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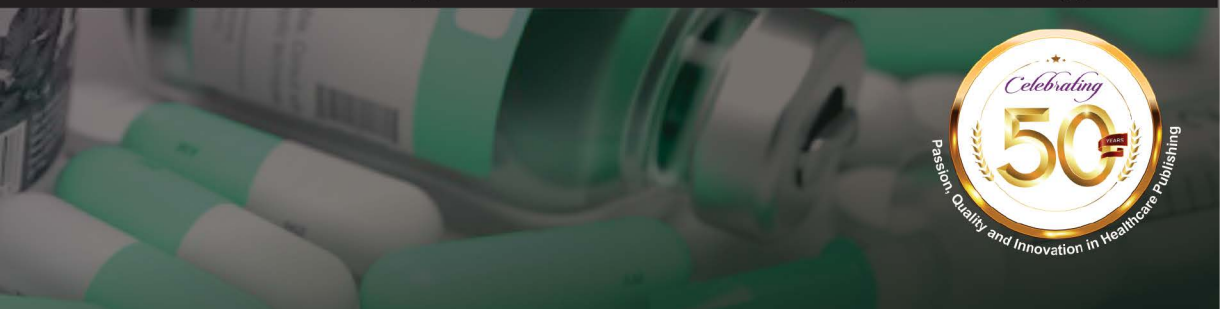

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Handbook of PHARMACOLOGY for the Anesthesiologists



Lopamudra Chowdhury

Foreword
Manjushree Ray

JAYPEE

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CHAPTER 4

Hypnotics and Sedatives

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DEFINITIONS

- **Sedatives:** Agents which depress central nervous system (CNS) activity producing a calming effect or drowsiness.
- **Hypnotics**: Agents which facilitate the onset and maintenance of sleep.

HISTORY

- Alcoholic beverages, laudanum and some herbs were used to induce sleep.
- Bromide was the first agent to be used as sedative hypnotic in the middle of the nineteenth century.
- Other agents like chloral hydrate, paraldehyde, sulfonal and urethane were also used.
- Phenobarbital was introduced in 1912.
- Chlordiazepoxide synthesized by Sternbach, actions explained by Randall, was introduced for use in 1961. Thus began the era of benzodiazepines.

All agents with sedative hypnotic effects may be broadly classified as benzodiazepines, barbiturates, nonbenzodiazepines or Z-compounds. Sedation may be an adverse effect of the other agents like antihistaminics, antipsychotics, or other central nervous system (CNS) depressants like alcohol.

CLASSIFICATION

Benzodiazepines

- Ultrashort acting (t½ <½ hr), e.g. Midazolam.
- Short acting (t½ <6 hr), e.g. Triazolam.
- Intermediate-acting (t½:6–24 hr), e.g. Temazepam.
- Longacting (t½: >24 hr), e.g. Diazepam.

Barbiturates

- *Ultrashort-acting*: Thiopentone sodium and methohexitone.

- *Shortacting*: Pentobarbitone and butobarbitone.
- *Long-acting*: Phenobarbitone.

Newer Nonbenzodiazepines or Z-compounds

Zolpidem, zaleplon and zopiclone.

Melatonin Congener

Ramelteon.

Others

Buspirone, chloral hydrate and paraldehyde.

MECHANISM OF ACTION

The $GABA_A$–BZD–Cl^- channel receptor is composed of five subunits of α, β, γ and any of δ, ε, θ, or Π subunits. There are multiple subtypes of the benzodiazepine receptor, of which $2\alpha_1$, $2\beta_2$, γ_2 pentamer is most common.

Benzodiazepines

Act selectively on benzodiazepine receptor, an integral part of $GABA_A$ receptor—chloride channel complex; binding site between two α_1 and γ_2 subunits interphase enhances presynaptic and postsynaptic inhibition by:

- Enhancing response to GABA.
- Facilitating opening of GABA-activated chloride channels.

Barbiturates

Act on α or β subunit of $GABA_A$ receptors in central nervous system (CNS), at sites different from that of benzodiazepines and increase the duration of opening of the chloride channels.

Nonbenzodiazepines

Act selectively on GABA receptor isoforms containing α_1 subunits and exert more selective action. As α_2 and α_3 subunits of $GABA_A$ receptor are associated with anxiolytic and muscle relaxant activity, these drugs are devoid of these effects.

Others

Alcohol, intravenous anesthetic agents like propofol,etomidate, thiopentone act on β_2, β_3 subunits of the $GABA_A$ receptor.

Antagonists bicuculline blocks GABA binding while flumazenil is a specific competitive antagonist at the benzodiazepine-binding site.

BENZODIAZEPINES

Pharmacokinetics

- All are absorbed orally.
- Have huge lipid-water distribution coefficient in nonionized form.

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- Rate of oral absorption differ according to lipophilicity; most barbiturates and newer hypnotics are absorbed rapidly into the blood.
- Extensive distribution crosses BBB, placental barrier and secreted in milk.
- Plasma protein binding varies markedly (e.g. 99% for diazepam while 10% for flurazepam).
- Metabolized in the liver, many produce active metabolites, e.g. flurazepam, diazepam, chlordiazepoxide, alprazolam.
- Ultrarapid elimination seen with triazolam and midazolam.
- Half-life 2–40 hours; long half-life as with diazepam, flurazepam, lorazepam and clonazepam.
- Metabolites are excreted in urine as glucuronide conjugates.

Actions

Anxiolysis and muscle relaxation produced by benzodiazepines are mediated through γ subunit, whereas its anticonvulsant action is mediated through α_1-subunit of $GABA_A$ receptor. The site of action of muscle relaxation is at spinal cord level and requires higher doses than the doses required for other actions.

- Reduction of anxiety and aggression.
- Sedation and induction of sleep.
- Reduction of muscle tone and coordination.
- Anticonvulsant effect.
- Anterograde amnesia.
- Do not have antidepressant effect; poor analgesia.
- May increase irritability and aggression in some individuals.
- Benzodiazepine withdrawal symptoms more commonly seen with short-acting compounds.

Hypnosis

- Hasten onset of sleep.
- Increase total duration of sleep.
- Proportion of rapid eye movement (REM) sleep is reduced.
- Duration of stage 2 non-rapid eye movement (NREM) is increased.
- Duration of stage 4 non-rapid eye movement (NREM) sleep is decreased.
- Growth hormone secretion remains unaffected.

  Abrupt cessation of drug may result in rebound in REM sleep; tolerance develops if drug is used for > 4–6 weeks.

Sedation

Sedation is a function of GABA receptors containing α_1 subunit.

- Calming effect at relatively low doses.
- Depressant effects on psychomotor and cognitive functions.
- Euphoria.
- Impaired judgement, loss of self-control.
- Dose-dependent anterograde amnesia.

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Other Actions

- *Anesthesia*: IV anesthesia, induction of anesthesia; diazepam, midazolam, lorazepam.
- *Muscle relaxation*: Inhibitory effect on polysynaptic reflexes and internuncial neurons; meprobamate and diazepam.
- *Anticonvulsant*: Clonazepam, diazepam, lorazepam and nitrazepam.
- *Respiratory and cardiovascular system*: Dose related depression of medullary respiratory center and or vasomotor center causing respiratory depression or circulatory collapse.
- Anxiolytic and anterograde amnesia are the most desired effects; also utilized in premedication.

Adverse Effects

- Dizziness, headache, vertigo and ataxia.
- Amnesia, delayed reaction time and impaired psychomotor skills.
- Weakness, blurring of vision, dry mouth and urinary incontinence.
- Paradoxical actions, e.g. Irritation, anger.
- Tolerance and cross-tolerance.

Drug Interactions

- Synergistic with alcohol and other central nervous system (CNS) depressants.
- CYP/3A4 inhibitors, e.g. ketoconazole, erythromycin, cimetidine, INH, oral contraceptive pills (OCP) retard benzodiazepine metabolism.

Uses

- *Anxiety states*: Generalized anxiety disorders, panic disorders and agoraphobia.
- *Sleep disorders*: Newer nonbenzodiazepine hypnotics are better.
- *Seizure disorders*: Diazepam, clonazepam.
- *IV anesthesia*: Midazolam, diazepam.
  Preanesthetic medication
  In short surgical procedures, e.g. bronchoscopy and diagnostic procedures
  To control symptoms of ethanol or other hypnotic sedative withdrawal.

BARBITURATES

Classification

- *Long-acting*: Phenobarbitone.
- *Short-acting*: Butobarbitone and pentobarbitone.
- *Ultrashort-acting*: Thiopentone and methohexitone.
- Barbiturates are substituted derivatives of barbituric acid; general CNS depressants; cause dose-dependent—anxiolysis, amnesia, hypnosis, anesthesia, coma and respiratory depression.

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Pharmacokinetics

- Half-life 4–60 hours.
- Orally absorbed and widely distributed.
- Onset of action dependent on lipid solubility.
- Plasma protein binding varies; cross-placenta.
- Termination of action depends on redistribution effect, metabolism and excretion.
- Barbiturates with low-lipid solubility are excreted unchanged in urine.
- Barbiturates induce hepatic microsomal enzymes.

Uses

- *Epilepsy*: Phenobarbitone.
- *Anesthesia*: Thiopentone.
- *Hypnotic*: Secobarbital.
- *Congenital nonhemolytic jaundice and kernicterus*: Phenobarbitone.

Adverse Effects

Hangover, tolerance, dependence, idiosyncrasy, precipitation of porphyria in susceptible patients.

NEWER HYPNOTICS

Special Features

- Rapid onset of hypnosis.
- Minimum incidence of hangover, amnesic or psychomotor depressant action.
- Sleep pattern is minimally affected; withdrawal effect is not seen on discontinuation.
- Anticonvulsant, antianxiety or muscle relaxation effects are not evident especially with zolpidem.
- Short duration of effect.
- No tolerance or dependence noted.

Drugs

Eszopiclone, zaleplon and zolpidem.

Uses

Insomnia especially with prolonged sleep latency.

Ramelteon

- Melatonin receptor agonist.
- Activates MT_1 and MT_2 melatonin receptors in suprachiasmatic nuclei of central nervous system (CNS).

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- Rapid onset of sleep; minimal rebound insomnia or withdrawal symptoms.
- Orally active; active metabolite.
- *Adverse effects*: Dizziness, fatigue, decreases testosterone, increases prolactin.
- Used for sleep onset insomnia.

Flumazenil

- Benzodiazepine analogue with minimum intrinsic activity.
- Acts on benzodiazepine receptor and reverses the activity of benzodiazepines and zolpidem, zaleplon and zopiclone, no other sedative—hypnotics.
- Used IV; short half-life; oral bioavailability 16%.
- After IV injection-action starts within seconds and lasts for 1–2 hours.
- Reverses the hypnogenic, psychomotor, cognitive and EEG effects.
- Used in benzodiazepine overdose—0.2 mg/min IV.

BUSPIRONE

- Partial agonist at $5HT_{1A}$ receptors, may have activity against D_2 receptors as well.
- Slow onset of action; 1–2 weeks; no withdrawal symptoms or abuse liability.
- Anxiolytic action with minimum psychomotor impairment.
- No additive effect when given along with central nervous system (CNS) depressant drugs.
- *Orally active*: Active metabolite; short ½ life.
- *Adverse effects*: Tachycardia, paresthesia and GI distress.

COMPARATIVE STUDY OF COMMONLY USED DRUGS

Barbiturates

Drug	*Indications*	*Dose*	*Comments*
Phenobarbitone	Generalized tonic-clonic seizure, partial seizure; sedative hypnotic	15–20 mg 2–3 times/day	Prolonged duration of action; induce hepatic microsomal enzymes
Thiopentone 25 mg/mL in solution + 1.5 mg/mL Na_2CO_3	Ultrashort-acting intravenous anesthetic	Induction dose 2.5% solution 3–5 mg/kg	Duration 5–8 min, Highly alkaline, pH 10–11
Methohexital 10 mg/mL in solution + 1.5 mg/mL Na_2CO_3	Ultrashort-acting intravenous anesthetic	Induction dose 4–7 mg/kg	Duration of induction 4–7 min; pH 10–11

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Benzodiazepines

Drug	*Indications*	*Dose*	*Comments*
Diazepam	As hypnotic sedative, anticonvulsant, IV anesthetic	Oral, IM, IV, rectal 0.1–0.2 mg/kg; max 60 mg/day 5–10 mg tab/day; 2.5–5 mg suppository; 0.3–0.5 mg/kg for induction	Several active metabolites, sedation, minimal drug interactions
Lorazepam	As sedative, hypnotic	Oral, IM, IV; 1–2 mg OD/BD	Slower onset, more potent, profound amnesia
Midazolam	As IV anesthetic for induction and maintenance; anti-hallucinatory and anti-convulsant	IV, IM; premedication 0.07–0.08 mg/kg IM; induction 0.15–0.3 mg/kg; infusion 0.02–0.1 mg/kg/hr	Rapid onset of action; duration 6–8 min; liable to abuse, rapid metabolism
Alprazolam	Anxiety disorders	Oral	Intermediate-acting, withdrawal effect, residual effect present
Clonazepam	Seizure disorders, acute mania	Oral	Tolerance may develop
Chlordiazepoxide	Insomnia, anxiety disorders, anesthetic premedication, alcohol withdrawal	Oral, IM, IV 0.3–0.5 mg/kg/day; 10– 25 mg tab BD	Long-acting, produce active metabolites
Flurazepam	Insomnia	Oral; 15–30 mg/day	Long-acting
Nitrazepam	Insomnia	Oral; 0 0.5–1 mg/kg/day OD/BD	Long-acting
Temazepam	Insomnia	Oral; 7.5–15 mg/day	Intermediate-acting

Newer Benzodiazepines

Zolpidem	Insomnia	Oral; 5–10 mg at bed time	↓ REM sleep
Zaleplon	Insomnia	Oral; 5–20 mg at bed time	Shortest acting
Eszopiclone	Insomnia	Oral; 1–3 mg at bed time	↑ total sleep time

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