Pharmacology to Optimize Reduction Success

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Objectives

• Understand goals and general approach for procedural sedation

• Review pharmacology of common medications used in procedural sedation

• Describe advantages and limitations of sedative agents
Objectives:

- Benzodiazepam + opiate
- Etomidate
- Propofol
- Ketamine
- Dexmedetomidine
- Methohexital

1. Pharmacology
2. Considerations
3. Utility

Availability $
Considerations

Department/Service
- Patient comfort
- Procedure success
- Provider/staff satisfaction

Procedure Duration
- Agent
- Pre-medications
- Support Staff

Ideal Medication
- Predictable
- Rapid onset
- Brief recovery
- Minimal complications
When talking about drugs...

“Half-life” vs “duration of effect”

- Multiple compartments → multiple half-lives
  - Distribution $t_{1/2}$
  - Elimination $t_{1/2}$

- Duration of effect
  - Varies with dose
Benzodiazepam + Opiate

• Midazolam + fentanyl
  • Typically dosed for light sedation

• Midazolam
  • Active metabolites increase duration

• Pediatric procedures:
  • Midazolam 0.4 mg/kg intranasal

**Curr Drug Metab. 2012;13(6):760-766.**
Propofol - Pharmacology

• $\text{GABA}_A$
• NMDA antagonism

• Directly vasoactive
  • Hypotension
Propofol

Duration of effect:
  Bolus
  5 – 10 minutes

Dose:
  Start with 0.5mg/kg
  aim for 1 mg/kg
  Needs to ‘saturate’
  Avoid “very slow titration”

Propofol - Considerations

Injection-site pain/burning
Inform patient

Propofol infusion syndrome
>48 hours / cumulative dose / risk factors

Dose variability
Regular cannabis use – 2x dose needed
Routine alcohol use – less certain, varies with age

Age
• 100 – age as initial dose

Ketamine - Pharmacology

“disconnects” cortical and limbic systems

- NMDA antagonist
- GABA agonist
  - $\text{GABA}_A$ (indirect)
  - $\text{GABA}_B$
  - $\text{GABA}_C$
- Opioid (mu, kappa)
- Muscarinic agonist
  - $\text{M}_1$ – $\text{M}_5$
- DA-2
- 5HT
- L-type Calcium

Ketamine – The Importance of Dose

Graphic: Salim Rezaie, MD on Twitter: “Special K: The Ketamine Brain Continuum & How to Reduce Feelings of Unreality for Patients

Ketamine – Considerations

- Catecholamine reuptake inhibition
  - Secondary catecholamine surge
  - Hypotension in catecholamine depletion?
  - Hypertension in uncontrolled HTN patients

- Hepatic metabolism
  - “Extensive”
  - Multiple pathways

**Major:**
- CYP2B6
- CYP3A4

**Minor:**
- CYP2C9
- CYP3A5
- CYP2A6

Mono-amine oxygenase
**Ketamine - Considerations**

**Oral secretions**
- Anticholinergics (atropine, glycopyrrolate)
- not routinely recommended

**Transient respiratory depression**
- Associated with rapid administration

**Emergence reactions:**
- More common in adults (varies widely)
- Related to extensive receptor types
- Screen for PTSD, military-combat service, psychiatric disorders

**Emesis**
- Can be delayed
Ketofol = Ketamine + Propofol

Reduces potential for:

Hemodynamic instability
Respiratory depression

Over 18 RCTs

*Most* show
Less hypotension
Less respiratory depression

Compatible in same syringe

Best to keep separate

0.75 – 1.0 mg/kg ketamine
Followed by propofol
0.5mg/kg and aliquots thereafter

Etomidate - Pharmacology

Mechanism:

Somewhat uncertain
Activity on GABA$_A$ receptors

Dose:

RSI: 0.3 mg/kg
Procedure: 0.1 – 0.2 mg/kg

Onset: rapid
Duration: 5 – 10 minutes

Hemodynamics

“Neutral”

Sedation can precipitate hypotension!
Etomidate - Considerations

High Osmolarity
4900 mosm/L
- burning/pain at injection site
- extravasation

Inhibits cortisol production

Myoclonus: 30 – 60%
- Masked in RSI paralysis

Lower seizure threshold?
- Poor quality studies, *inconclusive*
- Myoclonus from EPS disinhibition
- No seizure protection compared to propofol, phenobarb, methohexital
- Avoid or provide adjunct (GABA) in status

Etomidate – Clinical Utility

Not ideal for procedures requiring little movement
  • Reductions

RSI

Electrical cardioversion

Dexmedetomidine (Precedex®)
Pharmacology

MOA:
Central α-2 agonist
No analgesic property

Dose
High-level sedation: 1 mcg/kg over 10 minutes
Low-level sedation: 0.5 mcg/kg over 10 minutes

Pharmacokinetics
Onset: 10 minutes
Duration of effect: 1-2 h
Hepatic metabolism
Terminal t₁/₂: 2 hours
Dexmedetomidine (Precedex®) Considerations

Hypotension
Bradycardia

α-2, α-1

No respiratory depression
ICU - Wean off ventilator

Does not provide deep sedation

Not as expensive as previously
May be restricted / not readily available

<table>
<thead>
<tr>
<th>Procedural sedation</th>
<th>Dexmed</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>54 %</td>
<td>30 %</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>14 %</td>
<td>4 %</td>
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</tbody>
</table>

Dexmedetomidine (Precedex®)
Utility

Limited overall
Use adjunct for analgesia

Awake intubation?
Maintain respiratory drive

Pediatric procedures (light sedation)
2 – 3 mcg/kg
30 – 45 min prior to procedure
Intranasal administration

Behrle N, J Pediatr Pharmacol Ther. 2017
Methohexital (Brevital®)

Methohexital

MOA: Barbiturate

Onset: immediate

Duration:
  5 – 15 minutes
  Ultra-short acting

No analgesia

Moderate Hypotension

Limited supply?
Special Considerations

Special populations: Pregnancy

• One dose rarely if ever has effect on fetal mutation

• Most sedatives cross placenta
  • Relevant near term

• Consult pharmacist
Considerations - Which weight to use?

Scant literature
Rarely matters with titration

- Actual body weight
- Ideal BW
- Adjusted body weight

• Ideal Body Weight (Lean Body Weight)
  Propofol
  Ketamine

• Actual Body Weight:
  Etomidate
  (succinylcholine)

Propofol: PMID: 19520702
SUMMARY

Consider....

Premedication
  • Opiate
  • ‘pain-dose’ ketamine

Duration / metabolism

Co-morbidities

Adverse Effects
Questions - Discussion

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