

# Pharmacokinetic Aspects of Anxiolytic Drug Therapy

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**SUMMARY:** *Benzodiazepine derivatives are neuropharmacologically similar but may appear clinically distinct due to pharmacokinetic differences. The clinical effects of single doses depend mainly on rates of drug absorption and distribution, whereas drug accumulation is a major determinant of clinical action during multiple dosage. This paper outlines potential clinical implications of benzodiazepine pharmacokinetics.*

**RÉSUMÉ:** *Les dérivés des Benzodiazépines sont neuropharmacologiquement semblables, mais peuvent sembler cliniquement distincts à cause de différences pharmacocinétiques. Les effets cliniques de doses simples dépendent surtout des vitesses d'absorption et de distribution, tandis que l'accumulation de la drogue est un facteur déterminant de l'action clinique pour les dosages multiples. Le présent article décrit les implications cliniques possibles de la pharmacocinétique des benzodiazépines.*

Numerous benzodiazepine anxiolytics and hypnotics are available for clinical use. Although the neuropharmacologic profile of all these drugs is similar, they may appear to have different clinical action (Greenblatt and Shader, 1974). These differences may be partly explained by variations between drugs in patterns of absorption, distribution, and elimination (Greenblatt and Shader, 1978; Shader and Greenblatt, 1977). This paper reviews how these pharmacokinetic differences may influence apparent clinical action.

## SINGLE DOSES

The rate of onset and duration of action of a single dose of a benzodiazepine derivative is of importance in some but not all clinical situations (Breimer, 1979; Curry and Whelpton, 1979). Rapid onset of action is desirable for patients taking a benzodiazepine as a bedtime hypnotic, or in those experiencing acute anxiety who require rapid relief of symptoms. On the other hand, a slow onset of action is more desirable for patients who perceive the acute effects of single doses as unwanted drowsiness, sedation, or a feeling of being "spaced out". It is hypothesized that those benzodiazepines most prone to abuse by pleasure-seeking individuals are those with the most rapid onset of action, which abusers perceive as a "rush" or "high".

The most important determinant of onset of action is rate of absorption from the gastrointestinal tract. The most rapidly absorbed drugs are those that dissolve quickly in the stomach. Diazepam and clorazepate (serving as a precursor of desmethyl-diazepam) are notorious for their rapid onset of action. Prazepam (also a precursor of desmethyl-diazepam), oxazepam, and temazepam, are slowly absorbed drugs.

Chlordiazepoxide and lorazepam fall somewhere in between. These differences should be considered when a particular drug is chosen to meet the needs of an individual patient. It should be remembered that most of our knowledge of drug absorption rates is based on pharmacokinetic studies using volunteers in the fasting state with nothing in their stomach. Ingestion of benzodiazepines with food or with antacids can slow the rate of absorption, and thereby reduce the onset and intensity of clinical effects following single doses (Greenblatt et al, 1977, 1978).

The duration of action of a single dose is determined in large part by the rate and extent of drug distribution to body tissues, rather than the rate of elimination or biotransformation by the liver. Those drugs that are highly lipid soluble have large apparent volumes of distribution. The effects of a single dose may appear to "wear off" rapidly because of the rapid and extensive uptake into body tissues. Diazepam and desmethyl-diazepam are the best examples of such drugs.

Unless this relation of drug distribution to duration of action is well understood, pharmacokinetic data focusing only on elimination half-life may seem inconsistent with clinical observations. A single dose of lorazepam, for example, will have a much longer duration of action than will a single dose of diazepam, even though the elimination half-life of lorazepam (usual range: 8 to 25 hours) is much shorter than that of diazepam (usual range in young individuals: 20 to 70 hours). This is because diazepam is much more rapidly and extensively distributed to body tissues than is lorazepam; the distributional effect of diazepam leads to relatively rapid termination of action following single doses.

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## DRUG ACCUMULATION

In contrast to the clinical effects of single doses, the extent of drug accumulation is a major determinant of clinical effects following multiple dosage. Elimination half-life of the parent drug, and of any active metabolites that may be present, is in turn the major determinant of drug accumulation (Greenblatt and Shader, 1978). It is helpful to categorize benzodiazepines according to elimination half-life into a group of long-acting drugs, and another group of short and intermediate-acting drugs (Table 1). During multiple dosage with the long-acting drugs, there is exten-

sive accumulation of parent compound and/or any pharmacologically active metabolites that may be present. Accumulation proceeds until a steady state is reached, which generally takes from 5 days to 2 weeks after the initiation of therapy. Thus attainment of optimal anxiolytic effects may be somewhat delayed after initiation of therapy. It is possible that drug accumulation could also lead to cumulative and progressive sedation or drowsiness. However, this potential adverse effect may be partly or completely offset by the development of adaptation or tolerance to the non-specific central depressant effects of

the drug. After termination of treatment, drug washout occurs at a correspondingly slow rate; active substances may persist in the blood for many days or even weeks after termination of therapy. This can lead to a persistence of effects after termination of treatment, as well as a "protection" from abrupt return of symptoms.

Characteristics of the short- to intermediate-acting drugs are the reverse. The extent of accumulation is minimal, and steady state is attained within a few days of initiation of treatment. After therapy is stopped, blood levels return rapidly to zero. Table 2 summarizes the comparative properties of these two classes of benzodiazepines.

TABLE 1  
*Pharmacokinetic Strategy for  
Classification of Benzodiazepines*

Parent compounds	Important active metabolites
<u>Long-Acting Derivatives</u>	
Chlordiazepoxide	Desmethylchloridiazepoxide Demoxepam Desmethyldiazepam
Diazepam	Desmethyldiazepam
[Prazepam] <sup>a</sup>	Desmethyldiazepam
[Clorazepate]	Desmethyldiazepam
[Flurazepam]	Desalkylflurazepam
<u>Short- to Intermediate-Acting Derivatives</u>	
Oxazepam	—
Lorazepam	—
Temazepam	—
Alprazolam	—
Triazolam	—

a: Brackets indicate prodrugs or drug precursors, which do not reach the circulation in clinically important amounts.

TABLE 2  
*Implications of Benzodiazepine Kinetics  
During Multiple Dosage*

Properties:	Drug category:	
	Long	Short/Intermediate
Rate of accumulation	Steady-state slowly attained	Steady-rate rapidly attained
Extent of accumulation	Extensive	Not extensive
Once-daily anxiolytic therapy	Usually feasible	Usually not feasible
Drug elimination after treatment termination	Slow	Rapid
Symptom return after treatment termination	Usually slow	May be rapid

## COMMENTS

Understanding of pharmacokinetic differences among benzodiazepine derivatives may help clinicians in their attempt to choose the right drugs and dosage to meet the needs of a given patient. Pharmacokinetics, however, does not tell the whole story, due to unpredictable differences among individuals in response to drugs. The most important factor in optimizing anxiolytic therapy still remains the clinical judgement and the careful monitoring of the treating physician.

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