Pharmacology to Optimize Reduction Success

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Clinical Instructor – Department of Emergency Medicine – CU Anschutz

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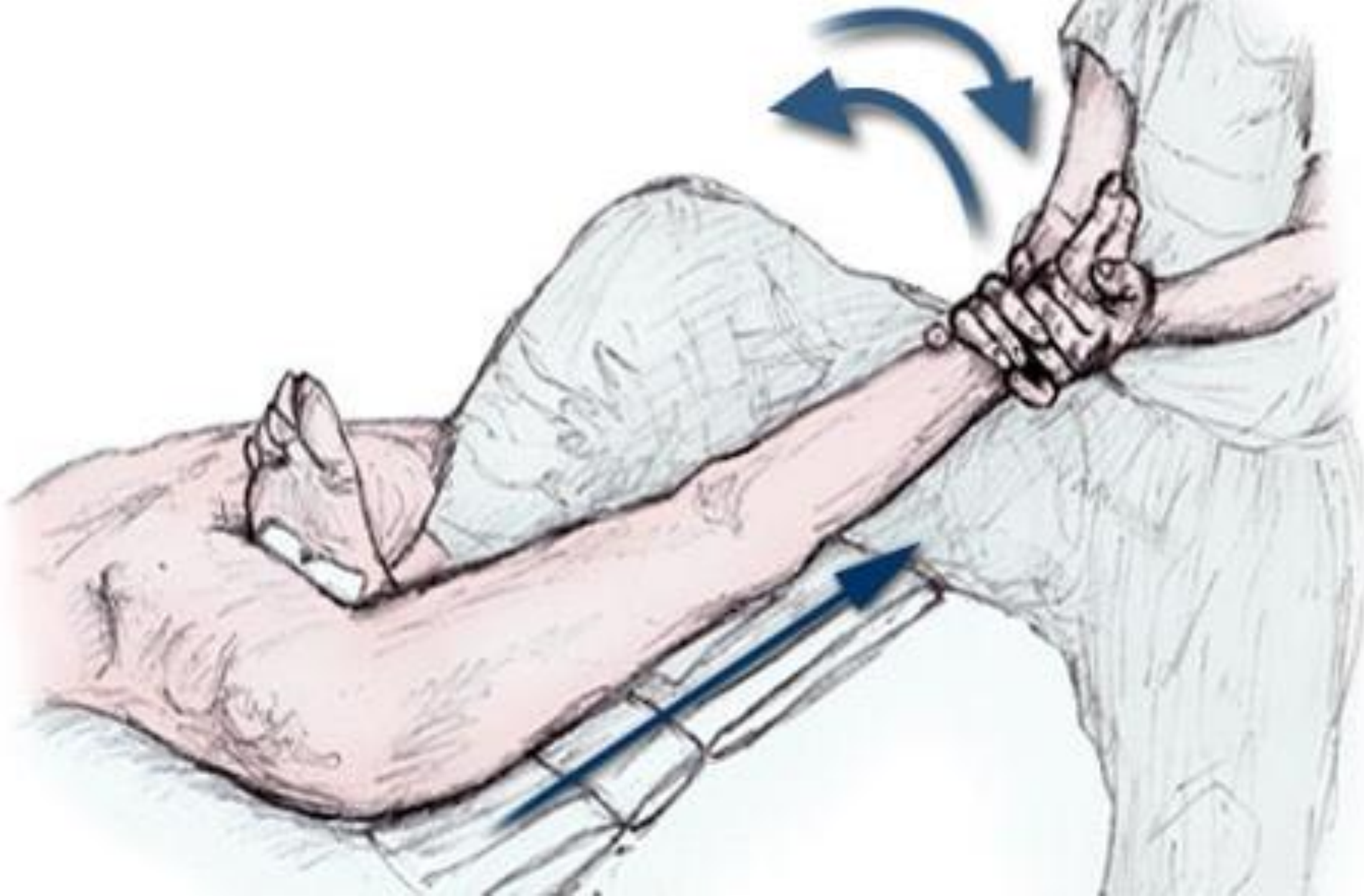
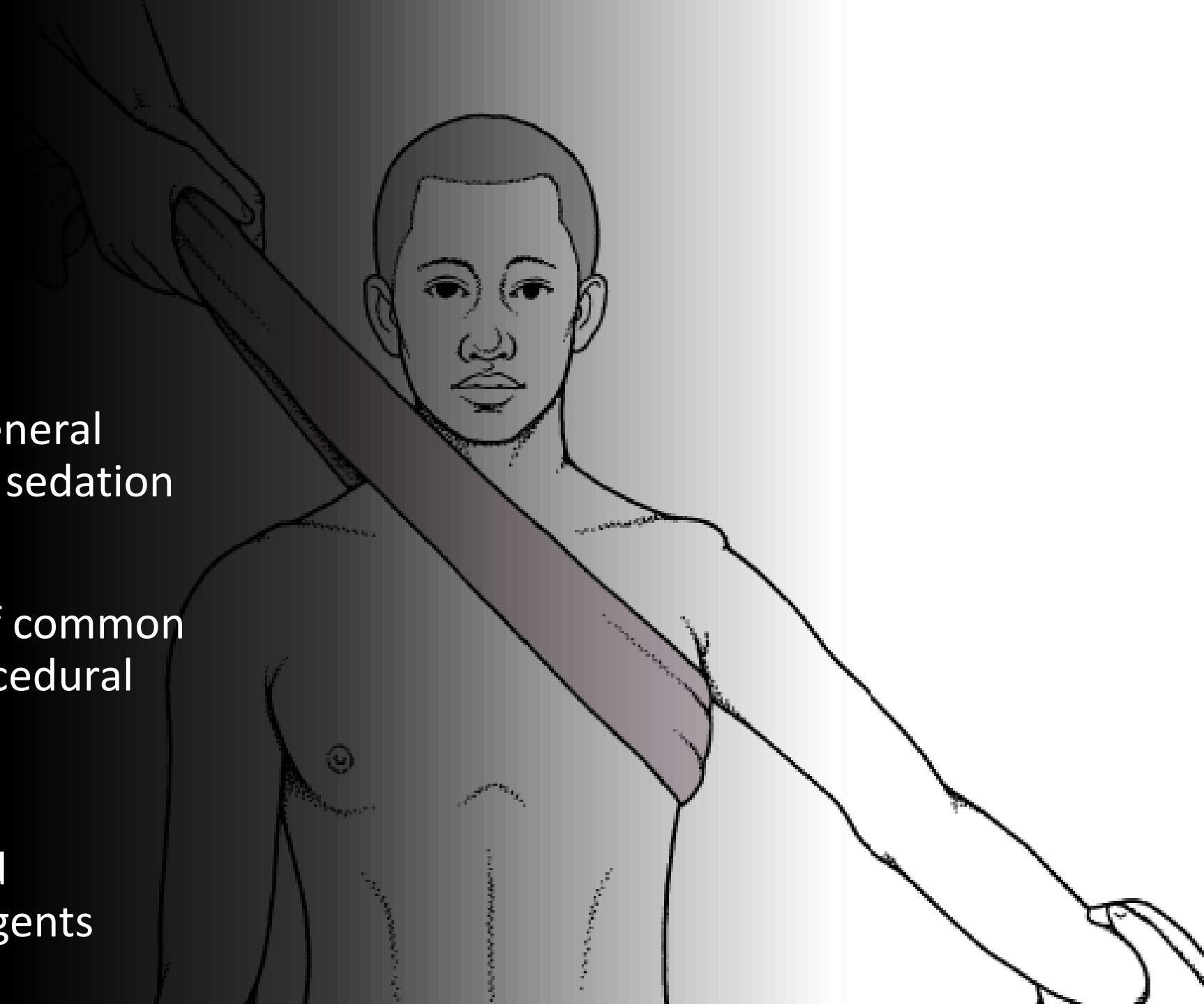
FOR LIFE'S JOURNEY



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

} Ketofol

- 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

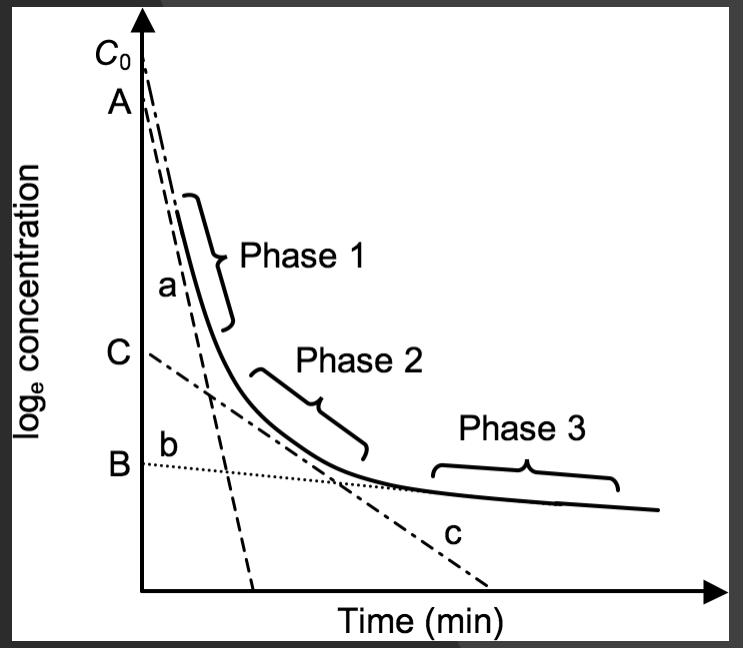
Provider specific ?

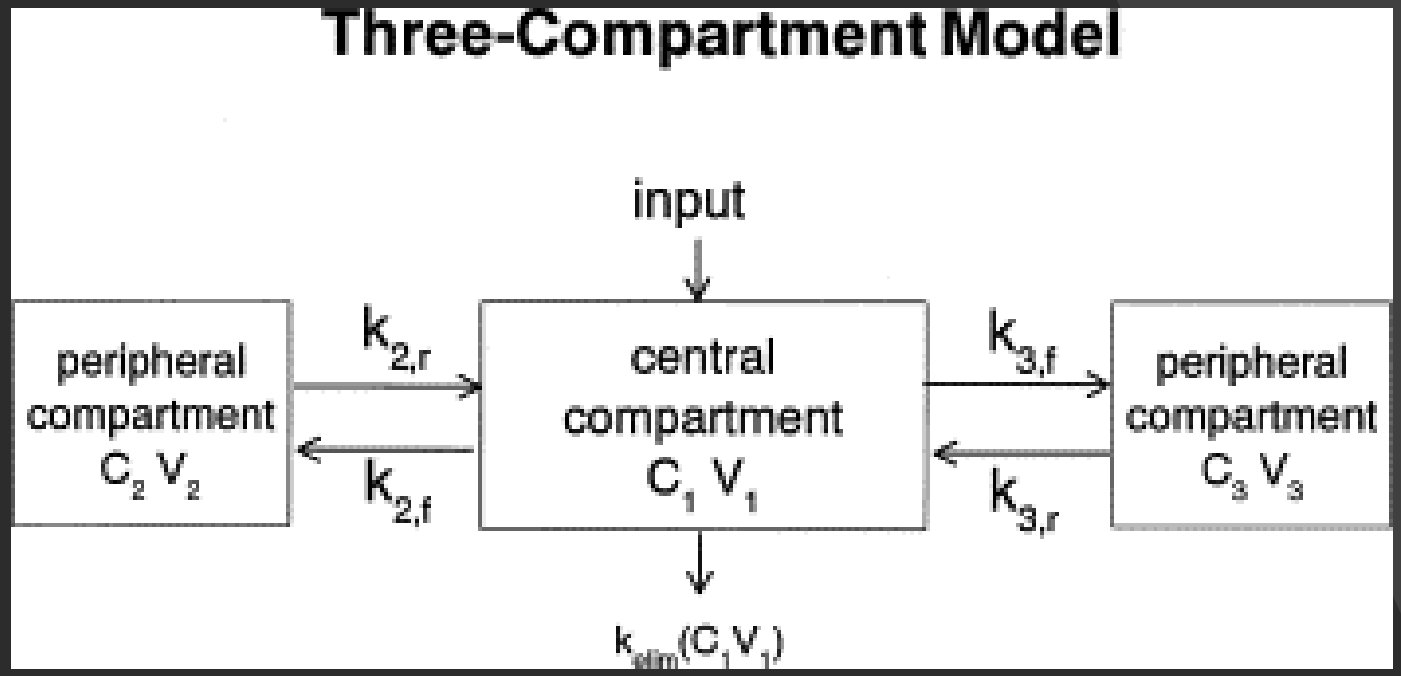
Ideal Medication

- 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

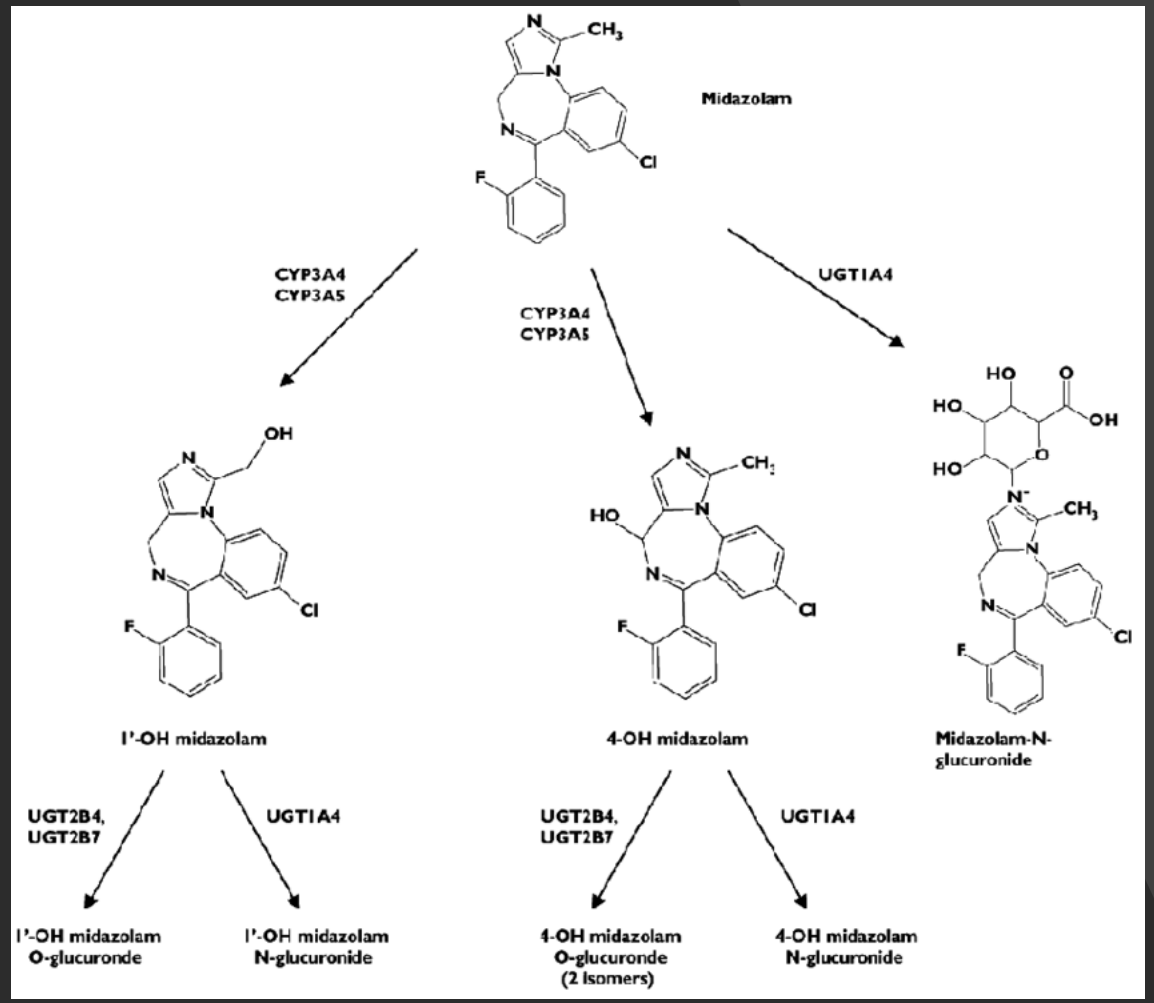




Marian, Seghezzi, et al. Ch4 – Ed. Lisa M. Plitnick, Danuta J. Herzyk, Nonclinical Development of Novel Biologics, Biosimilars, Vaccines and Specialty Biologics, Academic Press, 2013

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

- $GABA_A$
- 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”

Choon et al. Basic Clin Pharmacol Toxicol. 2013;113(2):126–31

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

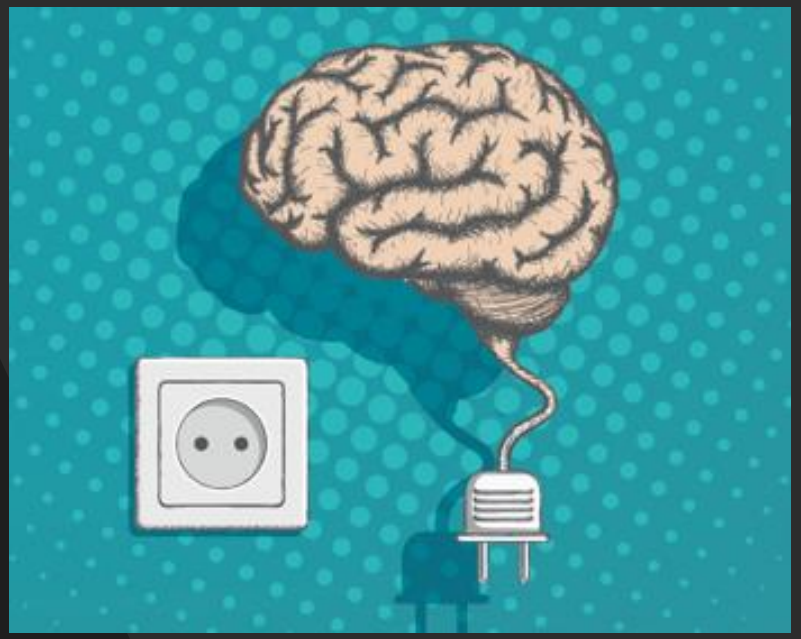
Routine alcohol use – less certain, varies with age

Age

- 100 – age as initial dose

Twardowski MA, et al. J Am Osteopath Assoc. 2019 Apr 15.
Imasogie N, et al. PLoS One. 2021 Mar 4;16(3):e0248062.
Liang C, et al. Acta Anaesthesiol Scand. 2011;55(9):1113–7.
Choon et al. Basic Clin Pharmacol Toxicol. 2013;113(2):126–31

Ketamine - Pharmacology

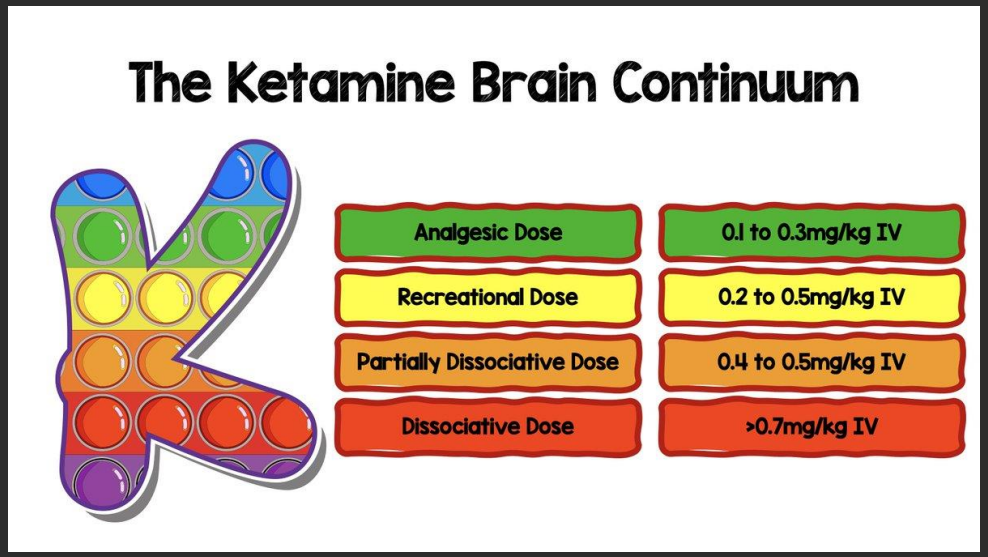


"disconnects" cortical and limbic systems

- NMDA antagonist
- GABA agonist
  - $GABA_A$(indirect)
  - $GABA_B$
  - $GABA_C$
- Opioid (mu, kappa)
- Muscarinic agonist
  - $M_1 – M_5$
- DA-2
- 5HT
- L-type Calcium

Green SM, et al 2011. Ann Emerg Med. 2011 May;57(5):449-61.
Zanos P,et al. Pharmacol Rev. 2018 Jul;70(3):621-66

Ketamine – The Importance of Dose



Lovett S, Rech MA et al. Acad Emerg Med. 2021 Jun;28(6):647-654.
Green SM, et al Clinical practice guideline for emergency department ketamine dissociative sedation: 2011. Ann Emerg Med. 2011 May;57(5):449-61.
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

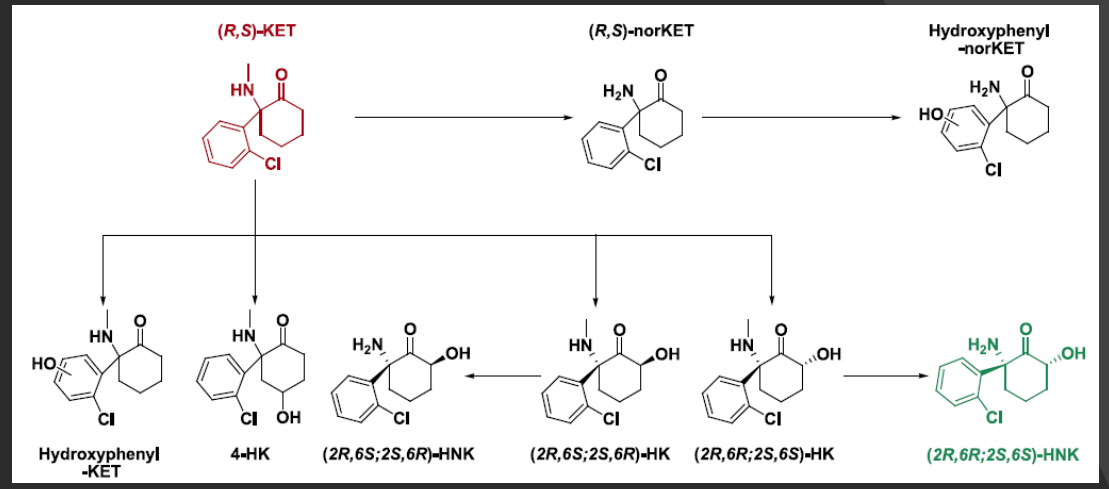
  “Extensive”

  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

Lovett S, Rech MA et al. Acad Emerg Med. 2021 Jun;28(6):647-654.
Green SM, et al Clinical practice guideline for emergency department ketamine dissociative sedation: 2011. Ann Emerg Med. 2011 May;57(5):449-61.
Graphic: Salim Rezaie, MD on Twitter: “Special K: The Ketamine Brain Continuum & How to Reduce Feelings of Unreality for Patients

Ketofol = Ketamine + Propofol

Reduces potential for:

- Hemodynamic instability
- Respiratory depression

Over 18 RCTs

- *Most* show
  - Less hypotension
  - Less respiratory depression

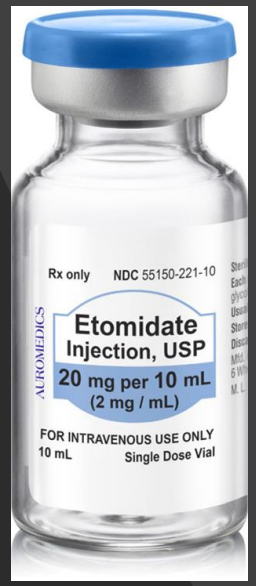
Compatible in same syringe

Best to keep separate

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

Jalili M, et al. Am J Emerg Med. 2016 Mar;34(3):558-69

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 !

Forman SA. 2011 Mar;114(3):695-707

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

Kosarek L, et al. Ochsner J. 2011 Summer;11(2):143-6
Wagner Rl, et al. N Engl J Med. 1984. 310:1536–1542
Butterworth et al in *& Mikhail's Clinical Anesthesiology, 5e.* New York, NY: McGraw-Hill; 2013.

Etomidate – Clinical Utility

Not ideal for procedures requiring little movement

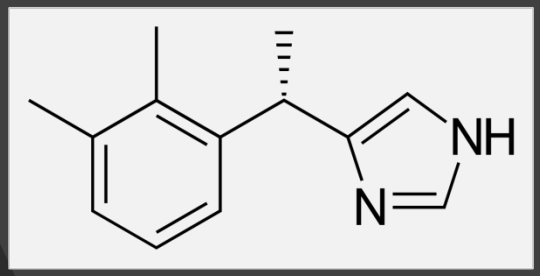
- Reductions

RSI

Electrical cardioversion

Chomrikh L, et al. BMC Anesthesiol. 2022 Jul 5;22(1):206.
Guldner G, et al. Acad Emerg Med. 2003 Feb;10(2): PMID: 12574010
Reddy RV, et al. Anesth Analg. 1993 Nov;77(5):1008-11.. PMID: 8214699

Dexmedetomidine (Precedex®) Pharmacology



MOA:

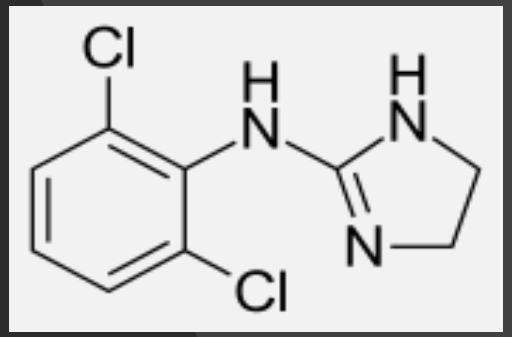
- Central α-2 agonist
- No analgesic property

Dose

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

Pharmacokinetics

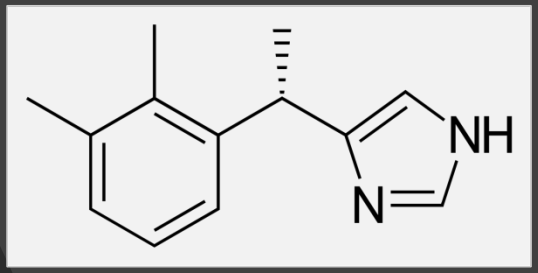
- Onset: 10 minutes
- Duration of effect: 1-2 h
- Hepatic metabolism
- Terminal $t_{1/2}$: 2 hours



Clonidine

Dexmeditomidine (Precedex). Product Insert. 2015 HQ Specialty Pharma Corporation. Paramus, NJ.
Weerink MAS, et al. Clin Pharmacokinet. 2017 Aug;56(8):893-913

Dexmedetomidine (Precedex®) Considerations



Hypotension
Bradycardia
} α-2, α-1

Procedural sedation	Dexmed	Placebo
Hypotension	54 %	30%
Bradycardia	14 %	4 %

No respiratory depression

ICU - Wean off ventilator

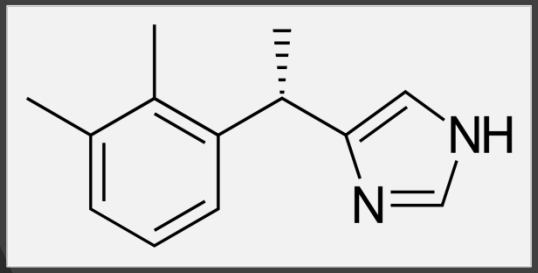
Does not provide deep sedation

Not as expensive as previously

May be restricted / not readily available

Dexmeditomidine (Precedex). Product Insert. 2015 HQ Specialty Pharma Corporation. Paramus, NJ.
Weerink MAS, et al. Clin Pharmacokinet. 2017 Aug;56(8):893-913

Dexmedetomidine (Precedex®) Utility



Limited overall

- Use adjunct for analgesia

Awake intubation ?

- Maintain respiratory drive

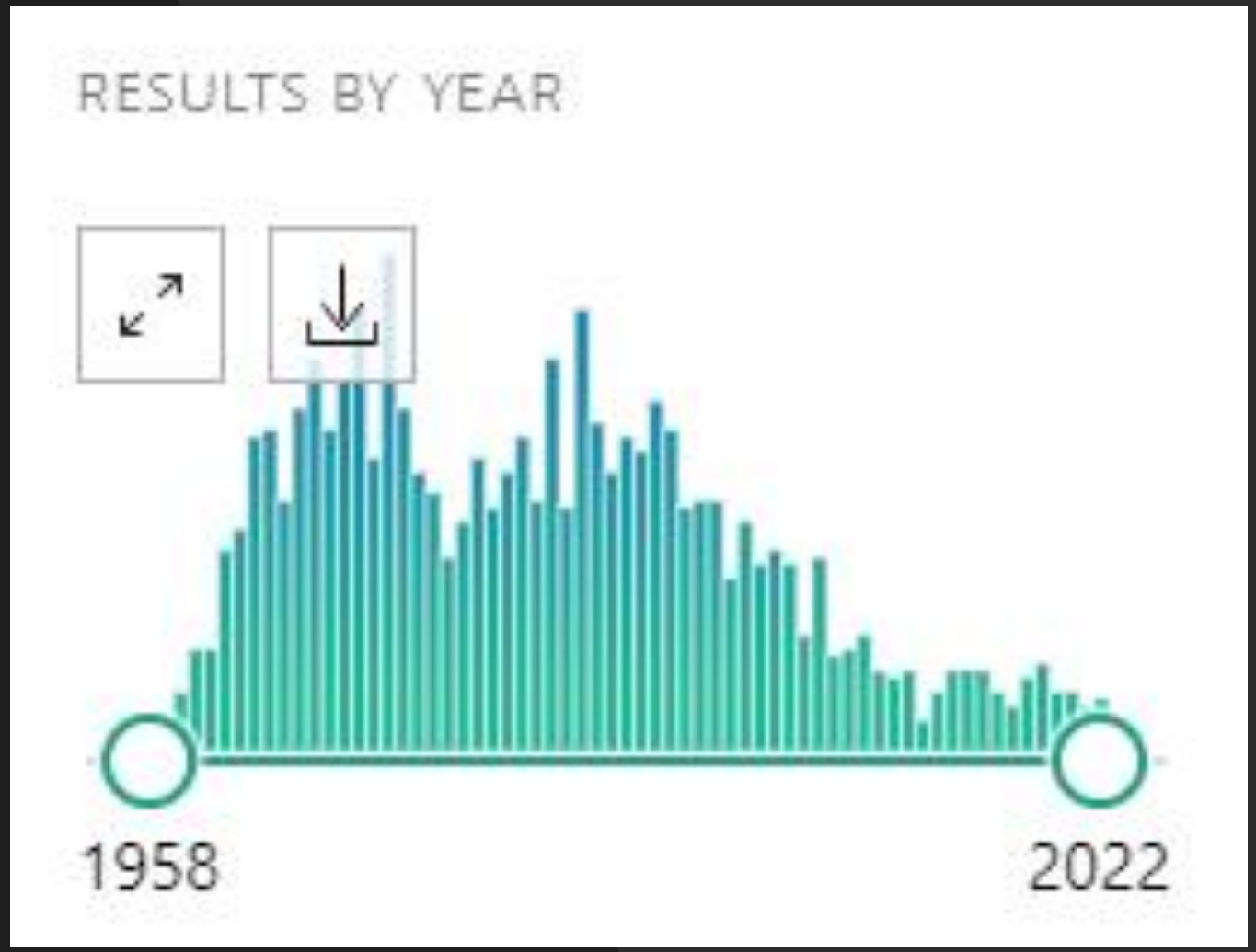
Pediatric procedures (light sedation)

- 2 – 3 mcg/kg
- 30 – 45 min prior to procedure
- Intranasal administration

Behrle N, J Pediatr Pharmacol Ther. 2017

Uusalo P, et al. 2020 Apr;130(4):949-957.

Methohexital (Brevital®)



Harry Daly Museum. https://ehive.com/collections/4493/harry-daly-museum

Methohexital

MOA: Barbiturate

Onset: *immediate*

Duration:

- 5 – 15 minutes
- Ultra-short acting

No analgesia

Moderate Hypotension

Limited supply ?

Zink BJ, et al. Ann Emerg Med. 1991 Dec;20(12):1293-8.
Brevital Product Insert. 2007. Monarch Pharmaceuticals, Inc., Bristol, TN
Gale DW, et al. Crit Care Med. 1993 Oct;21(10):1509-13.

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

- Ideal Body Weight (Lean Body Weight)

  Propofol

  Ketamine

- Actual Body Weight:

  Etomidate

  (succinylcholine)

- Actual body weight
- Ideal BW
- Adjusted body weight

Propofol: PMID: 19520702
Erstad, B.L., et al. *Crit Care* **24,** 315 (2020)

SUMMARY

Consider….

Premedication

- Opiate
- ‘pain-dose’ ketamine

Duration / metabolism

Co-morbidities

Adverse Effects

Questions - Discussion

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