Sedatives, Hypnotics & Anxiolytics

BARBITURATES

- Derivatives of Barbituric Acid
- Barbituric acid itself has no sedative effect
- No more used as sedative hypnotics but are applied as general anesthetics due to

1. Dec therapeutic index
2. Potent enzyme induction
3. Drugs of abuse
4. Risk of physical dependence
5. Severe withdrawl syndrome

CLASSIFICATION

- it is important to classify these drugs due to different DOA
- According to DOA;

i. LONG ACTING BARBITURATES (8-12hrs)
phenobarbital

ii. INTERMEDIATE ACTING (4-8HRS)
amobarbitone
secbarbitone
pentobarbitone

iii. Short acting barbiturates(2-4hrs)

Quinal barbitone

iv. Ultra short acting (15-30min)

Thiopentone sodium

Methohexitone

Thiamylal

PHARMACOKINETICS

- Generally IV in GA, others orally
- Absorption rapid
- Distribution rapid
- Ultra short acting more lipid soluble and cross BBB
- Once they entre brain, conc. Increases then redistributed along conc. gradient

- **REDISTRIBUTION**: is responsible for short duration of action of drugs/not met

The drug first goes to skeletal muscle then adipose tissue & then metabolized slowly by releasing form adipose tissue

If given repeatedly stores saturate and levels increase leading to toxicity

- METABOLISM: liver
- EXCRETION: inactive metabolite in urine

MOA

- GABA-ergic synapse
- RECEPTOR- GABA A
- Binding site different from BDZ
- Increase duration of Cl channel opening
- At high concentration they may be GABA-mimmetic
- Barbiturates can block excitatory glutamate receptors

- At high concentration they can block sodium channels giving anesthetic effect
- All these actions decrease neuronal activity

GROUP ACTIONS

- Sedation- reduced excitation
- Hypnosis- Decreased latency to fall asleep+ increase duration of sleep
- Anti epileptic- generalized and propagation of epileptiform action potential
- Anti convulsant
- Hyperalgesia- in presence of pain increase pain+ increase sensitivity to pain (given with aspirin)

- Amnesia
- Respiratory depression- hypoxic and chemoreceptor response to CO2 dec
- GIT- enzyme induction in liver
- Dependence- physical and psychological

THERAPEUTIC USES

1) General Anesthesia

Ultra short acting- thiopentone sodium for induction of GA in short duration surgery

2) Anti epileptics/ anti convulsants- phenobarbitone sp. for small children and infants. Used in febrile convulsions
3) Sedation and hypnosis
4) Neonatal jaundice and kernicterus

Enzyme induction causes metabolism of bilirubin, induce glucuronyl transferase for glucuronide conjugation

- the drugs are effective in premature infants for increased bilirubin formation or any hemolytic disease or if mothers are given sulfonamides in last trimester
- even in physiological jaundice that is not resolving

5) Anxiety- replaced by BDZ to relieve tension

when used as hypnotics they

supress REM sleep more than other stages

ADVERSE EFFECTS

1. CNS: drowsiness, impaired consciousness, mental and physical sluggishness

HANG OVER- at hypnotic doses produce feeling of tiredness after patient awakes. Impaired ability to work normally for many hours and occasionally nausea and vomiting

2. Attack of acute porphyria- D-ALA-synthetase induction

3. Enzyme induction

4. Drug dependence- anxiety, tremors, weakness, delirium, cardiac arrest.
WITHDRAWAL IS MUCH MORE SEVERE THAN OPIATES AND RESULT IN DEATH

5. Depression of fetal respiration

6. Drug automatism

Contraindication

- Hepatic failure
- Severe pulmonary insufficiency
- Acute intermittent porphyria

BARBITURATES HAVE NO ANTIDOTE

ACUTE POISONING

- Leading cause of death from drug overdose for many decades
- severe respiratory depression is accompanied with central cardiovascular depression resulting in shock-like state
- SYMPTOMS: shallow infrequent breathing, shock-like state, coma and death
- TREATMENT: Artificial respiration

- stomach wash
- Alkalinization of urine
- Hemodialysis