



Anxiolytic, Sedative and Hypnotic Drugs

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Anxiolytics: reduce anxiety

Sedatives: decrease activity, calming effect

Hypnotics: induce sleep

Some drugs have anxiolytic and
sedative/hypnotic effects.

CNS Depression

Sedation

Hypnosis

General Anesthesia

Poisoning

Death



Summary of Anxiolytic and Hypnotic Drugs

- Barbiturates.
- Benzodiazepines.
- Other anxiolytic drugs: buspirone, hydroxyzine and antidepressants.
- Other hypnotic agents: antihistamine, chloral hydrate, ethanol, ramelteon and zolpidem

Barbiturates

They have been largely replaced by the benzodiazepines, because Barbiturates:

- Induce tolerance
- Induce drug-metabolizing enzymes
- Physical dependence and
- Very severe withdrawal symptoms
- Narrow therapeutic index
- No specific barbiturate antagonist is available

Certain barbiturates, such as the very short-acting thiopental, are still used to induce anesthesia

Barbiturates are classified according to their duration of action into:

- Ultra-short acting :thiopental (20 minutes)
- Short acting: pentobarbital, secobarbital and amobarbital (3-8)hours
- Long acting: phenobarbital (1-2 days)

Mechanism of Action of Barbiturates

- The sedative-hypnotic action of the barbiturates is due to their interaction with GABA receptors, which enhances GABAergic transmission. The binding site is distinct from that of the benzodiazepines. Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride channel openings.
- In addition, barbiturates can block excitatory glutamate receptors.
- Anesthetic concentrations of pentobarbital also block high-frequency sodium channels. All of these lead to decreased neuronal activity.

Actions of Barbiturates:

- Depression of CNS: At low doses, the barbiturates produce sedation (calming effect, reducing excitement). At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation) and finally, coma and death. Thus, any degree of depression of the CNS is possible, depending on the dose.
- Barbiturates have no analgesic properties.

- Respiratory depression : over dosage cause respiratory depression and death.
- Circulatory collabs (by toxic dose)
- Enzyme induction: Barbiturates induce P450 microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are dependent on p450 metabolism example (phenytoin, anticoagulants)

Therapeutic uses of Barbiturates:

- **Anesthesia:** The ultra short-acting barbiturates, such as thiopental, are used intravenously to induce anesthesia.
- **Anticonvulsant:** Phenobarbital is used in long-term management of tonic-clonic seizures, status epilepticus, Phenobarbital has been regarded as the drug of choice for treatment of young children with recurrent febrile seizures.

- Anxiety: Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia. When used as hypnotics, they suppress REM sleep more than other stages. However, most have been replaced by the benzodiazepines.

Pharmacokinetics of Barbiturates

- Barbiturates are absorbed orally and distributed widely throughout the body. Barbiturates are metabolized in the liver, and inactive metabolites are excreted in the urine.
- They readily cross the placenta and can depress the fetus.

Adverse Effect of Barbiturates

1. CNS: Barbiturates cause drowsiness, impaired concentration, The CNS depressant effects of barbiturates synergize with those of ethanol.
2. Drug hangover: Hypnotic doses of barbiturates produce a feeling of tiredness well after the patient wakes. This drug hangover may lead to impaired ability to function normally for many hours after waking. Occasionally, nausea and dizziness occur.

3. Induce the P450 system and may decrease the duration of action of drugs that are metabolized by these hepatic enzymes.
4. Increase porphyrin synthesis, and they are contraindicated in patients with acute intermittent porphyria.
5. Physical dependence: Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, nausea, vomiting, seizures, delirium and cardiac arrest.
6. Poisoning: death resulting from drug overdoses because of severe depression of respiration and cardiovascular depression.



Potential
for Addiction



Vertigo



Drowsiness



Tremors



Nausea



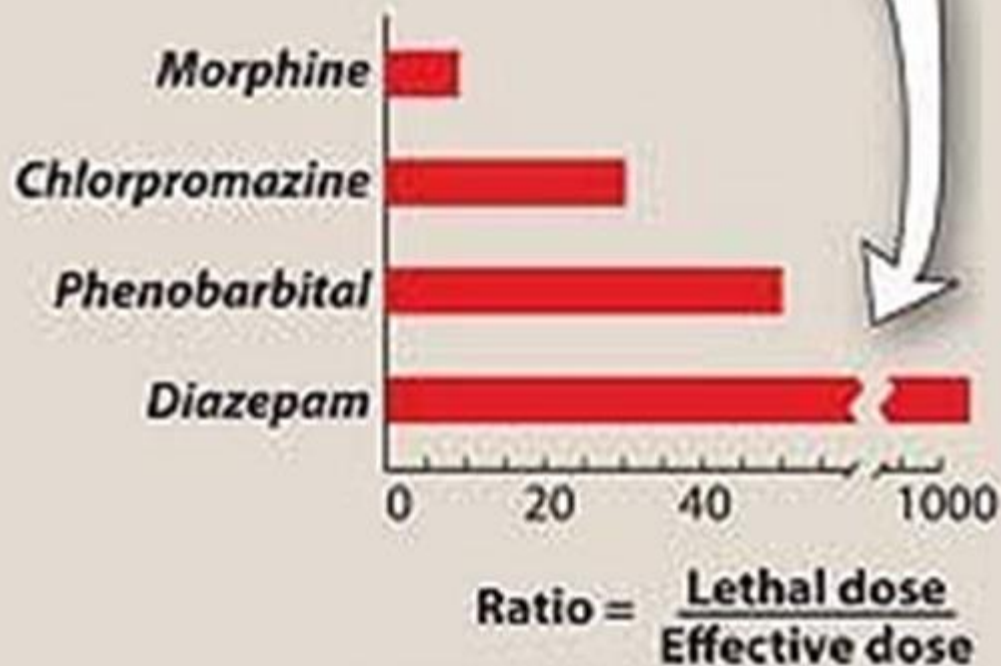
Enzyme
Induction

Treatment of Patient with Barbiturates Poisoning

- Artificial respiration
- purging the stomach of its contents if the drug has been recently taken
- Hemodialysis may be necessary if large quantities have been taken.
- Alkalinization of the urine often aids in the elimination of phenobarbital .

- Benzodiazepines are the most widely used anxiolytic drugs. They have largely replaced barbiturates because:
- The benzodiazepines are safer (have a wide therapeutic index) and more effective
- Not cause drug-drug interaction (not induce hepatic microsomal enzyme)
- Produce tolerance and psychological dependence but physical dependence and withdrawal symptom are less marked

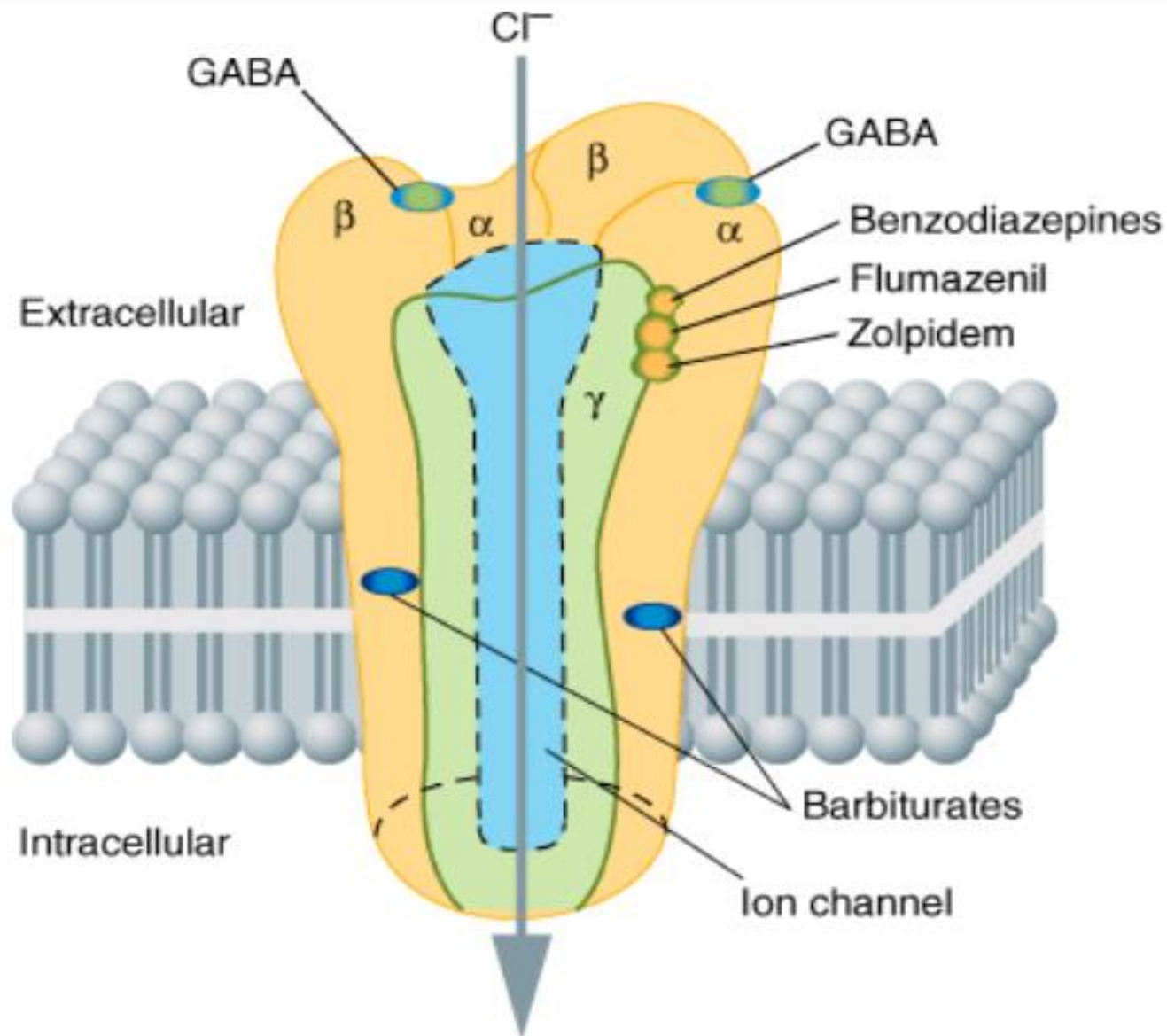
Benzodiazepines are relatively safe, because the lethal dose is over 1000-fold greater than the typical therapeutic dose.



Benzodiazepines are classified according to their duration of action into:

- Short-acting : Oxazepam, Triazolam (3-8) hours
- Intermediate-acting: Alprazolam, Lorazepam, Temazepam (10-20) hours
- Long-acting : Chlordiazepoxide, Diazepam and Flurazepam,

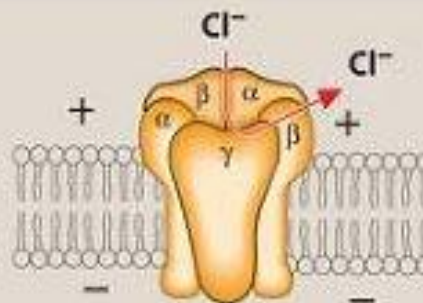
- Benzodiazepines
- **Anxiolytic:** Alprazolam, chlordiazepoxide, Diazepam and Lorazepam
- **Hypnotic:** Triazolam, Temazepam and Flurazepam.



Mechanism of Action:

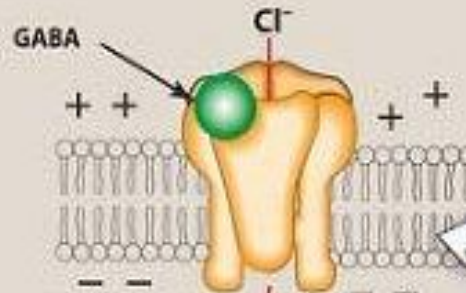
- Binding of GABA (the major inhibitory neurotransmitter in the central nervous system) to its receptor triggers an opening of a chloride channel, which leads to an increase in chloride conductance
- Benzodiazepines increase the frequency of channel openings produced by GABA. The influx of chloride ions causes hyperpolarization of the cell making it more difficult to depolarize and therefore reduces neural excitability

A Receptor empty
(no agonists)



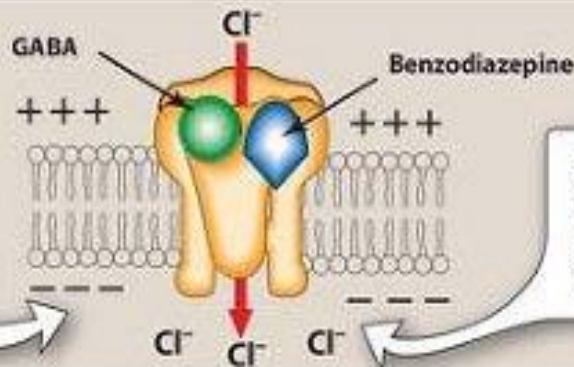
Empty receptor is inactive, and the coupled chloride channel is closed.

B Receptor binding GABA



Binding of GABA causes the chloride ion channel to open, leading to hyperpolarization of the cell.

C Receptor binding GABA and benzodiazepine



Entry of Cl^- hyperpolarizes the cell, making it more difficult to depolarize, and therefore reduces neural excitability.

Binding of GABA is enhanced by benzodiazepine, resulting in a greater entry of chloride ion.

Therapeutic uses:

- Anxiety disorders: Benzodiazepines are effective for the treatment of the anxiety. generalized anxiety disorder, specific phobias, such as fear of flying.
- The shorter-acting agents are used as premedication for anxiety-provoking and unpleasant procedures, such as endoscopic, bronchoscopic, dental procedures.

- Muscular disorders: Diazepam is useful in the treatment of skeletal muscle spasms, multiple sclerosis and cerebral palsy
- Midazolam is an injectable-only benzodiazepine also used for the induction of anesthesia

Seizures:

- Diazepam and lorazepam are the drugs of choice in terminating grand mal epileptic seizures and status epilepticus.
- Clonazepam is occasionally used in the treatment of certain types of epilepsy
- chlordiazepoxide, diazepam, and oxazepam are useful in the acute treatment of alcohol withdrawal

Sleep Disorders:

- Flurazepam: has a long-acting effect and causes no rebound insomnia.
- Temazepam: This drug is useful in patients who experience frequent wakening. the peak sedative effect occurs 1 to 3 hours after an oral dose; and should be given 1 to 2 hours before bedtime.
- Triazolam: short duration of action and, therefore, is used to induce sleep in patients with recurring insomnia.

Pharmacokinetics

- Completely absorbed after oral administration
- Most benzodiazepines, including chlordiazepoxide and diazepam, are metabolized to active compounds .
- The benzodiazepines are excreted in the urine as glucuronides or oxidized metabolites.
- Depress the CNS of the newborn if given before birth , nursing infants may also become exposed to the drugs in breast milk

Adverse Effects

- Drowsiness and confusion.
- Psychological and physical dependence on benzodiazepines can develop if high doses of the drugs are given over a prolonged period
- Withdrawal Symptoms, Including Confusion, Anxiety, Insomnia, Tension, Rarely and Seizures.

Benzodiazepine Antagonist

- Flumazenil (is a GABA-receptor antagonist) that can rapidly reverse the effects of benzodiazepines (competitively occupies a GABA-receptor without causing a functional change in CL channel) .
- For intravenous administration only.
- Rapid onset of action
- Short duration, with a half-life of about 1 hour.
- Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine

Side Effects:

1. Dizziness, nausea, vomiting, and agitation
2. Withdrawal in dependent patients
3. Seizures
 - If a benzodiazepine is used to control seizure activity
 - If the patient ingests tricyclic antidepressants

Other Anxiolytic Drugs (Buspirone, Hydroxyzine)

Buspirone

- Is useful in the treatment of generalized anxiety disorder
- Has efficacy comparable to that of the benzodiazepines.
- Mode of action differs from that of the benzodiazepines because:

The actions of buspirone appear to be mediated by

- Serotonin (5-HT_{1A}) receptors, buspirone displays some affinity for DA₂ dopamine receptors and 5-HT_{2A} serotonin receptors

Adverse Effects: Headaches, dizziness and nervousness

- Disadvantage: Buspirone has the slow onset of action

Hydroxyzine:

- An antihistamine with antiemetic activity.
- It is useful for patients with anxiety who have a history of drug abuse. It is also often used for sedation prior to dental procedures or surgery.
- Drowsiness is a possible adverse effect

Antidepressants:

Many antidepressants have proven efficacy in managing the long-term symptoms of chronic anxiety disorders and should be considered as first-line agents, especially in patients with concerns for addiction or dependence or a history of addiction or dependence to other substances.

The SSRIs, TCAs, venlafaxine, duloxetine and MAOIs all have potential usefulness in treating anxiety

Other Hypnotic Agents

Zolpidem

- Is not a benzodiazepine in structure, but it acts on a subset of the benzodiazepine receptor
- Zolpidem has no anticonvulsant or muscle-relaxing properties
- Adverse effects include nightmares, headache, gastrointestinal upset, dizziness and daytime drowsiness.

Ramelteon

- It is a selective agonist at the MT₁ and MT₂ subtypes of melatonin receptors
- Stimulation of MT₁ and MT₂ receptors by melatonin in the hypothalamus is able to induce and promote sleep
- Adverse effects of ramelteon include dizziness, fatigue, increase prolactin levels.

Chloral Hydrate

- The drug is an effective sedative and hypnotic
- Induces sleep in about 30 minutes and the duration of sleep is about 6 hours.
- Chloral hydrate is irritating to the gastrointestinal tract and causes epigastric distress

Antihistamines: Diphenhydramine

- They are effective in treating mild types of insomnia.
- They have numerous undesirable side effects such as anticholinergic effects (less useful than the benzodiazepines).