Sedatives in Critical Care

Dr. xeMeDAtiMe (PrECede) 1
Propofol 1
Etomidate 1
MIDAZOLAM (VERaX) 1
LORazepam (AtIVaN) 2
Ketamine 2
Others 2
CloMidiMeDAtiMe (d. ClOrehMeDiMeDAtiMe) 2
Remifentanil (FiniSTAR) 2
Chloral hydrate 2
Paraldehyde 2
Glucagon 3
Ethanol (ethyi alcohol) 3
Midazolam 3
Methohexitone (REMIX) 3
NonBenzodiazepine hypnotiMics 3
Zolpidem (Ambien), Zolpizide (B) 3
Zaleplon (Sonata) 3
Zopiclone 3
Zolpidem-Lumistar (Z) 3
Ramelteon (Zeromer) 3
Antihistamines 3
Sedatives in Critical Care

Muscarinic blockers – see p. 3905>
Opioids, NEUROLEPTANALGIESIA – see p. 3905>>
Sedation holidays – to evaluate ability to wean from ventilation.

DexmeDAtiMeDAtiMe (PrECede) 1
- relatively selective α-2-adrenergic receptor agonist with sedative properties.
  - useful for sedation of intubated (mechanically ventilated) patients in ICU
  - does not affect respiratory drive – easily extubate! (helps patients tolerate endotracheal tube without sedatives/harmonics to facilitate extubation)
  - no effect on lens examination – ideal in awake neurosurgery!
  - administered by continuous IV not to exceed 24 hours (longer use may cause withdrawal* if stopped abruptly).
  - may cause bradycardia & hypotension (hypotension during loading dose may be observed).

Propofol
- exact mechanism of action unknown.
- short half life with no active metabolites.
- popular for ambulatory surgery and in neurointensive care – rapid-acting (30-60 sec), short-acting (5-10 min), with smooth, absence-free emergence and clarity of mental status thereafter.
- excellent bronchodilation (via block of vagally mediated bronchoconstriction).
- decreases cerebral metabolism.
  - disadvantages:
    1) pain on injection.
    2) dose dependent BP, (cution in severe CAD, hypovolemia).
    3) poor analgesia (add opioids).
  - if administered for > 48 hours – great risk of PRIS (propofol-induced syndrome) - rhabdomyolysis
    - contraindications: liver injury.
  - propofol infusion syndrome
    - first identified in children but can occur in adults as well.
    - hyperkalemia, metabolic acidosis, hepatomegaly, lipemia, myocardial failure, rhabdomyolysis, and renal failure, resulting in death.
    - extreme caution must be taken when using doses greater than 5 mg/kg/hour, or when usage of any dose exceeds 48 hours in critically ill adults

ETOMIDATE (AmiDATE) 1
- benzodiazepine derivative - anesthetic and amnestic but no analgesic properties
- rapid onset of action (30-60 sec), ultra-short duration of action (4-6 min)
- absent hemodynamic changes – useful in cardiovascular disease.
- cerebrovascular constrictor – reduces CBV and ICP. Does not suppress brainstem activity.
- initial hopes for use as a cerebral protectant were abandoned based on experimental studies.
  - disadvantages:
    1) burning pain on injection
    2) no analgesia — abnormal muscular movements (myoclonus – may be confused with seizures)
    3) adrenal suppression (when given as prolonged sedation for critically ill patients).
  - impairs renal function.
    - contraindicated in children & pregnancy (embryocidal), renal failure

MIDAZOLAM (Versed) 1
- benzodiazepine with rapid onset of action (1-5 min), duration of action much shorter (< 30 min) than diazepam.
  - N.B. Catabolism in elderly may take 2-3 days!
- minimal hemodynamic changes – often selected in cardiovascular surgery.
  - powerful anxiolytic & antegrade amnesia (3-4 times more potent than diazepam) – used:
    a) to premedicate anxious patients
    b) for anesthesia induction
    c) as component of multimodal anesthetic.
**Midazolam Dosage**

- **Initial dose:**
  - Young, healthy patient: 1.0 mg
  - Elderly, frail, or pediatric patient: 0.5 mg

- **Redosing interval:** 2-3 minutes

- **Total dosages (common):** 2-6 mg per procedure

- **Total dose should NOT exceed 5 mg in 1 hour**

**LORAZEPAM (Ativan®)**
- **adverse effects:** propylene glycol (1,2-propandiol) toxicity (esp. in doses > 5.7 mg)
  - propylene glycol is **inadvertent** used to deliver lorazepam and diazepam IV.
  - incidence unknown
  - manifestations: unexplained anion gap / metabolic acidosis / hyperosmolality.

**KETAMINE**
- onset in < 1 min; duration 10-20 min.
- the only intravenous induction agent that: increases sympathetic tone! ↔ BP & heart rate?
  - useful in hypovolemic patients; avoid in CAD, hyperventilation, stroke.
  - increases cerebral blood flow! ↔ ICP?
  - no respiratory depression, bronchomotor tone! (via block of vagally mediated bronchoconstriction) - appropriate agent for asthma, respiratory failure patients (administer drying agent [e.g. glycopyrrolate] or premedicate with atropine because of copious oropharyngeal secretions).
  - SMDA receptor antagonist - produces dissociative anesthetia (catatelope, catatonia, profound amnesia and potent antinausea), but not necessarily complete unconsciousness! - patient appears awake but is unconscious, immobile (muscle tone↑) and feels no pain.
  - can be used as sole anesthetic for brief, superficial procedures (esp. in children and young adults).
  - laryngeal reflexes are maintained.
  - produces no muscular relaxation, does not control visceral pain, and may not completely control patient movement - not useful for abdominal cases or delicate surgery.
  - clinically important side effect - emergence delirium (H: supplemental benzodiazepines or volatile agents), contraindicated in psychiatric disorders.

**OTHERS**

**CLOMETHIAZOLE (S, CHLORMETHIAZOLE)**
- structurally related to thiamine (vit. B1) but acts like sedative, hypnotic, muscle relaxant and anticonvulsant.
- **mechanism of action:** 1) positive allosteric modulator at barbiturate/picrotoxin site of GABA-A receptor
  2) inhibits alcohol dehydrogenase! - helps to relieve sudden effects of alcohol withdrawal in alcoholics.
- **use:** 1) widely used in treating and preventing symptoms of acute alcohol withdrawal
  2) management of agitation, restlessess, short-term insomnia and Parkinson’s disease in elderly.
- **forms:** 192 mg capsule, syrup.
- **adverse effects:** tolerance and physical dependence (abrupt withdrawal → apnoeic tonic seizures).
  - overdosing (particularly toxic) - potentially fatal.

**BUSPIRONE (BUSPARE®)**
- unique chemically AZASPAN® (not chemically and pharmacologically related to benzodi azepines or barbiturates or other sedatives!)
  - partial agonist at serotonin 5-HT1A receptors.
  - affinity for D2 and D4-HT1A receptors.
  - **used as anxiolytic in long-term therapy of generalized anxiety disorders (efficacy comparable to benzodiazepines!).**
  - only minimal sedation! (esp. does not potentiate CNS depression of ethanol!)
  - most useful anxiolytic in elderly patients!
  - effectively eliminates episodic outbursts of aggression and agitation in brain-damaged patients.
  - minimal psychomotor and cognitive dysfunction.
  - no respiratory depression.
  - because higher doses cause dysphoria, patients do not escalate dose (dependence is unlikely, **low addiction potential**).

N.B. buspirone is not CNS depressant! cannot be directly substituted for benzodiazepines and does not suppress benzodiazepine withdrawal.

- at doses > 45 mg/d has antidepressant effect (but also at high doses may cause dysphoria).
  - no anticonvulsant, hypnotic-sedating, myorelaxant properties.
  - disadvantages slow onset of action! – must be given for 1 month before it is effective.
  - adverse effects (rare) - headaches, nervousness, dizziness, lightheadedness.
  - Little potential for abuse!

**CHLORAL HYDRATE**
- trichlorinated derivative of acetaldehyde.
  - must be metabolized by alcohol dehydrogenase to active metabolite TRICHLOROETHANOL.
  - weak but safe sedative-hypnotic! - induces sleep in 30 minutes and lasts 6 hours (T1/2 = 4-10 hrs).
  - relatively safe!
  - little reduction in REM sleep.
  - has anticonvulsant properties;
CHLORAL BETAINE

- mostly used for 1-3 nights to treat transient insomnia.
- adverse effects: unpleasant taste, GI tract irritation.
- CNS depressant effect potentiated by ethanol (combination CHLORAL ALCOHOLATE is dubbed “Mickey Finn”); addiction can occur!
- also used externally as rubefacient, anesthetic, and antiseptic.
- CHLORAL BUTYRATE is slowly hydrolyzed in GI tract to chloral hydrate.

PARALDEHYDE
- tinner of acetaldehyde (remembers CHLORAL HYDRATE).
- potent sedative-hypnotic - induces sleep in 15 minutes and lasts 4-8 hours. has anticonvulsant properties. can be administered orally (strong offensive odor and disagreeable taste + GI tract irritation!), parenterally, rectally.
- eliminated via lungs – does not depend on liver/kidney status!
- used exclusively for alcoholics undergoing withdrawal from alcohol. Do not use with PARALDEHYDE!

GLUTETHIMIDE
- very narrow therapeutic index - formerly used as hypnotic and as daytime sedative.

ETHANOL (ETHYL ALCOHOL)
- CNS depressant* with anxiolytic & sedative effects.
- synergizes with many other sedative agents and can produce severe CNS depression!
- N.B. toxic potential outweighs benefits?
- shallow dose-response curve (sedation occurs over wide dosage range with ultimately hypnotic and coma).
- about metabolism and DERFLURAM - see p. 702 >>

MEPROBAMATE
- propyl alcohol derivative (propanediol carbamate): hypnotic, muscle relaxant.
- depresses CNS as shorter acting barbiturates (+ phenobarbital).
- was widely used antianxiety agent → largely been replaced by benzodiazepines.
- well absorbed from GI tract.

METHOCARBAMOL (ROBAXIN®)
- carbamate derivative of guaifenesin (expectorant).
- CNS depressant with muscle relaxant properties (related to sedative properties, because drug has no direct action on contractile mechanism, motor end plate or nerve fiber).
- indication: as adjunct to rest, physical therapy, and other measures in acute painful musculoskeletal conditions.
- mode of action - not been clearly identified.
- may inhibit effect of anticholinesterase agents (pyridostigmine) - use with caution in myasthenia gravis.

NONBENZODIAZEPINE HYPNOTICS

ZOLPIDEM (AMBRIEN®, ZOLPIMIST®)
- DIAZAPROPRAZINE.
- selective for subtype 1 of benzodiazepine receptor (as QUIAZIDRAN).
- used as sedative-hypnotic (advantageous over benzodiazepines!)
- preserves sleep architecture:
  - does not cause memory disturbances (as benzodiazepines do);
  - minimal rebound insomnia;
  - no tolerance, no withdrawal effects with prolonged use.
- no anticonvulsant, no myorelaxant properties.
- rapidly absorbed from GI tract, rapid onset of action. T½ = 1.5-3 hours.
- Zolpimist® - FDA approved oral spray for short-term treatment of difficulty with sleep initiation.
- adverse effects - nightmares, agitation, headache, GI upset, dizziness, daytime drowsiness.

ZALEPON (SONATA®)
- PYRAZOLOPYRIMIDINE. = ZOLPIDEM.
- rapid onset of action with ultra-short duration.

ZOPICLONE
- CYCLOPYRROLONE.

ESZOPICLONE (LUNESTA®)
- CYCLOPYRROLONE.
- mechanism of action - interaction with GABA-receptor at binding domains close to (or allosterically coupled to) benzodiazepine receptors.
- used as hypnotic - likely to become first choice agent for treatment of insomnia.
- shows continued efficacy at 12 months of continued use.
- less addictive than benzodiazepines.
- rapidly absorbed from GI tract, rapid onset of action. T½ = 6 hr.
- higher doses (2-3 mg) are more effective for sleep maintenance; whereas lower doses (1-2 mg) are suitable for difficulty in falling asleep.

RAMELTEON (ROZEREM®)
- chemically related to MELATONIN.
- melatonin receptor agonist (high affinity and selectivity for MT1, and MT2 receptors, vs. MT3 receptors).
- T½ = 1-2.6 hrs.
- metabolized by liver.
- decreases [testosterone] and increases [progactin] in serum.
- used as hypnotic for sleep-onset insomnia (8 mg within 30 minutes of going to bed).
- does not cause rebound insomnia.
- does not cause dependence (drug is not controlled substance!).
- adverse effects: headache, somnolence, etc.
- should not be used with FLUVOXAMINE (ramelteon concentration ↑↑↑↑).

ANTIHISTAMINES

Nonprescription sedating antihistamines (DIPHENHYDRAMINE, DOXYLAMINE) are effective only in mild forms of situational insomnia.
OTHER SEDATIVES-ANXIOLYTICS

- anticholinergic side effects make them less useful than benzodiazepines.

HYDROXYZINE - antihistamine with antiemetic activity.
- low tendency for habituation - useful for anxiety with history of drug abuse.
- also used for sedation prior to dental procedures.

BIBLIOGRAPHY for “Sedatives, Hypnotics” — follow this LINK >>