

THE USE OF BENZODIAZEPINES IN CLINICAL PRACTICE

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Summary

- 1 The pharmacokinetic characteristics of the six benzodiazepine anxiolytic drugs available in the United States are reviewed.
- 2 Concern over the abuse potential of the benzodiazepine class of drugs is discussed.

Introduction

AFTER almost 20 years benzodiazepine derivatives remain as the most commonly prescribed anti-anxiety agents in world-wide clinical practice. Six benzodiazepine anxiolytics are currently prescribed in the United States, and additional ones are available in other parts of the world. All anxiolytic benzodiazepines have similar properties—they reduce anxiety, produce sedation and sleep, have anti-convulsant effects, and can produce muscle relaxation. The clinician may well ask how best to make a rational choice among the available derivatives. Despite similarities, there are differences of clinical value among benzodiazepines in patterns of absorption, distribution, and elimination by the human body. This clinically oriented review will summarize pertinent pharmacokinetic characteristics of benzodiazepine anti-anxiety agents available in the United States and highlight some aspects of the growing concern with their abuse potential.

Chlordiazepoxide

Chlordiazepoxide, the first available benzodiazepine, is generically available and offers the possibility of cost savings in some countries. The metabolic pathway of chlordiazepoxide in humans is complex, involving transformation into a series of pharmacologically active metabolites. Following oral administration, chlordiazepoxide is rapidly and completely absorbed from the proximal small bowel. Elimination proceeds with an apparent half-life ranging from 5 to 30 hours. Disappearance of chlordiazepoxide from blood is mirrored by appearance of its first pharmacologi-

cally active metabolite, desmethylchlordiazepoxide. Demoxepam, desmethyldiazepam and oxazepam are then formed, and with chronic administration all contribute to the net clinical effect.

An early lesson learned from kinetic research was that chlordiazepoxide given intramuscularly probably precipitates at the injection site. Intramuscular absorption can therefore be slow, erratic, and sometimes incomplete (Greenblatt *et al.*, 1974; Greenblatt, Shader, MacLeod, Sellers, Franke & Giles, 1978a). Oral use in the fasting state provides much more prompt and reliable clinical action, and intravenous infusion at a relatively slow rate is also effective. The metabolic clearance of chlordiazepoxide is reduced in elderly males and in patients with liver disease (Shader, Greenblatt, Harmatz, Franke & Koch-Weser, 1977; Roberts, Wilkinson, Branch & Schenker, 1978; Sellers, Greenblatt, Giles, Naranjo, Kaplan & MacLeod, 1979). This may partly explain the increased sensitivity of such individuals to the effects of the drug.

Diazepam

Diazepam is still the most widely used benzodiazepine. It has a pharmacokinetic profile somewhat similar to that of chlordiazepoxide. The major metabolic pathway of diazepam in humans involves N-demethylation, yielding its pharmacologically active major metabolite, desmethyldiazepam. After intravenous injection of diazepam, distribution of the parent compound is rapid and very extensive, and this may lead to rapid termination of the action of the parent com-

pound following a single intravenous dose. This property accounts for diazepam's prompt onset and short duration of action in the treatment of status epilepticus or during its adjunctive use in procedures such as sigmoidoscopy or cardioversion. Elimination of diazepam then proceeds with a relatively long half-life, usually greater than 24 hours. The onset of the disappearance of the parent compound is associated with the appearance of desmethyldiazepam. Orally administered diazepam is rapidly and completely absorbed from the proximal small bowel reaching peak blood concentrations shortly after the dose. This rapid onset property may explain the floating feeling or the brief 'buzz' described by some patients shortly after oral ingestion. It may also explain the misuse and abuse of diazepam by patients who are prone to addiction. Extensive distribution following the initial peak concentration of the parent compound dissipates these acute subjective effects after oral administration. Elimination proceeds slowly after distribution is complete. As with chlordiazepoxide, absorption of intramuscular diazepam is slow and erratic.

Multiple-dose therapy with diazepam leads to accumulation of diazepam and desmethyldiazepam. Steady-state concentrations of both compounds are generally reached within 5–15 d after initiation of multiple-dose therapy. The pharmacokinetic characteristics of diazepam make it quite suitable for once daily (at bedtime) anti-anxiety therapy. In some patients, accumulation of diazepam and desmethyldiazepam during multiple-dose therapy may be excessive and lead to unwanted clinical sedation. However, adaptation to the presence of these compounds in blood often counteracts the cumulative sedative effects that might be anticipated as blood concentrations increase. A most striking example of this adaptation is seen in overdosage cases in whom return to consciousness and adequate motor performance occurs relatively promptly (for example, within 8–48 h) despite continued high plasma concentrations of diazepam and its metabolites (lasting 10 or more days) (Greenblatt, Woo, Allen, Orsulak & Shader, 1978*b*). With multiple-dose therapy and with overdosage cases, plasma concentrations of two other metabolites, temazepam and oxazepam, may become measureable.

The clearance of diazepam is reduced in patients with cirrhosis and acute hepatocellular disease (Klotz, Avant, Hoyumpa, Schenker & Wilkinson, 1975). Any given dose may have a longer duration of action in such individuals, and it is therefore wise to administer diazepam (or any other sedative) with caution in patients with liver impairment. Elderly individuals seem to be more sensitive to diazepam as well as to other sedative-hypnotics. Recent data from our group indicate that the clearance of unbound diazepam is significantly reduced in the elderly

(Greenblatt, Allen, Harmatz & Shader, 1980, particularly in males. These data also indicate sex differences in other pharmacokinetic parameters.

When diazepam therapy at usual therapeutic doses is abruptly terminated, the drug is by no means rapidly eliminated from the body. Clinically important amounts of diazepam and desmethyldiazepam may persist in blood and in the body for many days and even weeks after therapy is terminated. In most patients, this intrinsic 'tapering-off' effect probably prevents rapid recurrence of anxiety symptoms after discontinuation of the drug. As with other benzodiazepines, however, objective withdrawal syndromes associated with diazepam therapy (that is, at prescribed dosage) do occur, but they are probably not common. After abrupt discontinuation, occasional patients show symptoms (after at least several days) which are suggestive of withdrawal. Some report insomnia or waking from sleep with sweating and nightmares. Other patients show a clinical picture consistent with the classical sedative-hypnotic withdrawal syndrome long associated with barbiturates, though occurring somewhat later in time.

We have previously reviewed the literature on the benzodiazepine withdrawal syndrome which typically consists of tremulousness, dysphoria, agitation, tachycardia and sweating, and sometimes includes hallucinations, psychosis and seizures (Greenblatt & Shader, 1978*a*). Most patients showing features of this syndrome exceeded standard therapeutic dosage ranges and took their benzodiazepine for extended time periods. Fruensgaard (1977) emphasizes the late onset of withdrawal symptomatology when describing its appearance in 15 patients, some of whom abruptly discontinued the drug prior to admission for surgery. In the United States it is not uncommon for patients to be prescribed a benzodiazepine to diminish preoperative anxiety and to promote sleep and then to receive a benzodiazepine postoperatively as well. This practice may obscure the incidence of withdrawal reactions from drug discontinuation associated with hospital admission. Fruensgaard restricts his case descriptions to patients showing psychotic features to their withdrawal and points out that some did not show withdrawal manifestations until 12–14 d after drug discontinuation. He also notes that the psychosis is generally not responsive to antipsychotic agents.

Pevnick, Jasinski, & Haertzen (1978) have described the development of withdrawal symptoms from the fifth to the ninth days following abrupt discontinuation of diazepam (30–45 mg daily for 20 months) and placebo substitution in a self-acknowledged chronic drug abuser. Tremor, dysphoria, muscle twitches and cramps, facial numbness, weight loss and orthostatic increases in pulse were prominent features. Hallstrom & Lader (1979) have

described two patients who underwent scheduled, gradual dosage reduction from 200 mg to 30 mg diazepam daily. Both patients developed a withdrawal syndrome in spite of the planned reduction. Important features of their clinical picture of withdrawal were perceptual changes including intolerance to bright lights and loud noises, a sense of numbness in certain body parts, and weight loss.

The difficulty in assessing cause-and-effect in such patients was recently brought home to us by a recent patient who had taken diazepam 30 mg daily for 10 years. On her own she had abruptly reduced her dosage to 5 mg per day. After two weeks, she began to experience 'strange things in my head,' a sense of 'going under,' 'electric shocks' on her skin and in her head, depersonalization and increased anxiety and dizziness. These feelings were omnipresent and were occasionally associated with visual phenomena including black dots, star-shaped flashes, and fully formed hallucinations. This picture had lasted for one year, when she presented for consultation. The patient denied having these symptoms previously, except for anxiety, and attributed them to diazepam withdrawal after recently reading Barbara Gordon's (1979) book, in which similar experiences were presented. Careful inquiry revealed an abnormal electroencephalogram with left temporal lobe spiking. Further investigation will be necessary to discover the relevant aetiology in this interesting and complex presentation.

Clorazepate and prazepam

Clorazepate (monopotassium or dipotassium) and prazepam are precursors or 'prodrugs' for desmethyldiazepam. Following oral administration to healthy individuals, clorazepate undergoes rapid acid-dependent hydrolysis and decarboxylation in the stomach to form desmethyldiazepam. Desmethyldiazepam is then absorbed from the gastrointestinal tract and seems to be the major compound present in blood after clorazepate ingestion. Only very small amounts of intact clorazepate are detected, and these traces persist for only a few hours. Antacids interfere with the amount of clorazepate hydrolysed to desmethyldiazepam and reduce the sedative effects of single doses (Shader, Georgotas, Greenblatt, Harmatz & Allen, 1978). Sodium bicarbonate has also been shown to reduce the amount and rate of desmethyldiazepam absorption (Arbruzzo, Macasieb, Weinfeld, Rider & Kaplan, 1977). These findings suggest that normal concentrations of gastric acid are necessary for the transformation of clorazepate into desmethyldiazepam. However, recent work from our group calls this into question, as conversion was not substantially reduced in patients after Billroth

gastrectomy and in two patients with pernicious anaemia and achlorhydria (Ochs, Greenblatt, Allen, Harmatz, Shader & Bodem, 1979).

After peak desmethyldiazepam levels are attained, rapid distribution of the compound occurs followed by a very slow phase of elimination. Desmethyldiazepam, regardless of what compound serves as its precursor, has the longest elimination half-life of benzodiazepines studied to date, ranging from 30–210 hours. It is evident that clorazepate is quite suitable for once daily anti-anxiety therapy and that multiple-dose therapy with this compound will lead to substantial accumulation of desmethyldiazepam before the attainment of steady-state.

Prazepam, following oral administration, undergoes almost complete 'first-pass' dealkylation of its N-1-cyclopropylmethyl substituent by the liver. Levels of intact prazepam in blood are nondetectable or reach only trace levels; therefore, desmethyldiazepam is responsible for prazepam's clinical activity. The rate of dealkylation of prazepam tends to be slow and quite variable in individual patients. The peak levels of desmethyldiazepam usually occur from 2.5–72 h after prazepam dosage; however, most patients range between 4–8 h. After attainment of peak levels, elimination of desmethyldiazepam proceeds with its characteristically long elimination half-life. As expected, subjects taking clorazepate and prazepam on separate occasions show approximately identical elimination half-lives. Prazepam, therefore, is another long-acting benzodiazepine; however, the rate of appearance in blood of desmethyldiazepam following oral administration of prazepam is very much slower than after oral clorazepate. For anxious patients prone (by history) to drug misuse or abuse, prazepam may offer some advantages over diazepam or clorazepate.

Age impairs the clearance of unbound desmethyldiazepam (whether it is derived from clorazepate or prazepam) in males, but not in females. For example, in a recent study of clorazepate, the correlation between age and intrinsic clearance in males was -0.62 , whereas in females it was $+0.28$ (Shader *et al.*, 1978).

Lorazepam and oxazepam

Lorazepam and oxazepam, though structurally related, have different pharmacokinetic characteristics from the longer-acting compounds already mentioned. Lorazepam and oxazepam, by virtue of their 3-hydroxy substitutions, are biotransformed by direct conjugation to glucuronic acid yielding a water-soluble glucuronide metabolite which is excreted in the urine. Active metabolic products are not produced. The elimination half-life of lorazepam is

shorter than those of the previously discussed compounds ranging from 10–20 h in most individuals (Greenblatt *et al.*, 1979a; Greenblatt *et al.*, 1979b). During multiple-dose therapy the extent of accumulation of lorazepam is considerably less than that observed with the four previously described benzodiazepines. Steady-state levels of lorazepam are generally achieved within two to three days after initiation of therapy. Conversely, termination of lorazepam therapy leads to complete elimination of the compound within several days (Greenblatt *et al.*, 1979c). The somewhat shorter elimination half-life of lorazepam makes it unsuitable for once daily therapy unless the patient's anxiety is confined to one portion of the day (for example, anxiety upon awakening or before going to sleep). A two or three times daily treatment regimen seems more suitable for most patients with pervasive anxiety symptoms.

Peak concentrations of lorazepam are generally reached within 2.5 h of dosage after oral administration. Studies comparing the pharmacokinetics of oral and intravenous lorazepam indicate that its absorption from the gastrointestinal tract is essentially complete. Intramuscularly injected lorazepam also is rapidly and nearly completely absorbed (Greenblatt *et al.*, 1979a; Greenblatt *et al.*, 1979b). This contrasts with the previously mentioned properties of intramuscular chlordiazepoxide and diazepam, which are absorbed much more slowly. A time-limited anterograde amnesia syndrome occurs in some patients receiving parenteral lorazepam (Greenblatt & Shader, 1978b). Although the frequency and duration varies with dose, clinical anecdotal experience suggests that anterograde amnesia may be somewhat more common with lorazepam than with diazepam. In selected clinical situations (for example, cardioversion or surgical procedures in which the patient may be awakened for a portion of the surgery) this anterograde amnesia may be therapeutically useful. In our limited research experience with lorazepam-induced amnesia (that is, after intravenous doses of 4 mg), the anterograde amnesia produced may be associated with confabulation. For example, some research subjects do not acknowledge any loss of memory and 'fill in' the lost time with plausible but inaccurate descriptions of what they have been doing. In this way the syndrome differs from that seen after acute alcohol intake, but resembles more, in simplified form, what may be seen in patients with Korsakoff's syndrome. The deliberate production of this condition may be a useful way to study certain aspects of memory dysfunction.

Oxazepam in capsule form reaches peak levels more slowly than lorazepam. In tablet form peaks range from 0.75–8 h with an average of 2.7 h. The elimination half-life of oxazepam usually ranges from 5–12 h, making it the most rapidly eliminated of currently available benzodiazepines in the United

States. Multiple-dose therapy with oxazepam leads to very little drug accumulation, and three or four daily doses are required to maintain adequate blood levels.

The effect of age and liver disease upon the pharmacokinetics of lorazepam and oxazepam have received only preliminary study. Reports on data suggest that the elimination of lorazepam or oxazepam is less influenced by these factors than is the elimination of the longer acting and more complex benzodiazepines (Shull, Wilkinson, Johnson & Schenker, 1976; Sellers, Greenblatt, Giles, Naranjo, Kaplan & MacLeod, 1979; Greenblatt *et al.*, 1979b).

Comment

An understanding of the pharmacokinetic characteristics of the six benzodiazepines currently available in the United States for the treatment of anxiety should assist the prescribing clinician in making appropriate individualized choices for specific patients.

Unfortunately, current pharmacokinetic findings do not provide complete insight into individual differences in responses to treatment. Additional understanding must be gained from studies of the pharmacokinetics of the unbound fractions of particular drugs (and their metabolites) and of the mechanisms of adaptation (perhaps at the receptor level) to particular drug concentrations. Further research must also focus on the individualized patterning of anxiety symptomatology. Perhaps the patient who shows daytime muscle tension and fatigue when anxious requires a different intervention than the patient with tachycardia and palpitations or the tremulous worrier who cannot fall asleep. The nature and aetiology of anxiety disorders must be further explored and linked to specific treatment interventions; pharmacokinetic research has more to contribute to this undertaking.

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