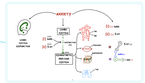
Anxiolytic and Hypnotic Drugs

Benzodiazepines

- features
  - Benzodiazepines has hypnogenic effect as E-max, whatever you increase the dose you won't reach anesthetizing or death level.
  - Physiological and physical dependence can developed if high doses of the drug are given over a prolonged period.
  - Sudden withdrawal of benzodiazepines results in withdrawal symptoms, and tension.
    - Benzodiazepine withdrawal syndrome is caused by stopping benzodiazepines or during dosage reduction.
    - Because of the long half-lives of some of the Benzodiazepine withdrawal symptoms may not occur until a number of days after discontinuation of therapy
    - Withdrawal symptoms including confusion, anxiety, agitation, insomnia, and tension.
  - There is a syndrome called: benzodiazepine dependance syndrome, which is caused by the desensitization or downregulation of GABA receptors during the treating of the anxiety patient, and due to the sudden withdrawal of the drug, the patient will get rebound anxiety, getting the patient to believe he can not live without the medication.
    - same syndome can occurs with ppl with insomnia
      - To treat insomnia with benzodiazepines we use half the dose we use for patients with anxiety, because the dependance and tolerance are higher.
  - overdose antidote
    - Flumazenil
      - is the only benzodiazepine receptor antagonist available for clinical use.
      - features
        - onset is rapid
        - short duration
        - half life
          - about one hour
      - route of administration
        - IV
          - only one available
- MOA
  - overview
    - Benzos Work on the frequency (times) of opening
  - enhances the affinity of GABA receptors for
    - Benzodiazepines bind to GABA receptors resulting in a more frequent opening of adjacent chloride channels specific, high affinity sites on the cell membrane, which are separate from but adjacent to the receptor for GABA.
  - GABA is the major inhibitory neurotransmitter in the CNS.
    - Binding of GABA to its receptors triggers the opening of chloride channel, which leads to an increase in the chloride conductance.
      - The influx of chloride ions causes a small hyperpolarization that moves the postsynaptic potential away from its firing threshold and thus inhibits the formation of action potentials.
- uses
  - reduction of anxiety (anxiolytic) at low dies
    - features
      - useful in treating the anxiety that accompanies some form of depression and schizophrenia.
      - these agents should not be used to alleviate the normal stress of everyday life, and should be reserved to sever anxiety.
      - Should be used for short periods of time because of the addiction potential
      - This drug puts the brain in a midzone between the excitatory- glutamate on NMDA receptor - and inhibitory- GABA- state.
      - anti-anxiety effects of the Benzodiazepines is less subject to tolerance than the sedative and hypnotic effects.
        - Tolerance is decreased responsiveness to repeated doses of drug-occur when used for more than one to two weeks
        - If more than 2 weeks, the inhibitory receptors will be downregulated, so the body "adapts" this drug which will make the excitatory effect predominates> rebound excitatory symptoms like anxiety and seizure.
          - cross tolerance exists among this group of agents and has been associated with a decrease in GABA receptors density
    - drugs
      - Diazepam
        - longer acting benzodiazepines
        - preferred with anxiety that may require treatment for prolonged periods of time.
  - muscular relaxant
    - drug
      - Diazepam
        - at high doses relax the spasticity of skeletal muscles probably by increasing presynaptic inhibition in the spinal cord.
        - useful in the treating a muscle spasm such as occur in muscle strain, and in treating spasticity from degenerative disorder such as multiple sclerosis.
  - sedative and hypnotic
    - all Benzodiazepines used to treat anxiety have some sedative properties and some can produce hypnosis. However, not all are useful as hypnotic agents.
      - a1 subunit is for limbic system
      - a2 for sleeping "melatonin pathway"
        - - The Cl- channel has 5 subunits, GABA binding on different subunits changes its effect
        - - "some" : increasing the doses increases the level of inhibition, however, increasing the level of inhibition on the limbic system doesn't cause hypnosis. But, affecting the suprachiasmatic center that inhibits GABA production inducing sleep and inhibits the arousal.
          - to reverse the hypnotic effect we use histamine or oroxine
        - Therefore, not all anti-stress medications have a hypnotic effect.
    - features
      - It is important to balance the sedative effect needed at bedtime with the residual sedation (hangover) on awakening.
      - hypnotics should be given for only a limited time
        - usually less than 2- 4 weeks
    - drugs
      - three most commonly prescribed fro sleep disorderders are
        - Flurazepam
          - long acting
            - Long-acting compounds (e.g. flurazepam) may ensure that a patient will sleep through the night, they also may cause cumulative effects resulting in daytime sluggishness or drug hangover
        - Temazepam
          - intermediate acting
        - Triazolam
          - short acting
            - doesn't produce much hangover effect, due to the continuous release of the drug from adipose tissue
              - the more the adipose tissue the more the hangover
            - Short-acting compounds (e.g. triazolam) avoid the hangover problem, but their use may be associated with early awakening and an increase in daytime anxiety
            - Flurazepam, bromozepam, lorazepam and trizolam are the best drugs that produce the hypnotic effect.
              - We use them when the patient has no induction of sleep, we either give him the ultra-short we talked about or triazolam.
              - We use it in intermittent sleeps "keeps waking up", or does not sleep for long periods at all.
              - Hangover effect, due to CNS depression effect of the drug, they wake up feeling sleepy and dizzy.
  - anticonvulsants
    - several Benzodiazepines have anticonvulsant activity and used to treat epilepsy and other seizure disorder.
    - drugs
      - clonazepam
        - useful chronic treatment of epilepsy
      - diazepam
        - terminating grand-mal epileptic seizes "status epilepticus, IM or IV injection, epileptic patient for more than 10-15 minutes".
        - We also use it for infants with febrile seizures "emergency cases, because we do not normally give them to infants.
  - anterograde amnesia
    - very high CNS depression
      - produces temporary impairment of memory
    - drugs
      - The short-acting agents are employed in premedication for endoscopic and bronchoscopic procedures such as angioplasty
  - adverse effects
    - Drowsiness and confusion
      - the two most common side effects
      - brain activity is inhibited, so they're not allowed to drive because the fine motor movements is not well functioning"
    - Ataxia
      - occurs at high doses and precludes activities that require fine motor coordination
    - Cognitive impairment can occur
      - can be used for people with dental-phobia.
      - Triazolam often show rapid development of tolerance ,early morning insomnia, daytime anxiety
  - interactions and precautions
    - (1) Used cautiously in treating patient with liver diseases.
    - (2) Should be avoid with acute narrow angle glaucoma.
    - (3) Alcohol and other CNS depressant enhance the sedative-hypnotic effect
      - becayse of the euphoria they produce (dopamine rewarding system)

Barbiturates

- features
  - these drugs are given gender-base, due to the difference of stress nature between men and women.
  - anxiety is an unpleasant state of tension and fear that seem to rise from unknown sources.
    - the symptoms of severe anxiety are similar to those of fear (such as tachycardia, palpitation) and involve sympathetic activation.
    - Sever anxiety may be treated with antianxiety drugs and/or some form of behavioral and psychotherapy.
      - Because all of the antianxiety drugs also cause sedation, the same drugs often function clinically as both anxiolytic and hypnotic (sleep-inducing).
        - it was thought that all anti-anxiety are hypnotic, this is not precisely correct because the insomnia takes place by another N.Tx' mechanism which is melatonin. As we all turn off the light and enter (seventh sleep) that comes by affecting GABA and other centres are worked on.
          - The point here is the melatonin induces the hypogenic state through activation and inhibition of other centres and areas instead of anxiety areas where anti-anxiety medications work.
    - extra
      - anxiety is basically a limbic system dysfunction due to a decrease in 2 types of neurotransmitter : GABA and 5-HT (serotonin)
        - this causes excessive excitation of the sympathetic nervous system ypsmtim,eating it thus causing other organs that is supplied by the sympathetic nervous system to get affected like
          - heart
            - increasing the HR
            - increasing the blood pressure
          - muscles
            - causing tremors
          - skin-sweat glands
            - diaphoresis
          - respiratory system
            - increase is respiratory rate
      - 
ANXIETY
GABA
Glutamate
Glycine
Cl-
Cl-
Cl-