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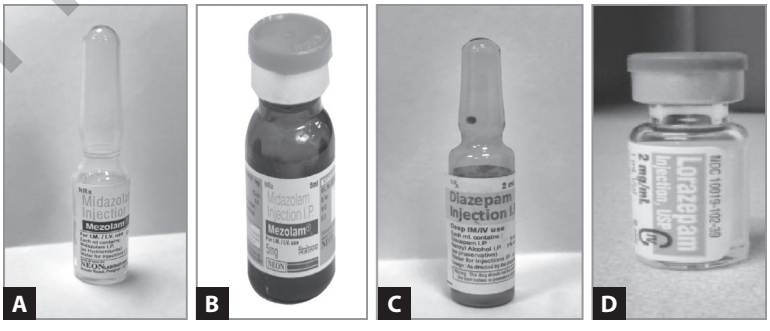
CHAPTER

4 Benzodiazepines

Amit Kumar, Nishkarsh Gupta

INTRODUCTION

- This class of drugs produces sedation, anxiolysis, hypnosis, anterograde amnesia, anticonvulsion, and centrally produced muscle relaxation. They do not have any analgesic properties.
- The most common intravenous benzodiazepines administered in the perioperative setting are midazolam, diazepam, and lorazepam **(Figs. 1A to D)**.
- These groups of drugs are frequently used for premedication, conscious sedation, and also for induction of general anesthesia in high doses.
- These drugs cause drowsiness, disorientation, unsteadiness, and acute confusional states. Also, postoperative cognitive dysfunction is seen especially in elderly patients.
- Side effects are rare (except for drowsiness and central depression), and may cause nightmares, nausea, skin rashes, and an increase in body weight when used for a prolonged duration. All of these drugs impair judgment, affect psychomotor behavior, increase reaction time, and may cause hangover effect on the day after their administration.
- These drugs alter the pattern of physiological sleep to increase stage 2 while decreasing stage 3, 4, and rapid eye movement REM sleep. There is a rebound phenomenon on stopping these drugs to compensate for earlier loss of REM sleep and associated with unpleasant dreams and nightmares.
- They do not induce hepatic microsomal enzymes and do not usually interact with



Figs. 1 to D: (A) Midazolam ampoule; (B) Midazolam vial; (C) Diazepam ampoule; and (D) Lorazepam ampoule.

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other drugs other than sedatives and hypnotics including alcohol use.
- Greater than 2–3 weeks of use may be associated with a significant risk of tolerance and drug dependence. Hypnotic effects get tolerance after 3–14 days of continual use. Physical dependence can be seen in up to 15% of patients on chronic use. In recent years, there is an increasing incidence of drug abuse for this group of drugs.
- There is a *benzene ring* in the chemical structure with a seven-member *diazepine ring*. Various substitutions on the rings distinguish individual drugs.
- Midazolam is water-soluble at low pH (3.5) and has aqueous preparations due to the imidazole ring; it increases lipid solubility at physiological pH by intramolecular rearrangement. The preserving agent, propylene glycol can cause venoirritation sometimes and can explain the pain on injection with midazolam. While intravenous diazepam and lorazepam contain propylene glycol which is water-insoluble and is associated with venous irritation.
- In supraclinical dosage, midazolam has antitumorigenic properties in certain types of cancers.
- Remimazolam an ultra-short acting $GABA_A$ agonist may be useful in future anesthesia practice.

MECHANISM OF ACTION

- Benzodiazepines act by enhancing γ-aminobutyric acid type A ($GABA_A$) receptors mediated inhibitory neurotransmission. These receptors are most numerous in the cerebral cortex, the cerebellar cortex, corpus striatum, and limbic system. Also, these receptors are present in the brainstem and spinal cord.
- $GABA_A$ receptors are transmembrane proteins with five subunits surrounding the intrinsic ion pore which is selective chloride ion permeable. These five subunits are derived from seven families and constitute 18 different types (α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, θ, and ρ_{1-3}).
- In the human brain >60% of GABA receptors contain three subunits in combination α_1, α_2, β_2, β_2, and γ_2. The receptors also contain barbiturates, steroids, and proconvulsive drug binding sites.
- Sedation, anterograde amnesia, and anticonvulsant effects are mediated via α_1 subunits of $GABA_A$ receptors. Anxiolysis and muscle relaxation are mediated via the α_2 subunits.
- Benzodiazepine binding site is at the interface between α and γ subunit close to histidine residue. Replacing histidine with arginine results in 1,000-folds decreased benzodiazepine affinity for the $GABA_A$ receptor.
- Benzodiazepines enhance and facilitate the effect of GABA by increasing affinity of GABA for the receptors. This increases the frequency of opening of a chloride channel in response to a given stimulus without increasing (or slight increase) the duration of channel opening resulting in neuronal hyperpolarization and inhibition.
- Depression of activity between the limbic system and reticular system causes decreased alertness and arousal reactions. Anticonvulsant effects occur due to inhibition of amygdaloid nuclei. Midazolam, diazepam, and lorazepam increase the seizure initiation threshold.
- Indirectly benzodiazepines may affect other neurotransmitters in central nervous system (CNS). They decrease 5-hydroxytryptamine (5-HT) and dopamine in specific regions of brain and prevent increase of stress-induced noradrenaline turnover.
- Intrathecal midazolam decreases the excitatory GABA mediated neurotransmission

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leading to a decrease in spinal dorsal horn neuron's excitability.
- The order for receptor affinity is lorazepam > midazolam > diazepam. Effects are dose-dependent. Receptor saturation can produce a ceiling effect.
- Flumazenil reverses the effects of benzodiazepines by acting as an antagonist on these same receptors.
- $GABA_B$ receptors which are mainly located in presynaptic sites in CNS and peripheral autonomic nerve terminals do not have high-affinity binding sites for benzodiazepines.
- The benzodiazepines preserve cerebral blood flow (CBF) to cerebral oxygen consumption ($CMRO_2$) ratio while decreasing the $CMRO_2$.
- Inverse agonist—some drugs when bind to benzodiazepine receptors may have proconvulsant effects (e.g., β-carboline esters) due to antagonism of spontaneous activity of benzodiazepine receptors. Benzodiazepine antagonist flumazenil may occasionally produce similar effects.

PHARMACOKINETICS

- These drugs are nonpolar and highly lipid-soluble. So, these are well-absorbed after oral administration, and have a large volume of distribution with high bioavailability.
- These are extensively bound to plasma proteins, but only an unbound fraction can cross the blood-brain barrier to have CNS effects.
- These drugs may be divided into hypnotics and sedatives/tranquilizers according to duration of action due to variation of half-lives. Hypnotics are with relatively short terminal half-life and sedatives/tranquilizers with relatively long half-lives.
- Diazepam and midazolam readily cross blood-brain barrier due to high lipid solubility and have onset of CNS effects within 2–3 minutes. Lorazepam has a slightly longer onset of action as it is moderately lipid-soluble. The effects of single dose are terminated within 3–10 minutes by redistribution **(Table 1)**.
- Metabolism of benzodiazepines via oxidation and glucuronide conjugation takes place in liver to transform these into water-soluble end products and minimal amounts are excreted unchanged. All benzodiazepines (except midazolam) have low intrinsic hepatic clearance which is not affected by liver blood flow.

TABLE 1: Physiochemical properties.

	Molecular weight (Da)	***pKa***	***Water solubility (g/L)***	***Lipid solubility (logP)***
Diazepam	284.7	3.4	0.051	2.801
Lorazepam	321.2	1.3	0.12	2.382
Temazepam	300.7	1.6,11.7	0.28	2.188
Midazolam	325.8 (hydrochloride 362.2)	6.0	0.004 (7.5, pH-1)	3.798
Remimazolam	439.3 (besylate 597.5)	5.3	0.008 (7.5, pH-1)	3.724
Flumazenil	303.3	0.86	0.042	2.15
Lipid solubility: Midaz > Remimazolam > diazepam > lorazepam > temazepam				
Water solubility: Midazolam = Remimazolam (at pH-1) > temazepam > lorazepam >diazepam > remimazolam > midazolam				

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- Midazolam has perfusion limited clearance due to a higher liver extraction ratio, whereas lorazepam and diazepam are cleared with dependence on enzymatic activity (capacity limited clearance).
- The metabolism of benzodiazepines may be impaired in liver function impairment and in presence of hepatic enzyme inhibitors. Cimetidine reduces metabolism of diazepam by binding to cytochrome P450. Erythromycin decreases the metabolism of midazolam. Heparin increases the unbound diazepam by displacing diazepam from protein binding sites.
- *Midazolam*:
  - Postoral ingestion, complete absorption. Peak plasma concentration achieved in 30–80 minutes.
  - Significant first-pass metabolism—> bioavailability <50%. Hepatic extraction ratio—0.30–0.40, metabolic clearance may be susceptible to hepatic blood flow.
  - Distribution half-life 6–15 minutes after intravenous administration.
  - 94–98% plasma protein binding.
  - Elimination half-life 1.7–3.5 hours.
  - Plasma clearance is 5.8–9.0 mL/kg/min— > higher compared to other benzodiazepines due to rapid oxidization of the fused imidazole ring.
  - It has pH dependent ring opening phenomenon. The commercial preparation has a pH of 3.5 in which the imidazole ring is closed making it water soluble but at pH of the blood which is more than 4, its ring opens and makes it highly lipophilic.
  - Factors affecting pharmacokinetics of midazolam include obesity, age, and hepatic cirrhosis.
  - It is metabolized by CYP3A4 and CYP3A5 to 1-hydroxymethylmidazolam and 4-hydroxymidazolam. 1-hydroxymidazolam has 60% less affinity to receptors than the parent compound.
  - These metabolites are rapidly conjugated and renally excreted. Profound sedation may be seen in patients with renal impairment.
- *Diazepam*:
  - Postoral ingestion has around 94% bioavailability. Peak concentration after around 60 minutes.
  - It is extensively protein bound and has a volume of distribution of 0.7–4.7 L/kg.
  - Plasma clearance ranges between 0.2 and 0.5 mL/kg/min.
  - Obesity, liver dysfunction, and age affect pharmacokinetics.
  - It is metabolized by CYP2C19 and CYP 3A4 producing metabolite N-desmethyldiazepam which is further metabolized to oxazepam. Also, diazepam is metabolized to temazepam which is conjugated to temazepam glucuronide. A smaller part of temazepam is demethylated to oxazepam which gets conjugated to oxazepam glucuronide. N-desmethyldiazepam has similar characteristics to diazepam but has a prolonged elimination half-life of 200 hours.
  - It is not eliminated with hemodialysis making its overdose very toxic.
  - It shows a secondary peak in plasma concentration at 6–12 hours with possible resedation due to enterohepatic circulation.
- *Temazepam*:
  - Orally active BZD used for insomnia owing to its less tolerance potential and almost complete absorption after oral administration.
  - Major part (90%) is conjugated by the liver to 3-oxy glucuronide which is inactive and excreted in the urine.

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- Minor amounts demethylated to oxazepam. It is eliminated as a glucuronide conjugate.

- *Lorazepam*:
  - High oral bioavailability of around 90%. Peak plasma concentration around 120 minutes after oral ingestion.
  - Elimination half-life ranges from 8 to 25 hours with a mean of 15 hours.
  - It is >90% plasma protein bound with a higher volume of distribution from 0.8 to 1.3 L/kg.
  - Its clearance is 0.8–1.8 mL/kg/min, clearance decreases with liver dysfunction.
  - Conjugated in liver to inactive conjugate and is excreted in urine.
- *Remimazolam*:
  - New short-acting $GABA_A$ agonist which degrades by nonspecific esterases to its carboxylic acid metabolite. It has first-order pharmacokinetic elimination.
  - It has a more rapid onset of action, greater depth of sedation, and more rapid recovery than midazolam with no accumulation after prolonged infusion.
  - It has a large volume of distribution of 34.8 ± 9.4 L and has a rapid clearance of 70.3 ± 13.9 L/hour.
  - Possible benefit of safe administration by endoscopists compared with propofol.

PHARMACODYNAMICS

Cardiovascular System

- Under normal circumstances, sympathetic nervous system is tonically inhibited dependent on GABAergic signaling.
- Slight reduction in arterial blood pressure resulting from a decrease in systemic vascular resistance.
- Induction of anesthesia with benzodiazepine preserves the heart rate, ventricular filling pressure and cardiac output. Heart rate may rise due to preservation of homeostatic reflex mechanism or vagolysis.
- Combination with an opioid will produce a greater decrease in systemic blood pressure and reduce sympathetic tone.
- There is a plateau plasma drug effect above, which there is little change in arterial blood pressure.

Respiratory System

- These drugs affect muscular tone resulting in upper airway obstruction.
- Depresses ventilatory response to carbon dioxide.
- Depress the hypoxic ventilatory response.
- Dose-related central respiratory depression [more pronounced in patients with chronic obstructive pulmonary disease (COPD), old age, debilitating diseases] and additive synergistic effect in combination with opioids.
- Depresses swallowing reflex and upper airway reflex activity.

Cerebral

- Moderate reduction of CBF which parallel reductions CMR. (Narcotics< benzodiazepines < barbiturates).
- With 15 mg diazepam, a 25% reduction in CBF and $CMRO_2$ was seen in head injury patients.
- Midazolam 0.15 mg/kg to healthy volunteers decreased CBF by 30–34%.
- Dose-related reduction in $CMRO_2$ and cerebral blood flow CBF.
- Normal ratio of $CMRO_2$ to CBF.
- Preserves cerebral vasomotor responsiveness to carbon dioxide (CO_2).
- Potent anticonvulsant but not neuroprotective.
- Safe to administer in intracranial hypertension provided that respiratory

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depression [associated increase in partial pressure of carbon dioxide ($PaCO_2$)] or hypotension do not occur.
- Increases the seizure threshold to local anesthetic.
- Does not produce a burst suppression isoelectric pattern on electroencephalography (EEG).
- At lower doses, these behave like propofol causing consolidation failure while leaving encoding intact, whereas at higher doses significant encoding impairment emerges. These may reduce REM sleep when used as sedation in intensive care unit (ICU).

USES

Premedication

- Midazolam, diazepam, and lorazepam are frequently used drugs for premedication **(Table 2)**. Given for anxiolysis, sedation, amnesia, sympathicolysis, and reduction of postoperative nausea and vomiting (PONV). Amnesia caused is anterograde and no retrograde memory is affected.
- Midazolam is commonly used short-acting sedative anxiolytic, whereas lorazepam is used when prolonged and intense anxiolysis is pursued.
- Respiration and oxygen saturation are affected minimally with midazolam even with doses up to 1.0 mg/kg with a maximum of 20 mg.

Sedation

- It causes anxiety relief and possibility of recall of unpleasant event during diagnostic which actually accounts for prerequisite for sedation.
- Midazolam has a peak effect at around 2–3 minutes, whereas diazepam takes slightly longer and lorazepam even longer for peak effect. Recovery is similar with midazolam and diazepam due to similar early plasma redistribution patterns while lorazepam has longer-lasting effects.
- Compared to propofol for sedation, midazolam has a similar profile except that propofol has a rapid recovery.
- Remimazolam is a newer agent useful for procedural sedation especially upper gastrointestinal endoscopy.
- Studies found single dose midazolam may be safe for cesarean section as minimal fraction is transferred to 24 hours breast milk.
- It has been used for ICU sedation due to its suitable profile of hemodynamic stability and amnesia but is not without disadvantages of potential lingering sedative effect and high prevalence of delirium.

TABLE 2: Frequently used drugs for premedication.

		Midazolam	***Diazepam***	***Lorazepam***
Oral premedication (usual adult dose)		7.5–15 mg	5–10 mg	2–4 mg
Intravenous	Sedation*	0.5–1 mg repeated dose	2 mg repeated dose	0.25 mg repeated dose
	Induction	0.05–0.15 mg/kg	0.3–0.5 mg/kg	0.1 mg/kg
	Maintenance	0.05 mg/kg PRN 1 µg/kg/min	0.1 mg/kg PRN	0.02 mg/kg PRN

*Sedation is given for anxiety relief and for lack of recall of unpleasant events during a diagnostic procedure or minor surgical procedure

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Induction and Maintenance of Anesthesia

- Among benzodiazepines, midazolam is induction agent of choice with a dose of 0.1–0.2 mg/kg in premedicated patients and up to 0.3 mg/kg in unpremedicated patients. This single anesthetic dose gives amnesia for a period of around 1–2 hours.
- It has onset of anesthesia within 30–60 seconds.
- It has synergistic effects with other anesthetic agents and opioids. Emergence time depends on the dose of midazolam and adjuvant anesthetic agents.
- Benzodiazepines do not possess analgesic properties so must be combined with analgesic agents.
- After continuous infusions, the recovery time is prolonged with benzodiazepines due to accumulation especially diazepam and lorazepam compared to midazolam (as midazolam has a shorter context-sensitive half-life).

Nausea and Vomiting Prophylaxis

- Intravenous midazolam 2 mg, 30 minutes before end of surgery has been shown to reduce the incidence of PONV comparable to ondansetron 4 mg.
- Children (4–12 years) posted for strabismus surgeries when given intravenous midazolam 0.05 mg/kg reduced PONV compared to placebo or intravenous dexamethasone.
- However, midazolam is not recommended due to sedation-related adverse effects.

Side Effects and Toxicity

- Respiratory depression is the major side effect. Diazepam and lorazepam also have venous irritation and thrombophlebitis related to poor aqueous solubility and propylene glycol vehicles for dissolution.
- Benzodiazepines have limited allergenic effects and do not suppress adrenal gland.
- It can cross placenta to cause neonatal depression.
- The incidence of cleft palate may be increased with administration during first trimester of pregnancy.
- When used for sedation or for induction and maintenance of anesthesia, benzodiazepines may cause undesirable postoperative sedation, amnesia, and less frequent respiratory depression. Flumazenil may be used to reverse the residual effects.

Flumazenil

- It is a competitive antagonist for benzodiazepines at GABA receptors and is highly specific.
- Reversal occurs in 2 minutes and it has a peak effect at 10 minutes and duration of action of 30 minutes.
- It is short-acting with a half-life of 1 hour and is rapidly metabolized in liver. Rebound sedation can be seen with respiratory suppression, but is less likely when it is used to reverse midazolam which has more rapid clearance compared to other benzodiazepines.
- When flumazenil is used in small dosage in presence of large dose of agonist, it attenuates deep CNS depression (loss of consciousness and respiratory depression) without reducing the agonist effect that occurs at low fractional occupancy of receptors (drowsiness, amnesia).
  Dose: 0.2 mg/kg IV bolus followed by 0.1 mg/kg subsequently at an interval of 60 seconds.
- The CBF, cerebral metabolic rates (CMR), and intracranial pressure (ICP) lowering actions of midazolam are reversed with this agent.

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- It should not be given to reverse benzodiazepine when benzodiazepines are used to treat convulsions. Also, in head injury patients with poor ICP control can get severe increase in ICP with flumazenil and so it should be used with caution in patients with impaired intracranial compliance.

QUESTION

Q. 1. Various routes of administration of benzodaizepines.

FURTHER READING

1. Calvey TN, Williams N. Principles and Practice of Pharmacology for Anaesthetists, 5th edition. United States: Wiley-Blackwell; 2008.
2. Flood P. Stoelting's Pharmacology and Physiology in Anesthetic Practice, 5th edition. Haryana: Wolters Kluwer India Pvt. Ltd; 2015.
3. Griffin CE, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system–mediated effects. Ochsner J. 2013;13(2):214-23.
4. Gropper MA, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Cohen NH, Leslie K. Miller's Anesthesia, 2-Volume Set, 9th edition. Amsterdam: Elsevier; 2019.
5. Kilpatrick G. J. Remimazolam: Non-clinical and clinical profile of a new sedative/anesthetic agent. Front Pharmacol. 2021;12: 690875.
6. Olkkola KT, Ahonen J. Midazolam and other benzodiazepines. Handb Exp Pharmacol. 2008;(182), 335-60.
7. Rudolph U, Davies FM, Barr J. Benzodiazepines. In Evers A, Maze M, Kharasch ED (Eds). Anesthetic Pharmacology: Basic Principles and Clinical Practice. United Kingdom: Cambridge University Press; 2011. pp. 466-77.

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