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Comparative Phamacokinetic and Pharmacodynamic of Beta Blocker and Benzodiazepine Drugs to Treat Anxiety

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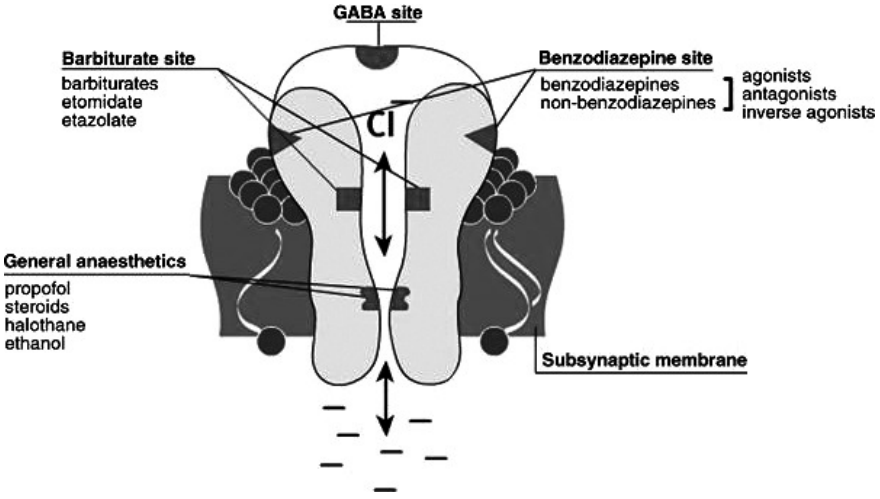
Abstract: *In the context of anxiety treatment, beta-blockers and benzodiazepines are distinct classes of medications with different pharmacological profiles. Beta-blockers, like propranolol, primarily act by blocking beta-adrenergic receptors, affecting physical symptoms of anxiety like palpitations and tremor. Benzodiazepines, on the other hand, like alprazolam, work by enhancing GABAergic neurotransmission, leading to sedation and anxiolysis. While both can be effective in reducing anxiety symptoms, their pharmacokinetic and pharmacodynamic properties differ significantly, influencing their suitability for different patients and anxiety presentations..*

Keywords: Adverse effects, benzodiazepines, central nervous system

I. INTRODUCTION

In the context of anxiety treatment, beta-blockers and benzodiazepines are distinct classes of medications with different pharmacological profiles. Beta-blockers, like propranolol, primarily act by blocking beta-adrenergic receptors, affecting physical symptoms of anxiety like palpitations and tremor. Benzodiazepines, on the other hand, like alprazolam, work by enhancing GABAergic neurotransmission, leading to sedation and anxiolysis. While both can be effective in reducing anxiety symptoms, their pharmacokinetic and pharmacodynamic properties differ significantly, influencing their suitability for different patients and anxiety presentations.



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Method

This review details the present knowledge about BZD mechanisms of action, drug profiles, clinical actions, and potential side effects. In addition, this review describes numerous types of BZD-mediated central nervous system effects.

Conclusion

For any patient taking a BZD, the prescribing physician must carefully evaluate the risks and benefits, and higher-risk patients require careful considerations. Clinically appropriate use of BZDs requires prudence and the understanding of pharmacology.

Introduction

Benzodiazepines (BZDs) are one of the most widely prescribed pharmacologic agents in the United States (more than 112 million prescriptions in 2007).[1] BZDs are used for numerous indications, including anxiety, insomnia, muscle relaxation, relief from spasticity caused by central nervous system pathology, and epilepsy. BZDs are also used intraoperatively because of their amnesic and anxiolytic properties. However, these properties become undesired side effects in nearly all other clinical instances.

The severity of BZD-induced adverse effects forces physicians to exercise caution and pay attention to side effects when prescribing this class of agents. Tolerance, dependence, age-related physiological changes, and drug-drug interactions are all important considerations. This review explains the mechanisms of action of BZDs, compares and contrasts popular BZDs on the market today, and describes specific BZD-mediated effects and side effects.

General/Pharmacodynamics

BZDs act as positive allosteric modulators on the gamma amino butyric acid (GABA)-A receptor. The GABA-A receptor is a ligand-gated chloride-selective ion channel.

GABA is the most common neurotransmitter in the central nervous system, found in high concentrations in the cortex and limbic system. GABA is inhibitory in nature and thus reduces the excitability of neurons. GABA produces a calming effect on the brain.[2] The 3 GABA receptors are designated A, B, and C. This article focuses primarily on the GABA-A receptor, with which BZDs interact.

The GABA-A receptor complex is composed of 5 glycoprotein subunits, each with multiple isoforms (Figure 1). GABA-A receptors contain 2 α subunits, 2 β subunits, and 1 γ subunit. Each receptor complex has 2 GABA-binding sites but only 1 BZD-binding site. The benzodiazepine binding site is in a specific pocket at the pairing (intersection) of the α and γ subunits. Within the α subunit of isoforms 1, 2, 3, and 5 resides a histidine residue (H101, H101, H126, and H105, respectively) that possesses a high affinity for BZDs.[3] Isoforms 4 and 6 of the α subunit contain an arginine residue and do not have an affinity for BZDs.[3] BZDs bind to the pocket created by the α and γ subunits and induce a conformational change in the GABA-A receptor, allowing GABA to bind. BZDs bind to the pocket created by α and γ subunits and induce a conformational change in the GABA-A receptor. This alteration, in turn, induces a conformational change in the GABA-A receptor's chloride channel that hyperpolarizes the cell and accounts for GABA's inhibitory effect throughout the central nervous system.[3]

Specific Benzodiazepine Receptors

The BZD receptor has been classified into several types, based on α subunit isoforms and clinical effects related to each type. The BZ1 receptor contains the α1 isoform. The BZ1 receptor is highly concentrated in the cortex, thalamus, and cerebellum;[4,5] it is responsible for the BZDs' sedative effects[6] and anterograde amnesia and for some of the anticonvulsive effects of diazepam.[7] Sixty percent of GABA-A receptors contain the α1 subunit. Therefore, amnesia is a common side effect of BZD use because the majority of GABA-A receptors contain the BZ1 receptor responsible for amnesia.[8] A major factor in predicting amnesia risk is lipid solubility; the greater the lipid solubility, the greater the risk of amnesia. BZDs with high lipid solubility have higher absorption rates and faster onset of clinical effects than BZDs with low lipid solubility.[2]

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BZ2 receptors contain the α2 isoform[4] and mediate the anxiolytic and, to a large extent, the myorelaxant effects of BZDs.[6] BZ2 receptors are highly concentrated in areas such as the limbic system, motor neurons, and the dorsal horn of the spinal cord.[7] The anxiolytic effects of BZDs are believed to be mediated through BZ2 receptors located in the limbic system, and myorelaxant properties are mediated via α2-containing receptors in the spinal cord and motor neurons.[7] Not all BZDs interact with the same type of BZ receptor or with equal affinity to a specific receptor. These differences in α subunit isoforms, BZ receptor type affinity, and location within the central nervous system account for the different effects of the various BZDs.[7]

Benzodiazepine Pharmacokinetics

The pharmacokinetic properties of a drug determine its onset of action and the duration of its effect. Specifically, pharmacokinetics describes the absorption, distribution, metabolism, and excretion of a drug (ie, what the body does to the drug). Pharmacodynamics describes the responsiveness of receptors to a drug and the mechanism by which these effects occur (ie, what the drug does to the body). Individuals respond differently to the same drug, and often these different responses reflect the pharmacokinetics and/or pharmacodynamics among different patients.

Pharmacokinetics (determination of the onset of action and the duration of drug effect) is affected by route of administration, absorption, and volume of distribution. BZDs can be administered via intramuscular, intravenous, oral, sublingual, intranasal, or rectal gel forms. Characteristics of the drug—including lipid solubility, binding to plasma proteins, and molecular size—influence the volume of distribution. Pharmacodynamics and pharmacologic drug effects are described in terms of dose-response curves that depict the relationship between the dose and the resulting pharmacologic effect. Dose-response curves predict the effect of the drug on the patient as doses increase. Titration of a drug should proceed based on the expected pharmacodynamics. Key considerations during titration of medications include making the appropriate choice for the patient's condition (eg, renal failure, liver failure, previous drug exposure), appropriate choice of incremental dosing (ie, time and quantity), and periodic monitoring.[9]

Preexisting disease processes and age-related changes affect elimination half-life, an especially important consideration when administering BZDs. Elimination half-life is the time necessary for plasma concentration of a drug to decrease to 50% during the elimination phase. Because elimination half-life is directly proportional to the volume of distribution and inversely proportional to its clearance, renal and hepatic disease (altered volume of distribution and/or clearance) affect elimination half-life.

Elimination half-life does not reflect time to recovery from drug effects. Elimination half-life is an estimate of the time needed to reduce the drug concentration in the plasma by half. After about 5 elimination half-lives, a drug is nearly totally eliminated from the body. Therefore, drug accumulation is likely if dosing intervals are less than this period of time.

From a pharmacological perspective, BZDs are usually well absorbed by the gastrointestinal tract after oral administration. After intravenous administration, BZDs quickly distribute to the brain and central nervous system. BZD activity is terminated by redistribution similar to that of the lipid-soluble barbiturates. Following intramuscular injection, absorption of diazepam or chlordiazepoxide is slow and erratic, whereas absorption of intramuscular administration of lorazepam or midazolam appears to be rapid and complete. Lorazepam is well absorbed after sublingual administration, reaching peak levels in 60 minutes.[2]

BENZODIAZEPINES IN CLINICAL PRACTICE

BZDs are classified in terms of their elimination half-life. Short-acting BZDs have a median elimination half-life of 1-12 hours, intermediate-acting BZDs have an average elimination half-life of 12-40 hours, and long-acting BZDs have an average elimination half-life of 40-250 hours.[2] As noted earlier, 5 half-lives are generally necessary for an agent to be eliminated from the body, making the number of hours that a drug is in the body considerably longer. The table lists various BZDs and their characteristics.[2]

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Benzodiazepines Commonly Prescribed in Clinical Practice

Drug	Protein Binding (%)	Half-Life Range (hr)	Major Active Metabolites (half-life in hr)	Time to Peak Plasma Concentration (hr)	Primary Elimination
Long half-life					
Chlordiazepoxide (Librium)	Very high (96)	5-30	Desmethylchlordiazepoxide (18) Demoxepam (14-95) Desmethyldiazepam (40-120) Oxazepam (5-15)	0.5-4	Renal (1-2), 3%-6% as conjugate
Clorazepate (Tranxene)	Desmethyldiazepam : Very high (95-98)	30-100	Desmethyldiazepam (40-120) Oxazepam (5-15)	0.5-2	Renal; fecal
Diazepam (Valium)	Very high (98)	20-80	Desmethyldiazepam (40-120) Temazepam (8-15) Oxazepam (5-15)	1-2 (Injection: intramuscular, 0.5-1.5; intravenous, within 0.25) (Sterile emulsion: intramuscular, >2; intravenous, 0.13-0.25) (Rectal gel: 1.5)	Renal
Flurazepam (Dalmane)	Desalkylflurazepam: Very high (97)	2.3	Desalkylflurazepam (47-100) *N*-1-hydroxyethylflurazepam (2-4)	0.5-1	Renal
Short to intermediate half-life					
Alprazolam (Xanax)	High (80)	6.3-26.9	None	1-2	Renal
Bromazepam (Lectopam)	High (70)	8-19	None	1-4	Renal
Clonazepam (Klonopin)	High (85)	18-50	None	1-2	Renal (<2)
Lorazepam (Ativan)	High (85)	10-20	None	1-6 (Intramuscular, 1-1.5; sublingual, 1)	Renal
Oxazepam (Serax)	Very high (97)	5-15	None	1-4	Renal; fecal
Temazepam (Restaril)	Very high (96)	8-15	None	1-2	Renal (<1)

Modified from Stoelting RK, Hillier S. *Pharmacology and Physiology in Anesthetic Practice*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006:140-153 and Barash PG, et al. *Clinical Anesthesia*. 6th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2009:586-588.

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