Pain and Sedation in the ICU

Dan Burkhardt, M.D.
Medical Director of Inpatient Pain Services
Associate Professor
Department of Anesthesia and Perioperative Care
University of California San Francisco
burkhard@anesthesia.ucsf.edu
Richmond Agitation-Sedation Scale (RASS)
Ely EW, JAMA 2003:289(22):2983

- +4  = Combative, violent
- +3  = Very agitated, pulls at catheters
- +2  = Agitated, fights the ventilator
- +1  = Restless
- 0   = Alert and calm
- -1  = Drowsy, >10 sec. eye open to voice
- -2  = Light sedation, <10 sec. eye open to voice
- -3  = Moderate sedation, movement to voice
- -4  = Deep sedation, movement to touch
- -5  = Unarousable, no response to touch
M-MAAS

- +3 = Dangerously agitated, uncooperative
- +2 = Agitated
- +1 = Restless and cooperative
- 0 = Calm and cooperative
- -1 = Responsive to touch or name
- -2 = Responsive only to noxious stimuli
- -3 = Unresponsive
How to "Sedate" in the ICU

- Identify goals:
  - analgesia
  - anxiolysis
  - amnesia
  - hypnosis
  - paralysis
- Choose a drug and titrate to effect
- Anticipate side effects
• "Daily Interruption of Sedative Infusions..."
• n=128, intubated, morphine plus either midazolam or propofol
• Daily interruption group:
  – shorter vent duration (4.9 vs. 7.3 day, p=0.004)
  – shorter ICU LOS (6.4 vs. 9.9 day, p = 0.02)
Wake Up And Breath

- 336 mechanically ventilated ICU patients prospectively randomized to getting a SAT or not before their SBT
- SAT+SBT group did better than SBT group
  - more ventilator free days (28 day study period, 14.7 vs. 11.6, p=0.02)
  - shorter ICU LOS (9.1 vs. 12.9 days, p=0.01)
  - lower 1 year mortality (HR 0.68, 95% CI 0.5 to 0.92, p=0.01)
**Bonus: Is A Daily Wake Up Bad?**

de Wit M et al. Crit Care 2008:12:R70

- RCT of Daily Interruption vs. Sedation Algorithm
  - Daily Interruption group did NOT use the algorithm
- Mechanically ventilated medical ICU patients
  - excluded neurocognitive dysfunction, paralytic use, or tracheostomy
  - did NOT exclude alcohol withdrawal
- Daily Interruption did worse (stopped at n=74 by DSMB)
  - longer duration of mechanical ventilation (6.7 vs. 3.9 days, p = 0.0003)
  - longer ICU LOS (15 vs. 8 days, p < 0.0001)
  - longer hospital LOS (23 vs. 12 days p = 0.01)
  - trend toward lower 28 day ventilator free survival (16.1 vs. 23.1 days, p = 0.0004 but NS with the preset alpha of 0.001 for the interim analysis)
- No propofol used in either group
- Daily interruption trended toward less fentanyl (0.5 vs. 1.2 mcg/kg/d) and less midazolam (0.2 vs. 0.4 mg/kg/d) but both were non-significant
"Sedation"

- Analgesia
- Anxiolysis
- Hypnosis
- Amnesia
- Paralysis
- Anti-psychosis
"Analgesia"
Sources of Pain in the ICU

- Surgical incisions
- Tissue injury from malignancy, infection, ischemia
- Indwelling catheters and monitors
- Discomfort from lying in bed in one position for hours or days
Assessment of Pain in the ICU:

- Patient Report
- Agitation (a "sedation scale")
- Grimacing, Tearing
- Splinting of the incision
- Pupil size
- Hemodynamic response to an opioid bolus
  - "If you give fentanyl, and the blood pressure drops, then you haven't given enough fentanyl"
Opioids

- The mainstay of analgesic therapy
- Do NOT reliably produce amnesia, anxiolysis, or hypnosis
  - Tend to preserve the neurologic exam
- Lots of side effects
- Very little direct organ toxicity, even with massive doses
Opioids: Side Effects

- Itching
- Nausea/Vomiting
- Constipation
- Euphoria/dysphoria (rare)
- Urine retention
- Myoclonus
- Respiratory Depression
Opioid Side Effects Are A Spectrum

• By varying the opioid dose you can move between:
  – Screaming in pain
  – Awake and comfortable
  – Nauseous, itching, “woozy”
  – Somnolent
  – Dead (from respiratory depression)

• You can get you to any point on the spectrum with any pure opioid agonist by changing the dose
  – Opioid antagonists can move you in the opposite direction

• Changing the pain intensity has the same effect as changing the opioid dose
  – Epidural infusion clogs --> Incisional pain --> IV fentanyl --> Comfort
    --> Epidural unclogged --> Respiratory Arrest
Opioids: How to Reduce Side Effects

• If the patient is comfortable, decrease the dose
  – Pain is a spectrum
• Change opioids
  – Fentanyl and Dilaudid may be better than morphine
• Add non-opioid adjuncts to reduce total dose
  – NSAIDS, acetaminophen, neuropathic pain treatments, regional anesthesia, dexmedetomidine, ketamine, etc.
• Reduce the source of pain so opioid requirements are less
  – Tracheostomy, for example
Opioids: Constipation

- Seen with essentially all opioid agonists
- Remarkable tendency **not** to develop tolerance over time to this effect
- Prevention:
  - Vigilance
  - Laxatives (especially multiple agents)
- Treatment:
  - PO naloxone
    - 8 mg PO QID
    - Oral antagonist not systemically absorbed failing late clinical trials
  - IV neostigmine
    - Neostigmine up to 2 mg IV with cardiac monitoring
    - IV atropine/glycopyrrolate at the bedside
  - ? Entereg (Alvimopan)
    - Peripherally acting opioid antagonist just FDA approved
IV Opioid Choices

- Morphine
  - Familiar
  - Multiple problems
    - histamine release
    - active metabolite accumulates in renal failure
    - ? more confusion in elderly
- Hydromorphone (Dilaudid)
  - Roughly the same onset and duration as morphine
- Fentanyl
  - Faster onset
    - Hard to use outside the ICU (large bolus = transient apnea)
  - Terminal elimination is similar to morphine
Short Acting Opioids: Remifentanil

- Ultra-short acting opioid
  - Rapid organ independent metabolism by plasma esterases
- Usual dose:
  - Light sedation = 0.01-0.05 mcg/kg/min IV
  - General anesthesia = 0.1 - 0.2 mcg/kg/min IV
- May be useful in neuro patients (especially with Propofol)
- Can precipitate SEVERE pain if the infusion suddenly stops
- Large boluses can cause transient bradycardia
  - Has lead to CPR in our ICU patients
- Expensive (~25-50% more than propofol, depending on tolerance)
- May induce the rapid development of opioid tolerance
Opioid Tips:
Long Acting Agents ... A Few Choices

- Extended release morphine, oxycodone, oxymorphone
  - Easy dose calculation for clinicians unfamiliar with opioids
  - Can't crush for FT
    - Impossible to give to an intubated patient
- Methadone
  - Cheap, available PO and IV
  - Takes 2+ days for dose change to take effect
  - QT prolongation, especially at high doses
- Fentanyl patch
  - Doesn't rely on IV or PO route
  - 12h++ onset and offset, fever causes increased absorption
  - Recent FDA warnings about use in opioid naive patients
Opioid Reversal: Naloxone

• If the patient has stable vital signs, titrate low doses of naloxone to reverse somnolence
  – 40 - 80 mcg IV q1-5 min.
• *Naloxone doesn't cause pain, a naloxone overdose does*
• Titrated carefully, side effects are very rare
  – Pulmonary edema has not been observed despite hundreds of uses in our practice
• Naloxone is shorter acting than any normal opioid
  – If it works, you need to start an infusion or the patient will become somnolent again
"Sedation"

- There are many components besides analgesia, including:
  - anxiolysis
  - amnesia
  - hypnosis
  - anti-psychosis or anti-delirium
  - paralysis
- Need to identify what your goals are in order to chose the proper therapy
Benzodiazepines

- Excellent anxiolysis, amnesia, hypnosis
- Little analgesia
- Anticonvulsant
  - useful for seizures, alcohol withdrawal
- Minimal hemodynamic effects
- Relatively less respiratory depression when used alone, but very synergistic with opioids
- May cause agitation in the elderly
Midazolam

• Infusion is more compatible with other drugs
• Rapid onset, short duration after single bolus dose
• Prolonged offset with some patients, especially after prolonged infusion
  – Cytochrome P450 3A4 elimination, so prolonged effect with fluconazole, ketoconazole, erythromycin, diltiazem, propofol, some anti-retrovirals, liver disease
• Preferred for sedation of <24 hours according to the consensus statements ... but this is widely disputed
Lorazepam

- No active metabolites
- Fewer drug interactions, more predictable offset
- Infusion not very compatible, precipitates
- Propylene glycol toxicity causes hyperosmolarity, acidosis, ATN
  - Worse in renal failure
  - Risk increased when daily dose exceeds 50-70 mg (2-3 mg/hr, as opposed to older discussions of 10 mg/hr) even with normal renal function
  - Monitor serum osmol gap QD or QOD when giving these doses
- The benzo of choice for sedation >24 hours according to consensus statements (an old recommendation that is widely disputed)
Benzodiazepine Reversal: Flumazenil

- Competitive antagonist
- Short duration
  - Like naloxone, at risk for reedation after use
- Risk of seizures
  - Unlike naloxone
- Transiently improves hepatic encephalopathy
  - So can’t use as a diagnostic trial of therapy
Speculation: Should Benzodiazepines Be Used in the ICU?

- Some practitioners suggest that benzodiazepines should not be used as first line therapy in critically ill adults
  - At least in patients at risk for delirium, which can be almost everyone in some ICUs
- The theory is that short acting hypnotics such as Propofol or Dexmedetomidine will cause less delirium
  - Benzo's can be reserved for patients with poor cardiac function or those at risk of withdrawal seizures
Propofol vs. Lorazepam

• Adult medical ICU patients expected to be intubated for >48 hours
• Randomized to lorazepam bolus or propofol infusion
• Daily interruption of sedatives in both groups
• Propofol group did better:
  – Fewer ventilator days (median 5.8 vs. 8.4, p = 0.04)
  – A strong trend toward greater ventilator-free survival (18.5 vs. 10.2 days, p = 0.06)
• Mean consumption 11.5 mg/d lorazepam vs. 24.4 mcg/kg/min propofol
  – Should be a minimal difference in hospital acquisition costs
Propofol Toxicities

- Pain on Injection
- Hypotension
- Myoclonus, seizure like activity
- Hypertriglyceridemia
- Pancreatitis
- Propofol Infusion Syndrome (metabolic acidosis)
Propofol Myocardial Depression:
Propofol during Cardiopulmonary Bypass
Xia Z et al. Anes Analg 2006;103:527

- 54 CABG patients randomized to 3 groups
  - Low-P: Propofol @ 60 mcg/kg/min throughout the case
  - Hi-P: Propofol @120 mcg/kg/min during CPB, and @60 the rest of the time
  - I: Isoflurane 1-3.5%
- Hi Propofol group did better (p<0.05 or better)
  - Significantly lower troponin I and cardiac index at 24hr vs. either LoP or I
    - HiP = 2.8 dyn/s/m2, LoP = 2.3, I = 2.2
  - Significantly lower vasopressors coming off CBP (HiP vs. I)
  - Significantly shorter ICU length of stay (HiP vs. I)
Propofol - Hypertriglycerideridemia

- Incidence estimates vary: up to 3-10% (Kang TM Ann Pharmacother 2002;36:1453-6)
- Risk factors likely include prolonged infusion and higher doses of lipid
- SCCM Clinical Practice Guidelines for the Sustained Use of Sedatives and Analgesics in the Critically Ill Adult - 2002
  - "Triglyceride concentrations should be monitored after two days of propofol infusion." Jacobi J et al. CCM 2002;30(1):119-41
- Areas of investigation
  - Higher concentrations (2% to 6%) to reduce total lipid dose
  - Alternative formulations (such as medium or long chain triglyceride based agents)
  - More soluble pro-drugs
Propofol - Hypertriglyceridemia
Practical Advice

- Limit long term infusion doses to less than 80 mcg/kg/min via the addition of supplemental agents
  - Analgesics such as opioids are particularly useful
  - Higher propofol doses are typically only needed for cerebral metabolic suppression therapy (brain injury, status epilepticus)
- Create institutional protocols and order sets for routine triglyceride monitoring
  - Perhaps q48 hours initially
  - Could also extrapolate frequency from local practice for TPN lipid infusions
Propofol Infusion Syndrome

• Severe metabolic acidosis
  – Progressing to hyperkalemia, rhabdomyolysis, hypotension, bradycardia, and death
• Risk factors are suspected to include
  – Prolonged infusion (>48 hrs) of higher doses (> 80 mcg/kg/min)
  – Steroid use
  – Catecholamine use
  – Brain Injury
  – Sepsis or other Systemic Inflammatory Response Syndrome
  – Pediatric patients
• May be associated with dysfunction of the mitochondrial energy metabolism
  – Pre-existing and/or drug induced
Propofol Infusion Syndrome:
Practical Advice

• Prevention
  – Minimize the dose administered (<80 mcg/kg/min), especially with prolonged infusion (>48 hours), through addition of supplemental agents
  – If acidosis develops
    • Discontinue propofol
    • Follow laboratory parameters (arterial blood gas, creatinine kinase, electrolytes, triglycerides)

• Treatment
  – Supportive care
  – (Possibly) hemodialysis/hemofiltration
Haloperidol

- Anti-psychotic
- Not FDA approved for IV administration or ICU sedation
- Relatively little respiratory depression compared with alternative sedatives
- Useful for management of agitation due to delirium
  - Controlling delirium may have an outcome benefit
Delirium is an Independent Predictor of Mortality in Mechanically Ventilated ICU Patients
(Ely EW et al. JAMA 2004)

• Prospective cohort study of 275 consecutive mechanically ventilated patients admitted to an adult medical and coronary ICU
• Delirium, measured by the Confusion Assessment Method for the ICU (CAM-ICU), was independently associated with a higher 6-month mortality after adjusting for covariates. (34 vs 15%, p=0.03)
• A recent survey of Canadian Critical Care practitioners indicated that only 3.7% routinely use a delirium scoring system (Mehta S et al. Crit Care Med 2006)
• This does not prove that there is any effective therapy
Haldol: Mortality Benefit?
Milbrandt EB, CCM 2005

- Retrospective chart review of 989 patients
  - Haldol within 2 days of initiation of mechanical ventilation (n = 83) against those who never received it (n = 906)
- Haldol group had a lower mortality (20.5% vs. 36.1%, p = 0.004)
  - Persisted after adjustment for age, comorbidity, severity of illness, degree of organ dysfunction, admitting diagnosis, and other potential cofounders
  - Haldol (broken down into low, medium and high doses) showed a dose response mortality benefit
Haloperidol: Side Effects

- Extrapyramidal effects
- QT prolongation leading to torsades-de pointes
  - Seen at total doses as low as 20-35 mg
  - Regular ECGs to assess for QT prolongation (printed on order form)
- Reduced seizure threshold
  - Increased mortality when used for alcohol withdrawal
  - Relative risk of mortality with neuroleptic treatment compared with sedative-hypnotic treatment of 6.6 (95% confidence interval, 1.2-34.7)
    Mayo-Smith MF, Arch Int Med 2004
- Neuroleptic Malignant Syndrome
  - Fever, rigidity, cognitive changes, tachypnea, tachycardia, diaphoresis, leukocytosis, elevated CK
  - Supportive care, discontinue inciting agent
  - Dopamine agonists (bromocriptine, amantadine, levodopa/carbidopa)
  - Dantrolene
"Atypical" Antipsychotics: Abilify, Zyprexa, etc.

- Don't prolong the QT interval
  - A controversial area: difficulty to measure accurately
- Usually not available IV (PO / SL / IM only)
- Beware drug interactions. For Abilify, for example
  - 2D6 inhibitors like Prozac or Paxil, and 3A4 inhibitors like itraconazole and erythromycin inhibit metabolism: reduce dose by half
  - 3A4 inducers like carbamazepine enhance metabolism: double dose
- Still cause NMS
Dexmedetomidine

- Selective alpha-2 agonist (IV infusion)
- Sedation, anxiolysis, analgesia, sympatholysis
- Not reliably amnestic
- Still arousable for neuro exam
- Not a major respiratory depressant
  - Can be used on extubated patients
- Alpha-2 agonists as a class may be associated with a cardiovascular protective effect with perioperative use
  - Metaanalysis of 23 studies of perioperative use of alpha-2 agonists showed a significant mortality reduction (RR=0.64, p=0.05) Wijeysundera DN et al. Am J Med 2003;114:742-52
Dexmedetomidine vs. Lorazepam
(Pandharipande PP et al. JAMA 2007)

- 103 adult medical and surgical ICU patients requiring mechanical ventilation for >24 hrs prospectively randomized to:
  - lorazepam 1 mg/hr IV titrated between 0-10 (no boluses allowed)
  - dexmedetomidine 0.15 mcg/kg/hr titrated between 0-1.5
- All patients received fentanyl boluses, or a fentanyl infusion if the max rate of study drug was reached.
- Continued until extubation or until FDA mandated endpoint of 120 hours, titrated to RASS. Patients assessed for delirium by CAM-ICU
- Dexmedetomidine group did better
  - More delirium and coma free days (7.0 vs. 3.0, p=0.01)
  - More time spent within one point of their target RASS (80% vs. 67%, P=0.04)
  - Trend toward lower 28 day mortality (17% vs. 27%, p=0.18)
- No difference in cortisol or ACTH levels 2 days after discontinuation
Dex: Problems

• Lack of SNS activity can lead to unopposed vagal activity
  – Episodes of bradycardia, sinus pauses, and even transient asystole in healthy unstimulated patients
  – Treatment is glycopyrrolate
• FDA approved only for 24 hours of use
  – Several studies report that up to 7 days of use is well tolerated
  – Concern about adrenal suppression
    • Dexmedetomidine had no effect on ACTH-stimulated cortisol release in dogs after a single dose; however, after the subcutaneous infusion of dexmedetomidine for one week, the cortisol response to ACTH was diminished by approximately 40%. (Package insert)
    • Unclear if this is clinically relevant in humans
• Expensive
  – FDA approved for doses up to 0.7 mcg/kg/hr, but often need doses above 1 mcg/kg/hr for intubated ICU patients, especially when used as monotherapy
Hospital Drug Acquisition Costs

Drug only ... does not include preparation, etc.
All costs are for 24 hours for a 70 kg patient

- **Propofol** 75 mcg/kg/min = $100
- **Dexmedetomidine** 1 mcg/kg/hr = $500
  - MICU patients needed 1 mcg/kg/hr (Venn RM et al. ICM 2003)
  - CABG patients on a 0-0.7 mcg/kg/hr dex protocol only reduced their Propofol dose from 20 to 5 mcg/kg/min
- **Midazolam** 2 mg/hr = $10
- **Fentanyl** 50 mcg/hr = $7
- **Remifentanil** 0.10 mcg/kg/min = $100
Dexmedetomidine: When to Use?

- The immediate peri-extubation period
  - Wean off other sedatives, and continue dex during extubation
- Agitation from drug withdrawal (like clonidine patch)
- Severe pain resistant to opioids
  - Another non-opioid adjunct for pain relief
  - Morphine sparing in multiple trials
- Patients at risk from adrenergic over-stimulation
  - Clonidine has a perioperative mortality like beta-blockers (Wallace AW, Anes 2004)
  - Dex provided a mortality benefit in a rat sepsis model (Taniguchi T, CCM 2004)
- Patients at risk for delirium (maybe)
Ketamine: A Unique Sedative

- Phencyclidine derivative (like PCP)
- NMDA receptor antagonist
- Dissociative hypnotic, amnestic
- Analgesic (the only potent analgesic without much respiratory depression)
- Useful for brief procedures (dressing changes) on unintubated patients
Ketamine: Problems

- Increases BP, HR, and possibly ICP because of sympathetic stimulation
  - Likely no increase in ICP in patients who are sedated and fully mechanically ventilated (Himmelseher S Anes Analg 2005)
- BUT is also a direct negative inotrope
- Causes unpleasant dreams and hallucinations
  - consider benzo use if dose is > 5 mcg/kg/min
- SNS stimulation my cause bronchodilation but the drug also increases secretions
- Maintains airway tone, but not necessarily airway reflexes
Ketamine: Last Resort Sedative

• For continuous sedation
  – 1 - 10 mcg/kg/min has been studied in post-op patients for pain relief (typically keep dose < 5 for awake patients)
  – up to 20 - 30 mcg/kg/min used at UCSF for "impossible to sedate" intubated patients to avoid paralysis
• Low doses (1-5 mcg/kg/min) may block the development of tolerance to opioids
• Low dose oral and IV ketamine is used outside the ICU by many centers (soon at UCSF).
Ketamine for Acute Postoperative Pain
(Bell RF et al. Cochrane Database 2006)

• Systemic review of randomized placebo controlled trials of adult patient undergoing surgery
• Low dose ketamine effective:
  – Reduced morphine requirements: Weighted Mean Difference (fixed) 15% (95% CI = 19 to 11%)
  – Significantly less nausea and vomiting (RR = 0.77, 95% CI 0.65 to 0.90)
• Minimal side effects
Neuromuscular Blocking Drugs

- Absolutely NO amnesia, hypnosis, analgesia, or anxiolysis
  - Actually quite anxio-genic
  - MUST administer amnestics/hypnotics
- Difficult to recognize pain/agitation
  - They are always an RASS of -5/5
  - Cannot titrate sedatives as all
- Can't recognize seizures or focal CNS deficits
  - Recognition and treatment won't happen in time to avoid permanent injury
- Can't withdraw the ventilator for comfort care
- May be associated with prolonged weakness due to critical illness polyneuropathy
  - Not clear that this is true
Paralytics

- Succinylcholine (1 mg/kg)
  - depolarizing
  - can't use in stroke/cord injury/paralysis, burn, or hyperkalemia
  - controversial for use in any long-term ICU patient
  - will likely completely disappear when new reversal agent arrives
- Rocuronium (1 mg/kg)
  - fastest onset of non-depolarizers
- Vecuronium (0.1 mg/kg)
  - cheap, but active metabolite accumulates in renal failure
- Cis-atracurium (0.2 mg/kg)
  - expensive, organ independent Hoffman elimination
- Pancuronium (0.1 mg/kg)
  - tachycardia, renal elimination, very long duration of action
Critical Illness Myopathy-Polyneuropathy: 
Lots of Theories, Little Data
De Jonge B, Cur Op Crit Care 2004

• Paralytics
  – Avoid long term use. Brief periods (like in the OR) don't seem to matter.
  – Monitor with twitch ("train of four") monitor

• Minimize Steroids

• Tight glycemic control

• Physical Therapy / Exercise
  – Avoid deep sedation
Take Home Messages

- Define your goals (analgesia, anxiolysis, hypnosis, amnesia, antipsychosis) and choose your drugs appropriately
- Titrate to effect
  - goal is “moderate” use of PRNs
  - frequently assess arousability (“wake up” test)
- Watch for side effects specific to that drug, and proactively treat
- (Maybe) avoid benzodiazepines in patients at risk for delirium