Sedation and delirium- drugs and clinical management

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Probability of transitioning from normal to delirium after lorazepam

Delirium Risk

<table>
<thead>
<tr>
<th>Lorazepam Dose</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Drug</td>
<td>0-1</td>
<td>1-2</td>
<td>2-3</td>
<td>3-4</td>
<td>4+</td>
<td></td>
</tr>
<tr>
<td>Log scale (mg)</td>
<td>0-2.7</td>
<td>2.7-7.4</td>
<td>7.4-20</td>
<td>20-55</td>
<td>55+</td>
<td></td>
</tr>
</tbody>
</table>

6 Month Mortality

Ely et al.

- Normal (n=17)
- Mild (n=68)
- Moderate (n=69)
- Severe (n=70)
Delirium and Chronic Cognitive Impairment

Mean Delirium Days (95% CI)

- Normal: 1.9
- Cognitively Impaired: 3.5

$P = 0.05$

Ely et al.

Neuropsychological Testing at 3 months
Richmond Agitation Sedation Scale (RASS)

4+ Combative
3+ Very Agitated
2+ Agitated
1+ Restless
0 Alert / Calm

-1 Drowsy  eye contact > 10 sec
-2 Light Sedation  eye contact < 10 sec
-3 Moderate  no eye contact
-4 Deep  physical stimulation required
-5 Unarousable  no response even with physical stimulation

Verbal  Physical

ABC Trial

Spontaneous Awakening Trial plus Spontaneous Breathing Trial

Vent Free Days: 15 vs 12
Hospital Days: 15 vs 19

Coma: 2 days vs 3

Self Extubation: 10% vs 4%
Re-intubation: 3% vs 2%

Tracheostomy: 13% vs 20%

Girard et al. Lancet 2008; 371;126
Sedation Practices

25 hospitals

251 patients

ANZICS Group AJRCCM 2012
Pain and Dyspnea Control First

- Morphine
  - Histamine release?

- Fentanyl
  - Tolerance
  - Infusion
No Sedative Agents

Mortality 36% no sedation, 47% sedation, p=0.27
Control group Ramsey score 3-4

Strom T. Lancet 2010
Sedative Agents

- Benzodiazepines
  - Midazolam
  - Lorazepam
  - Diazepam
- Propofol
- Dexmedetomidine
Midazolam

- **Rapid onset** and brief duration with initial dosing
- Rapid redistribution
- Defines the need for **daily interruption**
  - Accumulates in adipose tissue
  - Accumulates in hepatic and renal failure
- **High volume load**
Lorazepam

- Half-life: 12-15 hours
- Inactive metabolites
- Slower onset
- Intermittent bolus dosing preferred
  – (if used at all!)
Propofol

• Alkylphenol sedative and hypnotic
• Binds to a different $\gamma$-aminobutyric acid receptor than benzodiazepines
• General anesthetic at higher doses
• Rapid onset and offset
• Less reliable amnesia
  – Maybe a positive attribute?
Intermittent Lorazepam vs. Propofol

Randomized open label clinical trial
2 Medical ICUs
Subjects: 132 adult patients
• Expected to require MV for >48 hours
• Require > 10 mg or > 6 doses of lorazepam in 24 hours, or continuous sedation
Daily Awakening for both Groups
Morphine for both groups

**Drug Administration**

<table>
<thead>
<tr>
<th></th>
<th>Lorazepam n = 64</th>
<th>Propofol n = 68</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam/ Vent day</td>
<td>11.1 mg median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol/ Vent day</td>
<td></td>
<td>24 mcg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Morphine/ Vent day</td>
<td>22.5 mg</td>
<td>55.5 mg</td>
<td>0.001</td>
</tr>
<tr>
<td>Morphine Infusions, n</td>
<td>22</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>
## Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Lorazepam</th>
<th>Propofol</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vent days</td>
<td>8.4</td>
<td>5.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Vent days, survivors</td>
<td>9.2</td>
<td>4.4</td>
<td>0.004</td>
</tr>
<tr>
<td>ICU LOS, survivors</td>
<td>12.6</td>
<td>7.8</td>
<td>0.03</td>
</tr>
<tr>
<td>SBTs performed</td>
<td>90%</td>
<td>89%</td>
<td>NS</td>
</tr>
<tr>
<td>SBT f/VT</td>
<td>65.8 ± 30.9</td>
<td>48.8 ± 26.7</td>
<td>0.009</td>
</tr>
</tbody>
</table>
Cost effectiveness of Propofol

Versus Lorazepam


Versus Midazolam
Dexmedetomidine

• Alpha-2-adrenergic receptor agonist
• Analgesic effect in dorsal horn of spinal cord
• Sympatholysis via central & peripheral mechanisms
• Half-life: distribution phase: 9 min
• Half-life: elimination phase: 2 hr
Time spent at target

RASS > -3
74% Dex, 64% Mid/Pro

RASS < -3 (Deeper)
42% Dex, 62% Mid/Pro
Light to moderate sedation only, RASS 0 to -3

Jakob et al. JAMA 2012
Median ICU LOS 5.9 vs 7.6 days, p=0.24

Riker et al. JAMA 2009
Dex vs Midazolam - Delirium

Delirium free days 2.5 vs 1.7, p<0.002
MIND Study (Pilot)

Haloperidol vs Ziprasidone vs Placebo for Delirium Prevention/Treatment

120 Patients

Sedation protocol
Daily awakening
Daily SBTs

Girard et al. Crit Care Med 2010; 38:433
UNC Recommendation

• Sedation should be minimized and targeted to an objective endpoint using nurse protocol

• Continuous sedatives should be interrupted daily to allow awakening

• **Hypoxemic respiratory failure**: Begin with short acting, effective sedative
  – Propofol, supplemented by morphine
  – Consider dexmedetomidine during weaning

• **Ventilatory failure**: Low dose intermittent narcotics/midazolam or dexmedetomidine

• Assess for delirium
  – Consider haloperidol if agitated