INTRODUCTION

- Introduction
- Sedation
- Sleep
- Pain
- Review
- Questions
Objectives

• Explain why sedation is sometimes needed in the ICU
• List three drug options for treating ICU insomnia
• Name at least two contraindications to infusion of propofol
• Select an analgesic agent for the following scenario:

A 25-year-old man with traumatic brain injury, coma, and hypertension who is on 200 mcg/hour fentanyl, who has the following ABG: 7.47/32/150/24/0
Disclosures

• Conflicts: none

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  Penn: Provost’s Faculty Opportunity Fund
  McCabe Fund | Bach Fund
  Robert Wood Johnson Foundation
  NIH training grant (CC HSR)
  NIH Loan Repayment Program

• Off-label use: oh yeah

• Pathologic use of clip art
DEFINITIONS
HYPNOS
### Sedation, Hypnosis & related terms

<table>
<thead>
<tr>
<th>Word</th>
<th>Root</th>
<th>Similar word</th>
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<tbody>
<tr>
<td>sedation</td>
<td>sedare (Latin)</td>
<td>sedentary</td>
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<tr>
<td>hypnosis</td>
<td>hypno (Greek)</td>
<td>hypnotize</td>
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<tr>
<td>amnesia</td>
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<tr>
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<td>kines (Greek)</td>
<td>dyskinesia</td>
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<tr>
<td>areflexia</td>
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<td>surgical anesthesia</td>
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Pharmacology: basic principles

• Pharmacokinetics: how drugs get to the effect site
  • Route of administration: PO, IV, SC, IM, intranasal, transdermal
  • Elimination
  • Metabolism: first-pass metabolism, conjugation
  • Distribution / redistribution
  • Elimination

• Pharmacodynamics: drug effect as a result of receptor binding
  • Receptor agonist, antagonist, partial agonist
  • Genetic variability in receptor density and sensitivity
  • Dose response
  • Efficacy, potency, toxicity
Pharmacokinetics: basic principles

- **Pharmacokinetics**: how drugs get to the effect site
  - Think: route of administration: PO, IV, SC, IM, intranasal, transdermal
  - elimination
  - metabolism: first pass metabolism, conjugation
  - distribution: redistribution
  - elimination

- **Pharmacodynamics**: drug effect as a result of receptor binding
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  - dose response
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(1) Drug redistribution (2) Context-sensitive half time
1st concept: Drug redistribution

Important terms:
- Distribution half life
- Elimination half life

Miller’s Anesthesia, 7th edition.
2\textsuperscript{nd} concept: Context-sensitive half time

The longer you infuse a drug, the longer it takes to eliminate.

How are context-sensitive half time and drug redistribution related?

We essentially never get to steady state with very fat soluble drugs.
Why do sedatives and hypnotics work? (Pharmacodynamics)

Ascending arousal system

Any drug that affects these neurotransmitters can cause sedation

GABA | Galanin | Histamine | Serotonin
Norepinephrine | Acetylcholine | Dopamine
Why do we sedate people in the ICU?

Sedate or not?

• ARDS with a PaO2 of 50 mmHg on 100% FiO2
• Mechanical ventilation in a patient with RASS +3
• Mechanical ventilation in a patient with RASS 0
• ICP 25 in a vented patient with TBI
  • Bronchoscopy in a non-intubated patient
  • Bronchoscopy in an intubated / trached patient
ICU Sedation Indications

- Anxiolysis
- To facilitate procedures
  - Line placement, chest tube placement, IABP placement, intubation, tracheostomy, bronchoscopy
- To facilitate mechanical ventilation
- Paralysis needed
  - Severe ARDS (decrease $O_2$ consumption)
  - Therapeutic hypothermia
  - Surgical reason (e.g. hernia repair with component separation)
- Hyperactive delirium
- Seizure / status epilepticus
- Controlling vital signs?
Problems with ICU sedation

- Delayed emergence
- Delirium
- ICU-acquired weakness
- Post-traumatic stress disorder
- Tachyphylaxis
Sedative Agents

- Propofol (Diprivan®)
- Dexmedetomidine (Precedex®)
- Midazolam (Versed®)
- Lorazepam (Ativan®)
- Etomidate (Amidate®)
- Phenobarbital
- Inhaled anesthetics: sevoflurane, desflurane, isoflurane
PROPOFOL
(DIPRIVAN ®)

Introduction → Sedation → Sleep → Pain → Review → Discussion
Propofol: What do I need to know?

• Propofol is a milky white alkylphenol administered intravenously
  • Think: “milk of amnesia”
  • Contraindicated in egg allergy

• Developed in 1970s - rapidly became induction agent of choice
  • Used in ~95% of surgeries with general anesthesia

• Major use: induction of general anesthesia
  • Other uses: maintenance of general anesthesia
    procedural sedation
    ICU sedation
    off-label: anti-epileptic
    off-label: anti-emetic
    off-label: chronic headache therapy
    off-label: drug withdrawal
Propofol: Pharmacokinetics

- Pharmacokinetic features of propofol:
  - Redistribution $t_{1/2}$ is 2-8 minutes
  - Redistribution terminates effect after a single dose
  - Elimination $t_{1/2}$ is 4-23.5 hours

- Metabolism: hepatic, renal, and other
  - Most propofol is glucuronidated or sulfated prior to excretion
  - Lungs and small intestine probably contribute to metabolism

If central compartment increases in size, propofol concentration will drop. To maintain the same effect site concentration, dose must increase.

(Practical consequence: kids need higher doses/kg)
Propofol: Mechanism of action

• Propofol potentiates the effects of GABA
  • How? It’s complicated.
    – Binds to β subunit of the GABA$_A$ receptor
    – Also affects: α$_2$ adrenoreceptors
      NMDA glutamate receptors
      glycine receptors

• No effects on pain
Physiologic effects of propofol

- **Cardiovascular effects:**
  - Hypotension
    - Vasodilation (preload AND afterload)
    - Decreased sympathetic tone
    - Myocardial depression (maybe)
  - Heart rate: variable effects

- **Respiratory effects:**
  - Hypopnea or apnea
    - Decreased tidal volume, same or increased respiratory rate
  - Decreased response to hypercarbia and hypoxia
  - Bronchodilation

- **Neurologic effects:**
  - Decreased cerebral metabolic rate -> burst suppression
  - Decreased cerebral blood flow -> “brain relaxation”
Propofol dosing

- Weight-based dosing: mcg/kg/min
- In SICU, usually 10-80 mcg/kg/min
  - I usually start with 30-50

- Increase the dose:
  - Younger patients
  - People on chronic BZDs, AEDs
  - Redheads?

- Decrease the dose:
  - Older patients
  - Frail patients
Danger: Propofol Infusion Syndrome (PRIS)

• Refractory bradycardia (potentially asystole) plus
• One of the following:
  • Metabolic acidosis
  • Rhabdomyolysis
  • Hyperlipidemia
  • Enlarged/fatty liver
• Cause: propofol-mediated mitochondrial dysfunction
• Risk factors: age, CNS cause of critical illness (e.g. TBI), respiratory cause of critical illness (e.g. ARDS), mitochondrial disease, exogenous catecholamines, steroids, propofol dose and duration
• Diagnosis: RBBB with convex ST elevation in $V_1-V_3$
PRIS ECG findings

Propofol: adverse effects, contraindications

Adverse effects:
- Pain on injection
- Propofol infusion syndrome (PRIS)
- Hypertriglyceridemia and pancreatitis
- Urine discoloration (green, pink, white, brown)

Absolute contraindications:
- Allergy to propofol
- Allergy to egg protein

Relative contraindications:
- Hemodynamic instability
- Infusion duration >72 hours
- Awareness under anesthesia (for TIVA)
- Being at home
Propofol as a drug of abuse

• Rapid onset and offset
• Potent hypnotic
• Increases dopamine concentrations in nucleus accumbens
  • Like cocaine
    – Euphoria
    – Feeling of well-being
• Sexual dreams
• Not scheduled by DEA
DEXMEDETOMIDINE
(PRECEDEX ®)

Introduction → Sedation → Sleep → Pain → Review → Discussion
Dex: What do I need to know?

• Major clinical uses:
  • Sedation of “initially intubated and mechanically ventilated patients during treatment in an intensive care setting” (<24 hours)
  • Sedation of non-intubated patients before and/or during surgery
  • Sedation with dex resembles natural sleep
Dexmedetomidine: Pharmacokinetics and MOA

• $\alpha$-2 agonist
  • Sedation (like clonidine)
  • Analgesia (like clonidine, epinephrine)
Physiologic effects of dexmedetomidine

- Cardiovascular effects: biphasic, dose-dependent
  - Hypertension (loading dose) or hypotension (infusion)
  - Bradycardia, heart block, sinus arrest

- Respiratory effects: remarkably few
  - Respiratory depression: minimal to moderate

- Neurologic effects:
  - May decrease seizure threshold
Dexmedetomidine dosing

Dosing for intensive care setting sedation

<table>
<thead>
<tr>
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<th>Loading Dose</th>
<th>Maintenance Dose</th>
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</thead>
<tbody>
<tr>
<td>Adult patients</td>
<td>• 1 mcg/kg over 10 minutes*</td>
<td>• Followed by 0.4 mcg/kg/hr</td>
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<tr>
<td></td>
<td></td>
<td>• Titrate to effect with doses from 0.2–0.7 mcg/kg/hr</td>
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<tr>
<td></td>
<td></td>
<td>• Rate of infusion should be adjusted to achieve targeted level of sedation</td>
</tr>
<tr>
<td>Patients over 65 yrs</td>
<td>A dose reduction should be</td>
<td>• A reduction in maintenance dosage should be considered</td>
</tr>
<tr>
<td></td>
<td>considered</td>
<td></td>
</tr>
<tr>
<td>Patients with impaired</td>
<td>A dose reduction should be</td>
<td>• A reduction in maintenance dosage should be considered</td>
</tr>
<tr>
<td>hepatic or renal function</td>
<td>considered</td>
<td></td>
</tr>
</tbody>
</table>

- Reduce dex dosing if co-administered with other sedatives or hypnotics; titrate to effect
Dexmedetomidine:
Adverse effects, contraindications

**Adverse effects:**
- Hypotension, bradycardia, sinus arrest
- Dry mouth
- Tachyphylaxis after 24 hours

**Absolute contraindications:**
- Allergy to dexmedetomidine

**Relative contraindications:**
- Heart block
- Decreased ejection fraction

“Adverse reaction information is derived from the continuous infusion trials of Precedex for sedation in the Intensive Care Unit setting in which **1007 adult patients received Precedex**... The population was between 17 to 88 years of age, **43% ≥65 years of age**, **77% male and 93% Caucasian**. The most frequent adverse reactions were hypotension, bradycardia and dry mouth.”
LORAZEPAM
(ATIVAN®)
Lorazepam: Mechanism of action

Lorazepam potentiates GABA

- BZDs have their own binding site on the GABA channel
  - Z-drugs also bind here
- BZDs increase chloride ion conductance when GABA is already bound

http://www-hsc.usc.edu/~ddavies/
Lorazepam & Propylene Glycol

- Lorazepam’s preservative contains propylene glycol
- Prolonged lorazepam infusions can cause toxicity:
  - Lactic acidosis
  - Acute tubular necrosis
- Diagnosis:
  - Propylene glycol levels (slow, unreliable)
  - Osmol gap (shouldn’t be there)
- Treatment:
  - Stop the lorazepam
  - PG can be dialyzed out
Lorazepam: adverse effects, contraindications

**Adverse effects:**
- Propylene glycol toxicity
- Pardoxical excitatory reaction
- Depression

**Absolute contraindications:**
- Allergy to lorazepam

**Relative contraindications:**
- Metabolic acidosis
- Osmolal gap
- Delirium
ETOMIDATE
(AMIDATE®)

Introduction → Sedation → Sleep → Pain → Review → Discussion
Etomidate: What do I need to know?

Major clinical use: induction of general anesthesia
- Mostly used for known or anticipated hemodynamic instability
- Critical illness, cardiac anesthesia

Miller’s Anesthesia, 7th edition.
Etomidate: Pharmacokinetics and MOA

• Pharmacokinetic features of etomidate:
  • Redistribution $t_{1/2}$ is 2-8 minutes
  • **Redistribution** terminates effect after a single dose
  • Elimination $t_{1/2}$ is 3-5 hours
  • Metabolism: metabolized by liver, excreted in urine and bile
    – Metabolized by ester hydrolysis or $N$-demethylation

• Mechanism of action (MOA):
  • Probably potentiates the effects of GABA
  • No effects on pain
  • Also causes adrenocortical suppression

Miller’s Anesthesia, 7th edition.
Physiologic effects of etomidate

- Cardiovascular effects: remarkably few
  - Hypotension: minimal to moderate

- Respiratory effects: remarkably few
  - Respiratory depression: minimal to moderate

- Neurologic effects:
  - Decreased cerebral metabolic rate -> burst suppression
  - Decreased cerebral blood flow
  - Can also cause seizures
Etomidate: Adverse effects, contraindications

**Adverse effects:**
- Adrenal suppression, especially in critically ill patients
- Increased post-operative nausea/vomiting relative to propofol
- Myoclonus

**Absolute contraindications:**
- Allergy to etomidate

**Relative contraindications:**
- Adrenal insufficiency
- Critical illness, especially septic shock
- History of post-operative nausea/vomiting
SLEEP

Introduction
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Did your patients sleep last night?

• Why sleep is good:
  • Immune function improves
  • Delirium less likely
  • Less irritability
  • Better cognitive function

• How do we prevent sleep?
  • Noise
  • Lights
  • Vital signs
  • Medications
  • Bathing
  • Lab draws
How do we promote sleep?

• Non-pharmacologic:
  • Sleep hygiene, normal sleep-wake cycles
  • Light during the day, dark at night
  • Exercise, stimulation during the day

• Pharmacologic options
Bad sleep drugs

• Ineffective:
  • Chloral hydrate - also has daytime hangover

• Dangerous:
  • Diphenhydramine (Benadryl®) – also has daytime hangover
Sleep drugs from (the other) Dr. Schwab

Anxiolytics / hypnotics

- Benzodiazepines (short or medium ½ life)
- Z-drugs (zolpidem, zaleplon)
- Buspirone
- Trazodone
- Ramelteon
- Propofol (off-label)
- Dexmedetomidine (off-label)

Sedating antipsychotics:

- Haloperidol
- Atypicals (olanzapine, quetiapine)

Analgesics
Tell me what hurts...

- Surgical procedures
- Traumatic injuries
- Musculoskeletal pain
- Cancer
- Edema (legs, genitalia)
- Decubitus ulcers
- Pre-existing pain states
  - Fibromyalgia
  - Neuropathic pain
  - Headaches
- Devices
Drugs are Bad (Nonpharmacologic options)

- Repositioning
- Different bed
- Warm compresses
- Restful sleep
- Edema wrapping
- Hug pillow
- Abdominal binders
- Distraction
- Reassurance
That didn’t work.

- Opioids vs. all other analgesics

- Why do we like opioids?
  - Familiarity
  - Versatility
  - Predictability
  - Reversibility
  - No ceiling dose
Problems with Opioids

- Tachyphylaxis (fentanyl, sufentanil)
- Active metabolites (morphine)
- Seizures (meperidine)
- Histamine release (morphine)
- Respiratory depression
- Tolerance
- Nausea, vomiting
- Urinary retention
- Constipation
Non-Opioid Analgesics

- ketorolac
- ketamine (acetaminophen)
- local anesthetics (regional)
- acetaminophen
- gabapentin
- pregabalin
- ibuprofen
- baclofen
- clonidine
- fentanyl
- clonidine
- lidocaine
- lidocaine (ketamine)

() = not available at HUP
Pain tips and tricks from an anesthesiologist

- Figure out what hurts
- More opioid
  - Check for respiratory acid-base disturbances
  - Caution with impaired consciousness
- Different opioid
  - Dilaudid (hydromorphone) is not better than morphine
- Consider ketamine
  - Bolus vs. infusion
- Consider regional or neuraxial blockade
- Early pain consult
Objectives, revisited

• Explain why sedation is sometimes needed in the ICU
• List three drug options for treating ICU insomnia
• Name at least two contraindications to infusion of propofol
• Select an analgesic agent for the following scenario:

A 25-year-old man with traumatic brain injury, coma, and hypertension who is on 200 mcg/hour fentanyl, who has the following ABG: 7.47/32/150/24/0
For more information

• Evidence-Based Practice of Critical Care, Chapter 76: “What Is the Best Way to Sedate Critically Ill Patients?”
Thank you!

E-mail me (LaneMe@Upenn.edu) with:

- Questions
- Comments
- Concerns
- Typos, errors
  - Free coffee if you find one

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