Assessing and Managing Sedation in the ICU

Sandra Kane-Gill, PharmD, MSc, FCCM, FCCP  
Associate Professor  
University of Pittsburgh  
Pittsburgh, Pennsylvania

Faculty Disclosure

It is the policy of The France Foundation to ensure balance, independence, objectivity, and scientific rigor in all its sponsored educational activities. All faculty, activity planners, content reviewers, and staff participating in this activity will disclose to the participants any significant financial interest or other relationship with manufacturer(s) of any commercial product(s)/device(s) and/or provider(s) of commercial services included in this educational activity. The intent of this disclosure is not to prevent a person with a relevant financial or other relationship from participating in the activity, but rather to provide participants with information on which they can base their own judgments. The France Foundation has identified and resolved any and all conflicts of interest prior to the release of this activity.

Sandra Kane-Gill, PharmD, MSc, FCCM, FCCP, has received grant/research support from Cumberland Pharmaceuticals.

Learning Objectives

• Describe current guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit
• Use validated scales to measure sedation, pain, agitation, and delirium in critically ill patients
• Compare the benefits and limitations of available sedatives and analgesics in the acute care, procedural, and surgical settings
Current Guidelines

50 questions, statements, and recommendations

Sedation and Analgesia

Pain and/or Discomfort Should ALWAYS Be Considered a Cause of ICU Agitation

- “Mundane/routine” aspects of ICU care are the most troublesome for patients

1990
63% remembered moderate to severe pain

2007
77.4% recalled having pain and 50% remembered unmet analgesic needs

There has been little progress despite 17 years of focused attention on pain as an important clinical issue.
New Paradigm: Analgesia-based “Sedation”

- Also known as analgesedation or analgesia-first (A-1) sedation
- Acknowledges that discomfort is a common cause of agitation
  - Continuous infusion remifentanil or fentanyl
    - Rapid onset and offset
  - 30–74% require benzodiazepine/propofol rescue
  - Pure analgosedation = 10%
    - A1 still has a long way to go for acceptance


Pain

- Routine monitoring (+1B)
- Protocols and pain assessment can...
  - Reduce time on MV and ICU length of stay
  - Reduces severe pain
- Think of pain as a cause more frequently—analgesedation and pre-emptive treatment
- Recommend: IV opioid for non-neuropathic pain; add enteral gabapentin or carbamazepine for neuropathic pain
- Suggest: non-opioid analgesics
- Consider: non-pharmacologic treatments


Sedation and Agitation
The Fine Balance in Patient Comfort

Guidelines

- Maintaining light levels of sedation in adult ICU patients improves outcomes (B)
  - Shorter duration of MV
  - Shorter ICU length of stay
  - Incidence and duration of delirium
  - Long-term cognitive function
- Maintaining light levels of sedation increases physiologic response but not associated with incidence of myocardial infarction (B)
- Recommend light level of sedation in adult ICU patients, unless contraindicated (+1B) and recommend daily sedation interruption be routinely used in adult, MV ICU patients (+1B)

Deep Sedation

- 36 studies indicating the frequency of suboptimal sedation
- > 40% patients more deeply sedated than desired
- Drug-induced coma present during 32% of patient evaluations
  - Yet only 2.6% rated as “oversedated”

Olson D. RTI Proceedings. 2003;CS82:196.

Daily Sedation Interruption Decreases Duration of Mechanical Ventilation

- Hold sedation infusion until patient awake and then restart at 50% of the prior dose
- “Awake” defined as any 3 of the following:
  - Open eyes in response to voice
  - Use eyes to follow investigator on request
  - Squeeze hand on request
  - Stick out tongue on request


ABC Trial: Objectives

- To determine the efficacy and safety of a protocol linking:
  spontaneous awakening trials (SATs) & spontaneous breathing trials (SBTs)
  - Ventilator-free days
  - Duration of mechanical ventilation
  - ICU and hospital length of stay
  - Duration of coma and delirium
  - Long-term neuropsychological outcomes

ABC Trial: Main Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SBT</th>
<th>SAT+SBT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator-free days</td>
<td>12</td>
<td>15</td>
<td>0.02</td>
</tr>
<tr>
<td>Time-to-Event, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful extubation, days</td>
<td>7.0</td>
<td>5</td>
<td>0.05</td>
</tr>
<tr>
<td>ICU discharge, days</td>
<td>13</td>
<td>9</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital discharge, days</td>
<td>19</td>
<td>15</td>
<td>0.04</td>
</tr>
<tr>
<td>Death at 1 year, n (%)</td>
<td>97 (58%)</td>
<td>74 (44%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Days of brain dysfunction</td>
<td>3.0</td>
<td>2.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Coma</td>
<td>2.0</td>
<td>2.0</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Median, except as noted


ABC Trial: 1-Year Mortality


Avoiding Coma Impacts Outcomes

<table>
<thead>
<tr>
<th>Author (Reference No)</th>
<th>Tool</th>
<th>Study Design</th>
<th>Patients</th>
<th>Type</th>
<th>Benefits</th>
</tr>
</thead>
</table>
| Knaus et al. (1)      | RCT  |              | 128      | NC   | Reduced mortality to 0%
| Schuchardt et al. (2) |      |              | 125     | NC   | Reduced mortality to 0%
| De Jongh et al. (3)   |      |              | 102      | NC   | Reduced mortality to 0%
| Knaus et al. (3)      |      |              | 31       | NC   | Reduced mortality to 0%
| Brock et al. (4)      |      |              | 331      | NC   | Reduced mortality to 0%
| Batlle et al. (5)     |      |              | 295      | NC   | Reduced mortality to 0%
| Chiquet et al. (6)    |      |              | 239      | NC   | Reduced mortality to 0%

What about long-term outcomes?

# Drug Selection: Benefits and Precautions

## Sedatives

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Time to Onset (min)</th>
<th>T1/2 (hrs)</th>
<th>Lipophilicity</th>
<th>Primary Metabolism</th>
<th>Presence of Active Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmedetomidine</td>
<td>α₂ agonist</td>
<td>15</td>
<td>2-2.5</td>
<td>++</td>
<td>Glucuronidation</td>
<td>No</td>
</tr>
<tr>
<td>Diazepam</td>
<td>GABA, GABA receptor</td>
<td>2-5</td>
<td>20-50</td>
<td>+++</td>
<td>N-demethylation</td>
<td>Yes</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>GABA, GABA receptor</td>
<td>5-20</td>
<td>10-20</td>
<td>++</td>
<td>Glucuronidation</td>
<td>No</td>
</tr>
<tr>
<td>Midazolam</td>
<td>GABA, GABA receptor</td>
<td>2-5</td>
<td>3-12</td>
<td>+++</td>
<td>Hydroxylation</td>
<td>Yes</td>
</tr>
<tr>
<td>Propofol</td>
<td>GABA, GABA receptor</td>
<td>1-2</td>
<td>1-5-12</td>
<td>+++</td>
<td>Hydroxylation and glucuronidation</td>
<td>No</td>
</tr>
</tbody>
</table>


## Midazolam Pharmacodynamics

<table>
<thead>
<tr>
<th>GABA Agonist</th>
<th>Benzodiazepine Midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Effects</strong></td>
<td><strong>Adverse Effects</strong></td>
</tr>
<tr>
<td>• Sedation, anxiolysis, and amnesia</td>
<td>• May accumulate with hepatic and/or renal failure</td>
</tr>
<tr>
<td>• Rapid onset of action (IV)</td>
<td>• Anterograde amnesia</td>
</tr>
<tr>
<td></td>
<td>• Long recovery time</td>
</tr>
<tr>
<td></td>
<td>• Synergy with opioids</td>
</tr>
<tr>
<td></td>
<td>• Respiratory depression</td>
</tr>
<tr>
<td></td>
<td>• Delirium</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>GABA Agonist</th>
<th>Benzodiazepine Lorazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Effects</strong></td>
<td><strong>Adverse Effects</strong></td>
</tr>
<tr>
<td>• Sedation, anxiolysis, and amnesia</td>
<td>• Metabolic acidosis (propylene glycol vehicle toxicity)</td>
</tr>
<tr>
<td>• Commonly used for long-term sedation</td>
<td>• Retrograde and anterograde amnesia</td>
</tr>
<tr>
<td></td>
<td>• Delirium</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 60–80% MICU/SICU/TICU ventilated patients develop delirium</td>
</tr>
<tr>
<td>• 20–50% of lower severity ICU patients develop delirium</td>
</tr>
<tr>
<td>• Consequences</td>
</tr>
<tr>
<td>– Higher mortality</td>
</tr>
<tr>
<td>– Prolonged duration of ICU stay</td>
</tr>
<tr>
<td>– Prolonged cognitive impairment</td>
</tr>
<tr>
<td>– Greater health care costs</td>
</tr>
</tbody>
</table>

Benzodiazepine Concerns: Delirium

Benzodiazepines
- Independent risk factor for development of delirium
- Especially if used to induce even brief periods of coma
- Guidelines state:
  - Benzodiazepine may be a risk factor for delirium in adult ICU patients (B)


MENDS: Dexmedetomidine vs Lorazepam

- Dexmedetomidine resulted in more days alive without delirium or coma ($P < 0.01$) and a lower prevalence of coma ($P < 0.001$) than lorazepam
- Dexmedetomidine resulted in more time spent within sedation goals than lorazepam ($P = 0.04$)
- Differences in 28-day mortality and delirium-free days were not significant

GABA Agonist Propofol

<table>
<thead>
<tr>
<th>Clinical Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>Pain on injection</td>
</tr>
<tr>
<td>Hypnosis</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Anxiolysis</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Muscle relaxation</td>
<td>Decreased myocardial contractility</td>
</tr>
<tr>
<td>Mild bronchodilation</td>
<td>Increased serum triglycerides</td>
</tr>
<tr>
<td>Decreased ICP</td>
<td>Tolerance</td>
</tr>
<tr>
<td>Decreased cerebral metabolic rate</td>
<td>Propofol infusion syndrome</td>
</tr>
<tr>
<td>Antiemetic</td>
<td>Prolonged effect with high adiposity</td>
</tr>
<tr>
<td></td>
<td>Seizures (rare)</td>
</tr>
</tbody>
</table>

**α₂ Agonist Dexmedetomidine**

<table>
<thead>
<tr>
<th>Clinical Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Antihypertensive</td>
<td>• Hypotension</td>
</tr>
<tr>
<td>• Sedation</td>
<td>• Hypertension</td>
</tr>
<tr>
<td>• Analgesia</td>
<td>• Nausea</td>
</tr>
<tr>
<td>• Decreased shivering</td>
<td>• Bradycardia</td>
</tr>
<tr>
<td>• Anxiolysis</td>
<td>• Dry mouth</td>
</tr>
<tr>
<td>• Patient arousability</td>
<td>• Peripheral vasoconstriction at high doses</td>
</tr>
<tr>
<td>• Potentiate effects of opioids, sedatives, and anesthetics</td>
<td></td>
</tr>
<tr>
<td>• Decrease sympathetic activity</td>
<td></td>
</tr>
</tbody>
</table>


---

**Comparison of Clinical Effects**

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Propofol</th>
<th>Opioids</th>
<th>α₂ Agonists</th>
<th>Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Alleviate anxiety [1,2]</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analgesic properties [3,4]</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Promote arousability during sedation [3,4]</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Facilitate ventilation during weaning [3]</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Control delirium [4]</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>


---

**Comparison of Adverse Effects**

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Propofol</th>
<th>Opioids</th>
<th>α₂ Agonists</th>
<th>Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged weaning [1]</td>
<td>X</td>
<td>X</td>
<td>X *</td>
<td></td>
</tr>
<tr>
<td>Respiratory depression [1]</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension [1,2]</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Constipation [1]</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Deliriogenic</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia [1]</td>
<td>morphine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia [1]</td>
<td>fentanyl</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*Excluding remifentanil

**SEDCOM:**

**Dexmedetomidine vs Midazolam**

- Double-blind, randomized, multicenter trial comparing long-term (> 24 hr) dexmedetomidine (dex, n = 244) with midazolam (mz, n = 122)
- Sedatives (dex 0.2-1.4 μg/kg/hr or mz 0.02-0.1 mg/kg/hr) titrated for light sedation (RASS -2 to +1), administered up to 30 days
- All patients underwent daily arousal assessments and drug titration Q 4 hours

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Midazolam (n = 122)</th>
<th>Dexmedetomidine (n = 244)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in target sedation range, %</td>
<td>75.1</td>
<td>77.3</td>
<td>0.18</td>
</tr>
<tr>
<td>Duration of sedation, days</td>
<td>4.1</td>
<td>3.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Time to extubation, days</td>
<td>5.6</td>
<td>3.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Delirium prevalence</td>
<td>93 (76.6%)</td>
<td>132 (54%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Delirium-free days</td>
<td>1.7</td>
<td>2.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Patients receiving open-label midazolam</td>
<td>60 (49%)</td>
<td>153 (63%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Guidelines**

- **Suggestion**
  - Sedation strategies using non-benzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines to improve clinical outcomes in mechanically ventilated adult ICU patients (+2B)
- No pharmacologic prevention (-2C) for delirium but mobilization (+1B) may be appropriate
- Delirium
  - Routine monitoring, do not use rivastigmine (-1B), atypical antipsychotics may reduce duration of delirium (C), do not use antipsychotics in patients at risk for torsades de pointes (-2C), if patient has delirium not related to withdrawal then suggest use dexmedetomidine rather than benzos
Recent Study: Comparison

Dex vs. Midazolam vs Propofol: Long-term Sedation

- Study design
  - MIDEX-RCT @ 44 centers (dex n = 227; mid n = 233)
  - PRODEX-RCT @ 31 centers (dex n = 223; prop n = 214)
- Non-inferiority for maintaining sedation
- Superiority for MV duration
- Patients needing
  - More than 24h of MV
  - Light-to-moderate sedation


Dex vs. Midazolam vs Propofol—Long-term Sedation

- Comparison
  - Maintain sedation*
    - Time at target sedation measured by RASS
  - Duration of MV*
  - Time to extubation
  - Improve patient satisfaction
    - Visual analogue scale
    - Communication
    - Arousal
    - Cooperation
  - LOS and Mortality
- Results
  - Decimid ratio 1.07
  - Dex/prop ratio 1.00
  - Dec 123h; Mid 164h (P = 0.03)
  - Dec 99h; Prop 118h (P = 0.24)
  - Dec 107h; Mid 147h (P = 0.01)
  - Dec 69h; Prop 93h (P = 0.04)
  - Dec vs mid 19.7; Dec vs prop 11.2 (P < 0.001)
  - Dec vs mid 13.5; Dec vs prop 13.9 (P < 0.001)
  - Dec vs mid 17.5; Dec vs prop 9.2 (P < 0.001)
  - ICU LOS, hospital LOS, mortality similar

Patient Safety: AE Comparison

- Hypotension
- Bradycardia
- AV block
- Infections
- CIP

- Dex vs mid: 20.6% to 11.6% (P = 0.007); Dex vs prop: similar
- Dex vs mid: 14.2% to 5.2% (P < 0.001); Dex vs prop: similar
- Dex vs mid: same; Dex vs Prop 3.7% to 0.8% (P = 0.036)
- Same for new infections and pneumonias
- Dex vs Prop 2 pts vs 11 pts (P = 0.021)

BUT What About Drug Shortages…
Drug Shortage and Patient Safety: Propofol

- Impact of propofol shortage on duration of MV
- Patients MV > 48h administered sedative for > 24h
- 84% decrease in propofol use
- 50% increase in midazolam. 18% dexmedetomidine, 8% lorazepam
- Adjusted multivariate analysis failed to show before and after propofol periods as a significant indicator for MV


Monitoring: Scales

Assessment Is Important Because...

- Pain
  - Assessment – better pharmacologic treatment, MV, ICU
- Agitation
  - Sedation scales and protocols – lead to better outcomes: MV, ICU and hospital LOS, delirium
- Delirium
  - Negative outcomes are substantial so detection is critical

Recommendations

• Pain, sedation, and delirium should be routinely monitored in all adult ICU patients (+1B)
• Scale evaluation completed based on the psychometric properties - used scoring system
  • Pain
    – Behavioral Pain Scale (BPS) and the Critical Care Pain Observation Tool (CPOT) (B)


Risk Factors Specific for ICU Delirium

• Dementia
• Hypertension history
• Alcoholism
• Severity of illness
• Age (?pos /neg)
• Benzodiazepine use
• Coma (medical vs. pharmacologic)
• Morphone use (data unclear)

5. Greller LF, et al. Transl Care 2014;3:129

Scales for Monitoring Sedation

6 Delirium Screening Tools 
Validated in ICU Populations

- Cognitive Test for Delirium (CTD)
- Abbreviated CTD
- Confusion Assessment Method for the ICU (CAM-ICU)
- Intensive Care Delirium Screening Checklist (ICDSC)
- NEECHAM Scale
- Delirium Detection Score


Confusion Assessment Method 
(CAM-ICU)

1. Acute onset of mental status changes or a fluctuating course

and

2. Inattention

and

3. Altered level of consciousness

= Delirium


What Is the ABCDE Bundle?
We Need Coordinated Care

- Many tasks and demands on critical care staff
- Great need to align and support the people, processes, and technology already in ICUs
- ABCDE bundle is multicomponent, interdependent, and designed to:
  - Improve clinical team collaboration
  - Standardize care processes
  - Break the cycle of oversedation and prolonged ventilation

What Is the ABCDE Bundle?

Awakening and Breathing Trial coordination

Coordination/Choice of Sedation

Delirium Monitoring and Management

Early Mobility

---

Pharmacoeconomics

<table>
<thead>
<tr>
<th>Ref</th>
<th>Design</th>
<th>Sedatives Compared</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasilevskis EE, et al. Chest. 2010;138(5):1224-1233.</td>
<td>Randomized, open-label, single center</td>
<td>Remifentanil + propofol, midazolam + fentanyl</td>
<td>Similar sedation efficacy, time to extubation and time to ICU discharge shorter, yet higher drug costs with Remifentanil + propofol group. No difference in total cost of care</td>
</tr>
<tr>
<td>MacLaren R et al. Hypothetical decision-analysis model</td>
<td>Lorazepam, midazolam, propofol for short, intermediate and long-term therapy</td>
<td>Least costly sedative treatment varied by duration of therapy</td>
<td></td>
</tr>
<tr>
<td>Muellejans B et al. Randomized, open-label, single center cost consequence model of 80 cardiac surgery patients</td>
<td>Remifentanil + propofol, midazolam + fentanyl</td>
<td>Similar sedation efficacy, time to extubation and time to ICU discharge shorter, yet higher drug costs with Remifentanil + propofol group. No difference in total cost of care</td>
<td></td>
</tr>
<tr>
<td>Dasta J et al. Retrospective economic evaluation of an administrative database of cardiac surgery patients from 250 hospitals</td>
<td>Midazolam + propofol in 9996 patients, midazolam + propofol + dexmedetomidine in 356 patients</td>
<td>Dexmedetomidine cohort had lower hospital and ICU charges despite having higher pharmacy charges</td>
<td></td>
</tr>
<tr>
<td>Cox CE et al. Decision analysis model comparing value of sedatives from two randomized clinical trials, Monte Carlo simulation of 1000 scenarios</td>
<td>Propofol vs. intermittent lorazepam and propofol vs. midazolam</td>
<td>Propofol was cost effective compared to lorazepam. No difference in propofol vs. midazolam</td>
<td></td>
</tr>
</tbody>
</table>

---

Economic Analysis

- Equal sedation efficacy permitted a cost minimization analysis
- Compare costs of care between groups and select the therapy generating the lowest cost
- Investigators blinded to treatment group for all cost analysis
- Economic analysis performed post-hoc and from the institutional perspective
- Costs were estimated by multiplying actual resource used by US representative cost using Medicare schedules, peer-reviewed literature, and IMS drug prices

---

Total Post-randomization ICU Costs

- Components of total ICU costs
  - Cost of ICU stay
  - Cost of mechanical ventilation
  - Cost associated with adverse drug reactions probably or possibly related to study drug
  - Acquisition cost of study drugs
- For censored patients two strategies used
  - No imputation
  - Non-parametric imputation method (adjusted)
- Median regression approach was used

Lessons Learned from PE Studies

- Costs described in most studies have limitations
- Higher drug acquisition costs may not translate into increases in total hospital costs
- More expensive therapies can have overall economic benefit to the institution
- Selecting the least costly treatment may not be as easy as selecting one agent
Summary

• Recognize the importance of pain/discomfort
• Avoid drug-induced coma – go with light sedation
• Appreciate the need for daily sedation interruption
• Value pain/agitation/delirium assessment and management
• Understand the pros/cons of drug selection – potential ADEs
• Try not to complicate things
  – Avoid deliriogenic drugs when possible
• Consider total cost of therapy