Sedatives, Hypnotics and Anxiolytics

Anxiolytics: the drugs that relieve anxiety with little CNS depression

Sedatives: the drugs that quiet the excited or agitated patient

Hypnotics: the drugs that induce sleep and useful in the treatment of insomnia.

Drugs in this group include benzodiazepines, barbiturates, buspirone, chloralhydrate, and meprobamate

Other drugs include beta-blockers and H1-antihiatamines

I. Benzodiazepines:

Examples: diazepam, lorazepam, temazepam and nitrazepam , chlordiazepoxide, oxazepam. All these drugs act by the same mechanism and only differ in pharmacokinetic parameters as the half-life and route of metabolism

A. Mechanism of action of benzodiazepines:

The benzodiazepines are similar in chemical structure to the inhibitory neurotransmitter gamma amino butyric acid (GABA), an inhibitory neurotransmitter. They act by binding to the benzodiazepine site at the GABA receptors, which leads to the opening of chloride ion channels and the potentiation of the action of GABA. So benzodiazepines potentiate the actions of GABA. There are different sub-types of benzodiazepine receptors which mediate different actions. Benzodiazepines act on the brain reticular system and the limbic system. There are endogenous substances that can bind to benzodiazepine receptors and probably relieve anxiety. In addition there are endogenous substances called inverse agonists that can combine to the benzodiazepine receptors but produce anxiety as carbolines.

Benzodiazepine antagonist as flumazenil can also combine with benzodiazepine receptors and antagonize all the actions of benzodiazepines.

B. Pharmacokinetics of benzodiazepines:

Well absorbed when given orally. The absorption of intramuscular injection is less rapid and irregular, so it is not preferred to be given by this route while the intravenous injection produces rapid effect and useful in emergency. The benzodiazepines are highly protein bound (85%). The major site of metabolism is the liver, the metabolism include chemical biotransformation followed by conjugation with glucuronide to be excreted in the urine. Liver disease leads to reduced rate of metabolism and increased toxicity, in this case lorazepam and oxazepam are preferred as they are metabolised by conjugation only. Most of the metabolites of benzodiazepines are pharmacologically active and this leads to prolongation of their pharmacological action. The metabolism of benzodiazepines decreases with age, so the dose should be reduced in the elderly patients. Also the dose should be reduced in patients with liver disease.

C. Clinical uses of benzodiazepines:

1. Anxiety and panic state: both acute and chronic anxiety can be treated with benzodiazepines , the lowest effective dose should be used for the shortest possible time to avoid tolerance and dependence, drugs used include diazepam, chlordiazepoxide and lorazepam
2. Insomnia (difficulty to go to sleep), benzodiazepines reduce the latency to sleep and prolonged the sleeping time. They reduce rapid eye movement (REM) sleep but to a lesser extent than other hypnotics. Drugs with shorter half-life as nitrazepam are preferred to avoid prolonged sedation
3. Muscle relaxation, due to inhibition of polysynaptic reflexes in the spinal cord, they are especially useful in pain and muscle spasm associated with

injuries and inflammatory condition, diazepam is usually used. Benzodiazepines are also useful in tetanus to relieve muscle spasm

4. Anticonvulsants in status epileptics and in febrile convulsions in children, usually given intravenously or rectally as diazepam or lorazepam
5. In epilepsy as antiepileptic, like clonazepam which is useful in some form of epilepsy specially in children
6. Pre-an aesthetic medications to reduce anxiety before surgical operations and to produce anterograde amnesia (loss of memory after drug administration) for the procedure
7. Alcohol and hypnotics drug withdrawal state, to relieve the symptoms of withdrawal as chlordiazepoxide and diazepam

D. Adverse effects of benzodiazepines:

1. On the central nervous system, cause sedation, drowsiness, ataxia and amnesia, slowing of reaction time impair driving skill and predispose for accidents
2. Rapid intravenous injection may lead to respiratory and cardiovascular depression which may be fatal in patients with cardiac or respiratory diseases
3. Dependence and tolerance: prolonged use of benzodiazepines can lead to both physical and psychological dependence and withdrawal symptoms (occur when the patient suddenly stops taking the drug) characterized by severe anxiety, insomnia, tremor and convulsions associated with nausea, vomiting and loss of appetite. It is therefore recommended that these drugs stopped gradually by dose reduction with time specially after prolonged use

4. Overdose lead to CNS and respiratory depression followed by coma, which is much less severe than barbiturate. Benzodiazepines rarely cause death in overdose when ingested alone, but death might occur when taken with other CNS depressant drugs
5. Drugs interaction, benzodiazepines potentiate the effect of other CNS depressants as alcohol, antihistamines and barbiturates.

E. Benzodiazepine antagonist

Flumazenil

acts by binding to benzodiazepine receptors it can reverse the effects of benzodiazepine overdose and toxicity. It should be given by intravenous injection. Usually repeated doses are needed because it has a short half-life. Can also be used to terminate the benzodiazepines action when used in endoscopy and intensive care.

Flumazenil can precipitate withdrawal symptoms in benzodiazepines dependent patients and it may cause convulsion, so should be given with caution in these patients. It may cause brief anxiety

F. Drugs with anxiolytic effects

1. Barbiturates

Example; phenobarbitone, primidone, pentobarbitone and thiopentone

Mechanism of action: Like benzodiazepines enhance the action of GABA, but they bind to different sites on the GABA-receptors/chloride channels, and their action on the CNS is less specific leading to more CNS depression

Barbiturates are less commonly used as hypnotics, sedatives or anxiolytics

Because:

a. Barbiturates have low therapeutic index (can cause respiratory and cardiovascular depression even when given in therapeutic doses)
b. Can rapidly cause strong physical dependence with withdrawal symptoms
c. They are potent enzyme inducers which may lead to wide interaction with other drugs
d. Highly toxic in overdose and frequently lead to death due to respiratory and CNS depression.

   But still barbiturates have other clinical uses

A. Pharmacokinetics:

Rapidly absorbed after oral administration with variable plasma protein binding, are metabolized by the liver and can induce hepatic drug metabolizing enzymes

B. Clinical uses:

1. epilepsy as antiepileptic in tonic-clonic epilepsy (oral phenobarbitone and primidone)
2. induction of anesthesia (I.V thiopentone), to make the patient unconscious quickly. Thiopentone is highly lipid soluble and acts within seconds when given intravenously
3. neonatal jaundice, as enzyme inducer (oral phenobarbitone), which induces the liver enzymes, so increases bilirubin conjugation to water soluble compound and enhances it renal excretion

C. Adverse effects:

1. hypotension and reduction of cardiac output and myocardial depression
2. drowsiness, dizziness and confusion
3. respiratory depression especially in patients with asthma and bronchitis

4. physical and psychological dependence with withdrawal symptoms as tremor, weakness , dizziness, distorted vision, delirium and convulsions in severe cases
5. Allergic reaction as skin rash
6. drug interactions; potentiate the effect of other CNS depressants and also induce metabolism of other drugs and reduce their effects

2. Meprobamate

Has sedative, hypnotic and anxiolytic effects. May cause excessive sedation and dependence liability, so it is less used in anxiety.

It is well absorbed when given orally, metabolized by the liver and has a significant enzyme inducing effect. Meprobamate is used as a muscle relaxant mainly to relieve muscle spasm by inhibiting spinal reflexes, due to potentiating the effect of GABA inhibitory transmitter in the spinal cord

Adverse effects: excessive sedation, drowsiness, dependence and withdrawal symptoms lead to insomnia, anxiety and convulsions

3. Chloralhydrate:

is used mainly as a hypnotic to induce sleep, it is given orally as solution to reduce gastric irritation and improve its bad taste. It induces sleep within half hour of oral dose. It is relatively safe in therapeutic doses but in high doses causes respiratory depression. Chloralhydrate is well absorbed from the intestine, metabolized by the liver into trichloro-ethanol (the active form of the drug) by the action of the enzyme alcohol dehydrogenase. Used mainly as hypnotic especially in children.

It interacts with alcohol because they are metabolized by the same enzyme and this will lead to inhibition of alcohol metabolism and increase its concentration and toxicity

2. Buspirone:

   Relieves anxiety with less sedative or euphoric effect. Buspirone differs from benzodiazepines in mechanism of action. Acts as a partial agonist at serotonin 5HT1A and dopamine D2 receptors.

   Has minimal dependence and abuse potentials

   Has less psychomotor impairment effect in comparison with diazepam

   Fewer interactions with CNS depressant drugs

   Well absorbed from the GIT and extensively metabolized by the liver and highly bound to plasma proteins (95%)

   It is effective in anxiety but has no muscle relaxant or anticonvulsant effects and does not potentiate the effect of other CNS depressant drugs

3. Zopiclone

   Acts like benzodiazepines on benzodiazepines/GABA receptors. Have similar effects to benzodiazepines, causes less dependence and fewer withdrawal symptoms

4. Chlormethiazole

   is related in structure to vitamin B1 (thiamine). It may act by altering dopamine function in the brain. It is mainly useful in the treatment of withdrawal state of alcohol. It has sedative, hypnotic and anticonvulsant effects

5. Beta-blockers in anxiety:

Beta blockers are useful in the treatment of autonomic symptoms of anxiety as tremor, palpitation and excessive sweating. The highly lipid soluble beta-blockers as propranolol are most useful as they can pass to the brain more easily.

6. Antihistamines:

   As diphenhydramine and chlorpheniramine

   H1 antihistamine has sedative effects probably not related to their histamine antagonist effect; this can be therapeutically useful when anxiety associated with allergic disease.

   Their potent anticholinergic effect prevents their abuse.