Sedation for the ICU Patient

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Goals

• Why do we sedate patients
• How to sedate patients
  – How to measure sedation
  – What to sedate with
• How to wean sedation

Why Sedate Patients?

• Control the patient
  – Prevent extubation, line removal, etc
  – Improve hemodynamics
  – Improve oxygen consumption
  – Improve ICP
• Keep the patient comfortable
  – Painful procedures
  – Tissue injury
• Keep the nurses comfortable
How to Achieve Sedation in the ICU

• Measure adequacy of sedation
  – Sedation Scales
  – Depth of sedation monitors
• Choose a drug and titrate to effect
• Identify goals of sedation:
  – Analgesia
  – Anxiolysis
  – Amnesia
  – Hypnosis
  – Paralysis
• Anticipate side effects

Ramsey Sedation Scale

• 1 = Anxious, agitated, or restless
• 2 = Cooperative, oriented and tranquil
• 3 = Drowsy, but responsive to commands
• 4 = Asleep, brisk response to stimulus
• 5 = Asleep, sluggish response to stimulus
• 6 = No response to stimulus

Motor Activity Assessment Scale

• 6 = Dangerously agitated, uncooperative
• 5 = Agitated
• 4 = Restless and cooperative
• 3 = Calm and cooperative
• 2 = Responsive to touch or name
• 1 = Responsive only to noxious stimuli
• 0 = Unresponsive
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

Richmond Agitation-Sedation Scale (RASS)

- +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

Sedation Monitors: EEG

- Traditional EEG
  - Useful to detect seizures, especially in the paralyzed patient
  - Or to judge depth of a barbiturate coma
    - i.e. burst suppression or isoelectric EEG

- Processed EEG ("Bis Monitor")
  - 100=awake, 0=isolectric, 40-60=target
  - Used to judge depth of anesthesia in OR
  - Heavily promoted to prevent intra-op awareness
  - Cannot be used to rule out seizure activity
Goals of Sedation

- Analgesia
- Anxiolysis
- Amnesia
- Hypnosis
- (Paralysis)

Drug Classes to Achieve Goals

- Opioids
- Benzodiazepines
- Antipsychotics
  - Atypical antipsychotics
- Others
  - Hypnotics
  - Anesthetics
- Neuromuscular blocking agents

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
Opioids

- The mainstay of analgesic therapy
- Do NOT reliably produce amnesia, anxiolysis, or hypnosis
- Difficult to produce unconsciousness, even with very high doses
  - an advantage if you're trying to preserve the neurologic exam

Opioids: Hemodynamics

- Little negative inotropy
- Mild direct negative chronotropy with very large bolus injections
- Should be hemodynamically neutral
  - Morphine can precipitate histamine release, but this is probably not clinically relevant except in huge bolus doses

Opioid Overdose

- Raise CO2 threshold
  - may be desirable in respiratory alkalosis
  - can produce severe respiratory acidosis, even with normal O2 saturation
  - Diagnosis:
    - arousability (Sedation Scales)
    - ABG (from an arterial line)
    - or a trial of therapy (Naloxone)
Opioid Reversal: Naloxone

- For life threatening respiratory acidosis:
  - Treatment: Narcan
    - 0.4 mg / 1cc ampule
    - diluted into total volume of 10 cc (40 mcg/cc)
    - give 40-80 mcg IV q2-5min
  - May need infusion to avoid re-sedation

Opioids: Other Side Effects

- Itching (Benadryl, low dose Narcan)
- Nausea / Vomiting (antiemetics)
- Constipation (laxatives, physical activity, Narcan po, neostigmine IV)
  - Neostigmine up to 2 mg IV with cardiac monitoring and IV atropine/glycopyrrolate at the bedside
  - Follow stool production when on an opioid infusion
- Euphoria / dysphoria (rare)
- Urinary retention
- "Stiff Chest" syndrome (high dose IV Bolus)
- Myoclonus

Opioids: Reduce Side Effects

- Decrease dose
  - pain is a spectrum
- Change drugs
  - 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 stimulus
  - 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
  - $10\ mcg\ IV = 1\ mg\ Morphine\ IV$
  - Faster onset and offset (inconvenient for IV pm)
  - Terminal elimination is the same as 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
- Can cause significant bradycardia with boluses (even inadvertent ones)
  - Has led to CPR in our ICU patients
- Expensive (24 hours for 70 kg patient is $230 ... compared with $184 for Propofol at 50 mcg/kg/min)
- May induce the rapid development of opioid tolerance

Long Acting Opioids: Use Only One

- MS Contin, OxyContin
  - Easy dose calculation
  - Can't crush for FT
- Methadone
  - Cheap, available PO and IV
  - May have NMDA blocking activity
  - Takes 2+ days for dose change to take effect
- Fentanyl patch
  - Doesn't rely on IV or PO route
  - 12hr onset and offset, fever causes increased absorption
**Benzodiazepines**

- Excellent anxiolysis, amnesia, hypnosis
- NO analgesia
- Anticonvulsant
  - useful for seizures, alcohol withdrawal
- Minimal hemodynamic effects
- Minimal respiratory depression when used alone, but very synergistic with opioids
- May cause agitation in the elderly

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**Midazolam (Versed)**

- Rapid onset, short duration of bolus dose
- Water soluble, more compatible with other drugs
- Expensive (less so now that it is generic)
- Cytochrome P450 3A4 elimination, so prolonged effect with fluconazole, ketoconazole, erythro, diltiazem, propofol, some anti-retrovirals, liver disease
- Preferred for sedation of <24 hours according to the consensus statements ... but this is widely disputed

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**Lorazepam (Ativan)**

- Relatively inexpensive
- No active metabolites
- Fewer drug interactions
- Slower onset than midazolam, longer acting
- Infusion not very compatible, precipitates
- Propylene glycol toxicity causes hyperosmolarity, acidosis, ATN
  - Worse in renal failure
  - Keep dose under 15-20 mg/hr even with normal renal function
- The drug of choice for sedation >24 hours according to the consensus statements...
Diazepam (Valium)

- Cheap
- Very long acting active metabolites (oxazepam elimination half-life up to 96 hours)
- Propylene glycol vehicle is painful, scleroses veins
- Usually used as a "long acting" PO (akin to methadone's role)

Benzodiazepine Reversal: Flumazenil

- Competitive antagonist
- Short duration
  - like naloxone, at risk for reedation after use
- Risk of seizures
  - unlike naloxone
- Transiently improves hepatic encephalopathy

Antipsychotics: Haloperidol

- Anti-psychotic
- Useful for "sundowning" in elderly patients
- Patient appears calm and detached, but the experience may not be pleasant
  - Not usually first line therapy for agitation
- Dose variable from 1-2 mg to 1200 mg/d IV
- IV peak effect 11 min.
- Duration can be variable and prolonged
Haloperidol: Side Effects

- Extrapyramidal effects
  - Dystonia appears less with IV than PO administration
- QT prolongation leading to torsades-de pointes
  - Seen at doses as low as 20-35 mg (follow EKG’s)
- Reduces 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

"Atypical" Antipsychotics: Abilify, Zyprexa, etc.

- Don't prolong the QT interval
  - A controversial area: difficulty to measure accurately
- Available PO 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
- Use is rapidly expanding in the ICU to control agitation and delirium

Other Agents

- Propofol
- Ketamine
- Dexmedetomidine
- Clonidine
Propofol: Perfect Except.....

- Hypotension (negative inotropy & vasodilation)
- Respiratory depression (for intubated pts. only)
- Hypertriglyceridemia, risk of Pancreatitis
  - Follow triglyceride levels if use for > 48 hours (SCCM Guidelines, Jacobi J et al. CCM 2002)
- Lipid emulsion is infection risk (like TPN)
- Pain on injection (pretreat vein with lidocaine)
- Expensive
- Rare reports of severe metabolic acidosis (!)
  - More common in children

Ketamine

- 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
- 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: Continuous Infusion

- For continuous sedation
  - 2 - 20 mcg/kg/min has been studied in post-op patients for pain relief (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 prevent the development of tolerance to opioids Schmid RL, Pain 1999
- Doses as low as 0.15 mg/kg before incision have been shown to reduce opioid consumption by 50% Kwok

Ketamine for Perioperative Pain: Meta-analysis
Subramanian K et al. Anes Analg 2004

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<th>Study</th>
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<th>95% CI</th>
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Dexmedetomidine

- Selective alpha-2 agonist (IV infusion)
- Sedation, anxiolysis, analgesia, sympatholysis
- Not reliably amnestic
- Still arousable for neuro exam
- Not a major respiratory depressant
- Increases SVR / PVR at all dose ranges
- Hypertension with initial bolus
  - 0.5-1 mcg/kg over 10-20 min
- Hypotension with continuous infusion
  - 0.2-0.7 mcg/kg/hr
Dex: Heart Rate Response

Dex: Blood Pressure Response

Dex: CABG Patients

- RCT Dex vs. Propofol
  - 1 mcg/kg load over 20 min. at sternal closure, then 0.2-0.7 mcg/kg/hr, adding propofol if needed
  - Average Propofol consumption 20 mcg/kg/min in the Propofol group and 5 in the Dex group (11% needed rescue Propofol)
- Vent duration similar
- Dex group used less morphine, had fewer episodes of tachycardia, but MAP averaged 12 mmHg less

Herr DL JCTVA 2004
Hemodynamic Effects

Dex: Other Effects

- Dry mouth (useful for awake fiberoptic intubation)
- Decreased bowel motility
- Decreased oxygen consumption
- Prolonged local anesthetic action
- No effect on ICP, IOP

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 (have seen asystole in the OR)
  - Treatment is glycopyrrolate
- Under anesthesia the BP will sometimes rise with Dex
  - Propofol, epidurals, etc. have reduced SNS tone already and left peripheral vasoconstriction to predominate
Why Might Dexmedetomidine Be Useful

- "Wake up juice"
  - detox off other sedatives in the peri-extubation period
  - immediately post-op (coming up from the OR)
- May help treat drug withdrawal (like clonidine patch)
- Another non-opioid adjunct for pain relief
  - morphine sparing in multiple trials
- May prevent harm 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)

Dexmedetomidine and Delirium

- Delirium is an independent risk factor for mortality (Ely W JAMA 2004)
  - Prospective cohort 275 MICU and CCU pts
  - CAM-ICU scale
  - Delirium independent risk factor for 6 month mortality (hazard ratio 3.2, 95% CI 1.4-7.7, p=0.008), longer LOS, etc.
- Dex use associated with less delirium (Maldonado Anes 2003)
  - Prospective RCT in cardiac surgery pts (Dex vs. propofol vs. midaz/fent)
  - DSM-IV and Delirium Rating Scale
  - Dex 8%, Propofol 50%, Midaz 50%

Neuromuscular Blocking Drugs

- Absolutely NO amnesia, hypnosis, analgesia, or anxiolysis
  - actually quite anxiogenic
- MUST administer amnestics/hypnotics
- Difficult to recognize pain/agitation
  - they are always an M-MAAS of -3
  - 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
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

Critical Illness Polyneuropathy

- Prolonged weakness
  - can require months of rehabilitation

- Severe cases usually seen only after >24 hr. of paralysis

- Might be associated with corticosteroids

- Monitor ulnar nerve stimulator for thumb adduction (1 or 2 out of 4 “twitches”)
  - no evidence that this helps

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%
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

Weaning of Analgesics/Sedatives

- Plan for weaning should start when sedation started
- Acute withdrawal is a common problem after prolonged administration in the ICU
- After weaning to a comfortable but alert state, decrease no faster than 10% per day
- Clonidine may be a useful adjunct for sedation and control of sympathetic overstimulation during weaning
  - Or Dexmedetomidine if it's proven safe for long term use and gets cheaper

Weaning: Daily Interruption of Sedation

- \( n=128 \), intubated, morphine plus either midazolam or propofol
- Daily interruption group:
  - Decreased ventilator days: 4.9 vs. 7.3 day, \( p=0.004 \)
  - Decreased ICU LOS: 6.4 vs. 9.9 day, \( p = 0.02 \)
  - Less testing for AMS: 6 (9%) vs. 16 (27%), \( p=0.02 \)
  - Complications (extubation): 3 (4%) vs. 7 (4%), NS

Weaning: Use of Continuous Infusions

- N= 242 intubated ICU patients
- Continuous IV sedation vs. bolus or no sedation:
  - Increased duration of mechanical ventilation
    - 185±190 hrs vs. 55.6±75.6 hrs, p<0.001
  - Increased ICU length of stay
    - 13.5±33.7 days vs. 4.8±4.1 days, p<0.001
  - Increased hospital length of stay
    - 21.0±25.01 days vs. 12.8±14.1 days


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
- Convert to “floor regimen” prior to ICU d/c
- Plan for weaning early