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Review Article

Benzodiazepines in epilepsy: pharmacology and pharmacokinetics

Benzodiazepines (BZDs) remain important agents in the management of epilepsy. They are drugs of first choice for status epilepticus and seizures associated with post-anoxic insult and are also frequently used in the treatment of febrile, acute repetitive and alcohol withdrawal seizures. Clinical advantages of these drugs include rapid onset of action, high efficacy rates and minimal toxicity. Benzodiazepines are used in a variety of clinical situations because they have a broad spectrum of clinical activity and can be administered via several routes. Potential shortcomings of BZDs include tolerance, withdrawal symptoms, adverse events, such as cognitive impairment and sedation, and drug interactions. Benzodiazepines differ in their pharmacologic effects and pharmacokinetic profiles, which dictate how the drugs are used. Among the approximately 35 BZDs available, a select few are used for the management of seizures and epilepsy: clobazam, clonazepam, clorazepate, diazepam, lorazepam and midazolam. Among these BZDs, clorazepate has a unique profile that includes a long half-life of its active metabolite and slow onset of tolerance. Additionally, the pharmacokinetic characteristics of clorazepate (particularly the sustained-release formulation) could theoretically help minimize adverse events. However, larger, controlled studies of clorazepate are needed to further examine its role in the treatment of patients with epilepsy.

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Introduction

Much attention has been focused on the introduction of new antiepileptic drugs (AEDs) into the US market during the past 15 years. Nonetheless, benzodiazepines (BZDs), which have been used since the 1960s, remain important in epilepsy management and are the drugs of first choice for status epilepticus and seizures associated with post-anoxic insult. Benzodiazepines also continue to play major roles in treating other conditions such as febrile seizures, acute repetitive seizures and alcohol withdrawal seizures. The major clinical advantages of BZDs are high efficacy rates, rapid onset of action and minimal toxicity. Few other drugs possess comparable attributes.

All BZDs share similar neuropharmacologic properties including anxiety reduction, sedation, sleep induction, anticonvulsant effects and muscle relaxation (1). There are, however, differences among BZDs in affinity for receptor subtypes, which may produce different pharmacologic effects. Thus, some BZDs are more effective than others as anticonvulsants; few of the approximately 35 BZDs available worldwide (2) are used for managing epilepsy. Diazepam and lorazepam are primarily used for management of seizure emergencies, whereas clobazam, clonazepam and clorazepate are commonly used in chronic epilepsy management. Midazolam often is used as an alternative to diazepam and lorazepam in seizure emergencies and for treating refractory status

epilepticus. The BZDs also have widely varying pharmacokinetic profiles, with differences in absorption, onset and duration of action and formation of active metabolites. Thus, pharmacokinetic differences often dictate the use of specific BZDs, route(s) of administration and formulation(s). Additionally, the nature and importance of side effects and drug interactions have been identified and clarified in recent years.

The purpose of this review was to provide clinicians with information for selecting BZDs and for managing BZD therapy in their patients. The article considers BZD pharmacology, pharmacokinetics, use in epilepsy management, tolerance and withdrawal. Also included in this review is an analysis and discussion of the effects of missed daily doses of immediate- and extended-release clorazepate formulations on plasma *N*-desmethyldiazepam (DMD) concentrations.

Benzodiazepine pharmacology

There are three principal γ-aminobutyric acid (GABA) receptor subtypes. Ligand-activated ion channels that are selectively blocked by bicuculline and modulated by steroids, BZDs, and barbiturates are known as $GABA_A$ receptors (3). The second receptor subtype, $GABA_B$, consists of G-protein-coupled, seven-transmembrane receptors, which are selectively activated by (*R*)-(−)-baclofen and 3-aminopropylphosphinic acid and are blocked by phaclofen (3). Transmitter-gated chloride channels, $GABA_C$ receptors, are selectively activated by certain conformationally restricted GABA analogs and are not modulated by steroids, BZDs or barbiturates (3).

Benzodiazepines bind to $GABA_A$ receptors, ionotropic transmembrane proteins located in the neuronal membranes of the central nervous system (CNS) (3). The $GABA_A$ receptor consists of a pentameric structure with multiple subunits that are necessary for normal physiologic function. The receptor subunits are assembled from combinations of 19 polypeptides (i.e. α1–6, β1–3, γ1–3, δ, ε, π, θ and ρ1–3) (4); different subunit combinations determine the pharmacologic properties of the receptor (5, 6). The number and types of subunits vary depending on the location of the receptor in the CNS (7). The inhibitory neurotransmitter GABA binds to the receptor to open the chloride ion gates and produce an inhibitory current (6, 8). Binding of BZDs to the γ subunit of the receptor is important in the potentiation of GABAergic inhibition (9). Differentiation between BZDs and GABA is important. Benzodiazepines do not substitute for

GABA, but instead enhance the inhibitory effects of GABA. Benzodiazepines allosterically bind to the receptor at a different location than GABA does and enhance the chloride channel's conductance by increasing the *frequency* of gated channel opening (6, 7, 10–12).

In the search for BZD site ligands with higher therapeutic selectivity and a more favorable safety profile, $GABA_A$ receptor subtypes have long been considered promising targets (13). The pharmacologic relevance of $GABA_A$ receptor subtypes has been identified using a gene knock-in strategy in rodents. Based on *in vivo* point mutations, α-1-$GABA_A$ receptors have been found to mediate sedation and anterograde amnesia and to partially mediate anticonvulsant activity, whereas α-2-$GABA_A$ receptors mediate anxiolysis (14, 15).

The basic chemical structure of BZDs is formed from the fusion of a benzene ring and a seven-membered diazepine ring (16) (Fig. 1). Clobazam is an exception with its 1-5-BZD structure (17). The common chemical structure of the BZDs accounts for their similar mechanisms of action.

In pharmacologic terms, BZD potency refers to the *in vivo* affinity of the drug (or its active metabolites) for its receptor (18). Benzodiazepines are classified as low, medium (e.g. clorazepate and diazepam) or high (e.g. clonazepam and lorazepam) potency (18, 19).

Benzodiazepine pharmacokinetics

Benzodiazepines have differences in their physiochemical properties, most notably lipid solubility, which influence their rate of absorption and diffusion into tissue compartments and their pharmacokinetics. Each BZD has a unique pharmacokinetic profile that must be considered when the optimal agent is selected for a particular patient and condition. Key factors to consider include
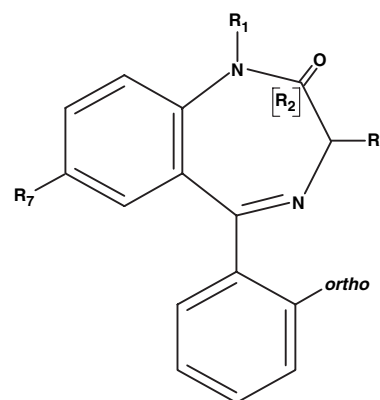

Figure 1. General chemical structure of 1,4- benzodiazepines.

route of administration, rate and extent of absorption, metabolism, formation of active metabolites, elimination and drug interactions (20).

Absorption and distribution

When orally administered, most BZDs are extensively and rapidly absorbed, with bioavailabilities varying from 80% to 100% and times to peak concentration ranging from minutes to several hours (Table 1). Midazolam is an exception, with low oral bioavailability due to metabolism by cytochrome P-450 (CYP) enzyme 3A5 in intestinal epithelial tissue, which can reduce by up to 50% the fraction of the dose reaching the bloodstream (24). Benzodiazepines cross the blood–brain barrier rapidly, although the diffusion rate into the brain varies by drug and is largely determined by lipophilicity (21). The faster the diffusion rate, the earlier is the onset of pharmacodynamic effects. Rapid entry of BZDs into the CNS and highly perfused tissues is consistent with their short distribution half-lives (21, 25). Following rapid uptake, BZDs redistribute into less well-perfused tissues; the rate of redistribution is the fastest for the most lipid-soluble drugs (25). After an intravenous (i.v.) BZD administration, BZD pharmacokinetics can be characterized by a multicompartmental mathematical model, with the first phase being distribution, followed by a longer elimination phase. Benzodiazepines also have large volumes of distribution, are highly bound to plasma proteins (Table 1) and readily cross into the placenta and breast milk (25).

Table 1 Summary of absorption and distribution pharmacokinetics of selected BZDs

Drug	F (%)	T_{max}	Protein binding (% bound)	Distribution half-life[a] (min)	V_d (l/kg)
Clobazam	87	1.3–1.7 h	82–90	NA	0.87–1.83
Clonazepam	>80	1–4 h	86	30 min (21)	1.5–4.4
Clorazepate[b]	PO: 100	PO: 0.5–2 h	96–98	6–29 min (22)	0.7–2.2
	IM: 91	IM: 2.7–11 h			
Diazepam	PO: 100	PO: 30–90 min	96–99	2–13 min (21)	0.95–2.0
	R: 90 (23)	IM: 30–60 min			
		R: 10–45 min			
Lorazepam	PO: 99	PO: 2.4 h	93.2	<11 min (21)	0.85–1.5
	IM: 96	IM: 1.2 h			
	SL: 94	SL: 2.3 h			
Midazolam	PO: 40	PO: 0.5–0.97 h	96	4–19 min (21)	0.7–1.7
	IM: 100	IM: 0.24–0.51 h			

Values refer to adults receiving monotherapy and are from Anderson and Miller (24) unless otherwise specified. BZD, benzodiazepine; F, bioavailability; T_{max}, time to maximum concentration; V_d, volume of distribution; NA, not applicable; PO, oral; IM, intramuscular; R, rectal; SL, sublingual.
[a]After intravenous administration.
[b]Pharmacokinetics for N-desmethyldiazepam after administration of clorazepate.

Metabolism and elimination

Benzodiazepines differ in their rates of elimination and the formation of pharmacologically active metabolites (Table 2). The elimination half-life ($t_{1/2}$) of a BZD or of its active metabolite is used to categorize BZD duration of effect: short acting (~< 10 h; lorazepam, midazolam), intermediate acting (10–24 h; clonazepam) or long acting (> 24 h; clobazam, clorazepate and diazepam) (43).

Benzodiazepine metabolism is primarily catalyzed by CYP-dependent hydroxylation, demethylation and nitroreduction (26, 44, 45). The CYP isoenzymes catalyzing these reactions include 3A4, 3A5, 2B6, 2C9 and 2C19 (Tables 2 and 3). Uridine diphosphate glucuronosyltransferase is also involved in the conjugation of some BZDs (Table 3).

Several BZDs have active metabolites. Diazepam and clorazepate are metabolized into the long-acting metabolite DMD (56). With multiple doses, the pharmacologic and toxic effects of diazepam are attributable to the parent drug, DMD, and other minor active metabolites (i.e. temazepam and oxazepam) (24). By contrast, clorazepate undergoes rapid and complete chemical conversion to DMD in the gastrointestinal tract; its pharmacologic effects are largely due to DMD (24, 56). N-Desmethyldiazepam undergoes glucuronidation to form a glucuronide conjugate (25%) and is hydroxylated (50%) by CYP 2C19 and CYP 3A4 to form oxazepam (24, 37). Approximately 5–9% of DMD is excreted unchanged in the urine (24). The $t_{1/2}$ of DMD ranges widely from 20 to 179 h (24, 33, 34, 38).

Other BZDs also have pharmacologically active metabolites. Clobazam is demethylated into an active metabolite (N-desmethylclobazam) (27). Midazolam is rapidly converted by CYP 3A4 and CYP 3A5 to 1-hydroxymidazolam, which contributes approximately 10% to the biologic activity of its parent drug (24, 41). Clonazepam and lorazepam undergo extensive metabolism, but no active metabolites are formed (18, 24).

Effects of pharmacokinetics and pharmacodynamics on BZD use – The differences in BZD pharmacokinetics and pharmacodynamics must be considered in order to use these drugs safely and effectively. Equivalent doses of BZDs differ as much as 20-fold because of differences in potency (57). The intensity of single-dose effects may vary, even if equipotent doses are used, because of varying oral absorption rates (58). Duration of action should be considered when choosing a BZD. When maintenance therapy is required (e.g. epilepsy and anxiety), long-acting BZDs are preferred because of their prolonged $t_{1/2}$, as effective drug concentrations can be maintained

Table 2 Summary of metabolism and elimination pharmacokinetics of selected BZDs

Drug	Primary metabolic pathway	Active metabolites	Elimination half-life of parent drug[a] (h)	Elimination half-life of active metabolites (h)
Clobazam	Demethylation (26)	N-desmethylclobazam (27)	10–30 (28)	36–46 (28)
Clonazepam	Nitroreduction (CYP 3A4), acetylation (NAT), hydroxylation (29–31)	NA	19–60 (32)	NA
Clorazepate	Decarboxylation, glucuronidation, hydroxylation (CYP 2C19 and 3A4) (24)	DMD (major), oxazepam (minor) (24)	NA	20–160 (24, 33, 34) Oxazepam: 6–24 (18)
Diazepam	Demethylation (CYP 2C9, 2C19, 2B6, 3A4, and 3A5), hydroxylation (CYP 3A4 and 2C19), glucuronidation (24, 35, 36)	DMD (major), oxazepam (minor), temazepam (minor) (24, 35, 37)	21–70 (23, 38)	DMD: 49–179 (33, 38) Oxazepam: 6–24 (18) Temazepam: 8–24 (18)
Lorazepam	Glucuronidation (24)	NA	7–26 (39, 40)	NA
Midazolam	Hydroxylation (CYP 3A4 and 3A5) (25, 41, 42)	1-hydroxymidazolam (minor) (24)	1–4 (24)	1 (24)

BZD, benzodiazepine; CYP, cytochrome P-450; NAT, N-acetyltransferase; NA, not applicable; DMD, N- desmethyldiazepam.
[a]Healthy subjects.

Table 3 Enzyme-mediated BZD metabolism and drug interactions

Enzyme associated with metabolism	BZD substrates	Inhibitors	Inducers
CYP 2C19	Diazepam (46)	Fluvoxamine (46) MHD (weak) (47) Omeprazole (46) Oxcarbazepine (46) Ticlopidine (46) Topiramate (46)	Dexamethasone (48) Phenobarbital (48) Phenytoin (49) Rifampin (46) St John's wort (50)
CYP 3A4	Clonazepam (29) Diazepam (46) Midazolam (46)	Azole antifungals (e.g. ketoconazole) (46) Cimetidine (46) Clarithromycin (46) Diltiazem (46) Erythromycin (46) Fluoxetine (51) Grapefruit juice (46) HIV protease inhibitor (46) Nefazodone (46) Sertraline (51)	Carbamazepine (46) Phenobarbital (48) Phenytoin (46) Rifabutin (46) Rifampin (52) Rifapentine (51) St John's wort (50)
UGT	Lorazepam (53) Oxazepam (54)	Valproate (55)	Carbamazepine (55) Lamotrigine (weak) (55) Phenobarbital (55) Phenytoin (55) Rifampin (52)

BZD, benzodiazepine; CYP, cytochrome P-450; MHD, monohydroxy derivative; HIV, human immunodeficiency virus; UGT, uridine diphosphate glucuronosyltransferase.

without the need for frequent dosing (56). Short-acting BZDs are preferred for intermittent hypnotic therapy, when the duration of action of the drug should be restricted to night-time, allowing patients to awaken feeling refreshed, without hangover effects (56).

Drug–drug interactions

Benzodiazepines interact with other drugs such as certain antidepressants, AEDs (e.g. phenobarbital, phenytoin and carbamazepine), sedative antihistamines, opiates, antipsychotics and alcohol (44, 57, 59), which may result in additive sedative effects.

As discussed earlier, BZD metabolism is complex and largely catalyzed by CYP isoenzymes. Consequently, there is potential for interactions between BZDs and drugs that induce or inhibit CYP isoenzymes. The clinical importance of these interactions depends on the net effect of inhibition or induction on the metabolic pathway of a particular BZD. For example, inhibition of a minor pathway may have little impact on drug concentration, whereas inhibition of a major pathway may result in enhanced clinical effect or toxicity. By contrast, addition of an enzyme-inducing drug that affects even a relatively minor pathway may lead to a clinically important reduction in plasma BZD concentration. For BZDs with active metabolites, the addition of an inhibitor or inducer may affect only the parent drug, only the metabolite, or both. Clinicians should exercise particular caution when using BZDs with selective serotonin reuptake inhibitors, cimetidine, macrolide antibiotics and antimycotics; these drugs may inhibit reactions catalyzed by certain CYP isoenzymes and, therefore, inhibit the metabolism of many BZDs, which results in increased plasma BZD concentrations (44). Conversely, potent enzyme inducers (e.g. phenytoin, phenobarbital and carbamazepine) substantially increase clearance and reduce the $t_{1/2}$ of certain BZDs (44). For a detailed review of pharmacokinetic drug interactions involving BZDs, see Tanaka (44).

Oral contraceptive steroids may inhibit the metabolism of some BZDs that undergo oxidative metabolism or nitroreduction and accelerate the metabolism of some BZDs that are conjugated. Interactions between BZDs and oral contraceptives are described in detail by Back and Orme (60).

Special populations

Elderly patients – Pharmacokinetics in older individuals differ from those in younger individuals because of age-related changes in physiology and the likelihood of concurrent diseases. Elderly individuals often have variable drug absorption, decreased plasma protein–drug binding due to lower albumin concentrations, and reduced hepatic and renal clearance (61). Additionally, many elderly individuals take multiple medications, which increase their risk of drug–drug interactions. Therefore, treatment of the elderly can be challenging.

Increased sensitivity of older patients to BZDs is partly due to reduced drug metabolism (when compared with younger adults), which can result in drug accumulation (62). Furthermore, BZD pharmacologic effects appear to be greater in elderly patients than in younger patients even at similar plasma BZD concentrations (63, 64), possibly because of age-related changes in drug–receptor interactions, post-receptor mechanisms and organ function. When a BZD is prescribed for an elderly patient, the initial maintenance dose should be half that recommended for younger adults (57), and BZD use should be only short term (limited to 2 weeks) (65). A short-acting BZD may be preferable for treating an elderly patient because such a drug is better tolerated than is a BZD or BZD active metabolite with a long $t_{1/2}$ (64).

Pediatric patients – Limited information is available regarding BZD absorption in children. Often, before children are administered medications, the tablet is crushed or the capsule is opened, and the contents are mixed with food or drink. Food and beverages may affect BZD bioavailability, but studies investigating this issue in children are lacking.

Drug metabolism is variable in children and depends on the biotransformation pathway. Cytochrome P-450-catalyzed metabolism tends to be low at birth, but exceeds adult values by age 2–3 years; thereafter, CYP-catalyzed metabolism decreases, reaching adult levels around puberty (66). Metabolism via glucuronidation tends to be low in neonates, reaching adult levels by age 3–4 years (66). In neonates, the $t_{1/2}$ of clorazepate is prolonged and clearance is decreased (67). Infants have reduced hydroxylation metabolism, which results in a decreased clearance of diazepam (68). The $t_{1/2}$ of midazolam is shorter in children than in adults: 0.79–2.83 h in children (69) vs 1.36–4 h in adults (24). Clinicians should consider how patient age may affect BZD clearance, because clearance will affect BZD dosing.

Special formulations of BZDs

Extended-release drug formulations can help patients with epilepsy achieve their primary treatment goals of controlling seizures while reducing side effects by minimizing fluctuations in drug concentration and by improving compliance. Extended-release formulations may also improve quality of life and patient satisfaction with treatment, in part by simplifying dosage regimens (70). Currently, clorazepate is the only BZD available in both a sustained-release, single-dose (Tranxene®-SD, Ovation Pharmaceuticals, Deerfield, IL, USA) formulation (11.25- and 22.5-mg tablets) and an immediate-release formulation that requires multiple doses per day (Tranxene® T-Tab; 3.75-, 7.5- and 15-mg tablets) that is approved in the USA for the treatment of seizures. Some BZDs are also available as oral liquids [diazepam (Diazepam Intensol; 5 mg/ml), lorazepam (Lorazepam Intensol; 2 mg/ml) and midazolam (generic only; 2 mg/ml)], disintegrating tablets [clonazepam (Klonopin® Wafer; Roche Pharmaceuticals, Nutley, NJ, USA; 0.125-, 0.25-, 0.5-, 1- and 2-mg tablets)] or a rectal gel [diazepam (Diastat® AcuDial; Valeant Pharmaceuticals International, Costa Mesa, CA, USA; 2.5-, 10- and 20-mg delivery systems)].

Effect of extended-release formulations on plasma BZD concentrations: pharmacokinetic simulations with clorazepate – Our group has performed simulation studies of plasma DMD concentrations over time to investigate differences between clorazepate formulations and to characterize the effect of missed doses with or without replacement doses under steady-state conditions when using the sustained-release and immediate-release formulations (71). These simulations were briefly described by Kaplan and DuPont (72), but detailed results are reported herein. The following simulations were performed for both formulations using WinNonlin® (Pharsight Corporation, version 4.1: Mountain View, CA, USA) software and a two-compartment, first-order, oral-absorption pharmacokinetic model: (1) steady-state conditions, (2) missed dose(s) without replacement and (3) missed dose(s) with replacement at the next scheduled dose. The following dosing schedules for the sustained-release and immediate-release formulations were entered to attain steady-state conditions (> 7 days): clorazepate sustained-release 22.5 mg – one tablet orally every 24 h for 20 days; and clorazepate immediate-release 7.5 mg – one tablet orally three times daily (given 6 h apart) for 20 days. The resulting simulated plasma DMD

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