

## Other Sedatives-Anxiolytics

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### SEDATIVES IN CRITICAL CARE

MUSCULAR BLOCKERS – see p. 3905 >>

OPIOIDS, NEUROLEPTANALGESIA – see p. 3905 >>

**Sedation holidays** – to evaluate ability to wean from ventilation.

#### DEXMEDETOMIDINE (Precedex®)

- relatively selective  $\alpha_2$ -adrenoceptor agonist with sedative properties.

- used for **sedation of intubated** (mechanically ventilated) patients in ICU
- **does not affect respiratory drive** – can easily extubate! (helps patients tolerate endotracheal tube without sedatives/narcotics to facilitate extubation)
- **no effect on neuro examination** – ideal in awake neurosurgery!
- administered by continuous IVI not to exceed 24 hours (longer use may cause withdrawal\* if stopped abruptly). \*similar to CLONIDINE withdrawal
- may cause bradycardia & hypotension (hypertension 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 (30-40 sec), short-acting (5-10 min), with smooth, nausea-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↓** (caution in severe CAD, hypovolemia).
  - 3) **poor analgesia** (add opioids).
  - 4) 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®)

- 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.
- **cerebrovasoconstrictor** - reduces CBF 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).
  - 4) impairs renal function
- **contraindicated** in children & pregnancy (embryocidal), renal failure

#### MIDAZOLAM (Versed®)

- benzodiazepine with rapid **ONSET** of action (1-5 min); **DURATION** of action much shorter ( $\approx$  30 min) than diazepam.  
N.B. catabolism in **elderly** may take 2-3 days!
- **minimal hemodynamic changes** - often selected in cardiovascular surgery.
- powerful **anxiolysis & anterograde amnesia** (3-4 times more potent than diazepam) – used:
  - a) to premedicate anxious patients
  - b) for anesthesia induction
  - c) as component of multidrug anesthetic.

#### LORAZEPAM (Ativan®)

- **adverse effects:** **propylene glycol (1,2-propanediol) toxicity** (esp. in doses > 5-7 mg)
  - propylene glycol is **solvent used to deliver** lorazepam and diazepam IV.
  - incidence unknown
  - manifestations: unexplained anion gap / metabolic acidosis / hyperosmolality.

#### KETAMINE

- onset in  $\approx$  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, hypertension, stroke.
- **increases cerebral blood flow** → **ICP↑**.
- **no respiratory depression, bronchomotor tone↓** (via block of vagally mediated bronchoconstriction) - appropriate agent for asthmatics, respiratory failure patients (administer drying agent [e.g. glycopyrrolate] or premedicate with atropine because of copious oropharyngeal secretions).
- NMDA receptor antagonist - produces **DISSOCIATIVE ANESTHESIA** (catalepsy, catatonia, **profound amnesia** and **potent somatic analgesia**, 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**

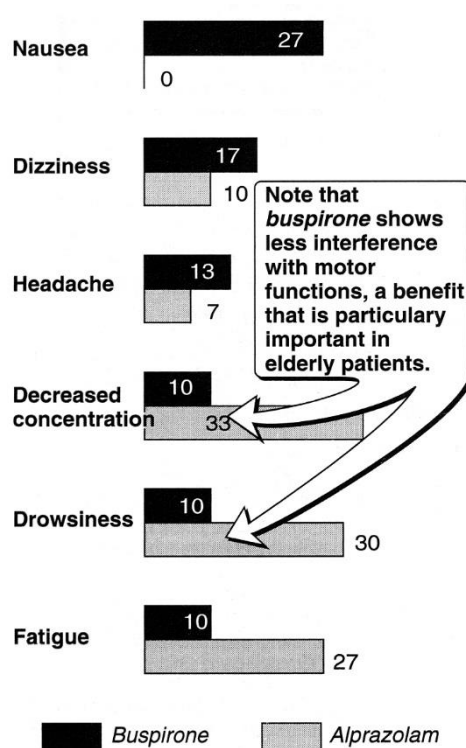
**CLOMETHIAZOLE (S. CHLORMETHIAZOLE)**

- 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.
- uses:
  - 1) widely used in treating and preventing symptoms of **acute alcohol withdrawal**.
  - 2) management of agitation, restlessness, 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).
- overdose (*particularly toxic*) - potentially fatal.

**BUSPIRONE (BUSPAR®)**

- unique chemically **AZASPIRONE** (not chemically and pharmacologically related to benzodiazepines or barbiturates or other sedatives!).

- partial agonist at **serotonin 5-HT<sub>1A</sub> receptors**; some affinity for **D<sub>2</sub>** and **5-HT<sub>2</sub> receptors**.
  - used as **anxiolytic** in long-term therapy of generalized anxiety disorders (efficacy comparable to benzodiazepines!).
    - only **minimal sedation!** (+ 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.
  - disadvantageous **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 (T<sub>1/2</sub> = 4-10 hrs).
  - relatively safe;
  - little reduction in REM sleep;
  - has anticonvulsant properties;
  - 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 BETAINE** is slowly hydrolyzed in GI tract to chloral hydrate.

**PARALDEHYDE**

- trimer of acetaldehyde (resembles **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 **DISULFIRAM!**

**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 hypnosis and coma).
- about **metabolism** and **DISULFIRAM** – see p. 702 >>

### MEPROBAMATE

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

### METHOCARBAMOL (ROBAXIN®)

- carbamate derivative of guaifenesin (expectorant).
- CNS depressant with **musculoskeletal 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 (AMBIEN®, ZOLPIMIST®)

- **IMIDAZOPYRIDINE**.
- selective for **subtype 1 of benzodiazepine receptor** (as **QUAZEPAM**).
- 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,  $T_{1/2} \approx 1,5-3$  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.

### ZALEPLON (SONATA®)

- **PYRAZOLOPYRIMIDINE**;  $\approx$  **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.
- $T_{1/2} \approx 6$  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  $MT_1$  and  $MT_2$  receptors, vs.  $MT_3$  receptors).
- $T_{1/2} \approx 1-2,6$  hrs.
- metabolized by liver.
- decreases [testosterone] and increases [prolactin] 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  $\uparrow\uparrow\uparrow$ ).

## ANTI-HISTAMINES

**Nonprescription sedating antihistamines** (**DIPHENHYDRAMINE**, **DOXYLAMINE**) are effective only in *mild forms of situational insomnia*.

- 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"  $\rightarrow$  follow this [LINK >>](#)