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

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Research Grant Recipient and Consultant: Hospira

Management of Pain in the Intensive Care Unit

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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)

Breen et al. Crit Care 2005;9:R200

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

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

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

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

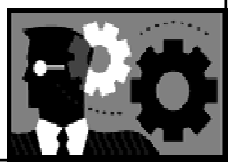
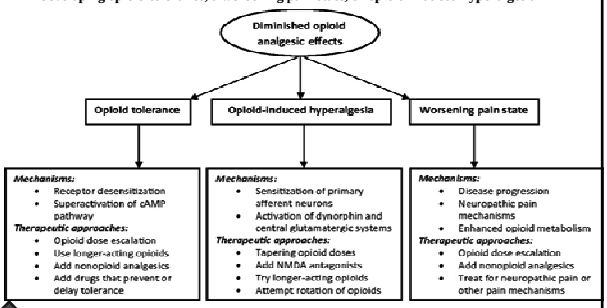


FIGURE 2 Algorithm showing that clinical signs of diminished opioid analgesia may result from developing opioid tolerance, a worsening pain state, or opioid-induced hyperalgesia



Anand, K. J. S. et al. Pediatrics 2010;125:e1208-e1225

PEDIATRICS

SNPs Altering Morphine Analgesia

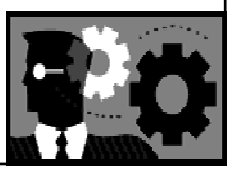
Gene Variant	Frequency in Population	Direction and Magnitude of Needed Dose Modification
OPRM1 (μ receptor)		
118A→G exon 1	12%	Increase by 2.2
C→T intron 1	6%	Increase by unknown factor
COMT		
472G→A exon 4	46%	Decrease by 0.67
UGT2B7		
211G→T exon 1	15	Unknown
802C→T exon 2	54	Unknown

Anand, K. J. S. et al. Pediatrics 2010;125:e1208-e1225

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



Opioid Comparisons

Opioid	t ½ß(h)	Cl (mL/kg/min)	V_c/V_{dss}(L)	logP[a]
Morphine[b]	1.5-5	14	25/225	1.2
metabolite renal failure	25-50	(6-glucuronide- slow CNS transfer but will accumulate)		
Hydromorphone[b]	3	20	25/300	1.2
Fentanyl[c]	1.3-3	13	15/325	4.1
Remifentanil[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

Camu & Vanlsersberghe. Best Prac Res Clin Anesth 2002;16:475
de Leon Casasola et al. Anesth Analg 1996;83:867

Morphine in Renal Failure- Dialysis

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)

Carson et al. Crit Care Med 2006;34:1326

Opioid Comparisons

Opioid	Cost	Metabolism	Adverse Effects[a]
Morphine	< $1	Demethylation[b] (active metabolite)	↓ BP/HR; bronchospasm
Hydromor	< $1	Demethylation[b]	Dosing errors?
Fentanyl	< $1	Demethylation	Muscle rigidity[c]
Remifent	$10/mg	Esterases	Bradycardia/hypotension

[a] Refers to adverse effects that are somewhat unique to a particular opioid- does not include ADEs common to all opioids (e.g., CNS depression)
[b] Has 3-glucuronide metabolite that has neuroexcitatory effects in animal models
[c] Possibly just a function of higher doses since noted with morphine and meperidine, albeit less commonly; rigidity may not be seen as much in ICU vs. OR due to concomitant benzo or NMBA (or less likely, naloxone) use

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

Hong et al. Anesth Analg 2008;107:1384

Case Presentation

- 50 y/o obese woman post-pancreatectomy, post-auto-islet cell transplantation
  - PMH: chronic pancreatitis, fibromyalgia, depression
  - FH/SH/DH: not significant; morphine SR 100 mg every 8 h; fentanyl patches 200 mcg/h (every 72 h), hydromorphone 2-4 mg every 4 h prn pain, citalopram 40 mg daily, pregabalin 150 mg twice daily, tramadol 100 mg h.s. insomnia
  - 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 prn (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

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?

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

*Adapted from Erstad et al. CHEST 2009;135:1075; * Christenson & Marjala. Ann Pharmacother 2010;44:207*

Medications Involved in Actual, Preventable ADEs in ICU Studies

Adult Observation n=22
Cardiovascular 32%
Sedation/analgesia 27%
GI agents 18%
Renal 14%

MEDMARX
Insulin 10.2%
Heparin 6.3%
Morphine 5%
Dopamine 3.6%

Peds Observation n=7
Cardiovascular 28%
Sedation/analgesia 28%
Renal 28%
Electrolytes 14%

Cullen SICU
Sedation/analgesia n=115
Antibiotics n=97
Cardiovascular n=88
GI agents n=82

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 ≈ 50% of errors in adults and ≈ 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

Smith & Lesar. J Pain 2011;12:29

Opioid Near-Miss Prescribing Errors

- 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 ānalgesic")
  - 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)

Smith & Lesar. J Pain 2011;12:29

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

	Morphine (M)
Morphine	M iv ↔ M po = 1 : 2-3
Hydromorphone	M iv → HM iv = 4-7 : 1
Hydromorphone	M po → HM po = 5-8 : 1
Fentanyl	M iv → F iv ~ 50 100 : 1
Fentanyl	M po → F transd = 70-150 : 1
Methadone	<90 mg/day M po → ME po = 4-9 : 1
Methadone	90-300 mg/day M po → ME po = 8-10 : 1
Methadone	>300 mg/day M po → ME po = 12-14 : 1

Adapted from Patanwala et al. Ann Pharmacother 2007;41:255

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 > 1-1.5 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

Nesher et al. CHEST 2009;136:245

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