Dexmedetomidine: the various roles and utilization strategies

Julie Belfer, PharmD
September 2014
Disclosure

• No disclosures concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation.
Objectives

1. Define the role of dexmedetomidine in managing pain, agitation and delirium in the intensive care unit.
2. Evaluate the use of dexmedetomidine in treating alcohol withdrawal syndrome.
3. Describe appropriate utilization of dexmedetomidine in non-intubated patients.
DEXMEDETOMIDINE (DEX)
Dexmedetomidine

- FDA approval in 1999
  - Indication – continuous sedation for intubated, mechanically ventilated, ICU patients for up to 24 hours
- Centrally acting alpha₂ agonist

*Am J Health-Syst Pharm* 2013;70:767-77
*Pharmacotherapy* 2013;33(2):165-186
Mechanism of Action

alpha$_2$/alpha$_1$ binding affinity: 1620/1
Dexmedetomidine

- FDA approved dosing for sedation
  - Loading dose: 1 mcg/kg IV over 10 minutes
  - Maintenance infusion: 0.2 – 0.7 mcg/kg/hr continuous IV infusion titrated to desired clinical effect for a MAX of 24 hours
  - Safety and efficacy established for longer duration (up to 28 days) and at higher doses (up to 1.5 mcg/kg/hr)
Dexmedetomidine

Pharmacokinetics

- Onset: 15-30 min
- Biphasic half-life
  - Distribution $t_{1/2} = 6$ min
  - Terminal $t_{1/2} = 2$ hours
- Metabolism: hepatic
- Excretion: 95% urine
Side Effects

- Hypotension 24-56%
- Bradycardia 5-42%
- Tachycardia 2-5%
- Cardiac Arrhythmias <10%
- Transient Hypertension 28%

References:

Am J Health-Syst Pharm 2013;70:767-77
Pharmacotherapy 2013;33(2):165-186
Pain, Agitation and Delirium

DEXMEDETOMIDINE
Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

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Crit Care Med 2013; 41:263-306
Pain, Agitation & Delirium

Strength of recommendations based on quality of evidence and risks and benefits across all clinical outcomes

- Strong (1) or weak (2)
- In favor of (+) or against (-)
- No recommendation (0)

TABLE 1. Factors That Affect the Quality of Evidence

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Quality of Evidence</th>
<th>Type of Evidence</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>High quality RCT</td>
<td>Further research is unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>RCT with significant limitations (downgraded) or high-quality OS (upgraded)</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>OS</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
</tbody>
</table>

Crit Care Med 2013; 41:263-306
Alpha$_2$-agonist

- Sedative and anxiolytic effects
  - Facilitated through locus coeruleus in the central nervous system
  - Locus coeruleus – high density of adrenergic receptors (alpha$_{2A}$)
    - Alpha$_{2A}$ receptors: antinociceptive, sedative, sympatholytic, hypothermic and behavioral actions
  - Induces a state of arousable sedation
    - Allows for easy awakening
    - Facilitates routine patient assessment
Guideline Recommendations

• “Choice of sedation strategies using nonbenzodiazepines sedatives (either propofol or DEX) may be preferred over sedation with benzodiazepines (BZD) to improve clinical outcomes in mechanically ventilated adult ICU patients (2B+)”
• Limited data comparing propofol and DEX
DEX vs propofol or midazolam

• Jakobi et al.
  • Two phase 3 multicenter, randomized, double-blind trials
  • Evaluating efficacy of DEX versus midazolam (MIDEX) or DEX versus propofol (PRODEXX)
    • Maintaining sedation at target sedation level
    • Reducing duration of mechanical ventilation (MV)
  • Continuous sedation, daily sedation interruptions and spontaneous breathing trials

JAMA 2012;307:1151-1160
# MIDEX Results

<table>
<thead>
<tr>
<th></th>
<th>DEX (n=249)</th>
<th>Midazolam (n=251)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time at target sedation goal (%)</td>
<td>60.7</td>
<td>56.6</td>
<td>0.15</td>
</tr>
<tr>
<td>Duration of MV (hrs), median (IQR)</td>
<td>123 (67-337)</td>
<td>164 (92-380)</td>
<td>0.03</td>
</tr>
<tr>
<td>ICU LOS (hrs), median (IQR)</td>
<td>211 (115-831)</td>
<td>243 (140-630)</td>
<td>0.27</td>
</tr>
<tr>
<td>Hypotension, n (%)</td>
<td>51 (20.6)</td>
<td>29 (1.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Bradycardia, n (%)</td>
<td>35 (14.2)</td>
<td>13 (5.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LOS = Length of stay

*JAMA* 2012;307:1151-1160
## PRODEX Results

<table>
<thead>
<tr>
<th></th>
<th>DEX (n=247)</th>
<th>Propofol (n=249)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time at target sedation goal (%)</td>
<td>64.6</td>
<td>64.7</td>
<td>0.97</td>
</tr>
<tr>
<td>Duration of MV (hrs), median (IQR)</td>
<td>97 (45-257)</td>
<td>118 (48-327)</td>
<td>0.24</td>
</tr>
<tr>
<td>ICU LOS (hrs), median (IQR)</td>
<td>164 (90-480)</td>
<td>185 (93-520)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hypotension, n (%)</td>
<td>32 (13)</td>
<td>33 (13.4)</td>
<td></td>
</tr>
<tr>
<td>Bradycardia, n (%)</td>
<td>32 (13)</td>
<td>25 (10.1)</td>
<td>0.328</td>
</tr>
<tr>
<td>1st degree AV block, n (%)</td>
<td>9 (3.7)</td>
<td>2 (0.8)</td>
<td>0.036</td>
</tr>
</tbody>
</table>
Take Away Points

• DEX was not inferior to midazolam or propofol in maintaining light to moderate sedation
• DEX reduced duration of MV compared with midazolam
  • No difference in ICU length of stay
• Greater number of adverse effects were associated with DEX
Alpha$_2$-agonist

• Effects on delirium
  • Possibly related to alpha$_{2A}$ receptor selectivity and activation
    • Selectivity permits minimal disruption of neurotransmitter pathways, → decreasing likelihood of delirium
    • Activation results in blockade of norepinephrine
      • May lead to changes in the noradrenergic system decreasing development of delirium
  • DEX promotes physiologic sleep-wake cycles
    • GABAergic agents are believed to interfere with physiologic sleep patterns
Outcomes of Delirium

- Increased mortality (A)
- Prolonged ICU and hospital LOS (A)
- Post-ICU cognitive impairment (B)

Crit Care Med 2013; 41:263-306
Risk Factors

- Preexisting dementia (B)
- Hx of HTN or EtOH (B)
- High severity of illness (B)
- Coma (B)
- Opioids (B)
- BZD (B)

Delirium

*Crit Care Med 2013; 41:263-306*
Risk Factors

• “In MV adult ICU patients at risk for developing delirium, DEX infusions administered for sedation may be associated with a lower prevalence of delirium compared to benzodiazepines (B)”
  • Two RCTs comparing sedation with BZDs vs. DEX
    • SEDCOM and MENDS
    • Reported a ~20% lower prevalence of delirium in DEX group
  • Take away points
    • BZDs may be a risk factor for delirium
    • Does not prove BZD cause or DEX protects against delirium
Delirium Prevention

• “No recommendations for the use of dexmedetomidine to prevent delirium in adult ICU patients, as there is not compelling evidence regarding its effectiveness in these patients (0,C)”
Delirium Treatment

• “We suggest that in adult ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal, continuous IV infusions of dexmedetomidine rather than benzodiazepines infusions be administered for sedation to reduce the duration of delirium in these patients (2B+).”
  
• Data extrapolated from SEDCOM and MENDS trial
• Insufficient data to make recommendations regarding the risk and benefits of using other non-bzd sedatives (i.e., propofol)

Crit Care Med 2013; 41:263-306
JAMA 2009; 301:489-499
Crit Care 2010; 14:R38
Alpha$_2$-agonist

- Analgesic effects
  - Theorized to occur via activation of the alpha$_{2c}$ receptor
    - Synergistic analgesic effect with opioid receptors
  - Opioid sparing effect has been demonstrated
  - Monotherapy with DEX does not meet total analgesic requirements for ICU patients
True or False

• Sedation strategies using dexmedetomidine is preferred over sedation with midazolam to improve clinical outcomes in mechanically ventilated adult ICU patients.

True
Dexmedetomidine

ACUTE ALCOHOL WITHDRAWAL
• 42 yo male
• Admitted for hemorrhagic stroke
• Drinks 24+ beers/day
• CIWA protocol initiated
  • PRN lorazepam IV/CiWA score
  • Folic acid, thiamine, MVI
• Day 3
  • Dexmedetomidine infusion initiated overnight due to increasing agitation

• Appropriate utilization of dexmedetomidine?
Alcohol Withdrawal Syndrome (AWS)

- Prevalence of EtOH abuse among inpatients: 21-42%
- Prevalence of EtOH abuse among ICU patients: 10-33%
- Development of AWS among ICU patients: 18%

*Chest 2010;128(4):994-1003*
Pathophysiology

- Main central nervous system neurotransmitters affected
  - Inhibitory: gamma-aminobutyric acid (GABA) binds to GABA_\text{A} receptor
  - Excitatory: Glutamate binds to N-methyl-d-aspartate (NMDA) receptor

*CNS Drugs* 2014;28:401-410
Pathophysiology

**Acute Exposure**
- ↑ GABA activation
- ↓ glutamate activation

**Chronic Exposure**
- ↓ GABA levels
- ↓ GABA\(_A\) receptors and sensitivity
- ↑ NMDA receptors

**Abrupt Cessation**
- ↑ Glutamate binding to NMDA receptors
- ↓ GABA binding to GABA\(_A\) receptors

*Chest* 2010;128(4):994-1003
*CNS Drugs* 2014;28:401-410
Clinical Manifestation

**Autonomic Hyperactivity**
- Diaphoresis
- Nausea/vomiting
- Anxiety
- Tremor
- Agitation
- Tachycardia

**Hallucinations**
- Visual
- Tactile
- Less common - auditory

Lasts: 1-6 days in 30% of patients

**Withdrawal Seizures**
- Generalized tonic-clonic
- May occur as early as 2 hours (10%)

**Delirium Tremens / Acute Withdrawal Delirium**
- Disorientation
- Agitation
- Hallucinations
- Tachycardia
- Hypertension
- Fever

May last up to 7 days

Time of first onset of symptoms (days)

1 2 3

EtOH Cessation

References:
- Chest 2010;128(4):994-1003
- CNS Drugs 2014;28:401-410
Assessment Severity

• Clinical Institute of Withdrawal Assessment for Alcohol (CIWA-Ar)
  • Developed for non-ICU patients and not validated in ICU patient
  • Includes 10 items requiring patient participation
  • CIWA-Ar >10 warrants management and reassessment
    • Score 10-18 correlates with moderate to severe
    • Score >20 consistent with severe

BR J Addict 1989;84:1353-1357
Assessment Severity

- Validated ICU sedation scales used in AWS studies
  - Included mechanically ventilated patients
  - Riker Sedation-Agitation Scale (SAS)
    - Score $\geq 5$ triggered pharmacologic therapy with target goal 3 to 4
    - Assessment intervals varied from every hour to every 4 hours
  - Richmond Agitation-Sedation Scale (RASS)
    - Used to titrate pharmacologic therapy to goal 0 to -1
- Confusion Assessment Method-ICU (CAM-ICU)
  - Validated tool to detect delirium but not used solely to manage AWS
Management of AWS

- Supportive care
- Benzodiazepines
- Ethanol
- Adrenergic agents
- Barbiturates
- Propofol
Current Management Pitfalls

• Agitation and autonomic hyperactivity control is essential in severe AWS and delirium tremors
• BZD monotherapy may be insufficient for control
  • Decreased respiratory drive $\rightarrow$ intubation $\rightarrow$ increase ICU stay
• Drawbacks to alternative sedative therapy
  • Risk for respiratory depression requiring MV
  • Hemodynamic instability
• Dexmedetomidine
  • Provides sedation and decreases autonomic activity
  • No effect on respiratory function
  • Evidence based??
DEX vs. Placebo

• Mueller et al.
  • Prospective, randomized, double-blind, placebo-controlled trial
  • Severe AWS: CIWA >15 and lorazepam 16+ mg/day
  • Outcomes
    • Change in total lorazepam (LOR) requirements over a 24-hr period pre and post-study drug
    • Cumulative LOR dose over the 1st seven days of AWS

Crit Care Med 2013;41:263-306
## Results

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=8) Median (IQR)</th>
<th>DEX (n=16) Median (IQR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hr prior LOR (mg)</td>
<td>39 (31-91)</td>
<td>82 (42-150)</td>
<td>0.28</td>
</tr>
<tr>
<td>24-hr post LOR (mg)</td>
<td>77.1 (10.3-182)</td>
<td>22.3 (9.3-53.3)</td>
<td>0.33</td>
</tr>
<tr>
<td>24-hr pre-post LOR (mg)</td>
<td>-8 (-31.3 to -76.2)</td>
<td>-56.4 (-94.5 to -16.8)</td>
<td>0.027</td>
</tr>
<tr>
<td>7-d LOR (mg)</td>
<td>180.6 (73.6-455.1)</td>
<td>159.1 (62.4-257.1)</td>
<td>0.58</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>4 (1.9-7.1)</td>
<td>4.7 (2.4-10)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>7.4 (4.8-14.3)</td>
<td>10 (5.2-12.8)</td>
<td>0.71</td>
</tr>
<tr>
<td>Bradycardia, n (%)</td>
<td>0 (0)</td>
<td>4 (25)</td>
<td>0.26</td>
</tr>
<tr>
<td>Hypotension, n (%)</td>
<td>0 (0)</td>
<td>3 (18.75)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

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

- Statistically significant reduction in lorazepam requirements in the first 24 hours
- Non-statistical significant decrease in LOR requirements over 7 days
• Retrospective review of 33 critically ill patients
  • Primary diagnosis – AWS
• Protocol – BZD/DEX administered at provider discretion
• Endpoints
  • Difference in cumulative BZD requirements and hemodynamic 12 hours pre- and post-DEX
Results (n=33)

- 85% male
- Median age: 47 years
- Median baseline CIWA-Ar: 15

<table>
<thead>
<tr>
<th></th>
<th>Before DEX</th>
<th>After DEX</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td></td>
</tr>
<tr>
<td>BZD (mg)</td>
<td>30 (23-56)</td>
<td>8 (2-20)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>116 (107-129)</td>
<td>99 (85-108)</td>
<td>p=0.03</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>153 (130-169)</td>
<td>135 (117-170)</td>
<td>p=0.07</td>
</tr>
</tbody>
</table>

- DEX dosing: 78% received ≤ 0.7 mcg/kg/hr
  - 13/33 received a bolus dose
- Development of AWS complications
  - 6/33 – Pneumonia
  - 3/33 – seizure

*J Crit Care* 2014; 29:298-302
Conclusion

• Adjunctive utilization of DEX resulted in decreased BZD administration

• Limitations
  • Did not evaluate DEX use and need for mechanical ventilation
  • Lack of standardization
    • Absence of a consistent definition for severe refractory AWS
    • Utilization of DEX was inconsistent

*J Crit Care* 2014; 29:298-302
Continuous DEX vs BZD

• Crispo et al.
• Retrospective cohort
• Compared the efficacy and safety of continuous infusion BZD or DEX in non-intubated patients with severe AWS
• Individualized treatment at clinicians discretion
• Outcomes
  • Rate of respiratory distress requiring mechanical ventilation or EtOH withdrawal seizure
  • Total BZD dose before and during administration of study drug
  • Occurrence of adverse events including bradycardia and hypotension
  • Cost comparison (hospital stay and study drug)
# Results

<table>
<thead>
<tr>
<th></th>
<th>BZD (n=33)</th>
<th>DEX (n=28)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory distress, n (%)</strong></td>
<td>3 (9.1)</td>
<td>2 (7.1)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td><strong>Seizure, n (%)</strong></td>
<td>0</td>
<td>1 (3.6)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Duration of infusion (hrs), median (IQR)</strong></td>
<td>55.5 (30-72.8)</td>
<td>45.9 (23.8-85.3)</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Cumulative BZD dosing during infusion (mg), median (IQR)</strong></td>
<td>105 (60-199.5)</td>
<td>3.5 (0-12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Bradycardia, n (%)</strong></td>
<td>5 (15.2)</td>
<td>13 (46.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Hypotension, n (%)</strong></td>
<td>4 (12.1)</td>
<td>12 (42.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Total cost of hospitalization (US$), mean + STD</strong></td>
<td>11467.60 ± 1568.48</td>
<td>17014.62 ± 2180.62</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Study drug cost, (US$) mean + STD</strong></td>
<td>227.74 ± 32.54</td>
<td>771.59 ± 221.38</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Length of hospital stay, (days), mean + STD</strong></td>
<td>9.7 ± 7</td>
<td>10.2 ± 8</td>
<td>0.88</td>
</tr>
</tbody>
</table>
Conclusions

• Utilization of DEX required lower BZD to manage AWS
• 1/3 of the pts in the DEX group did not receive concomitant BZDs following initiation of DEX, increasing risk of progressing AWS and seizure
  • One of these patients resulted in seizure resulting in terminal and irreversible encephalopathy
Take Away Points

• BZD remain the mainstay in treatment of AWS
• Adjunctive DEX reduces autonomic symptoms
  1. In those uncontrolled with BZD alone
  2. In those experiencing respiratory depression from BZD
• Safety has been demonstrated by weak evidence
  • DEX does not treat or prevent seizures or delirium tremens
• Appropriate rate of infusion still needs to be determined
• Continued studies will help define the appropriate place in therapy
Review Question

All of the following scenarios are appropriate to recommend dexmedetomidine as an adjunctive treatment option except:

A. Patient A continues to score >20 on the CIWA-Ar despite multiple doses of lorazepam (cumulative dose of 20 mg)

B. Patient B received lorazepam 3 mg IV x 4 per hospital policy based on CIWA-Ar. The nurse calls prior to giving the next lorazepam dose with concerns of increased respiratory depression observed with the administration of the lorazepam dose.

C. Patient C admitted from the ED to the neurocritical care for traumatic brain injury, ethanol level on admission was 186 mg/dL. Patient is currently receiving fentanyl IV and propofol IV for sedation.
In the non-intubated patient

DEXMEDETOMIDINE
Alpha$_2$-agonist

- Does not exhibit respiratory depressive effects
  - Opioid analgesic-sparing allows for less opioid-induced respiratory depression
- Additional indication FDA-approved in 2008
  - Non-intubated patients prior to and during surgical and other procedures
  - Only sedative approved for administration in non-intubated patients
  - Allows for use before, during and after extubation
  - Based on the results of two RCT: the MAC and AWAKE

*Crit Care Med* 2013; 41:263-306
To evaluate the safety and efficacy of DEX for sedation during a broad range procedures requiring monitored anesthesia care (MAC)

- DEX 0.5 mcg/kg, DEX 1 mcg/kg or saline placebo (2:2:1)
  - DEX 0.2-1.0 mcg/kg/hr titrated to a targeted level of sedation
  - Midazolam prn to achieve target sedation levels and fentanyl prn for pain
AWAKE

- Randomized, double-blind, multicenter, Phase IIIb FDA study
- To evaluate the safety and efficacy of DEX compared to placebo as the primary sedative for awake fiberoptic intubation
- DEX vs saline (+ rescue midazolam) to achieve target sedation before and throughout intubation

<table>
<thead>
<tr>
<th></th>
<th>DEX</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rescue midazolam</td>
<td>47.3%</td>
<td>86.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rescue midazolam (mg)</td>
<td>1.07 ± 1.05</td>
<td>2.85 ± 3.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Am J Ther 2010; 17(6):586-595*
Clinical Application

• Safety and efficacy has been demonstrated
  • Extrapolated data applied to many clinical scenarios
• Proceed with caution
  • Administration in ICU or OR setting with continuous monitoring
  • May cause loss of oropharyngeal muscle tone $\rightarrow$ airway obstruction
    • Continuous respiratory monitoring for both hypoventilation and hypoxemia is indicated
Review Question

Which of the following is an FDA-labeled indication for dexmedetomidine:

1) During anesthetic procedures in non-intubated patients
2) Agitation and delirium in non-intubated patients
3) Alcohol withdrawal syndrome requiring high-dose benzodiazepines
4) Anesthesia during awake craniotomy
Take Home Points

• Sedation with nonbenzodiazepines may improve clinical outcomes in mechanically ventilated adult ICU patients
  • Limited data comparing propofol and DEX
• DEX may be associated with lower prevalence of delirium but is not recommended as a preventative measure
• DEX may be used as an *adjunct* to BZD for the treatment of AWS
  • DEX does not treat or prevent seizures or delirium tremors
• DEX may be utilized in non-intubated patients in a controlled environment with continuous monitoring and trained personnel (i.e., ICU, OR)
References


References


• Product Information: Precedex(TM) intravenous injection, intravenous injection concentrate , dexmedetomidine HCl intravenous injection, intravenous injection concentrate . Hospira, Inc. (per FDA), Lake Forest, IL, 2013.


Dexmedetomidine: the various roles and utilization strategies

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