The Difficult to Sedate ICU Patient

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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
- Don’t forget: laxatives, laxatives, laxatives!

IV Opioid Choices

- Morphine
  - Familiar
  - Multiple problems
    - histamine release
    - active metabolite accumulates in renal failure
    - 7 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, hydromorphone
  - 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
  - 12hr++ 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

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**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)

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**Propofol vs. Benzo in Vented ICU Pts**


- Retrospective review of 2,250 propofol-midazolam and 1,054 propofol-lorazepam matched cohorts of ICU patients
- Significantly lower mortality with propofol
  (Death at 28 days)
  - 19.2 vs 28.0%, p<0.001 for midaz
  - 19.1 vs 24.6%, p<0.0018 for loraz

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**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 - Hypertriglyceridemia

- 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

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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 0.15
- 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=0.006)
**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 prn agitation
  - Fentanyl 0.5 - 1 mcg/kg iv q15mr prn pain
  - Haloperidol 1 - 5 mg iv q10-20min prn delirium

**Dexmedetomidine vs. Midazolam**
(Riker RR et al. JAMA 2009)

- 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 Adrenal Suppression**
(Riker RR et al. JAMA 2009)

- Mean dose of 0.83 mcg/kg/hr x 3.5 days
- 1/244 dex patients had adrenal insufficiency (0/122 in midaz group)

**Dex vs. Propofol**
(Jakob SM et al. JAMA 2012)

- RDBRCT 590 ICU pt. on mechanical ventilation who need >24 h sedation. Rx for up to 14 days.
  - Dex 0.2 - 1.4 mcg/kg/hr (mean 0.925 x 42h)
  - Propofol 5 – 67 mcg/kg/hr (mean 29.2 x 47h)
  - Fentanyl for pain, bolus midazolam for rescue
- No difference
  - Vent duration (D vs. P) 4.0 vs. 4.9 d (p=0.24)
  - ICU LOS, mortality, hemodynamics
  - Neurocognitive AE requiring rx: 28.7% vs. 26.8% (p=0.689)
  - CAM-ICU Positive: 11.9% vs. 13.9% (p=0.393)
- Dex had less critical illness polyneuropathy (0.8% vs. 4.4% p=0.02)
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 = $75
- Dexmedetomidine 1 mcg/kg/hr = $500
  - MICU patients needed 1 mcg/kg/hr (Veness RM et al. ICM 2003)
  - CABG patients on a 0.6-0.7 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

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.

Metaanalysis Benzo vs. Non-Benzo

Bardel et al. CCM 2013

Ketamine: A Unique Sedative

- Phencyclidine 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 intubated 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 (Himmelscher 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 IV (< 5 mcg/kg/min) is used anywhere in the hospital
• Oral ketamine used on outpatients

Polysubstance Abuse

• Alcohol / Benzodiazepines
  – Withdrawal is difficult to manage with a high morbidity / mortality
  – Watch for seizures, don’t use only neuroleptics, etc.
• Opioids
  – Titrated 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!”
**Neuromuscular Blocking Drugs**

- 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

**DeJonghe JAMA 2002**

- 95 consecutive ICU patients, intubated for at least 7 days, who were still alive 7 days after waking up
- 25% had “severe muscle weakness”
  - <48 on 0-60 scale of limb strength
- All had sensorimotor axonopathy on EMG
- Independent risk factors: female gender, corticosteroid use, days on a ventilator, days with 2+ organ dysfunction
- Trend toward more paralytic use: 62% vs. 41%
  - mean duration of paralysis 3.3 vs. 2.1 days

**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
- **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

**Paralytics for ARDS**

- Randomized 340 patients with ARDS to paralytics for two days.
- 90 day in-hospital mortality lower in the NMB group (0.68, 0.48 – 0.98)
- No difference in long term weakness (29% vs. 32% as defined by Medical Research Council Scale <48 at 28 days)
Paralytics for ARDS
Papazian L et al. NEJM 2010

- Sedation Protocol:
  - Keep unresponsive to stimuli for 48 hours using benzo and opioid. Add propofol or ketamine if plateau pressure > 32 cm H₂O
- Problems:
  - The non-paralyzed group received inappropriately deep sedation
  - Both groups received the evil drug: benzodiazepines

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.

Don’t Need Daily Wake-Up
Mehta S et al. JAMA 2012

- 430 intubated ICU patients on protocolized sedation randomized to daily wake-up (then restart at half previous dose) vs. not
- No difference
  - Vent duration 7 vs. 7 days
  - ICU LOS 10 vs. 10 days
  - Unplanned extubation 4.7% vs. 5.8%
- Midazolam dose HIGHER in wake-up group
- Benzo’s BAD
Reprints / Questions

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