 5 mg of ketamine bolus doses by PCA) have found reductions in morphine doses and overall consumption while maintaining pain control

### Conclusions
- Pain management in the ICU has unique issues compared to management in other settings
- Much of the data extrapolated from studies in other areas
- Increasing evidence that analgo-sedation is preferred to sedato-analgesia in the ICU
- Opioids remain the standard of comparison for severe pain in the ICU
- Differences between opioids for dose-related ADEs often overstated, but there are good reasons for choosing one over another (e.g., renal failure)
- Nonopioid analgesics have a role but also have unique considerations when used in critically ill patients

### Question

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