PHARMACOKINETICS OF THE HYPNOTIC BENZODIAZEPINE, TEMAZEPAM

P. BITTENCOURT & A. RICHENS

Department of Clinical Pharmacology, St Bartholomew's Hospital, London EC1A 7BE, UK

P.A. TOSELAND & J.F.C. WICKS

Department of Clinical Chemistry, Guy's Hospital, London, UK

A.N. LATHAM

Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berks SL6 0PH, UK

THE ever increasing number of benzodiazepines with subtle changes in molecular structure has led to the subdivision of these compounds into two main therapeutic groups, the rapidly absorbed, rapidly eliminated, short-acting compounds which are appropriate as hypnotics and the more slowly absorbed longer acting derivatives which may be preferable as anxiolytics. In this context recent studies with temazepam are of interest, as they suggest that this benzodiazepine has a pharmacokinetic profile which is particularly appropriate for its use as an hypnotic. Nicholson & Stone (1976) have observed that temazepam in a solution of polyethylene glycol contained in a soft gelatin encapsulated formulation markedly reduced sleep onset latency and prolonged total sleep time, whereas Harry & Johnson (1978), in a multicentre clinical evaluation of a similar formulation (Normison®, Wyeth) as an hypnotic, have shown that it leads to rapid sleep induction and improved quality of sleep without the drowsiness.

Fuccella *et al.* (1977) have shown that temazepam from a soft gelatin liquid filled capsule formulation (Euhypnos®) achieved peak plasma concentrations in 50 min with a subsequent elimination $T_{1/2}$ of 8.35 hours. The present study was to determine the

absorption and elimination kinetics of temazepam from Normison® soft gelatin capsules.

Six healthy male volunteer subjects between 20 and 30 years of age and free of other medications for at least 1 week before the trial received 20 mg (2×10 mg capsules) orally with a glass of water and on an empty stomach. A light lunch was permitted 3 h later. Venous blood samples (10 ml) were withdrawn at appropriate intervals during a 32-h period. Following centrifugation, plasma was removed and deep frozen before assay. Plasma concentrations of temazepam were measured by the gas-chromatographic method of Belvedere *et al.* (1972) which was modified by the use of *O*-methyl temazepam (125 ng/ml plasma) as internal standard. Drugs were chromatographed on a Hewlett Packard 5710A gas chromatograph fitted with an electron capture ^{63}Ni detector.

The plasma concentrations (Y) obtained for each subject were related to the time (t) at which the blood samples were taken by the expression

$$Y = -Ce^{-\gamma t} + Ae^{-\alpha t} + Be^{-\beta t}$$

for a monoexponential absorption and biexponential elimination process. The terms C (absorption), A and B (elimination) have dimensions of concentration

Table 1 Pharmacokinetics of temazepam (Normison®) in six healthy subjects.

Subject	$T_{\max}$ (min)	Peak (ng/ml)	$T_{1/2\text{abs}}$ (min)	$T_{1/2\alpha}$ (min)	$T_{1/2\beta}$ (h)	K_{el} (h^{-1})	AUC (mg/lh)	App V_d [area] (l)	App Cl (l/h)
1	50	854	5.4	90.6	10.1	0.238	4.56	63.7	4.4
2	30	363	3.6	19.8	3.3	0.746	0.92	102.0	21.3
3	15	703	24.6	30.0	6.1	0.438	4.92	36.0	4.1
4	50	672	8.4	98.4	9.4	0.160	5.04	54.5	4.0
5	75	559	17.4	21.6	13.4	0.486	7.34	52.7	2.7
6	50	856	18.0	34.2	7.4	0.313	7.01	30.8	2.9
Mean	45	668	12.9	49.1	8.3	0.397	4.97	56.6	6.6
s.e.m.	8	77	3.4	14.5	1.4	0.086	0.94	10.4	3.0

and γ , α and β are the appropriate rate constants. Their values were computed from a programme modified from a Simplex method described by Nelder & Meade (1965). The derived temazepam absorption and elimination pharmacokinetic parameters are given in Table 1. Apparent volumes of distribution and clearance values are included for completeness but the accuracy of these results may be limited by the fact that the drug was administered orally rather than intravenously. Data obtained for subject number 2 differed considerably from those of the remaining subjects but there was no obvious explanation for this discrepancy.

Our results confirm the findings of Fuccella *et al.* (1977) for the pharmacokinetics of temazepam

administered during the daytime in the form of a soft gelatin liquid-filled capsule formulation. Thus, temazepam from Normison® was absorbed and eliminated rapidly after oral administration. Both the rapid rate of absorption and short elimination half-life are properties required of an hypnotic and correlate with the rapid sleep induction and absence of residual drug effects on waking found with the therapeutic use of temazepam. With a mean half-life of 8.3 h minimal accumulation on repeated daily use of the drug would be expected.

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