SEDATIVE-HYPNOTIC DRUGS

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Sedative drug is the drug that reduce anxiety (anxiolytic) and produce sedation and referred to as *minor tranquillisers*.

Hypnotic drug is the drug that induce sleep

This drug classification is based on clinical uses rather than on chemical structure because of variable chemical nature of these drugs.

An effective sedative (anxiolytic) agent should reduce anxiety and exert a calming effect with minimum CNS depression (alertness)
A hypnotic drug should produce drowsiness and encourage the onset and maintenance of a state of sleep with more CNS depression.

Certain sedative agents can become hypnotics simply by increasing the dose.
The $\text{GABA}_A$-Benzodiazepine receptor complex: GABA is probably the most important inhibitory transmitter in CNS, control the state of excitability in all brain areas. The balance between excitatory inputs (most glutamatergic) and the inhibitory GABAergic activity determine the prevailing level of neuronal activity.

Increase GABA activity lead to sedation, amnesia, muscle relaxation, nervous and anxiety reduction.

While decrease GABA activation or increase excitatory activity elicit arousal, anxiety, restlessness and insomnia.
When GABA binds with the GABA<sub>A</sub>-Benzodiazepine receptor complex, the permeability of the central pore of the receptor to chloride ions increases, allowing more ions to come in to the neurons and decreasing excitability.

Classical benzodiazepines (BDZ) enhances the effectiveness of GABA by lowering the concentration of GABA required for opening the channel while barbiturates increase duration of action of GABA so both act as agonist and there is an antagonist (flumazenil) which prevent agonist from binding. Drugs act as agonist at this receptor are used mostly in anxiety and sleep disorder.
Benzodiazepines (BDZs): they are the most widely used anxiolytic drugs. They have largely replaced barbiturates in the treatment of anxiety since they are more effective and safe.

Actions they have no antipsychotic activity, no analgesia and no autonomic effects.

1- at low doses, they reduce anxiety by agonist effect on GABA<sub>A</sub> - Benzodiazepine receptor complex.

2- all BDZs have sedative activity and at high doses certain BDZs produce hypnosis.

3- several BDZs have anticonvulsant activity.

4- BDZs relax the spasticity of skeletal muscle by increasing presynaptic inhibition in spinal cord.
Uses:

1- anxiety disorders: for severe, chronic and anxiety disorders that accompany depression and schizophrenia. Used for short period because of addiction potential. Longer acting agent (diazepam) used in patients required long term treatment or high-potency, intermediate-duration (lorazepam). Help people to cope with stress.

For panic disorder alprazolam is effective.
2- muscle disorder: (reduction of muscle tone and coordination) diazepam is useful in treatment of skeletal muscle spasm e.g. muscle strain and spasticity of degenerative muscle diseases. Has influence on manual skills (!)

3-epilepsy: by increasing seizure threshold. Clonazepam is useful in chronic treatment of epilepsy while diazepam is drug of choice in status epilepticus.
4-sleep disorder: Three BDZs are effective hypnotic agents; long acting flurazepam, intermediate acting temazepam and short acting triazolam. They decrease the time taken to get to sleep and increase the total duration of sleep.

5-control of alcohol withdrawals symptoms include diazepam, chlordiazepoxide, clorazepate and oxazepam.

6-in anesthesia: as preanesthetic amnesic agent (also in cardioversion) and as a component of balanced anesthesia.
Flurazepam significantly reduce both sleep induction time and numbers of awakenings and increase duration of sleep and little rebound insomnia. It may cause daytime sedation.

Temazepam useful in patients who experience frequent awakening, peak sedative effect occur 2-3 hr. after an oral dose.

Triazolam used to induce sleep in recurring insomnia and in individuals have difficulty in going to sleep, tolerance develop within few days and withdrawals result in rebound insomnia therefore the drug used intermittently.
Pharmacokinetics:
The BDZs are lipophilic and are rapidly and completely absorbed after oral dose.

$\frac{t_1}{2}$ have important therapeutic usefulness and they divided into short, intermediate and long acting, the longer acting agents have active metabolites, BDZs metabolized by hepatic microsomal system through hydroxylation and conjugation with glucuronic acid
Short-Term Effects
(Low Doses)

- **Euphoria**
  - “Being in a happy world”

- **Fatigue**
  - Feeling drowsy

- **Shallow breathing**
  - Not being able to take full, deep, normal breaths

- **Trouble coordinating your movements**
Short-Term Effects (High Doses)

- **Paranoia**: Having an unrealistic perception of something, someone, or some place in relationship to the world and you.
- **Aggression**
- **Easily agitated**
- **Difficulty remembering**
- **Irritability**
Cognitive Effects

- Memory impairment/Amnesia
- Confusion
- Sleepiness
Effects in Overdose

- Unconsciousness
- Respiratory depression
- Collapse of heart and heart functions
- Walking difficulty
- CNS depression
- Shallow breathing
  - Not being able to take full, deep, normal breaths
The use of benzodiazepines can lead to abuse, whether they are taken properly or for the wrong reasons.

- **Dependence**: Psychological and physical dependence on BDZs can develop if high doses of the drugs are given over a prolonged period. Abrupt discontinuation of the BDZs result in withdrawal symptoms. Short acting BDZs induce more abrupt and severe withdrawal reactions.
Withdrawal Symptoms

- Tachycardia – increase in heart rate
- Severe headaches
- Panic attacks can occur
- Tremors
- Changes in perception – not fully in tune with, or aware of, everything going on around you
- Weight loss
- Parasthesias
  - Pins and needles/tingling feeling
Tolerance: (gradual escalation of dose needed to produce the required effect), it occurs with all BDZs as dose dependence which is their main drawback and appears to represent a change at the receptor level.

It is less marked than it is with barbiturates which produce pharmacokinetic tolerance because of induction of hepatic drug metabolizing enzyme
Benzodiazepine antagonist **flumazenil** it is a GABA receptor antagonist that can rapidly reverse the effect of BDZs. It is available by i.v. administration only, onset is rapid and duration is short \( t_{1/2} \) is 1 hr., frequent administration may be necessary to maintain reversal of a long acting BDZs. It may precipitate withdrawal symptoms in dependent patients and may cause seizures if BDZ is used to control seizures. Side effects include dizziness, nausea, vomiting and agitation.
Non-BDZ anxiolytic:

1- Zolpidem: It is not related to BDZs group but act on the same receptor, has no anticonvulsant or muscle relaxing properties. It shows no withdrawal effects, exhibits minimal rebound insomnia with little or no tolerance. It is rapidly absorbed after oral administration and has rapid onset of action with short t_{1/2}. Side effects include nightmares, agitation, headache, GI upset, dizziness and daytime drowsiness.

2- Zopiclone: rapid onset of action (1hr.), effective for insomnia with few side effects and less withdrawal reactions, action prolonged in hepatic insufficiency and in elderly.
3-**Zaleplon** rapid onset and short duration of action, no effect on psychomotor skills like driving.

4-**Buspirone** structurally unrelated to BDZs, mode of action is by selective activation of the inhibitory presynaptic $5\text{HT}_{1A}$-receptor not like BDZs, used for generalized anxiety disorder with no anticonvulsant or muscle relaxant effects. Causes minimal sedation and less side effects and dependence is unlikely. It has short onset of action. Side effects nausea, dizziness, headache and restlessness.
5-Hydroxyzine antihistamine with antiemetic activity, useful for patients with anxiety who have history of drug abuse and for sedation prior to dental procedure or surgery.

miscellaneous other drugs-
older sedative-hypnotics:
  meprobamate, glutethimide
  rarely used
Barbiturates: They were formerly the mainstay of treatment used to sedate the patient or to induce and maintain sleep. They have been replaced nowadays by BDZs because they induce tolerance, drug metabolizing enzymes, physical dependence and very severe withdrawal symptoms and cause coma in toxic doses.

Mode of action: they interfere with Na\(^+\) and K\(^+\) ions transports across cell membrane lead to inhibition of reticular activating system and increase duration GABA action.
They are classified according to their duration of action; long acting, short acting and ultra short acting.

e.g. **thiopental** acts within seconds and duration of action is 30 minutes used for i.v. induction of anesthesia.

**Phenobarbital** duration of action greater than a day is useful in treatment of seizures. **Pentobarbital**, **secobarbital** and **amobarbital** are short acting effective as hypnotic rather than sedative (antianxiety) agents.
Actions

1- depression of CNS: at low doses, they produce sedation and at high doses produces hypnosis followed by anesthesia, coma and death, with no analgesic effect.

2- respiratory depression: barbiturates suppress the hypoxic and chemoreceptors response to CO2 and in over doses lead to decrease respiratory rate and death.

3- enzyme induction: barbiturates induce P-450 microsomal enzymes in the liver, so chronic barbiturates administration diminishes the action of many drugs that are depend on P-450 enzymes in metabolism to reduce their concentrations.
4-Drug hangover: hypnotic doses of barbiturates produce a feeling of tiredness well after the patient awaken. This drug hangover leads to impaired ability to function normally for many hours after waking.

5-Increase porphyrin synthesis so it is contraindicated in acute intermittent porphyria.

6-Abrupt withdrawal may cause tremors, anxiety, weakness, nausea, vomiting, delirium and cardiac arrest.
Uses:
1- anesthesia
2- anticonvulsant
3- sedative and hypnotic but largely replaced by BDZs.
Non-barbiturate sedatives:

1- **Chloral hydrate** is trichlorinated derivative of acetaldehyde that is converted to trichlorethanol in the body. It induces sleep in about 30 minutes and lasts up to 6 hr. It is irritant to GIT and produce unpleasant taste sensation.

2- **Ramelteon** melatonin receptors are thought to be involved in maintaining circadian rhythms underlying the sleep-wake cycle. Ramelteon is an agonist at MT1 and MT2 melatonin receptors, useful in patients with chronic insomnia with no rebound insomnia and withdrawal symptoms.
3- **Ethanol (alcohol)** it has antianxiety sedative effects but its toxic potential outweighs its benefits. Ethanol is a CNS depressant producing sedation and hypnosis with increasing dose.

Absorption of alcohol taken orally is rapid, it is highly lipid soluble, presence of food delayed its absorption, maximal blood concentration depend on total dose, sex, strength of the solution, the time over which it is taken, the presence of food and speed of metabolism.
Alcohol in the systemic circulation is oxidized in the liver principally 90% by alcohol dehydrogenase to acetaldehyde and then by acetaldehyde dehydrogenase to products that enter the citric cycle.

Alcohol metabolism by alcohol dehydrogenase follows first order kinetics in the smallest doses.
Once the blood concentration exceeds about 10 mg/100 ml, the enzymatic processes are saturated and elimination rate no longer increases with increasing concentration but become steady at 10-15 ml/ 1 hr. in occasional drinkers. Thus alcohol is subject to dose dependant kinetics i.e. saturation or zero order kinetics.
Actions

**Ethanol** acts on CNS in a manner similar to volatile anesthetic. It also enhances GABA so stimulating flux of chloride ions through ion channels. Other possible mode of action involve inhibition of Ca-channels and inhibition of excitatory NMDA receptors.

Ethanol has non selective CNS depressant activity. It causes cutaneous vasodilatation, tachycardia and myocardial depression,
Ethanol increases HDL-cholesterol to LDL-cholesterol ratio in plasma so it reduces coronary heart diseases risks.

It has irritant effect on lung and nasal tissue.

On GIT it stimulates gastric acid secretion,

On kidney it inhibits ADH release,

On sex increases desire but inhibits performance,

On fetus causes small babies and congenital malformations.
Uses: antiseptic, counterirritant and appetite stimulator.

Side effects: nausea, vomiting, hangover, disulfiram like reaction (disulfiram this drug inhibits acetaldehyde dehydrogenase results in accumulation of acetaldehyde and other keton bodies leading to flushing, burning sensation, headache, vomiting, postural hypotension and collapse, some other drugs have this effect if administrated together with alcohol like griseofulvin, sulfonylurea and metronidazole).
Tremor of limbs is usual manifestation in alcohol drinker and thought to be due to consumption of vit.B6, administration of vit.B6 will restore the nervous tone. acute intoxication with alcohol results in hypotension, collapse, coma, respiratory failure and death.

Other drugs that have sedative effects include: antipsychotics, antidepressants and antihistamines.