Other Sedatives-Anxiolytics

Last updated: April 21, 2019

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 α_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 (≈ 30 min) than diazepam.
  N.B. catabolism in elderly may take 2-3 days!
- **minimal hemodynamic changes** - often selected in cardiovascular surgery.
- powerful **anxiolysis & antegrade 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 ≈ 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)

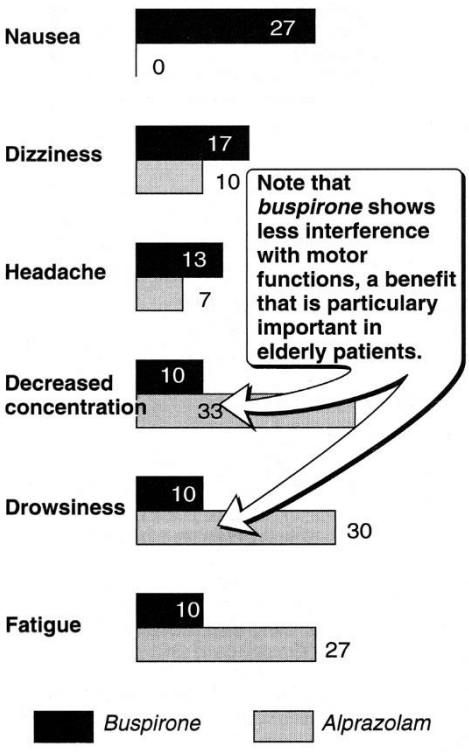
- structurally related to thiamine (vit. B1) but acts like sedative, hypnotic, muscle relaxant and anticonvulsant.
- mechanism of action:
  1) positive allosteric modulator at barbiturate/picrotoxin site of **GABA-A receptor**.
  2) inhibits **alcohol dehydrogenase** - helps to relieve sudden effects 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$_{1A}$ receptors**; some affinity for **D$_2$** and **5-HT$_2$ 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 ($T_{1/2}$ = 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** (≈ 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 **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**; ≈ 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↑↑↑).

ANTIHISTAMINES

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" → follow this LINK >>