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BENZODIAZEPINES: A SUMMARY OF PHARMACOKINETIC PROPERTIES

D.J. GREENBLATT, R.I. SHADER, M. DIVOLL & J.S. HARMATZ

Division of Clinical Pharmacology, Departments of Psychiatry and Medicine, Tufts University School of Medicine, New England Medical Center Hospital, 171 Harrison Avenue, Boston, Massachusetts 02111, USA

1 The onset and duration of action of benzodiazepines after single oral doses depend largely on absorption rate and the rate and extent of distribution, respectively.

2 The rate and extent of accumulation during multiple dosage depend on elimination half-life and clearance. A framework is proposed for classification of benzodiazepines according to elimination half-life.

3 Long-acting benzodiazepines have half-life values usually exceeding 24 hours. Drugs in this category have long-acting pharmacologically active metabolites (often desmethyldiazepam), accumulate extensively during multiple dosage, and may have impaired clearance in the elderly and those with liver disease.

4 Intermediate and short-acting benzodiazepines have half-life values from 5–24 hours. Active metabolites are uncommon. Accumulation during multiple dosage is less extensive than with the long-acting group, and diminishes as the half-life becomes shorter. Age and liver disease have a small influence on metabolic clearance.

5 The half-life of ultrashort acting benzodiazepines is less than 5 hours. These drugs are essentially non-accumulating.

6 Pharmacokinetic classification may assist in understanding of differences among benzodiazepines, but does not explain all of their clinical actions.

Introduction

THE pharmacologic properties of benzodiazepine derivatives are at the same time very similar and very different. Most studies assessing their intrinsic neuropharmacology indicate that all benzodiazepines possess anxiolytic, sedative-hypnotic, anticonvulsant, and muscle-relaxant effects (Greenblatt & Shader, 1974). Once differences in milligram potency among individual compounds are accounted for, the overall similarity of the drugs in pharmacological profile is far more striking than the differences.

However, it is clear that the effect of these drugs on the brain is dependent in large part, though not entirely, upon drug concentrations at the receptor site of action. In clinical terms, this means that physicians must choose not only a particular drug, but also the dose, interval between doses, and route of administration such that the desired brain concentration is achieved and maintained for an appropriate period of time. High concentrations may lead to excessive central nervous system depression, whereas receptor site concentrations that are too low may be therapeutically ineffective. The pharmacokinetic properties of the benzodiazepines are important determinants of the time-course and intensity of clinical action. In pharmacokinetic terms, there are major differences among the benzodiazepine derivatives.

Pharmacodynamics of single compared with multiple doses

The pharmacokinetic determinants of acute benzodiazepine effects may be quite different from determinants of clinical effects during long-term treatment.

Single-dose effects

Following oral dosage, the *absorption rate* is a major determinant of the subjective effect of a single dose. A rapid rate of absorption is associated with rapid onset of clinical effects such as anxiety reduction, drowsiness, and relaxation. When the absorption rate is slow, these acute subjective perceptions are attenuated or eliminated (Greenblatt, Shader, Harmatz, Franke & Koch-Weser, 1977; Shader,

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Georgotas, Greenblatt, Harmatz & Allen, 1978). The desirability of a slow or rapid absorption rate depends entirely upon the clinical circumstances. When a benzodiazepine is to be taken as a hypnotic, or if the drug is used to treat acute situational anxiety, rapid absorption is desirable. On the other hand, a fast absorption rate may be unfavourable if acute drug effects are perceived as unwanted drowsiness or as a dysphoric, disconnected ('spaced-out') sensation. Currently available data suggest that diazepam and clorazepate are among the most rapidly absorbed benzodiazepines, prazepam and oxazepam the least rapidly absorbed, with chlordiazepoxide, lorazepam, and flurazepam falling in between. Although diazepam and clorazepate are promoted mainly as anxiolytics, it is not surprising that they also are widely used as hypnotics.

The *duration* of action of a single dose depends upon the rate and extent of drug distribution, as well as the rate of elimination once distribution is complete. It is difficult to predict how these factors will interact. A single dose of diazepam, for example, may seem to have a short duration of action (George & Dundee, 1977) although its elimination half-life is long, ranging from 20–80 h even in young, healthy individuals (Greenblatt, Allen, Harmatz & Shader, 1980; Mandelli, Tognoni & Garrattini, 1978). This is attributable to the rapid and extensive distribution from blood into fatty tissues, causing prompt diminution or termination of single-dose effects. Lorazepam, on the other hand, has a much shorter elimination half-life averaging 15 hours (Greenblatt *et al.*, 1979*a*; Greenblatt *et al.*, 1979*b*), but the effective duration of a single dose of lorazepam may be relatively long, as its distribution is much less extensive and effective concentrations can persist in plasma and brain for many hours (George & Dundee, 1977).

Multiple-dose effects

The clinical effects of benzodiazepines during chronic or multiple-dose therapy depend in part upon the rate and extent of drug accumulation, which in turn are related to elimination half-life and clearance. After initiation of multiple-dose therapy, accumulation *rate* varies inversely with half-life—the longer is half-life, the slower is the rate of accumulation. In general, the steady-state condition is more than 90% attained after an interval of at least four times the half-life has elapsed since the start of treatment (Greenblatt & Koch-Weser, 1975). The *extent* of accumulation also is determined by half-life, as well as by the drug dosage and volume of distribution. The relative amount of accumulation—that is, the plasma concentration at steady-state relative to that at the start of therapy—becomes larger as half-life increases. Thus, drugs with long half-lives accumulate extensively and slowly, whereas short half-life implies that accumulation is not extensive and is completed rapidly.

It should be emphasised that clinical drug effects do not necessarily increase in direct proportion to plasma concentration during multiple-dose therapy. Adaptation or tolerance may balance or even outweigh the pharmacokinetic effects of drug accumulation. This is particularly true in the case of nonspecific central nervous system depression. For example, patients experiencing unwanted drowsines early in the course of diazepam therapy sometimes find that the sedative effects wane despite continued administration of the same dose and clear biochemical evidence of drug accumulation (Hillestad, Hansen & Melsom, 1974).

Pharmocokinetic classification

A useful approach to classification of benzodiazpine derivatives subdivides the drugs according to ranges of elimination half-life (Table 1). The scheme is only approximate, since half-life for any given drug may vary considerably among individuals. The categories also may overlap somewhat—nitrazepam and flunitrazepam, for example, may actually belong in the long-acting category. Finally, since research on benzodiazepine pharmacokinetics is very active, the availability of new information may necessitate substantial changes in our scheme.

Long

The long-acting benzodiazepines have a net biochemical half-life of 24 h or longer in the majority of individuals. Either the parent compound, or one or more of its pharmacologically active metabolites, account for this effectively long half-life. The half-life of chlordiazepoxide, for example, generally ranges from 5–30 h, but the half-life for the metabolites—particularly desmethyldiazepam—is considerably longer.

Endogenous biotransformation of long-acting benzodiazepines yields pharmacologically active metabolite products. The number of metabolites may be large—chlordiazepoxide and medazepam, for example, each have at least three active metabolic products (Table 1). Desmethyldiazepam, which itself has a long half-life reaching 200 h or more, is a metabolite of four long-acting benzodiazepines listed in Table 1, and also of several other benzodiazepines (halazepam, ketazolam, fosazepam, clazepam) for which precise kinetic data are not yet available. It is clear that desmethyldiazepam plays an important role in the clinical action of many benzodiazepines. Two derivatives, in fact (clorazepate and prazepam), do not reach the systemic circulation as such, and serve as prodrugs or drug precursors of desmethyl-

Table 1 Pharmacokinetic classification of benzodiazepine derivatives*

Parent compound	*Clinically important active metabolites*	*Selected references*
Long (effective half-life usually > 24 h)		
Chlordiazepoxide (5–30)	Desmethylchlordiazepoxide	
	Demoxepam	Greenblatt *et al.* (1978)
	Desmethyldiazepam (36–200)	
Diazepam (20–100)	Desmethyldiazepam (36–200)	Mandelli *et al.* (1978)
		Greenblatt *et al.* (1980)
[Clorazepate]†	Desmethyldiazepam (36–200)	Greenblatt & Shader (1978)
[Prazepam]†	Desmethyldiazepam (36–200)	Allen *et al.* (1979)
Medazepam	Desmethylmedazepam	Viukari & Linnoila (1977)
	Diazepam	deSilva & Puglisi (1970)
	Desmethyldiazepam (36–200)	
Clobazam (12–60)	Desmethylclobazam	Hanks *et al.* (1979)
[Flurazepam]†	Desalkylflurazepam (40–250)	(unpublished data)
Intermediate—short (half-life 5–24 h)		
Nitrazepam (15–38)		Breimer *et al.* (1977); Kangas *et al.* (1979)
Flunitrazepam (20–30)	Desmethylflunitrazepam	(unpublished data)
Estazolam (10–30)	? of hydroxylated metabolite	Allen *et al.* (1979)
Bromazepam (10–20)	? 3-hydroxybromazepam	Kaplan *et al.* (1976)
Alprazolam (6–20)		Unpublished data
Lorazepam (10–20)		Greenblatt *et al.* (1979*a*, 1979*b*, 1979*c*)
Temazepam (8–22)		Lader *et al.* (1979)
Oxazepam (4–15)		Shull *et al.* (1976); Chinnery & Sandwall (1978)
Ultrashort (half-life <5 h)		
Triazolam		Metzler *et al.* (1977)
Midazolam		Brown *et al.* (1979)

*Approximate range of elimination half-life values is shown in parentheses when the data are available.

†Brackets indicate prodrugs or drug precursors that do not reach the systemic circulation as such in clinically important amounts.

diazepam. This is not to say that clorazepate and prazepam are identical—they differ in the rate at which desmethyldiazepam reaches the blood after a single dose (rapid for clorazepate, slow for prazepam). This could cause important differences in acute effects following single doses. The hypnotic agent flurazepam is also a drug precursor or prodrug for another extremely long-acting, pharmacologically active metabolite, desalkylflurazepam (Figure 1).

Drug accumulation during multiple-dose therapy with long-acting benzodiazepines is a well documented phenomenon. Parent drugs and metabolic products may accumulate at different rates and to different extents, depending on the half-life and clearance of each compound (Figure 2). After termination of treatment, the rate of 'washout' of active substances parallels the slow rate of accumulation. When very long-acting compounds (such as desmethyldiazepam or desalkylflurazepam) are present, reappearance of pre-treatment symptoms of anxiety or insomnia is usually correspondingly slow even after abrupt discontinuation of the drug. However, this is not always true, particularly among individuals with severe underlying disease or in those who have developed considerable drug tolerance.

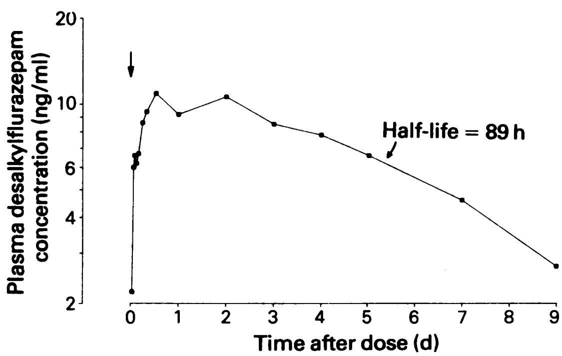

Figure 1 Plasma desalkylflurazepam concentrations for 9 d after a single dose of flurazepam hydrochloride 15 mg (at arrow) taken by a healthy elderly volunteer (female, 66 yr).

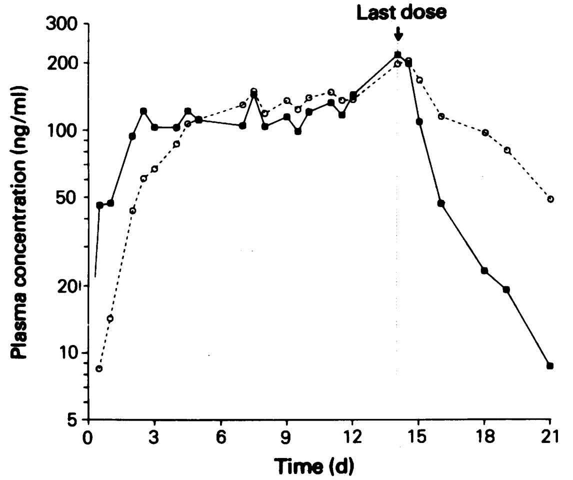

Figure 2 Plasma concentrations of diazepam (■) and desmethyldiazepam (O) in a 28-yr-old female volunteer who ingested diazepam 2.5 mg twice daily for 15 days.

The pattern of accumulation during treatment with long-acting benzodiazepines has both benefits and disadvantages. The possibility of single bedtime dosage may be a very desirable option for patients with anxiety not marked by severe within- and between-day fluctuations in symptomatology, or in those with symptoms of both anxiety or insomnia. A single daily dose of diazepam, clorazepate or flurazepam administered at bedtime may be sufficient for such patients. Furthermore, occasional omissions of dosage—whether deliberate or inadvertent—should not lead to acute reappearance of symptomatology. On the other hand, observed patterns of drug accumulation have caused concern regarding unwanted daytime drowsiness and impairment of psychomotor performance (Solomon, White, Parron & Mendelson, 1979). As discussed above, such effcts are at least partially offset by adaptation or tolerance. It is also possible that overall performance on relatively complex psychomotor tasks (such as automobile driving) is actually improved in patients receiving long-acting benzodiazepines whose performance would otherwise be impaired by the underlying condition of anxiety or insomnia if left untreated. Neverthless, it is prudent that patients taking long-acting benzodiazepines on a chronic basis be carefully informed both of the pharmacokinetic consequences of treatment, as well as the balance between risks and benefits.

The endogenous metabolic pathway of all long-acting benzodiazepines involves the hepatic oxidative reactions of N-demethylation, hydroxylation, or both. The efficiency of these reactions is importantly influenced by the age of the patient and by the status of hepatic function. Individuals over the age of 60 yr—even when they are healthy, ambulatory, and free of identifiable disease—have an impaired capacity to complete the hepatic biotransformation reactions of N-demethylation and hydroxylation. Thus, the half-life of long-acting benzodiazepines tends to be prolonged, and total metabolic clearance reduced, in elderly as opposed to young individuals. The magnitude of the age-related decrement can vary from slight to very marked, depending on the drug and the gender of the patient. For unknown reasons, the metabolic impairment among elderly males is considerably greater than that of females. Metabolic changes in old age have been documented for all long-acting benzodiazepines studied to date: chlordiazepoxide (Shader *et al.*, 1977; Roberts, Wilkinson, Branch & Schenker, 1978), diazepam (Klotz, Avant, Hoyumpa, Schenker & Wilkinson, 1975; Kanto, Maenpaa, Mantyla, Sellman & Valovirta, 1979; Greenblatt *et al.*, 1980), desmethyldiazepam (unpublished data) and flurazepam (unpublished data). Impaired metabolism could explain part of the increased sensitivity of elderly individuals to the effects of these drugs. Similarly, clearance of long-acting benzodiazepines is impaired in patients with cirrhosis or acute hepatitis (Klotz *et al.*, 1975; Roberts *et al.*, 1978; Sellers *et al.*, 1979).

Intermediate to short

The intermediate to short-acting benzodiazepines are characterized by half-life values ranging from 5–24 h (Table 1). The properties of benzodiazepines change progressively as the half-life becomes shorter. Active

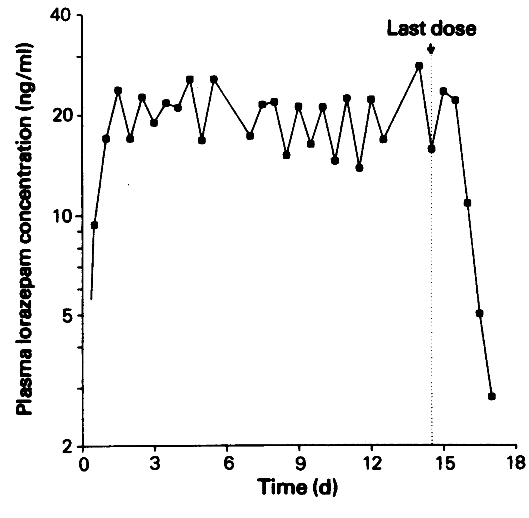

Figure 3 Plasma concentrations of lorazepam in the same volunteer who ingested lorazepam 3 mg daily in divided doses for 15 .5 days.

metabolites become uncommon—only flunitrazepam, and possibly estazolam and bromazepam, have active metabolites present in clinically important amounts. Thus, clinical activity is generally determined only by the parent compound. Because the half-life is shorter, accumulation during multiple-dose therapy is not extensive and the steady-state condition is attained relatively rapidly after initiation of therapy (Greenblatt *et al.*, 1979*c*). Drug washout after termination of treatment is correspondingly rapid. The shorter the half-life, the less feasible is once-daily anxiolytic therapy. In the case of oxazepam, anti-anxiety therapy is most appropriate with three or four divided daily doses.

Metabolic biotransformation of intermediate to short-acting benzodiazepines can involve non-oxidative metabolic pathways, including nitroreduction (for nitrazepam and the active metabolite of flunitrazepam) and glucoronide conjugation (for lorazepam, temazepam, and oxazepam). Insofar as studied, these pathways seem to be relatively uninfluenced by old age and by liver disease (Greenblatt *et al.*, 1979*b*; Shull, Wilkinson, Johnson & Schenker, 1976; Kraus *et al.*, 1978; Kangas *et al.*, 1979).

Provided absorption properties are favourable, short or ultrashort (see below) benzodiazepines probably should be prescribed for patients needing a hypnotic and for whom avoidance of any residual daytime effects is essential, or for those needing intermittent, short-term treatment of acute anxiety with minimum likelihood of prolonged drug effects. Multiple daily dose therapy with an intermediate or short-acting benzodiazepine may also be of value in patients with chronic anxiety who benefit from the feeling of 'mastery' derived from taking multiple pills, or those in whom the option of rapid drug washout should be maintained. On the other hand, short-acting benzodiazepines are probably not appropriate for poorly compliant patients who may experience acute reappearance of symptomatology when one or more doses are missed.

Ultrashort

Triazolam and midazolam are two benzodiazepines with 'ultrashort' half-life values of less than 5 hours. These drugs are essentially non-accumulating during multiple dosage. Triazolam is used as a hypnotic, whereas midazolam is under study as a short-acting anesthetic induction agent (Brown *et al.*, 1976). Earlier published data on temazepam suggested that it belongs in the short or ultrashort category (Fuccella, Bolcioni, Tamassia, Ferrario & Tognoni, 1977), but recent results from our laboratory and elsewhere (Lader, Makin & Nicholson, 1979) indicate that the half-life of temazepam is in the intermediate range (Table 1).

Comment

The proposed scheme for pharmacokinetic classification of benzodiazepine derivatives is not precise or perfect, but provides a framework for understanding the similarities and differences among the many benzodiazepine derivatives now in clinical use. Many more benzodiazepines are likely to become available in the near future, and it is hoped that pharmacokinetic classification will facilitate assessment of the potential clinical benefits that new drugs may or may not provide.

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