The Difficult to Sedate ICU Patient

Dan Burkhardt, M.D.
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

Titrate to Effect: Kress JP NEJM 2000

- "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)

Do I Really Have to Wake Them Up?

- 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)
But ... That’s Not What The Talk Is Supposed To Be About ...

• My “easy to sedate” patients should be titrated to the minimum dose necessary, and have a daily wake-up. Got it.
• What about my difficult to sedate patients?

Case: The ASF Won’t Sit Still

• 58 year old male who remains intubated in the ICU with upper airway edema immediately after a multilevel anterior cervical spine fusion who is sedated with a propofol infusion
• He is alternating between hypotension and agitation with propofol titration.
• What’s wrong?

Case: The TKR Just Kicked Me

• 52 year old male POD #1 from a left total knee replacement, who is hypertensive, tachycardic, agitated, and delirious. He just kicked the RN with his left leg.
• Low dose fentanyl does nothing. High dose fentanyl causes transient hypoxia and unresponsiveness.
• What is wrong?

How to "Sedate" in the ICU

• Identify goals:
  – Analgesia
  – Anxiolysis
  – Amnesia
  – Hypnosis
  – Paralysis
• Choose a drug and titrate to effect
• Anticipate side effects
## "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
- ICU sedation algorithms always start with “Does the patient have pain? → Treat it.”
  - If you can’t ask the patient:
    - Guarding of wound
    - Pupil size (to assess opioid tolerance)
    - Trial of therapy

## Opioids

- The mainstay of analgesic therapy
- Do NOT reliably produce amnesia, anxiolysis, or hypnosis
- Lots of side effects (itching, nausea, constipation, urine retention, myoclonus, respiratory depression)
- Very little direct organ toxicity

### Opioids: How to Reduce Side Effects

- If the patient is comfortable, decrease the dose
- Change opioids
  - Fentanyl and Dilaudid may be better than morphine
- Add non-opioid adjuncts to reduce opioid dose needed
  - NSAIDS (PO or IV), acetaminophen (PO or IV), neuropathic pain treatments (PO only), regional anesthesia, dexmedetomidine, ketamine, isoflurane etc.
- Reduce the source of pain
  - Tracheostomy, for example

### 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
  - 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

---

**Opioid Tips:**

**Long Acting Agents ... A Few Choices**

- Extended release morphine, oxycodone, oxymorphone
  - Can't crush for FT
  - Just divide up total daily dose and give IR version per FT at frequent intervals
- 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
  - Regulatory hassle

---

**"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
- Minimal hemodynamic effects
- Anticonvulsant (useful for seizures or alcohol withdrawal)
- Little analgesia
- Cause delirium
  - Lorazepam was an independent risk factor for transition to delirium in ICU patients (OR 1.2, 95% CI 1.2-1.4), while fentanyl, morphine, and propofol were not (Pandharipande P et al. Anes 2006, 104:21-26)
**Benzodiazepines Are Bad!**

- Should not be used in ICU patients
  - At least those at risk for delirium, which is basically everyone
- Benzodiazepines can be reserved for patients with
  - Very very poor cardiac function
  - Alcohol or benzodiazepine withdrawal
- Use propofol or dexmedetomidine instead
  - We routinely use propofol with phenylephrine for prolonged periods in SAH patients

**Propofol vs. Lorazepam**  
(Carson SS et al. *Crit Care Med* 2006)

- 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)

**Case: Propofol Works Great, but.......**

- 48 year old morbidly obese male intubated for altered mental status and high ICP after SAH.
- Sedated well on propofol 90 mcg/kg/min (based on actual body weight)
- Triglyceride level 482 mg/dL.

**Propofol - Hypertriglyceridermia**

- Incidence estimates vary: up to 3-10% (Kang TM *Ann Pharmacother* 2002;36:1453-6)
- Risk factors likely include prolonged infusion (> 80 mcg/kg/min for > 24 hrs)
  - Especially in obese patients dosed according to actual body weight
- 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
- May not need to stop the drug, just reduce the dose (add fentanyl)
**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
- Treatment
  - STOP the drug

**Dexmedetomidine**

- Selective alpha-2 agonist (IV infusion)
- Sedation, anxiolysis, analgesia, sympatholysis
- Not reliably amnestic at low doses
- Still arousable for neuro exam
- No significant respiratory depression
  - Can be used on extubated patients
- No more hemodynamically stable than propofol

---

**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 infusion if necessary
- Continued until extubation or until FDA mandated endpoint of 120 hours
- **Dexmedetomidine group did better**
  - More delirium and coma free days (7.0 vs. 3.0, p<0.01)
  - Trend toward lower 28 day mortality (17% vs. 27%, p=0.18)
- **Dexmedetomidine group received significantly more fentanyl** (575 vs. 150 mcg/24h, p<0.001)
- **No difference in cortisol or ACTH levels 2 days after discontinuation**

**Dexmedetomidine vs. Midazolam**

(Riker RR et al. JAMA 2009)

- **PDBRCT 375 intubated med/surg ICU patients expected to require ventilation for at least 3 more days**
  - Dex 0.2 - 1.4 mcg/kg/hr vs Midaz 0.02 - 0.1 mg/kg/hr until extubation or 30 days
  - Excluded (among other things) hypotension defined as SBP < 90 despite 2 vasopressors
  - **Also**
    - Study drug boluses prn
    - Open-label midazolam 0.01-0.05 mg/kg iv q10-15min pm agitation
    - Fentanyl 0.5-1 mcg/kg iv q15mr pm pain
    - Haloperidol 1-5 mg iv q10-20min pm delirium
Dex vs. Midazolam

- Dex group did better
  - Less delirium (54% vs. 76.6%, p<0.001)
  - Shorter time to extubation (3.7 vs. 5.6 days, p=0.01)
- No difference
  - ICU LOS (5.9 vs. 7.6 days, p=0.24)
  - 30 day mortality (22.5% vs 25.4%, p=0.60)
- Dex had more bradycardia (42.2% vs. 18.9%, p<0.001)
- Dex mean dose of 0.83 mg/kg/hr for average duration of 3.5 days
  - 1/244 dex patients had adrenal insufficiency (0/122 in midaz group)

Hospital Drug Acquisition Costs

- Propofol 75 mcg/kg/min = $75
- 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 = $250

Other Ways to Prevent/Treat Delirium

- Promote sleep (quiet ICU at night)
  - Yakometer sound monitor
- Exercise (so they are exhausted at night)
  - We ambulate on ECMO (V-V)
- Antipsychotics
  - Not prophylactic
  - Haloperidol
    - Daily EKG
  - Atypical antipsychotics
    - Seroquel popular for insomnia

Case: The Last Resort

- 25 year old male with severe pancreatitis and ARDS. Progressive worsening of hypoxia and agitation since admission 2 weeks ago.
- Oxygen saturation 85% on FiO2=1.0 and PEEP=20. Frequent coughing leading to desaturations down to 60% despite fentanyl at 1000 mcg/hr IV and midazolam 20 mg/hr IV.
Ketamine: A Unique Sedative

- Phenacyclidine derivative (like PCP)
- NMDA receptor antagonist
- Dissociative hypnotic, amnestic
- Analgesic
  - The only potent analgesic without much respiratory depression
  - One of the few non-opioid analgesics that can be given IV
- Classically used for brief procedures (such as dressing changes) on unintubated patients
- Little to no tolerance

Ketamine: Problems

- Increases BP and HR via sympathetic stimulation
  - But actually a direct negative inotrope
- May increase in ICP, also because of sympathetic stimulation
  - But not in patients who are sedated and mechanically ventilated (Himmelseher S Anes Analg 2005)
- Causes unpleasant dreams and hallucinations
  - Consider benzo use if dose is > 5 mcg/kg/min IV
- Increases bronchodilation by sympathetic stimulation
  - But also increases secretions

Ketamine: Last Resort Sedative

- For continuous sedation in the ICU
  - 1 - 10 mcg/kg/min IV used in post-op patients for pain relief (typically keep dose < 5 for awake patients)
  - Up to 20 - 30 mcg/kg/min IV used at UCSF for “impossible to sedate” intubated patients to avoid paralysis
- Low dose oral (<50 mg po TID) and IV (< 5 mcg/kg/min) ketamine is used outside the ICU by many centers
- Oral ketamine also used on outpatients by Pain Clinics

Polysubstance Abuse

- Alcohol / Benzodiazepines
  - Withdrawal is difficult to manage with a high morbidity / mortality
  - Watch for seizures, don’t use only neuroleptics, etc.
- Opioids
  - Titrate opioid dose up to effect
  - Withdrawal is relatively benign
- Amphetamine / Cocaine
  - Main problem is fatigue
  - Withdrawal is relatively benign
- Marijuana
  - Consider oral marinol
  - Withdrawal is relatively benign
What About Paralytics?

- They are NOT sedatives
  - No analgesia
  - No amnesia
  - No anxiolysis
- They don’t belong in a “how to sedate” talk
  - Morally no different than putting your hands over your eyes and saying “Look! No more agitation!”

Take Home Messages

- Define your goals (analgesia, anxiolysis, hypnosis, amnesia, antipsychosis) and choose your drugs appropriately
- Titrate to effect (with daily wake ups)
- Watch for side effects specific to that drug, and proactively treat
- Don’t use benzodiazepines
  - Unless the problem is alcohol or benzo withdrawal.

Reprints / Questions

burkhard@anesthesia.ucsf.edu