

We are grateful to Dr Jennifer Jowsey, Mayo Clinic, Rochester, Minnesota, for the bone histological studies, to Dr L. Galante, Royal Postgraduate School of Medicine, Hammersmith, London, for the parathyroid hormone and calcitonin assays, and to Dr M. Nelson for the cytogenetic investigations.

This investigation was supported by grants from the South African Medical Research Council, the University of Pretoria Research Fund and the University of Cape Town Staff Research Fund.

REFERENCES

1. Beighton, P., Davidson, J., Durr, L. *et al.* (1977): *Clin. Genet.*, **11**, 1.
2. Beighton, P., Durr, L. and Hamersma, H. (1976): *Ann. intern. Med.*, **84**, 393.
3. Beighton, P., Cremin, B. and Hamersma, H. (1976): *Brit. J. Radiol.*, **49**, 934.
4. Beighton, P. and Hamersma, H. (1979): *S. Afr. med. J.*, **55**, 783.
5. Deftos, L. J., Powell, D., Parthemore, J. G. *et al.* (1973): *J. clin. Invest.*, **52**, 3109.
6. Tashjian, A. H. jun., Wolfe, H. J. and Voelkel, E. F. (1974): *Amer. J. Med.*, **56**, 840.
7. Walker, D. G. (1966): *Endocrinology*, **79**, 836.

Review Article

Which Benzodiazepine, Why and How?

J. L. STRAUGHAN

SUMMARY

While no major differences with regard to psychopharmacological actions are to be found among the benzodiazepines, certain pharmacokinetic differences are known. These differences allow the benzodiazepines to be classified as cumulative or non-cumulative; the differences between these two groups are further dissected and evaluated, in an attempt to rationalize therapy with these agents.

S. Afr. med. J., **55**, 1110 (1979).

Rational use of drugs demands a certain minimum base of hard data. The enquiring prescriber will hunt out such data as he thinks pertinent and useful, but the vast majority of prescribers require reviews to enable them to obtain with relative ease and in a minimum of time the essentials of the relevant information.

This review aims to draw some distinctions between the various benzodiazepines, which hopefully may be of value in an area of therapeutics that seems beset with a superfluity of agents looking for conditions to treat!

Anxiety is the most common 'dis-ease' encountered in

medical practice; this has ensured that pharmaceuticals promising respite from this experience find a ready market. For several decades the barbiturates were widely used as sedative, anti-anxiety agents. Nothing really new was forthcoming until about 1960, when the benzodiazepines appeared on the pharmacotherapeutic scene.

The benzodiazepines were innovative, particularly with regard to their safety, both in normal doses and in large overdoses. They have several other advantages over the barbiturates: by careful adjustment of dosage, the anti-anxiety effect may usually be obtained with minimal sedative effect; tolerance and dependence are less prevalent; and there is no significant induction of hepatic microsomal enzymes, and thus no accelerated biotransformation of endogenous substances or other exogenous substances also metabolized by these enzymes.

Thus, it is easy to understand why this group of drugs has become a worldwide best-seller. Nevertheless, it is salutary to bear in mind that the therapeutic spectrum of the benzodiazepines is not very different from that of the barbiturates.

ARE THE BENZODIAZEPINES A HOMOGENEOUS GROUP?

With regard to their pharmacological actions, there is very little of major importance to differentiate the various benzodiazepines on the market in the Republic of South Africa. Once variations in potency and dosage have been taken into account, these agents have remarkably similar

Department of Pharmacology, University of Stellenbosch, Parowvallei, CP

J. L. STRAUGHAN, B.S.C. (PHARM.), M.B. CH.B., B.S.C. HONS., Senior Lecturer

Date received: 27 December 1978.

pharmacodynamic properties. However, at a time when the introduction of yet more benzodiazepines is imminent, it is increasingly important to make some comments which might assist in rationalizing benzodiazepine therapy, or which might at least provoke some reassessment of their usage.

DIFFERENCES IN METABOLISM AND ELIMINATION

It is very largely on the basis of pharmacokinetic data that marked differences among the benzodiazepines may be discerned and choices may be made in a more rational manner. The pharmacokinetic properties that reflect marked differences among the various benzodiazepines are those of biotransformation (metabolism) and elimination. If we examine the pharmacokinetic properties of the benzodiazepines, it is evident that they may usefully be divided into two classes: group 1 — short-acting, with very little tendency to accumulate, e.g. temazepam (Levanxol); oxazepam (Serepax); lorazepam (Ativan) (this group is characterized chemically by possessing a hydroxyl group in the 3 position); and group 2 — long-acting, with a considerable tendency to accumulate, e.g. diazepam (Valium);

chlordiazepoxide (Librium); chlorazepate (Tranxene); flurazepam (Dalmadorm); medazepam (Nobrium).

In Table I some common benzodiazepines are listed and their major active metabolites and their respective plasma half-lives are indicated, in accordance with the above-mentioned classification.

It should be noted that the biotransformation products of the short-acting benzodiazepines are directly conjugated. These conjugated products are essentially inactive, water-soluble and very readily cleared by the kidneys. The longer-acting benzodiazepines are biotransformed via a cascade of other active products, most of which have long plasma half-lives. The active biotransformation products are formed sequentially to a large extent; for instance, when diazepam is administered as a single dose, the benzodiazepine-type effect is produced for a period related to (*inter alia*) the sum of the individual plasma half-lives of each of the active products. Fig. 1 illustrates these points.

Such long duration of action makes the prescription of these agents on a 2, 3, or 4 times-a-day basis look quite nonsensical. From a pharmacotherapeutic viewpoint the agents might very advantageously be administered once a day, and several of them could well be administered

TABLE I. SOME COMMON BENZODIAZEPINES, THEIR MAJOR ACTIVE METABOLITES AND RESPECTIVE PLASMA HALF-LIVES

	Parent drug	Active biotransformation product/s	Plasma half-life* (h)	
Group 1 — short-acting	Oxazepam (Serepax)	None	5 - 10	
	Temazepam (Levanxol)	Oxazepam (very small amounts)	6 - 8	
			5 - 10	
	Lorazepam (Ativan)	None	8 - 20	
	Diazepam (Valium)		20 - 90	
		Desmethyldiazepam	36 - 200	
		Temazepam	6 - 8	
	Group 2 — long-acting	Chlordiazepoxide (Librium)	Oxazepam	5 - 10
				5 - 30
			Desmethylchlordiazepoxide	30 - 90
K-chlorazepate (pro-drug) (Tranxene)		Desmethyldiazepam	36 - 200	
		Oxazepam	5 - 10	
		Demoxepam	15 - 95	
		Medazepam (Nobrium)	Oxazepam	5 - 10
				evanescent†
			Desmethyldiazepam	40 - 100
		Prazepam (Demetrin)	Diazepam	20 - 90
	Desmethyldiazepam		36 - 200	
			uncertain	
	Nitrazepam (Mogadon)	Desmethyldiazepam	36 - 200	
Oxazepam		5 - 10		
Flurazepam (Dalmadorm)		20 - 38		
	? — but probable	?		
	Desalkylfurazepam	1 - 4		
		50 - 100		

* Published values may vary somewhat. These values seem to represent the expected range.

† Converted by the acid pH of the stomach to desmethyldiazepam, before absorption, therefore described as a pro-drug. Preparations or surgical operations that diminish gastric acidity may be expected to reduce and delay the systemic absorption of this product.†

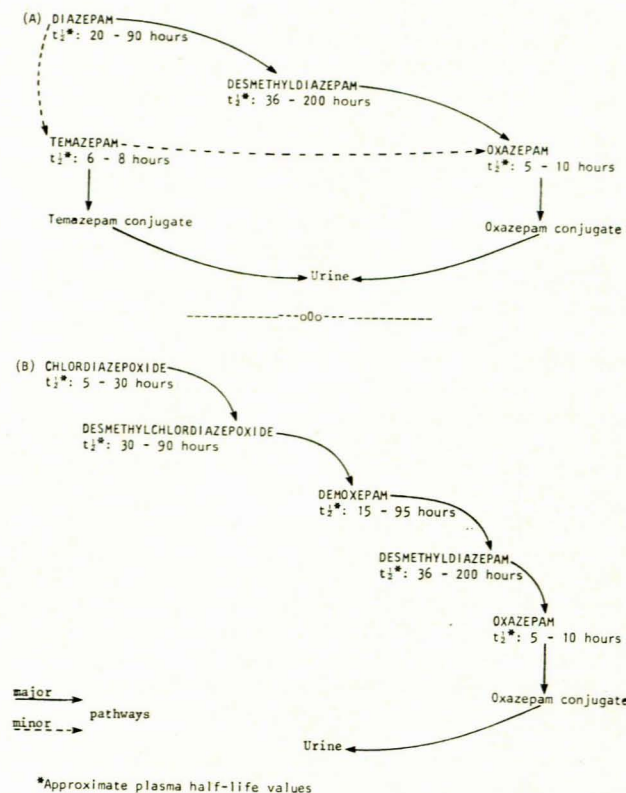


Fig. 1. The main biotransformation pathways of (A) diazepam (Valium) and (B) chlordiazepoxide (Librium).

every other day, without the occurrence of any major fluctuations in their plasma levels! Furthermore, if it is borne in mind that the duration of their pharmacological action is usually appreciably longer than their plasma half-life, it becomes all the more apparent that the agents are prescribed at unnecessarily short intervals, and probably in unnecessarily high daily dosages.

These long-acting agents should be prescribed in a once-a-day 'before bedtime' dose; in this way the plasma level of the parent compound reaches a peak during the night. This should help to promote sleep, and might help to reduce unnecessary and perhaps undesirable and excessive daytime sedation.

STEADY-STATE CONDITIONS, AND THEIR IMPLICATIONS

Short-Acting Benzodiazepines

When a short-acting benzodiazepine such as oxazepam is administered in a dose of, for example, 10 mg 3 times a day, the plasma and tissue levels of the drug attain a fairly stable state about 2 days after initiation of the regimen. Thus, the effects of a particular dosage soon become evident and maximal. This set of circumstances makes it fairly simple to adjust dosages to suit a particular person.

The interval of a couple of days before oxazepam attains steady-state conditions (when plasma levels and elimination processes attain fair constancy with constant dosage) is of that order because pharmacokineticists have demonstrated that, as a general rule, steady-state conditions are established after about 4 or 5 half-lives have elapsed since initiation of therapy. Thus for oxazepam, with a plasma half-life of approximately 10 hours, it would require about 2 days (5×10 hours) to establish steady-state conditions.

Long-Acting Benzodiazepines

However, when a long-acting agent such as diazepam is administered in a regular dosage of, say, 2 mg morning and evening, and if the plasma half-life of diazepam is 40 hours, it will be about a week before diazepam has attained steady-state conditions! The diazepam story is in fact much more complicated, because its major metabolite, desmethyldiazepam, has a much longer plasma half-life than the parent diazepam.² With a value of, say, 100 hours for the plasma half-life of desmethyldiazepam, it would take about a fortnight for the plasma levels of desmethyldiazepam to reach some constancy; because the desmethyldiazepam derives from diazepam, which itself slowly attains a steady state over about a week, it is apparent that desmethyldiazepam levels will attain constancy only some 3 or more weeks after initiation of diazepam therapy. Fig. 2 illustrates this relationship.

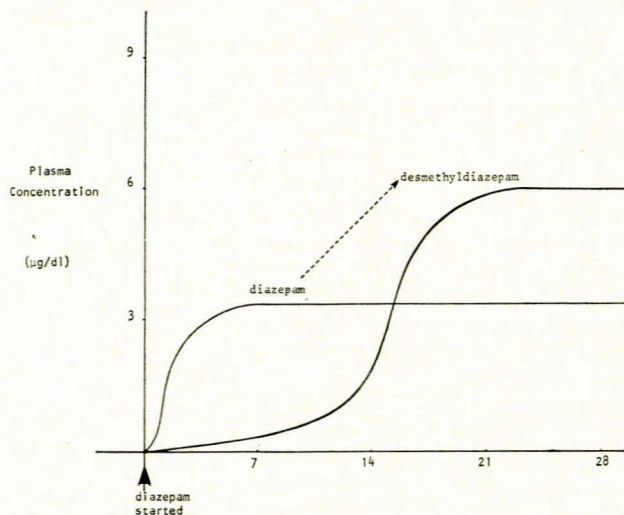


Fig. 2. Graphic representation of the relationship of the plasma levels of diazepam, and its chief metabolite desmethyldiazepam, during the first few weeks after initiating diazepam administration at e.g. 5 mg/d.

It should also be noted that it is the desmethyl metabolite that becomes the dominant anxiolytic. It is thus apparent that the effects of a particular dosage regimen with the long-acting benzodiazepines cannot be expected to be fully evident before some considerable time has elapsed — about 3 or 4 weeks, in the case of diazepam.

Therefore, when it comes to making appropriate alterations in the dosage of the long-acting benzodiazepines, the situation is much more complex than with the short-acting members. The initial dosage used with a long-acting benzodiazepine might well be suitable for the first week or so, but may then become quite in excess of what is required as the parent drug and its metabolites accumulate.

I would make so bold as to suggest that a rational way of prescribing the long-acting benzodiazepines, such as diazepam, would be to initiate therapy with a dosage of 2, 5, or 10 mg diazepam (according to the immediate needs of the patient) morning and evening for about 7 days, and then to 'back off' and halve the initial dosage by giving a single dose in the evening for the next 2 weeks or so. At this stage it might well be possible to discontinue the medication altogether; if not, the dosage regimen should again be carefully reassessed, bearing in mind that the effective anxiolytic dosage is often well below the sedative dosage.

Such an approach should make it possible to arrive at the lowest effective dosage regimen. This is the dosage that will minimize impairment of motor and cognitive processes, and produce the best psychotherapeutic results, at the least financial cost to the patient.

This type of approach takes cognizance of the peculiar pharmacokinetics of the long-acting benzodiazepines, and makes it possible to individualize dosages by making adjustments at appropriate intervals.

In the elderly, who do not eliminate the long-acting benzodiazepines as readily as younger people, this approach is particularly to be advocated, so as to avoid unnecessary over-sedation, with all its repercussions, in the age group that is most inclined to develop such problems.

The accumulation of the long-acting benzodiazepines, while perhaps subtle in most everyday circumstances, is very dramatically evident when diazepam is used in high and frequent dosage, as in the management of tetanus patients.³ In these cases diazepam and its chief metabolite accumulate very markedly, so that days after muscle relaxation is no longer required the patient is still comatose or stuporous, because doses too high and too frequent have been administered for too long. Bearing in mind the pharmacokinetic data presented above, it should be possible to solve this prolonged recovery problem.

When fine control of dose-effect relationship is desirable, the short-acting benzodiazepines have a decided advantage over the longer-acting members of this drug family. In the light of the foregoing, prescribers should familiarize themselves with all the pertinent data about one or two representatives from each of the two groups of benzodiazepines.

HYPNOTICS

With regard to the use of benzodiazepines as hypnotics, I can find no pharmacological justification for singling out nitrazepam (Mogadon) and flurazepam (Dalmadorm) as hypnotics, i.e. as 'sleeping tablets'! No data of which I am aware suggest that these two products should be marketed specifically for this role.

Indeed, I would express the opinion that there are two other agents, temazepam (Levanxol) and oxazepam (Serepax), that should be considered as benzodiazepines of choice for 'sleeping tablets'. (Perhaps lorazepam (Ativan), another 3-hydroxybenzodiazepine, should also be included in this category?) As hypnotics these agents cause fewer 'hangover' effects, for they do not tend to accumulate. The conjugation process of oxazepam and lorazepam in the elderly, even in the presence of hepatic dysfunction, is not prolonged.⁴⁻⁶ This might be expected to apply to the other short-acting benzodiazepine, temazepam. Accumulation of the benzodiazepines in elderly people is a particular hazard. Elderly people metabolize and/or eliminate the long-acting benzodiazepines more slowly than younger persons, and, in any case, are more prone to fall and be unsteady on their legs; thus, long-acting benzodiazepines are especially liable to cause confusion, lethargy, drowsiness, weakness and unsteady gait in elderly folk, if the cumulative propensity is not taken fully into consideration.

Lorazepam, despite the ease with which it can be conjugated and eliminated, does have a longer duration of action than either oxazepam or temazepam (see Table I). The halogen in lorazepam confers greater milligram-potency, presumably as a result of better penetration of the central nervous system, so longer pharmacological action might also be expected. At the doses in which it is available and prescribed, lorazepam is also more sedative than either oxazepam or temazepam, and would thus be very useful when overt sedation is desirable, and accumulation remains undesirable.

On the basis of such data, I would suggest that from among the benzodiazepines the short-acting members — temazepam and oxazepam, and probably lorazepam — seem to be ideally suited for prescription as hypnotics.

When an extended daytime anti-anxiety effect is required, the non-cumulative agents may be prescribed 2-4 times a day. Unless there are reasons such as old age and/or hepatic disease, it would seem more rational to prescribe one of the long-acting benzodiazepines on a simple 'before bedtime' regimen, thus making multiple daily dosing unnecessary.

ADVERSE WITHDRAWAL EFFECTS

The opinion seems to be fairly prevalent that lorazepam gives rise to more dependence or 'addiction' than the other benzodiazepines. I shall try to indicate why this opinion might be prevalent. Because of its considerable sedative action (at the dosages usually employed), lorazepam is frequently prescribed for those persons whose anxiety levels are high, and who are then the very candidates to feel anti-anxiety agent withdrawal effects more acutely and extensively than less neurotic or less anxious persons. Additionally, because lorazepam has no tendency to accumulate, on abrupt withdrawal of the drug there is a sudden decline of plasma and tissue levels (such as is experienced, for example, with ethanol). Thus, if a person has been receiving lorazepam for any length of time and is 'dependent' on the drug for its anti-anxiety effectiveness, abrupt withdrawal must, on pharmacological grounds,

be expected to give rise to withdrawal problems. Jitteriness, jumpiness, shakiness, sweating, disturbed sleep, 'full head', etc., have been described. Rebound anxiety and rebound insomnia, occurring upon withdrawal, are very real entities, therefore people receiving lorazepam or any other short-acting benzodiazepine for periods longer than a few days should probably have the drug withdrawn, with step-wise reductions, over a week or more.

Group 2 benzodiazepines do not give rise to notable withdrawal effects because of their long duration of action, their cumulative tendency and the biotransformation 'cascade' of active products; all these militate against sudden lowering of plasma and tissue levels of anti-anxiety substances. Nevertheless, even when administration of these agents is abruptly stopped there might be some mild withdrawal symptoms and signs, such as described above. Gradual reduction in dosage might thus also be advisable with long-acting agents, particularly for those whose personalities and/or disorders make this desirable.

PARENTERAL BENZODIAZEPINES

Chlordiazepoxide, diazepam and clonazepam (Rivotril) are available in forms suitable for intravenous administration. This gives them a special place in the emergency or critical (for whatever reason) situation. They are useful in many situations, e.g. in the management of convulsions, ethanol withdrawal or acute anxiety 'crisis'. It would be remiss not to mention that the intramuscular route for the administration of these benzodiazepines is most unsatisfactory; absorption, and therefore onset of action after intramuscular administration (which is painful) is known to be erratic, and also slower than that obtained after oral ingestion!^{1,8} The intravenous route is the route of choice, should a rapid, incisive effect be desired. The duration of action of single intravenous doses of diazepam is short, because rapid and extensive redistribution of the agent within the body occurs.

BUCCAL ADMINISTRATION

It is being reported that sublingual or buccal administration of the benzodiazepines might be expected to produce effects less rapidly than intravenous administration, but more rapidly than oral ingestion. Several of the tablet preparations available are suitable for administration via the buccal route, the tablet being allowed to disintegrate in the mouth.

An advantage of the buccal route is that the partial but immediate breakdown of the ingested benzodiazepine within the gastro-intestinal tract and in the liver after absorption (first-pass effect), is bypassed, and thus more of the parent drug is available for a more rapid onset of effect in the central nervous system. Perhaps more attention should be given to the formulation of tablets suitable for administration via this route?

OTHER PARENTERAL BENZODIAZEPINES

It has also been opined that there is a niche in the benzo-

diazepine market for a parenteral form of a non-cumulative agent. Such a product might be especially useful as a sedative for minor surgical procedures, for the management of delirium tremens and less severe alcohol withdrawal states, and for anxiety crises. A parenteral form of lorazepam has been investigated, and in view of its reported prompt efficacy via the intramuscular route,⁹ might be a useful addition to the therapeutic range.

NEW BENZODIAZEPINES

There are already more than a dozen different benzodiazepines available in South Africa. Various new benzodiazepines and closely related agents are champing at the bit, waiting to be released! If these agents are truly innovative, pharmacodynamically, they might be welcomed; if not, let the cry go out: 'Enough! Enough!'

CONCLUSION

Because the benzodiazepines enjoy very wide use, they deserve to be explained in better detail to, and understood in greater depth by medical practitioners. I believe that the pharmaceutical firms that market these products have promoted them as though they are not a pharmacodynamically homogeneous group of agents, and have therefore not concentrated on the pharmacokinetic differences (the real differences). It is hoped that the data and ideas presented here might assist the medical practitioner when prescribing benzodiazepines, or might at least provoke some reassessment of prescribing patterns.

ADDENDUM

Since this article was prepared, there has appeared on the South African market a new benzodiazepine derivative, triazolam (Halcion). This triazolobenzodiazepine has a plasma half-life of the order of 3 hours, and has no highly active metabolites. It must therefore be ranked among the short-acting benzodiazepines and is very suitable as a hypnotic.¹⁰

I express my gratitude to colleagues in the Department of Pharmacology for their constructive criticism, and also to the Merck Foundation, as it was during the tenure of a Merck International Fellowship in Clinical Pharmacology in the USA that my interest in the benzodiazepines was nurtured.

REFERENCES

1. Shader, R. I. and Georgotas, A. (1978): *Clin. Pharmacol. Ther.*, **24**, 308.
2. Eatman, F. B., Colburn, W. A. and Boxenbaum, H. G. (1977): *J. Pharmacokinet. Biopharm.*, **5**, 481.
3. Kendall, M. J. and Clarke, S. W. (1972): *Brit. med. J.*, **1**, 354.
4. Hoyumpa, A. M. (1978): *Sth. med J. (Bgham, Ala.)*, **71**, 23.
5. Kraus, J. W., Desmond, P. V., Marshall, J. P. *et al.* (1978): *Clin. Pharmacol. Ther.*, **24**, 411.
6. Schull, H. J., Wilkinson, G. R., Johnson, R. *et al.* (1976): *Ann. intern. Med.*, **84**, 420.
7. Hillstad, L., Hansen, T., Melsom, H. *et al.* (1974): *Clin. Pharmacol. Ther.*, **16**, 479.
8. Greenblatt, D. J., Shader, R. I., Kock-Weser, J. *et al.* (1974): *New Engl. J. Med.*, **291**, 1116.
9. Greenblatt, D. J., Joyce, T. H., Comer, W. H. *et al.* (1977): *Clin. Pharmacol. Ther.*, **21**, 222.
10. Vogel, G., Thurmond, A., Gibbons, P. *et al.* (1975): *Psychopharmacologia (Berl.)*, **41**, 65.