Pharmacodynamic correlates of modified absorption: studies with lormetazepam

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- 1 The bioavailability, pharmacokinetics, and effects on performance of lormetazepam (1 mg) have been compared using soft gelatin capsule and tablet formulations.
- 2 Lormetazepam was more rapidly absorbed from the soft gelatin capsule ($t_{\max} = 1.0 \pm 0.2$ h) than from the tablet ($t_{\max} = 2.4 \pm 0.4$ h), and the plasma concentration-time curve for the capsule was shifted to the left. Bioavailability and elimination kinetics did not differ between the formulations.
- 3 The number of substitutions in the digit symbol test was reduced between 0.5 and 1.5 h for both formulations ($P < 0.001$), but the degree of impairment at 0.5 h was greater after the capsule than after the tablet ($P < 0.01$). Visuo-motor co-ordination was impaired from 0.5 to 1.5 h after the tablet and the capsule ($P < 0.01$), and extended to 5.5 h after the tablet ($P < 0.05$). These observations reflect the differences in the plasma concentration-time curves.

Keywords lormetazepam pharmacokinetics formulation performance

Introduction

Lormetazepam is a 3-hydroxy-benzodiazepine (Figure 1) closely related to temazepam and oxazepam, and is metabolized to the 3-*o*-glucuronide with an elimination half-life of around 10 h (Humpel *et al.*, 1979). However, these compounds tend to be relatively slowly absorbed with maximum plasma concentrations around 2–3 h after ingestion, and such a pharmacokinetic profile is less likely to be useful for sleep onset insomnia if doses free of residual effects the next day are appropriate.

Temazepam has been formulated in polyethylene glycol in a soft gelatine capsule and is absorbed more quickly with peak plasma concentrations around 1 h after ingestion (Bittencourt *et al.*, 1979; Fuccella, 1979). In view of the structural similarity of lormetazepam to temazepam it would be reasonable to expect that a similar modification may also lead to faster absorption of this compound also. It is in this context that we have compared the pharmacokinetic and pharmacodynamic activity of lormetazepam ingested orally in two separate preparations which may have different rates of absorption.

Figure 1 Structure of lormetazepam (7-chloro-5-(2-chlorophenyl)-3-hydroxy-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one).

Methods

Pharmacokinetic studies

Subjects Subjects were seven healthy male volunteers, aged 18–45 years who had taken no psychotropic drugs or known enzyme-inducing agents for 2 weeks and no alcohol for 24 h. Before entering the study, all underwent a physi-

cal and haematological examination (packed cell volume, red and white cell counts). They were fasted overnight but were allowed to take a light breakfast 1 h after drug administration. In view of anticipated psychomotor impairment, they were asked to refrain from driving for 12 h.

Drug administration Lormetazepam 1 mg, was administered in two formulations, each taken with 50 ml water, i.e. a soft gelatin capsule, containing a solution of the drug in polyethylene glycol 400 (Loramet[®], Wyeth Laboratories) and a wet granulation tablet (Noctamid[®], Schering AG). Each subject received both formulations in a cross-over design with treatments separated by an interval of 1 week. The formulations were administered to each individual on a random basis.

Sample collection Blood samples (6 ml) were withdrawn from the cubital vein into heparinized glass tubes at the following times after drug administration: Pre-treatment, 0.33, 0.67, 1, 2, 3, 4, 6, 8, 12, 24 and 36 h.

Plasma was separated from red cells by centrifugation.

Drug analysis Concentrations of lormetazepam in plasma were determined by electron-capture gas chromatography. Drug and the internal standard, temazepam (1 ng), were extracted into 3 ml toluene containing 1.5% isoamyl alcohol from 0.5 ml plasma acidified with 0.2 ml of 2 N sulphuric acid. The organic phases were evaporated to dryness under a stream of nitrogen at 45°C and trimethyl silyl ether derivatives prepared by reconstitution in a 10% solution of bis-trimethyl silyl acetamide (BSA, Phase Separations Ltd, Queensbury, Clwyd) in ethyl acetate (25 µl). The extraction efficiency of lormetazepam under these conditions was 89%.

Chromatography of 0.5–1 µl aliquots of the BSA solutions was performed on a Pye 204 gas chromatograph fitted with a ⁶³Ni electron-capture detector. The column was 3% OV-17 on Chromosorb W HP (100–120 mesh), 4 mm i.d. × 1.5 m and conditions as follows: column temperature 280°C, detector temperature 300°C, injection port temperature 300°C, nitrogen carrier gas at flow rate 50 ml/min. Under these conditions, the retention times of the trimethylsilyl ethers of temazepam and lormetazepam were respectively 3.5 and 4.2 min. The standard curve relating peak area ratio to concentration was linear over the range 0.2–10 ng/ml (for $n = 7$, correlation coefficient 0.99). Relative standard deviations for 10 samples each determined at 0.2 and 10 ng/ml respectively were 5.8% and 3.8%.

Pharmacokinetic analysis The following model-independent pharmacokinetic parameters were calculated:

$t_{\max}$ = time of observed maximum plasma concentration (h).

$C_{p\max}$ = observed maximum plasma concentration (ng/ml).

% $C_{p\max}(t)$ = percentage of maximum plasma concentration present at time t (h) after dosing.

$t_{1/2}$ = β -phase disposition half-life, determined by linear regression analysis of the linear terminal phase of the plasma concentration-time curve.

AUC trap (0–36 h) = area under plasma concentration-time curve up to 36 h after dosing, calculated by the trapezoidal method (ng ml⁻¹ h).

AUC_{0-∞} = total area under plasma concentration-time curve after addition of the portion beyond 36 h, calculated by use of the terminal phase half-life.

CL_p = plasma clearance corrected for systemic bioavailability (F) of 80% (Humpel *et al.*, 1980), calculated as follows:

$$CL_p = \frac{F \times \text{Dose}}{100 \times AUC_{0-\infty}} \quad (\text{Wilkinson \& Shand, 1975})$$

Plasma concentration data at individual times and values for each model-independent parameter were compared for the two formulations by paired t -tests.

Pharmacodynamic studies

The subjects were six healthy females aged between 21 and 34 (mean 25.8) years, weighing between 42 and 72 (mean 56.8) kg. They abstained from alcohol and caffeine from 1900 h on the day preceding an experiment, and retired at their usual bedtime. No coffee or other beverages containing caffeine were consumed on an experimental day when subjects were provided with decaffeinated coffee. A light breakfast was consumed after the first performance session.

Each subject ingested 1 mg lormetazepam on two occasions, given by soft gelatine capsule or tablet formulation, and on two occasions placebos. The placebos matched the separate formulations and a double-dummy technique was used. Medication was therefore identical in appearance and treatments were arranged double-blind in a random order, at least 1 week separating each assessment. Drug or placebo ingestion was at 08.00 h, and the immediate effects on performance were assessed at 0.5, 1.5, 3.5, 5.5 and 8.0 h. Comparisons between the post-drug and post-placebo measures, and between those resulting from the two formulations, were made using analysis of variance.

Subjects were trained on a visuo-motor co-ordination task until they reached steady performance. They were required to position a spot inside a randomly moving circle displayed on an oscilloscope, using a hand-held stick, and an error signal proportional to the distance between the spot and the centre of the circle controlled the difficulty of the task by modulating the mean amplitude of the movement of the circle. The position of the circle and spot, and so the radial error, were recorded. Each experimental run lasted 10 min. The subjects reached a plateau performance within 100 s, after which scoring began. The laboratory was sound-attenuated and air-conditioned (Borland & Nicholson, 1974).

Digit symbol substitution (DSS) was also tested. A series of 100 different sheets each with 200 randomized digits (0–9) arranged in 10 rows was presented. Under each digit there was a space where the subjects were required to write the appropriate symbol indicated by a code at the top of the page. The code was different for each of the 100 sheets. In each session subjects were given two sheets, and were allowed 2 min per sheet to complete as many substitutions as possible. In all tests and for all subjects errors

were extremely rare, and so only the number attempted was analysed. Subjects were trained on the test until they reached steady performance and DSS was measured immediately after the visuo-motor co-ordination sessions (Nicholson & Stone, 1982).

Results

Pharmacokinetics

Plasma concentrations of lormetazepam are given in Table 1, and the derived model-independent parameters in Table 2. Inter-subject variation in plasma concentrations at individual times after dosing was low. The standard errors for $C_{p_{max}}$ were 7% and 3% of its mean value for the tablet and gelatin capsule respectively. Concentrations of lormetazepam 20 min after the gelatin capsule were 45% of its maximum value and were about four times that of the tablet ($P < 0.05$), and at 40 min were 93% of its maximum value and nearly twice that of the tablet ($P < 0.05$). $C_{p_{max}}$ was achieved at $1.0 \pm$

Table 1 Plasma concentrations of lormetazepam following a 1 mg oral dose by gelatin capsule or Schering tablet

Time after dosing (h)	Lormetazepam (ng/ml)							Mean $\pm$ s.e. mean
	S1	S2	S3	S4	S5	S6	S7	
Gelatin capsule								
0.33	2.3	5.2	1.3	3.7	1.3	2.8	0.7	2.5 $\pm$ 0.6*
0.67	6.7	5.2	5.5	5.1	6.0	4.7	7.5	5.8 $\pm$ 0.4*
1	5.8	5.8	3.7	6.3	5.7	8.1	10.6	6.6 $\pm$ 0.8
2	6.4	5.3	5.0	6.6	5.4	7.9	8.3	6.4 $\pm$ 0.5
3	6.7	4.5	4.7	5.6	4.4	8.3	7.0	5.9 $\pm$ 0.6
4	5.5	2.9	5.1	4.3	4.4	5.2	6.6	4.9 $\pm$ 0.4
6	3.2	2.6	4.2	2.9	3.3	4.1	5.0	3.6 $\pm$ 0.3*
8	2.8	2.2	3.7	2.1	3.3	2.9	3.9	3.0 $\pm$ 0.3
12	1.4	1.4	2.3	1.7	1.6	1.8	2.6	1.8 $\pm$ 0.2
24	0.3	0.8	1.2	0.5	0.6	0.7	1.6	0.8 $\pm$ 0.2
36	<0.2	0.3	0.8	0.5	<0.2	0.3	0.8	0.4 $\pm$ 0.1
Tablet								
0.33	0.9	0.6	<0.2	1.7	<0.2	0.4	0.4	0.6 $\pm$ 0.2
0.67	2.3	6.0	1.5	4.7	1.5	0.5	0.9	2.5 $\pm$ 0.8
1	3.9	6.9	2.1	5.5	7.2	3.7	3.5	4.7 $\pm$ 0.7
2	4.6	6.7	4.5	6.3	8.7	6.4	7.1	6.3 $\pm$ 0.5
3	5.0	5.9	6.7	4.9	5.1	6.6	6.9	5.9 $\pm$ 0.3
4	5.8	4.9	5.1	4.4	4.5	5.6	5.6	5.1 $\pm$ 0.2
6	4.0	3.7	3.9	3.8	3.5	4.2	5.8	4.1 $\pm$ 0.3
8	2.6	2.8	1.8	3.0	2.4	3.4	4.4	2.9 $\pm$ 0.3
12	2.0	1.9	3.6	1.7	1.4	1.8	2.2	2.1 $\pm$ 0.3
24	0.7	1.0	0.7	0.2	0.6	0.9	2.1	0.9 $\pm$ 0.2
36	<0.2	0.5	<0.2	<0.2	<0.2	0.4	0.8	0.2 $\pm$ 0.1

* ($P < 0.05$)—Significantly different from values obtained after tablet administration

Table 2 Model-independent pharmacokinetic variables following a 1 mg oral dose by gelatin capsule or tablet

	<i>S1</i>	<i>S2</i>	<i>S3</i>	<i>S4</i>	<i>S5</i>	<i>S6</i>	<i>S7</i>	<i>Mean</i> $\pm$ <i>s.e. mean</i>
<i>Gelatin capsule</i>								
<i>t</i> _{max} (h)	0.67	1.0	0.67	2.0	0.67	1.0	1.0	1.0 $\pm$ 0.2*
<i>C</i> _{pmax} (ng/ml)	6.7	5.8	5.5	6.6	6.0	8.3	10.6	7.1 $\pm$ 0.7
% <i>C</i> _{pmax} (0.33 h)	34.3	89.7	23.6	56.1	21.7	33.7	6.6	38.0 $\pm$ 10.3*
% <i>C</i> _{pmax} (0.67 h)	100.0	89.7	100.0	77.3	100.0	56.6	70.8	84.9 $\pm$ 6.5**
<i>AUC</i> _{trap} (0–36 h) (ng ml ⁻¹ h)	58	56	79	60	59	73	101	69 $\pm$ 6
<i>AUC</i> _{0-∞} (ng ml ⁻¹ h)	58	60	97	69	59	77	116	76 $\pm$ 8
<i>t</i> _{1/2,z} (h)	5.2	10.0	15.8	12.3	6.9	8.7	13.0	10.3 $\pm$ 1.4
<i>CL</i> _p (ml min ⁻¹)	229	223	137	192	225	173	115	185 $\pm$ 17
<i>Tablet</i>								
<i>t</i> _{max} (h)	4.0	1.0	3.0	2.0	2.0	3.0	2.0	2.4 $\pm$ 0.4
<i>C</i> _{pmax} (ng/ml)	5.8	6.9	6.7	6.3	8.7	6.6	7.1	6.9 $\pm$ 0.3
% <i>C</i> _{pmax} (0.33 h)	15.5	8.7	<3.0	27.0	<2.3	6.1	5.6	9.0 $\pm$ 3.6
% <i>C</i> _{pmax} (0.67 h)	39.7	87.0	22.4	74.6	17.2	7.6	12.7	37.3 $\pm$ 11.9
<i>AUC</i> _{trap} (0–36 h) (ng ml ⁻¹ h)	58	73	71	54	59	70	98	69 $\pm$ 6
<i>AUC</i> _{0-∞} (ng ml ⁻¹ h)	58	81	71	54	59	76	111	73 $\pm$ 7
<i>t</i> _{1/2,z} (h)	8.3	11.7	7.3	4.4	8.4	11.1	11.3	8.9 $\pm$ 1.0
<i>CL</i> _p (ml min ⁻¹)	229	164	188	247	225	176	120	193 $\pm$ 17

* ($P < 0.05$), ** ($P < 0.01$) Significantly different from values obtained after tablet administration.

0.2 h with the gelatin capsule, and at 2.4 ± 0.4 h with the tablet ($P < 0.05$).

The shift of the plasma concentration-time curve to the left with the capsule was accompanied by a reduction in the plasma concentration 6 h after dosing ($P < 0.05$), but there was no difference in the rates of elimination between the two formulations. The half-lives of the elimination phase (*t*_{1/2}) were 10.3 ± 1.4 h and 8.9 ± 1.0 h, and the clearances (*CL*_p) were 184 ± 17 ml min⁻¹ and 193 ± 17 ml min⁻¹ for the capsule and tablet respectively.

The bioavailability of the two formulations was the same, as indicated by the areas under the plasma concentration-time curves (*AUC*_{trap} 0–36 h = 69 ± 6 ng ml⁻¹ h).

Performance

Effects of the capsule and tablet formulations of lorazepam on performance are given in Tables 3 and 4. There was a marked impairment of performance 0.5 and 1.5 h after ingestion with both preparations. Visuo-motor co-ordination was impaired at 0.5 h ($P < 0.001$) and 1.5 h ($P < 0.01$) after ingestion of tablet and capsule, and the decrement in performance ($P < 0.05$) persisted to 5.5 h with the tablet, but not with the capsule. Impairment at 0.5 h appeared greater after the capsule than after the tablet, but the difference just failed to reach statistical significance. The number of substitutions on the digit symbol task was decreased by both capsule and

Table 3 Change in performance on visuo-motor co-ordination (arbitrary units) after lorazepam compared with placebo (means for six subjects)

	<i>Time (h) after ingestion</i>				
	0.5	1.5	3.5	5.5	8.0
Lorazepam					
1 mg capsule	-1.70***	-0.85**	-0.43	-0.28	+0.18
1 mg tablet	-1.10***	-0.94**	-0.71*	-0.72*	-0.13

Least significant differences (LSD) from placebo for means of six are:

* $P < 0.05 = 0.63$

** $P < 0.01 = 0.84$ arbitrary units

*** $P < 0.001 = 1.10$

Table 4 Change in the number of substitutions on digit symbol substitution after lormetazepam compared with placebo (means for six subjects)

	Time (h) after ingestion				
	0.5	1.5	3.5	5.5	8.0
Lormetazepam					
1 mg capsule	-29.0***	-16.1***	-7.1	-7.0	+2.0
1 mg tablet	-17.3***	-17.6***	-7.1	0.8	-4.5

Least significant differences (LSD) from placebo for means of six are:

* $P < 0.05 = 8.5$

** $P < 0.01 = 11.4$ arbitrary units

*** $P < 0.001 = 15.2$

tablet at 0.5 and 1.5 h ($P < 0.001$), and at 0.5 h the decrement was greater with the capsule than with the tablet ($P < 0.01$).

Discussion

In the present study pharmacokinetics and pharmacodynamic measures were obtained in groups of different sex, but comparisons were not prejudiced as gender does not appear to affect the disposition of lormetazepam (Humpel *et al.*, 1980). Plasma concentrations and derived pharmacokinetic parameters (C_{pmax} , t_{max} , $t_{1/2}$, AUC and CL_p) after oral administration of the tablet were also consistent with those observed previously (Humpel *et al.*, 1980).

However, the relative rates at which plasma concentrations were achieved indicated that absorption took place more quickly from the capsule than from the tablet. Accordingly, the intensity of the central effects was greater 0.5 h after the capsule, and this would suggest that a more rapid onset of sleep may be possible with

this formulation. This is important as though the dose of 1 mg lormetazepam in the tablet formulation is free of residual effects the next day, it does not reduce the prolonged sleep onset latency of poor sleepers (Oswald *et al.*, 1979). The somewhat longer duration of impairment after the tablet was consistent with the plasma concentrations around 6 h, but in all other respects the formulations were bioequivalent and there was no difference in the elimination rates.

This study has shown that the different formulations of lormetazepam may lead to different pharmacokinetics and that in turn such modified pharmacokinetics may lead to pharmacodynamic changes of clinical relevance. The more rapid absorption of the soft gelatin capsule leads to a quicker onset of central effects as indicated by impaired performance, and so a more rapid onset of hypnotic action can be expected, which would be useful for patients who have difficulty in falling asleep.

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