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Clinical Pharmacokinetics of Diazepam

Marinella Mandelli, Gianni Tognoni and Silvio Garattini

Istituto di Ricerche Farmacologiche 'Mario Negri', Milan

Summary

Diazepam is still one of the most used of the benzodiazepine group of drugs. Extensive studies over 10 years have defined a fairly complete profile of its kinetics. Minor aspects relating to patterns of its metabolism and excretion in certain age groups and in some disease states remain to be described quantitatively. However, there is more than sufficient kinetic information available for the requirements of good clinical practice.

For optimum clinical benefit with minimum side-effects the following kinetic properties should be borne in mind: (a) there is a large interindividual variation (up to 30-fold) in dose/blood level ratios, especially when treatment is short-term; (b) the elimination half-life is prolonged in the elderly and the newborn and in some cases of liver disease; (c) there is accumulation of the active N-desmethylated metabolite during long-term treatment; and (d) administration of diazepam to pregnant women leads to rapid distribution from the maternal to fetal compartment: accumulation of both diazepam and desmethyldiazepam could cause prolonged sedation in the newborn. As there does not appear to be any clear relationship between the concentration of diazepam in the plasma and clinical effect, measurement of blood levels, other than for research purposes, is unnecessary.

Based on kinetic data, a single administration of diazepam at night should be adequate for hypnotic and anxiolytic effects in most patients.

There are many excellent articles on the benzodiazepines, their properties, uses and patterns of disposition (Garattini et al., 1973a, 1975; Tyrer, 1974; Greenblatt and Shader, 1974; Costa and Greengard, 1975; Lasagna, 1977). The pharmacokinetics of diazepam, still probably the most widely prescribed conpound in this group, have been extensively investigated. The purpose of this review is to show how the results of these studies may be applied in general clinical practice. Previous articles in the journal have discussed the kinetic properties of diazepam relevant to its use in epilepsy (Hvidberg and Dam, 1976) and anaesthetic practice (Ghoneim and Kortilla, 1977).

There is general agreement that neither chemical manipulation of the basic diazepam molecule, nor use of its active metabolites (fig. 1) has lead to any substantial gain in therapeutic efficacy (Kesson et al., 1976; Shader and Greenblatt, 1977). However, side-effects in groups at risk because of age and/or associated disease states, may be minimised by the application of kinetic principles: either by adjusting the dosage regimen, or by choosing a benzodiazepine with a shorter half-life (and possibly no after-effects), such as oxazepam or methyloxazepam (Nicholson and Stone, 1976; Fuccella et al., 1977).

The kinetic and metabolic patterns of diazepam have been extensively investigated using sensitive and

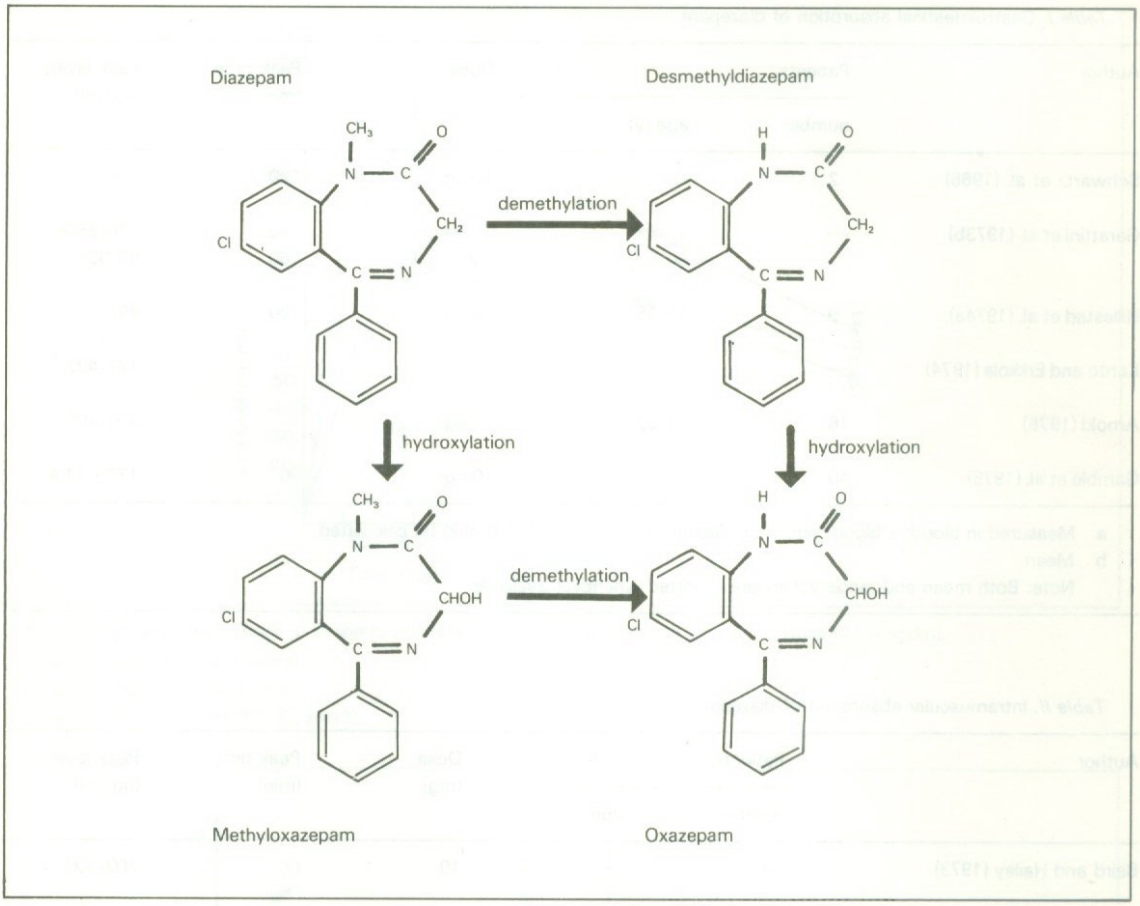

Fig. 1. Biotransformation pathways of major active metabolites of diazepam.

specific analytical techniques (Marcucci et al., 1968a; Van der Kleijn et al., 1971; Belvedere et al., 1972; Zingales, 1973; Arnold, 1975). Diazepam may be considered almost a classical model for the study of the various factors known to influence the disposition of a drug in the body. By far the most clinically relevant information to emerge has been the absence of any evidence of a correlation between plasma levels and therapeutic effect. Thus, measurement of blood levels is unnecessary except in a patient where knowledge of the concentration of the drug could help in clarifying an unexpected reaction, or where changes in the metabolic pattern of diazepam might be considered as a marker of other biological events, such as enzyme induction (Garattini et al., 1973b; Hvidberg and Dam, 1976; Bond et al., 1977).

1. Fundamental Pharmacokinetic Properties

1.1 Absorption

Table I summarises some of the studies dealing specifically with the absorption of diazepam follow-

Table I. Gastrointestinal absorption of diazepam

Author	Patients		Dose	Peak time (min)	Peak levels (ng/ml)
	number	age (y)			
Schwartz et al. (1965)	2	—	10mg	120	70[a]
Garattini et al. (1973b)	—	17-59	0.25mg/kg	60	140-250[a]
		60-80	0.25mg/kg	60	80-90[a]
Hillestad et al. (1974a)	9	19-35	20mg	30	492
Kanto and Erkkola (1974)	—	—	—	—	177-492
Arnold (1975)	16	21-57	10mg	—	300-400
Gamble et al. (1975)	40	32[b]	10mg	90	177 ± 11.4

a Measured in blood: a blood/serum or plasma ratio of about 0.6 should be calculated.
b Mean.
Note: Both mean and range values are reported whenever available.

Table II. Intramuscular absorption of diazepam

Author	Patients		Dose (mg)	Peak time (min)	Peak level (ng/ml)
	number	age (y)			
Baird and Hailey (1973)	4	—	10	60	200-300
Hillestad et al. (1974a)	9	19-35	20	60	293
Gamble et al. (1975)					
Buttock (nurses)[a]	31	32[b]	10	90	43 ± 7.8
Buttock (doctors)[a]	10	33[b]	10	90	100 ± 5.1
Thigh (doctors)[a]	33	28[b]	10	90	149 ± 3.7

a See text for explanation.
b Mean.

ing various routes of administration. Where no contraindications exist, the oral is preferable to the intramuscular or rectal route of administration.

Absorption after oral administration is rapid and complete; peak plasma levels being reached within 30 to 90 minutes. Age is a major factor influencing absorption; an earlier peak is seen in children, a delayed and lower one is observed in the elderly (fig. 2; Garattini et al., 1973b). In chronic alcoholic cirrhosis, a substantially lower (44% at 2 hours), but not delayed, absorption peak has been observed (Sellman et al., 1975a).