Critical Care Pharmacotherapy: What Do You Need to Know?

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Objectives

- Review pertinent pharmacotherapy common to the critically ill patients
- Discuss new developments in the pharmacotherapy of critically ill patients
- Identify relationship between respiratory therapists and pharmacist in the care of critically ill patients
What's New?

Tranexamic Acid

Intensive Insulin Therapy

Relative Adrenal Insufficiency

Early Goal Directed Therapy

Daily Awakenings

Vasopressor Selection

Sleep Cycles

Role of Nutrition Support

ECMO

Tidal Volumes

Choice of Fluid Resuscitation Agent

Delirium

Relative Adrenal Insufficiency
2 Key Publications

- Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit
  - Crit Care Med 2013; 41:263-306
  - Update from 2002 guidelines

- Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012
  - Crit Care Med 2013; 41:580-637
  - Update from 2008 guidelines
Pain, Agitation, Delirium Guidelines

- All encompassing for ICU patients
- Greatly effects both of our jobs
- As those with experience know...it is an art...not necessarily a science
Pain

Incidence

- Not readily addressed in 2002 guidelines
- ICU patients routinely experience pain – at rest & with care
- Procedural pain common
- Specified 2 patient populations
  - Cardiac surgery pain is common & poorly treated
  - More pain in female patients undergoing cardiac surgery

Assessment

- Use vital signs to cue further assessment
- Utilize valid scoring systems
  - Behavioral Pain Scale (BPS)
  - Critical-Care Pain Observation Tool (CPOT)

*Crit Care Med 2013; 41:263-306*
Behavioral Pain Scale

Table 1. The Behavioral Pain Scale (11)

| Item                      | Description                                           | Score |
|---------------------------|-------------------------------------------------------|-------|
| Facial expression         | Relaxed                                               | 1     |
|                           | Partially tightened (e.g., brow lowering)             | 2     |
|                           | Fully tightened (e.g., eyelid closing)                | 3     |
|                           | Grimacing                                             | 4     |
| Upper limb movements      | No movement                                           | 1     |
|                           | Partially bent                                        | 2     |
|                           | Fully bent with finger flexion                        | 3     |
|                           | Permanently retracted                                 | 4     |
| Compliance with mechanical ventilation | Tolerating movement                                  | 1     |
|                           | Coughing but tolerating ventilation for the most of time | 2     |
|                           | Fighting ventilator                                   | 3     |
|                           | Unable to control ventilation                         | 4     |

- Baseline score should be 3 (but studies show it may be 4)
- Scoring increases during painful procedures (6 – 7)
## Critical-Care Pain Observation Tool

| Indicator                                      | Description                                                                 | Score            |
|------------------------------------------------|-----------------------------------------------------------------------------|------------------|
| **Facial expression**                          | No muscular tension observed                                               | Relaxed, neutral | 0    |
|                                                | Presence of frowning, brow lowering, orbit tightening, and levator contraction | Tense            | 1    |
|                                                | All of the above facial movements plus eyelid tightly closed                | Grimacing        | 2    |
| **Body movements**                             | Does not move at all (does not necessarily mean absence of pain)           | Absence of movements | 0    |
|                                                | Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements | Protection       | 1    |
|                                                | Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed | Restlessness     | 2    |
| **Muscle tension**                             | No resistance to passive movements                                          | Relaxed          | 0    |
| Evaluation by passive flexion and extension of upper extremities | Resistance to passive movements                                             | Tense, rigid     | 1    |
|                                                | Strong resistance to passive movements, inability to complete them          | Very tense or rigid | 2    |
| **Compliance with the ventilator** (intubated patients) | Alarms not activated, easy ventilation                                    | Tolerating ventilator or movement | 0    |
|                                                | Alarms stop spontaneously                                                  | Coughing but tolerating | 1    |
|                                                | Asynchrony: blocking ventilation, alarms frequently activated              | Fighting ventilator | 2    |
| **OR**                                         |                                                                             |                  |
| **Vocalization** (extubated patients)          | Talking in normal tone or no sound                                          | Talking in normal tone or no sound | 0    |
|                                                | Sighing, moaning                                                           | Sighing, moaning | 1    |
|                                                | Crying out, sobbing                                                        | Crying out, sobbing | 2    |
| **Total, range**                               |                                                                             |                  | 0-8  |
Pain – Treat It

- Use preemptive analgesia when possible
  - Prior to painful procedures
- Intravenous opioids
  - First line for non-neuropathic pain
  - All are effective if titrated appropriately
## Opioid Pharmacology

| Opiate          | Onset (IV) | Elimination Half-Life | Intermittent Dosing                  | Infusion Rates | Comments                                                                 |
|-----------------|------------|-----------------------|-------------------------------------|----------------|--------------------------------------------------------------------------|
| Fentanyl IV     | 1-2 m      | 2-4 h                 | 0.35 – 0.5 mcg/kg q 0.5 -1 h         | 0.7 – 10 mcg/kg/hr | Less BP ↓ Accumulates in fat Chest wall rigidity                           |
| Hydromorphone IV| 5-15 m     | 2-3 h                 | 0.2 – 0.6 mg q 1- 2 h                | 0.5 – 3 mg/h    | Accumulates in renal & liver failure                                      |
| Morphine IV     | 5-10m      | 3-4 h                 | 2 – 4 mg q 1 – 2 h                  | 2 – 30 mg/h     | Accumulates in renal & liver failure Histamine release                   |
| Methadone IV    | 1-3d       | 15-60 h               | IV: 2.5 – 40 mg q 6 –12h             | N/A            | Unpredictable!                                                            |
| Remifentanil IV | 1-3 m      | 3-10 m                | N/A                                 | Load 1.5 mcg/kg then 0.5 – 15 mcg/kg/hr | Watch dosing in obese pts                                                 |

Crit Care Med 2013; 41:263-306
### Non-Opioid Pharmacology

| Opiate          | Onset (IV) | Elimination Half-Life | Dosing                                      | Comments                                           |
|-----------------|------------|-----------------------|---------------------------------------------|----------------------------------------------------|
| Ketamine (IV)   | 30 – 40 s  | 2 – 3 h               | 0.1 – 0.5 mg/kg then 0.05 – 0.4 mg/kg/h     | Emergency reactions Hallucinations                 |
| Acetaminophen   | PO: 30 – 60 m IV: 5 – 10 m | 2 – 4 h 2 h | 325 – 1000 mg q6h max 4 g/d 1000 mg q 6h max 4 g/d | Caution in liver failure                           |
| Ketorolac IV    | 10 m       | 2 – 9 h               | 15 – 30 mg iv q 6h x max of 5 days          | Caution in renal failure & bleeding risk           |
| Gabapentin (PO) | 25 min     | 1 – 3 h               | Start 100 mg q8h & titrate to 100 – 200 mg q6h (up to 1200 mg/d) | May cause sedation & ataxia                        |

*Crit Care Med 2013; 41:263-306*
Sedation

- Don’t just sedate people...
- Attempt to identify underlying cause of anxiety & agitation
  - Pain
  - Delirium
  - Hypoxemia
  - Hypoglycemia
  - Hypotension
  - Alcohol or drug withdrawal
Sedation

- Depth: Light = good
- Assessments
  - Use Richmond Agitation-Sedation Scale (RASS) or Sedation-Agitation Scale (SAS)
  - Objective measuring techniques (Bispectral Index, etc.)
    - Not recommended as primary method of assessment
    - Adjunctive assessments in paralyzed pts or when subjective assessment is unobtainable
  - Use EEG monitoring for seizing pts

*Crit Care Med 2013; 41:263-306*
| Agent            | Onset (IV) | Elimination Half-Life | Intermittent or loading doses | Infusion Rates | Adverse Effects                     |
|------------------|------------|-----------------------|-------------------------------|----------------|-------------------------------------|
| Midazolam        | 2 – 5 m    | 3 – 11 h              | 0.01 – 0.05 mg/kg             | 0.02 – 0.1 mg/kg/h | Respiratory depression, Hypotension |
| Lorazepam        | 15 – 20 m  | 8 – 15 h              | 0.02 – 0.04 mg/kg load 0.02 – 0.06 mg/kg q 2 – 6 h prn | 0.01 – 0.1 mg/kg/h | Respiratory depression, Hypotension |
| Diazepam         | 2 – 5 m    | 20 – 120 h            | 5 – 10 mg load 0.03 – 0.1 mg/kg q 0.5 – 6 h prn | N/A            | Respiratory depression, Hypotension |
| Propofol         | 1 – 2 m    | Short term: 3 – 12h Long term: 50 – 70 h | 1 mg/kg                      | 5 – 50 mcg/kg/min (or up to 100) | Lots... Hypotension, TG ↑, Acidosis; Pancreatitis..... |
| Dexmedetomidine  | 5 – 10 m   | 1.5 – 3 h             | 1 mcg/kg over 10 min          | 0.2 – 0.7 mcg/kg/h | Bradycardia, hypotension, hypertension with loading dose |
Benzodiazepines

- Anxiolytic, amnestic, sedating, hypnotic, anticonvulsant effects
- Highly lipid soluble: diazepam & midazolam
  - Quicker onset
  - Larger volume of distribution
- Can hang around forever in certain patients
  - Elderly
  - Liver dysfunction
  - Renal dysfunction

*Crit Care Med 2013; 41:263-306*
Propofol

- Sedative, hypnotic, anxiolytic, amnestic, antiemetic, & anticonvulsant effects
- Quick on, quick off...BUT
- Long term use = saturation of peripheral tissues & prolonged effect
- Dose dependent hypotension
- Propofol infusion syndrome
  - Worsening metabolic acidosis, ↑TG, ↓BP, & arrythmias
  - Generally associated with prolonged duration of higher dose (> 70 mcg/kg/min)

*Crit Care Med 2013; 41:263-306*
Dexmedetomidine

- Selective alpha-2 agonist
- Sedative, analgesic/opioid sparing, & sympatholytic properties
- Pts are more easily arousal & minimal respiratory depression
- Often requires higher dosages than general “approved” dose
Sedation Choice

“We suggest that sedation strategies using nonbenzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred over benzodiazepines (either midazolam or lorazepam) to improve clinical outcomes in mechanically ventilated adult ICU patients”

Class +2B recommendation
Data

Lorazepam vs. Propofol (Carson et al)
- Compared duration of ventilation
- Pts expected to require > 48 hrs ventilation
- Daily awakenings
- N=132 pts
- Lower ventilator days in propofol vs. lorazepam group (5.8 vs. 8.4, p = 0.04)

SEDCOM: Dexmedetomidine vs. Midazolam
- Primary endpoint = % time within RASS -2 to +1
- Pts expected to require > 24 hrs ventilation
- N = 366 pts
- No difference in time within RASS goal
- BUT...

Carson et al. Crit Care Med 2006; 34: 1326 – 1332
SEDCOM. JAMA 2009; 301: 489 – 499
SEDCOM Secondary Objectives

- Decrease in time to extubation with dexmedetomidine group (1.9 day difference)
  - Dexmedetomidine: 3.7 days [95% CI 3.1 – 4.0]) vs. Midazolam: 5.6 days [95% CI 4.6 – 5.9]; p = 0.01
- Prevalence of delirium in dexmedetomidine (54%) decreased by 22% vs. midazolam (76/6%) p< 0.001

JAMA 2009; 301: 489 – 499
Cost Analysis for Dexmedetomidine

- Nested pharmacoeconomic evaluation of SEDCOM
- Prices used: 200 mcg vial of dexmedetomidine = $58; 5 mg vial of midazolam = $1.50
- Median total intensive care unit cost savings of $9679 (CI, $2314 - $17,045) with dexmedetomidine compared with midazolam
- Primary cost drivers
  - Reduced cost of ICU stay (median savings $6584)
  - Reduced costs of mechanical ventilation (median savings $2958)
Sedation Conclusions

- Guidelines exist
- Most of us don’t follow them
- Data are there...but likely need more
- Change is hard...
Delirium

- Syndrome characterized by acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattention, and either disorganized thinking or altered level of consciousness.
- Does not require hallucination or delusions.
- Pts can fluctuate between 2 types:
  - Hyperactive: agitated
  - Hypoactive: calm and lethargic

_Crit Care Med 2013; 41:263-306_
Delirium Symptoms

- Disturbed level of consciousness (reduced clarity of awareness of surroundings)
- Memory deficit
- Disorientation
- Language disturbance
- Perceptual disturbance like hallucinations or delusions
- Fear
- Anxiety
- Anger
- Depression
- Apathy
- Euphoria
Delirium...So What?

- May affect up to 80% of mechanically ventilated adult ICU pts
- Costs $4 to 16 billion annually in US alone
- Associated with increase in mortality, prolonged ICU & hospital length of stay
- We still really don’t understand why and how it happens
- Not great data on how to treat it

*Crit Care Med 2013; 41:263-306*
Delirium Assessment

- Most important thing...identify it early...before it gets too bad
- Confusion Assessment Method for the ICU (CAM-ICU) Scoring
- Needs to part of standard ICU assessments
1. Acute Change or Fluctuating Course of Mental Status:
   - Is there an acute change from mental status baseline?  OR
   - Has the patient’s mental status fluctuated during the past 24 hours?
     - YES  →  NO  →  CAM-ICU negative NO DELIRIUM
     - NO  →  CAM-ICU positive DELIRIUM Present

2. Inattention:
   - “Squeeze my hand when I say the letter ‘A’.”
     - Errors: No squeeze with ‘A’ & Squeeze on letter other than ‘A’
   - If unable to complete Letters → Pictures
     - > 2 Errors  →  CAM-ICU negative NO DELIRIUM

3. Altered Level of Consciousness
   - Current RASS level
     - RASS = zero  →  CAM-ICU negative NO DELIRIUM
     - RASS other than zero  →  CAM-ICU positive DELIRIUM Present

4. Disorganized Thinking:
   - 1. Will a stone float on water?
   - 2. Are there fish in the sea?
   - 3. Does one pound weigh more than two?
   - 4. Can you use a hammer to pound a nail?
   - Command: “Hold up this many fingers” (Hold up 2 fingers)
     - OR “Now do the same thing with the other hand” (Do not demonstrate)
     - OR “Add one more finger” (If patient unable to move both arms)
     - > 1 Error  →  CAM-ICU negative NO DELIRIUM
     - 0 - 1 Error  →  CAM-ICU negative NO DELIRIUM

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Delirium Prophylaxis

- No great data exist to recommend pharmacologic agents to prevent delirium
- Non pharmacologic recommendations
  - Early mobilization & aggressive mobilization
Delirium Treatment

- Vitamin “H” : “no published evidence that treatment with haloperidol reduces the duration of delirium in adult ICU patients”
- Atypical antipsychotics may be of use
  - Small study suggests quetiapine may reduce duration of delirium

_Crit Care Med 2013; 41:263-306_
Sleep...It’s a Good Thing

“We recommend promoting sleep in adult ICU patients”
**Current Events**

**Expert: Michael Jackson went 60 days without real sleep**

By Alan Duke, CNN
updated 11:15 AM EDT, Mon June 24, 2013

Michael Jackson didn’t get good night’s sleep in two months leading up to 'This Is It' tour: expert

Dr. Charles Czeisler, a Harvard sleep researcher, said Jackson’s propofol-induced slumber induced by Conrad Murray wasn’t providing the pop star enough REM sleep. He also said that lab rats exposed to the same lack of REM often died after five weeks. Czeisler was testifying during the wrongful-death suit against concert promoter AEG Live, brought on by Jackson’s mother, Katherine.

Comments (11)

BY CORKY SIEMASZKO / NEW YORK DAILY NEWS
FRIDAY, JUNE 21, 2013, 5:29 PM

**Michael Jackson trial: How long can you survive without sleep?**

By Megan Gannon / Published June 24, 2013 / LiveScience

http://www.nydailynews.com/
http://www.foxnews.com
www.cnn.com
Normal Circadian Rhythm

**Wake**
- Inhibition of melatonin release
- ↑ orexin, acetylcholine, serotonin, norepinephrine, dopamine, histamine, adenosine

**Sleep**
- Diurnal secretion of melatonin
- ↓ adenosine

Kamdar BB, et al. J Intensive Care Med. 2012;27(2):97–111.
Normal Sleep Architecture

- Normal sleep cycle lasts approximately 90 minutes

- Continuous cycling between Non-Rapid Eye Movement (NREM) and Rapid Eye Movement (REM) sleep stages

Kamdar BB, et al. J Intensive Care Med. 2012;27(2):97–111.
# Normal Sleep Architecture

| Sleep Stage                        | Description of Sleep | Percentage of Total Sleep |
|------------------------------------|----------------------|---------------------------|
| Stage I (N1)                       | Light                | 2-5%                      |
| Stage II (N2)                      | Light                | 45-55%                    |
| Slow wave sleep (SWS)              | Deep sleep           | 15-20%                    |
| REM                                | Deep sleep           | 20-25%                    |

Kamdar BB, et al. J Intensive Care Med. 2012;27(2):97–111.
Sleep Disturbances in the Intensive Care Unit (ICU)

Gabor JY, et al. Am J Respir Crit Care Med 2003;167:708–15.
Patient Perception of Sleep Quality in the ICU

Degree of Disruption (Severe: 10 to None: 0)

- All activities
- Vitals
- Phlebotomy
- Noise
- Diagnostics
- Nursing
- Light
- Medication

Freeman NS, et al. Am J Respir Crit Care Med. 1999;159:1155-62.
Consequences of Sleep Deprivation

- Fatigue, anxiety, impaired cognition and concentration
  - Potential risk factor for development of delirium
- Increased activation of the hypothalamic-pituitary-adrenal axis
  - Tachycardia, hypertension, increased cortisol
- Alterations in nitrogen balance, protein catabolism
  - Increased insulin resistance
- Immune system dysfunction

Boyko Y, et al. Acta Anaesthesiol Scand.2012;56(8):950-8.
Mechanical Ventilation and Sleep Quality

- Same alteration of sleep architecture in mechanically-ventilated patients
- Pressure support vs. pressure assist control
  - Less central apneas improved sleep quality
  - Weaning should occur during daytime hours
- Non-invasive ventilation
  - Limited studies

Cooper AB, et al. Chest 2000;117:809-818.
Cabello B, et al. Crit Care Med. 2008;36(6):1749-55.
Alexopoulou C, et al. Intensive Care Med. 2013;39:1040–1047.
Roche-Camp F, et al. Crit Care Med 2013; 41:1637–1644.
Comparison of Sleep and Sedation

| Similarities                                      | Differences with Sleep                      |
|---------------------------------------------------|---------------------------------------------|
| • Altered sensorium and mentation                  | • Spontaneous                               |
| • Muscle hypotonia                                 | • Rhythmic                                  |
| • Temperature dysregulation                        | • Essential                                 |
| • Disconjugate eye movements                       | • Reversible with stimuli                  |
| • ↓ respiratory rate                               |                                             |

Kondili E, et al. Intensive Care Med. 2012;38(10):1640-6.
## Propofol and Sleep Quality

### Study Design
- Randomized, crossover
- Medical ICU (single center)

### Inclusion
- Mechanical ventilation (assisted modes) > 48 hours, hemodynamic stability, no concomitant sedation or analgesia
- Glasgow coma scale < 11, APACHE II > 15, presence of delirium, neurologic disease, sleep apnea, sepsis, detectable plasma levels of sedative drugs

### Exclusion

### Outcomes
- Sleep architecture using PSG

Kondili E, et al. Intensive Care Med. 2012;38(10):1640-6.
Overnight Intervention (20:00 to 07:00)

Night 1
- N = 13
- No propofol

Night 2
- Propofol 0.01-0.05 mg/kg bolus followed by infusion titrated to Ramsey scale of 3

Kondili E, et al. Intensive Care Med. 2012;38(10):1640-6.
Baseline Characteristics

| Characteristic                                      | Result |
|-----------------------------------------------------|--------|
| Male sex, %                                         | 50     |
| Age (years), median                                 | 73     |
| Admission APACHE II, median                         | 23     |
| Mechanical ventilation (days), median               | 18     |
| Mechanical ventilation mode, %                      |        |
| Pressure support ventilation                        | 84     |
| Continuous positive pressure airway pressure        | 8      |
| Proportional assist ventilation +                   | 8      |
| Propofol infusion dose, (mcg/kg/min) median         | 15     |

Kondili E, et al. Intensive Care Med. 2012;38(10):1640-6.
## Sleep Architecture Results

| Endpoint, median (IQR) | No Propofol | Propofol  | p value |
|------------------------|-------------|-----------|---------|
| TST (min)              | 214         | 260       | 0.37    |
| Sleep efficiency (% TST) | 62.6       | 76.3      | 0.37    |
| SWS (% TST)            | 0 (0-0)     | 0 (0-5.8) | 0.75    |
| REM (% TST)            | 1.4 (0-13)  | 0 (0-0)   | 0.04    |

Kondili E, et al. Intensive Care Med. 2012;38(10):1640-6.
## Influence of Medications on Sleep Quality

| Medication                 | Sleep latency | TST | N1, N2 | SWS | REM |
|----------------------------|---------------|-----|--------|-----|-----|
| Benzodiazepines            | ↓             | ↑   | ↑      | ↓   | ↓   |
| Propofol                   | ↓             | ↑   | ↑      | -   | ↓   |
| Dexmeditomidine            | -             | ↑   | ↑      | -   | -   |
| Dopamine antagonists       | ↓             | ↑   | -      | ↑   | -   |
| Opioid agonists            | -             | ↓   | -      | ↓   | ↓   |
| Corticosteroids            | ↑             | -   | -      | ↓   | ↓   |
| Vasopressors               | -             | -   | -      | ↓   | ↓   |

Kamdar BB, et al. J Intensive Care Med. 2012;27(2):97-111.

Hardin KA. Chest.2009;136(1):284-94.
Treatment of Sleep

- No great pharmacologic options
- Utilize non-pharmacologic techniques
- Ultimately...get ‘em out of the unit
The Men & Women Keeping Us All Together
Conclusions

- Guidelines exist...
- Change is hard
- Try to minimize sedation as much as possible
- Utilize analgesia as first option for treatment
- Watch for delirium
- Be mindful of effects of sleep deprivation on patients

**SHOOT FOR THE MOON**

Even If You Miss, You’ll Land Among the Stars.
Of Course, Then Your Eyeballs Will Boil and Your Lungs Explode from Decompression. But That’s What You Get for Being a Damn Showoff.