

SEDETIVES AND HYPNOTYIC DRUGS

INTRODUCTION

- When ANXIETY becomes excessive and disproportionate to the situation, it becomes a pathological condition and needs treatment.
- Anxiety involves both, Mental features (like worry, fear, difficulty in concentration, sleep problems) and physical symptoms (like tachycardia, nausea, shortness of breath, trembling, pacing).
- Anxiety can be treated by using sedatives and hypnotics.
- SEDATION refers to decreased responsiveness to any level of stimulation and is associated with decreased motor activity and ideation.

- SEDATIVE is a drug that subdues excitement and calms the subject without inducing sleep.
- HYPNOTIC is a drug that induces and/or maintains sleep, similar to normal arousable sleep.
- Sedatives and hypnotics are CNS depressants with somewhat differing time-action and dose-action relationship.
- Hypnotics have quicker onset, shorter duration and steeper dose response curves.
- Sedatives have slower onset, longer duration and flatter dose response curves.
- Hypnotics at lower doses may act as sedatives.
- Hypnotics at higher dose may act as general anaesthesia. Ex: Diazepam.

SLEEP

- Hypnotics induce sleep. The different phases of sleep and their characteristics are as follows:
 - STAGE 0 (Awake): From lying down to falling asleep and occasional nocturnal awakenings. It constitutes 1-2% of sleep time. EEG shows alpha activity when eyes are closed and beta activity when eyes are open.
 - STAGE 1 (Dozing): Alpha activity is interspersed with theta waves. Eye movements are reduced, but there may be bursts of rolling. Neck muscles relax. Occupies 3-6% of sleep time.

- **STAGE 2 (Unequivocal sleep):** Theta waves with interspersed spindles, K-complexes can be evoked on sensory stimulation; little eye movements, subjects are easily arousable. It comprises 40-50% of sleep time.
- **STAGE 3 (Deep sleep transition):** EEG shows theta, delta and spindle activity, K complexes can be evoked with strong stimuli only. Eye movements are few; subjects are not easily arousable, comprise 5-8% of sleep time.

- **STAGE 4 (Cerebral Sleep):** delta activity predominates in EEG, K-complexes cannot be evoked. Eyes are practically fixed, subjects are difficult to arouse. It comprises 10-20% of sleep.
- **REM Sleep (Paradoxical sleep):** EEG has waves of all frequency, K-complexes cannot be elicited.

CLASSIFICATION OF DRUGS

1 Barbiturates

Long acting	Short acting	Ultra-short
acting Phenobarbitone	Butobarbitone	
Thiopentone		
pentobarbitone	Methohexitone	

2. Benzodiazepines

Hypnotic : Diazepam Flurazepam Nitrazepam Alprazolam
Temazepam Triazolam

Antianxiety : Diazepam Chlordiazepoxide Oxazepam
Lorazepam Alprazolam

Anticonvulsant : Diazepam Lorazepam Clonazepam
Clobazam

3. Newer nonbenzodiazepine hypnotics : Zopiclone, Zolpidem Zaleplon

BARBITURATES

- Barbiturates are substitute derivative of barbituric acid .
- They have variable lipid solubility, the more they slouble once are more potent and shorter acting
- They are insoluble in water but their sodium salts dissolve yielding highly alkaline solution.
- Example : phenobarbitone, butobarbitone, methohexitone, pentobarbitone

MECHANISM OF ACTION

- interact with GABA receptors, the binding site is distinct from that of the BZs.
- potentiate GABA action on Cl^- entry into the neuron by increase the duration of Cl^- ion channel opening.
- In addition, barbiturates can block excitatory glutamate receptor (sub anesthetic dose).
- at high doses (anesthetics conc. of pentobarbital-reticular activating system inhibition), also
 - open Cl^- ion channels directly
 - and block high frequency Na^+ channels).

PHARMACOLOGY

CNS : barbiturates produces dose dependent effects :

Sedation  sleep  anaesthesia  coma

- Hypnotic dose shortens the time taken to fall asleep and increases sleep duration. The sleep is arousable. Night awakenings are reduced. The effects on sleep become progressively less marked if the drug is taken every night consecutively.
- Sedative dose (smaller dose of a longer acting barbiturate) given at daytime can produce drowsiness, reduction in anxiety and excitability. However, barbiturates do not have selective antianxiety action.
- Higher dose of a barbiturate induce a predominance of slow, high voltage EEG activity.

- **RS** : respiration is depressed by relatively higher doses. Neurogenic, hypercapneic and hypoxic drives to respiratory centre are depressed in succession. Barbiturates do not have selective antitussive action.
- **CVS** : Hypnotic doses of barbiturates produce a slight decrease in BP and heart rate: magnitude of change not differing from that during normal sleep. Toxic doses produce marked fall in BP due to ganglionic blockade, vasomotor centre depression and direct decrease in cardiac contractility. Reflex tachycardia can occur.
- **Skeletal muscle** : Hypnotic doses have little effect but anaesthetic doses reduce muscle contraction by depressing excitability of neuromuscular junction.

- **Smooth muscles:** Tone and motility of bowel is decreased slightly by hypnotic doses; more profoundly during intoxication. Action on bronchial, ureteric, vesical and uterine muscles is not significant.
- **Kidney :**Barbiturates tend to reduce urine flow by decreasing BP and increasing ADH release. Oliguria attends barbiturate intoxication.

ADME :

- Barbiturates are well absorbed from the GI tract.
- They are widely distributed in the body. The rate of entry into CNS is dependent on lipid solubility. Plasma protein binding varies with the compound, e.g. thiopentone 75%, pentobarbitone 35%, phenobarbitone 20%. Barbiturates cross placenta and are secreted in milk; can produce effects on the foetus and suckling infant.
- Metabolism Drugs with intermediate lipid-solubility (short-acting barbiturates) are primarily metabolized in liver by oxidation, dealkylation and conjugation. Their plasma t_{1/2} ranges from 12-40 hours.
- Excretion Barbiturates with low lipid-solubility (long-acting agents) are significantly excreted unchanged in urine.

Barbiturates induce hepatic microsomal enzymes and increase the rate of their own metabolism as well as that of many other drugs.

- **ADR :**

Mental confusion, excitement, precipitation of porphyria, rashes, swelling of eye lids, tolerance and dependence may occur

- **USES :**

- phenobarbitons are used in epilepsy
- Thiopentone are used as anaesthesia.

BENZODIAZEPINES

- This class of drug has proliferated and has replaced barbiturates as hypnotic and sedative, because-
 1. BZDs produce a lower degree of neuronal depression than barbiturates . They have high therapeutic index.
 2. Hypnotic doses do not affect respiration or cardiovascular functions. Higher doses produce mild respiratory depression & hypotension which is problematic only in patients with respiratory insufficiency or cardiac/haemodynamic abnormality

3. BZDs have practically no action on other body systems. Only on IV injections the BP falls and cardiac contractility decreases. Fall in BP in case of diazepam and lorazepam is due to reduction in cardiac output.

BENZODIAZEPINE MECHANISMS OF ACTION

Affect neurons that have receptors for the neurotransmitter GABA

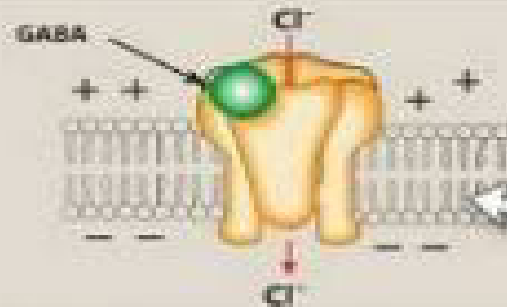
BZs potentiate GABA → increase frequency of Cl⁻ ion channel opening → causes hyperpolarization → raise firing threshold → and thus inhibits the formation of action potentials → inhibitory effect on different sites of the brain especially motor cortex, and limbic system.

A Receptor empty
(no agonists)



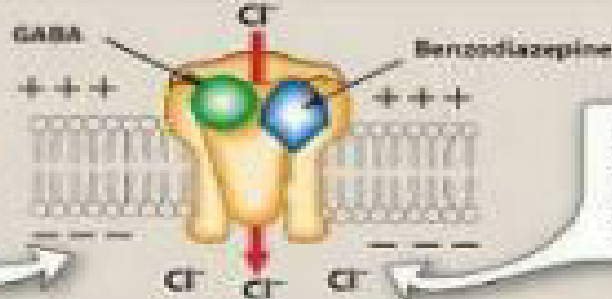
Empty receptor is inactive, and the coupled chloride channel is closed.

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.

PHARMACOKINETICS

- Most of them are well absorbed orally.
- Bzs are lipid soluble and widely distributed
- Redistribution from CNS to skeletal muscles, adipose tissue.
- Cross placental barrier during pregnancy and are excreted in milk (Fetal & neonatal depression).
- Highly bound to plasma protein.

PHARMACOKINETICS

- All Bzs are metabolized in the liver
 - Phase I: (liver microsomal system)
 - Phase II: glucouronide conjugation and excreted in the urine.
- Many of Phase I metabolites are active: Increase elimination half life of the parent compound , cumulative effect with multiple doses.
- EXCEPT No active metabolites are formed for (LEO) Lorazepam, Estazolam, Oxazepam.

PHARMACOLOGY

- In contrast to barbiturates, they are not general depressants, but exert relatively selective anxiolytic, hypnotic, muscle relaxant and anticonvulsant effects in different measures
- The antianxiety action of BZDs is probably not dependent on their sedative property; with chronic administration relief of anxiety is maintained, but drowsiness wanes off due to development of tolerance. they hasten onset of sleep, reduce intermittent awakening and increase total sleep time Time spent in stage 2 is increased while that in stage 3 and 4 is decreased. They tend to shorten REM phase.
- BZDs produce centrally mediated skeletal muscle relaxation without impairing voluntary activity. Clonazepam and diazepam have more marked muscle relaxant property. Very high doses depress neuromuscular transmission.

- Clonazepam, diazepam, nitrazepam and flurazepam have more prominent anticonvulsant activity than other BZDs. However, their utility in epilepsy is limited by development of tolerance to the anticonvulsant action.

Given i.v., diazepam (but not others) causes analgesia. In contrast to barbiturates, BZDs do not produce hyperalgesia

- Other actions Diazepam decreases nocturnal gastric secretion and prevents stress ulcers. BZDs do not significantly affect bowel movement. Short-lasting coronary dilatation is produced by IV diazepam

NON-BENZODIAZEPINE HYPNOTICS

- Act on a specific subset of BZD receptors. Their action is competitively antagonised by the BZD antagonist flumazenil, which can be used to treat their overdose toxicity. The non-BZD hypnotics act selectively on $\alpha 1$ subunit containing BZD receptors and produce hypnotic- amnesic action with only weak anxiolysis, muscle relaxant and anticonvulsant effects.
- Example : zopiclone, zolpidem, zaleplon

- **USES :**

- 1. Used as anxiolytic and for day time sedation.**
- 2. Used as anticonvulsant.**
- 3. Used as centrally acting muscle relaxants.**