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Temazepam elixir: comparative bioavailability with a capsule formulation

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Summary

Ten healthy male volunteers took part in a single oral dose cross-over study receiving both 'Euhypnos' Forte (20 mg) and temazepam elixir (20 mg) on separate occasions and in random order. There was no significant difference in the extent of drug absorption from the two formulations as determined by the area under the plasma concentration vs time curve and the peak plasma concentration. There was evidence of a more rapid absorption of drug from the elixir as determined by the higher plasma concentrations 20 min after dosage, suggesting that a more rapid onset of activity should be possible with this formulation. In accordance with theory the terminal phase half-life for the drug did not differ significantly for the two formulations. The short half-life determined (5–15 h) compared with other benzodiazepines suggests no prolongation of sedative effect with either formulation.

Introduction

Temazepam is a benzodiazepine particularly employed as a sleep inducer but also possessing powerful anxiolytic, muscle relaxant and anti-convulsant activity. It

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belongs to a small group of benzodiazepines characterised by a hydroxyl group in the 3 position, others in the group being oxazepam, lorazepam and lormetazepam. Over recent years it has become increasingly clear that the rate of absorption of 3-hydroxy benzodiazepines (and perhaps of other benzodiazepines also) from the gut after oral administration is formulation dependent. When given in solid dose forms, as tablets or as capsules containing dry powder, dissolution of the drug is slow and the drug is therefore poorly available to the gut mucosa for absorption (Divoll et al., 1981).

Taking, by contrast, the pharmacokinetics of temazepam from a solution-filled soft gelatin capsule formulation (Fucella et al., 1977), the time to peak plasma level has been reported to be 40–60 min and the peak plasma concentration of around 900 ng/ml is easily adequate for sleep induction, being generated by only a 20 mg dose. If temazepam could be presented as, for example, an elixir which has no shell requiring dissolution, the time to onset of action might be reduced further. Such a formulation would also be useful for patients for whom the capsules were regarded as unsuitable.

In considering such a formulation two approaches were initially considered. Since temazepam is sensitive to the presence of moisture an anhydrous base, a triglyceride preparation based on fractionated coconut oil, was investigated. While stability of temazepam in this vehicle was excellent, it proved very difficult to disguise the oiliness of the base and this was felt to be unsatisfactory. A more conventional elixir-type base was therefore used consisting of glycerol, ethanol and sorbitol as the main components of the vehicle. The use of sorbitol syrup instead of anhydrous sorbitol in this vehicle does lead to the inclusion of a few percent of water but this was found to be desirable from the point of view of reducing the stickiness of the vehicle in the mouth. The use of a buffer (pH 7.7) to maintain the pH at an appropriate level enabled the stability of temazepam to be maintained in spite of the presence of this amount of water. The vehicle is hyperosmotic and this might be expected, in case of overdosage, to result in emesis thus limiting absorption following suicidal attempts.

The purpose of this study was to compare the rate and extent of absorption of temazepam from the elixir formulation with an established, solution-filled capsule formulation, Euhypnos Forte.

Materials and Methods

Subjects

Ten healthy male volunteers (aged 20–24 years) within 15% of ideal body weight participated in the study. Subjects receiving any course of drug therapy within 4 weeks of the study were excluded. In addition, no alcohol or other drugs were allowed within 48 h of each study day. All subjects passed routine clinical, haematological and biochemical tests and signed a Form of Consent prior to commencement of the study.

Study design

The study was designed as a single oral dose cross-over with 7 days between dosage of two formulations: soft gelatin capsules (20 mg) and temazepam elixir (20 mg).

Ethical review

The protocol for the study was submitted to members of an independent Ethical Committee for their consideration, comment and guidance; they agreed that the study was scientifically and ethically justified.

Conduct of study

After a standard light evening meal at 19.00 h no further food or drink was permitted. Dosing commenced at 22.00 h with water (100 ml), the times being staggered to facilitate subsequent blood sampling.

On day 1 of the study, 5 subjects received the capsule and five the elixir formulation, randomly allocated. Volunteers remained seated for at least one hour after dosage before retiring to bed. Standard meals were provided at 08.00 h and 13.00 h on day 2 of each study weekend. Subjects returned one week later and received the alternative formulation under identical conditions.

Blood specimens

Venous blood (20 ml) was collected immediately before dosage and subsequently (10 ml) at 20, 40 min and 1, 2, 3, 4, 6, 8, 12, 15, 24, and 33 h after dosage. Volunteers were awakened during the night to provide samples between 2 and 8 h after dosing. Blood was centrifuged immediately and the plasma stored at $-20°C$ to await analysis.

Analytical procedure

Temazepam plasma concentrations were determined by gas chromatography with electron-capture detection. This procedure was adopted in preference to high-performance liquid chromatography to provide the high sensitivity required for drug determination after a single oral dose of the drug. The method used was based on that of Belvedere et al. (1972) and involved diethyl ether extraction of drug from plasma (together with diazepam as internal standard), followed by silylation of the dried extract using N,O-bis-trimethylsilyl acetamide. Pyridine was incorporated as solvent/catalyst as described by Fucella et al. (1977).

All samples (both formulations) from a single volunteer were analyzed as a single batch, together with a calibration series spiked with between 0 and 1000 ng/ml temazepam and prepared using the same subject's plasma (predose).

Pharmacokinetic calculations

For each volunteer and each formulation the terminal phase half-life ($t_{1/2\beta}$) was calculated by standard procedure from the least-squares regression line through the terminal phase log data points. The area under the plasma concentration vs time plot from time zero to infinity ($AUC_{0\rightarrow\infty}$) was calculated using the trapezoidal rule up to

33 h and adding on the area contribution from 33 h onwards which was calculated using the equation:

$$AUC_{33\rightarrow\infty} = \frac{C_{33} \times t_{1/2\beta}}{0.693}$$

where C_{33} is the plasma concentration after 33 h.

The half-life of the "distribution phase" ($t_{1/2\alpha}$) was calculated from the slope of the line drawn by the method of residuals (Gibaldi and Perrier, 1975).

Results

All volunteers completed the study in a satisfactory manner. One subject (Volunteer 1) complained of a severe headache at 06.00 h (8 h after capsule dosage), which was not considered to be drug-related.

Individual plasma concentrations of temazepam after capsule and elixir formulation are presented in Table 1. Mean data for the two formulations are illustrated graphically in Fig. 1. Pharmacokinetic data are summarized in Table 2 and indicate a mean peak concentration of 444 ng/ml compared with 411 ng/ml after the elixir.

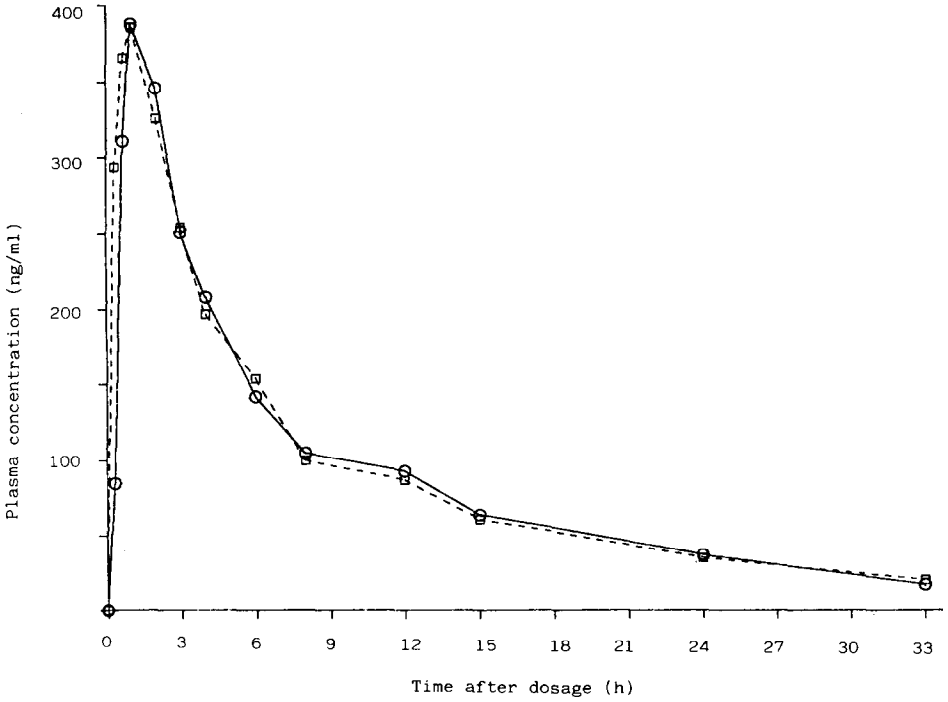

Fig. 1. Mean temazepam plasma concentrations (ng/ml) following oral dosage of 20 mg capsule (—○—) and elixir (--□--) formulations to 10 volunteers.

TABLE 1

PLASMA CONCENTRATIONS OF TEMAZEPAM (ng/ml) FOLLOWING ORAL DOSAGE OF (a) CAPSULE, AND (b) ELIXIR FORMULATION TO 10 VOLUNTEERS

Volunteer no.		Time after dosage (h)											
		0.33	0.67	1	2	3	4	6	8	12	15	24	33
1	a	187	476	533	326	206	181	143	93	77	71	39	20
	b	212	275	318	264	225	194	146	107	83	63	31	21
2	a	41	151	232	349	324	239	170	122	68	41	33	23
	b	202	293	306	341	247	179	129	96	62	41	50	17
3	a	23	617	622	433	259	183	115	98	81	76	34	16
	b	384	408	482	374	251	190	116	83	59	58	35	15
4	a	114	461	499	336	180	116	76	47	61	31	18	6
	b	442	476	426	447	220	137	89	72	79	40	18	7
5	a	20	70	246	368	263	218	128	84	67	31	29	14
	b	271	321	406	322	247	179	186	83	58	33	28	29
6	a	352	549	565	398	300	319	226	161	235	156	92	35
	b	441	654	631	451	396	301	193	141	177	125	78	37
7	a	4	113	208	385	263	210	163	92	61	60	46	20
	b	259	278	315	337	267	220	235	114	89	83	38	18
8	a	11	71	86	143	204	230	175	158	117	120	36	23
	b	83	103	106	106	172	210	221	155	129	94	43	27
9	a	18	284	460	315	210	179	118	121	83	25	17	3
	b	192	289	302	258	236	192	144	87	63	43	11	5
10	a	81	319	424	406	298	208	108	74	75	25	26	12
	b	450	563	569	358	275	163	83	61	72	28	17	23
Mean	a	85	311	388	346	251	208	142	105	93	64	37	17
	b	294	366	386	326	254	197	154	100	87	61	35	20
S.E.M.	a	35	65	57	26	15	17	13	11	17	14	7	3
	b	41	51	48	32	18	14	17	9	12	10	6	3

TABLE 2

PHARMACOKINETIC DATA DERIVED FOLLOWING TEMAZEPAM DOSAGE (20 mg) TO 10 VOLUNTEERS

Volunteer no.	Capsule						Elixir					
	T_{max} (h)	C_{max} (ng/ml)	β (h^{-1})	$t_{1/2\beta}$ (h)	$AUC_{0\rightarrow\infty}$ ($ng \cdot h\ ml^{-1}$)	$t_{1/2\alpha}$ (h)	T_{max} (h)	C_{max} (ng/ml)	β (h^{-1})	$t_{1/2\beta}$ (h)	$AUC_{0\rightarrow\infty}$ ($ng \cdot h/ml$)	$t_{1/2\alpha}$ (h)
1	1	533	0.063	11.0	3399	1.3	1	318	0.067	10.4	3123	2.1
2	2	349	0.045	15.3	3352	2.7	2	341	0.057	12.2	3060	1.8
3	1	622	0.073	9.5	3455	0.8	1	482	0.068	10.2	3134	1.1
4	1	499	0.085	8.1	2167	0.9	0.67	476	0.093	7.5	2643	0.5
5	2	368	0.067	10.3	2613	1.3	1	406	0.067	10.3	2872	1.5
6	1	565	0.086	8.1	5940	*	0.67	654	0.071	9.8	5653	*
7	2	385	0.055	12.7	3184	1.3	2	337	0.075	9.2	3608	1.3
8	4	230	0.081	8.6	3442	**	6	221	0.078	8.9	3503	**
9	1	460	0.136	5.1	2429	*	1	302	0.131	5.3	2331	*
10	1	424	0.077	9.0	2726	1.0	1	569	0.090	7.7	2630	1.1
Mean	1.6	444	0.077	9.8	3271	1.3	1.6	411	0.080	9.2	3256	1.3
(±S.E.M.)	0.3	37	0.008	0.9	331	0.2	0.5	42	0.007	0.6	294	0.2

* Insufficient data.

** No apparent distribution phase.

The mean time to peak concentration was 1.6 h for both capsule and elixir formulations. Seven of the 10 volunteers showed marginally higher peak concentrations following the capsule but this was not statistically significant (paired t-test; $P > 0.3$). The time to peak level was also not statistically different (Wilcoxon paired rank test) for the two formulations. However, 20 min after dosage in all 10 volunteers, the elixir produced significantly higher plasma concentrations than in the capsule ($P < 0.01$) (Table 1 and Fig. 1). In 3 volunteers (nos. 4, 6 and 10) both formulations showed a plasma concentration after 12 h (about 2 h after breakfast on day 2) in excess of that after 8 h (Fig. 2). This was reflected in only a small drop in mean concentration at 12 h (Fig. 1).

All but one volunteer (No. 8) showed evidence of biexponential pharmacokinetics (Fig. 3). a 'distribution' phase being evident up to approximately 8 h (range 5–10 h), with a mean half-life ($t_{1/2\alpha}$) of 1.3 h for both capsule and elixir. Volunteer 8 showed a late peak plasma concentration. The distribution phase was therefore unclear in this subject.

The mean drug terminal phase half-life ($t_{1/2\beta}$), calculated from a mean of 5 data points for the 10 volunteers, was 9.8 h (capsule) and 9.2 h (elixir). Differences were not significant (paired t-test; $P > 0.2$).

The mean area under the plasma concentration vs time plot was 3271 ng · h · ml^{-1}

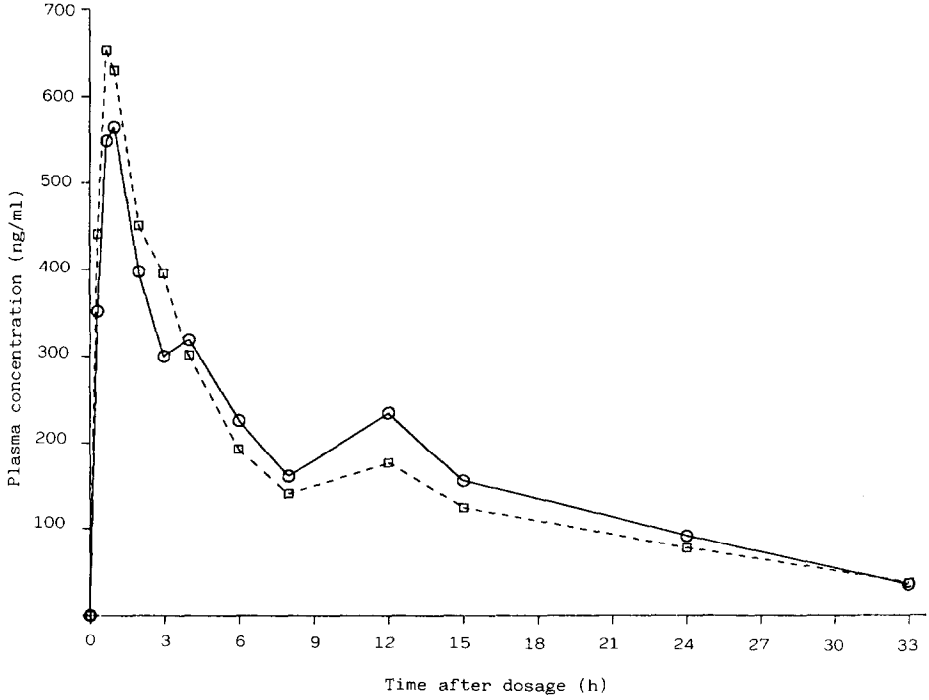

Fig. 2. Plasma concentration of temazepam (ng/ml) in Volunteer 6 showing the rise in levels 12 h post-dosing with both capsule (—○—) and elixir (--□--) formulations.

for the capsule and 3256 $ng \cdot h \cdot ml^{-1}$ for the elixir (Table 2), also statistically insignificant (paired t-test, $P > 0.8$).

Discussion

The lack of significant difference in area under the curve data and in peak plasma concentration data would suggest no difference in the extent of drug absorption between capsule and elixir. However, the highly significant difference in concentration 20 min post-dosing would suggest that the dissolution of the capsule shell is critical in terms of drug absorption. The high levels achieved 20 min after elixir administration suggest that a more rapid onset of activity is possible with this formulation.

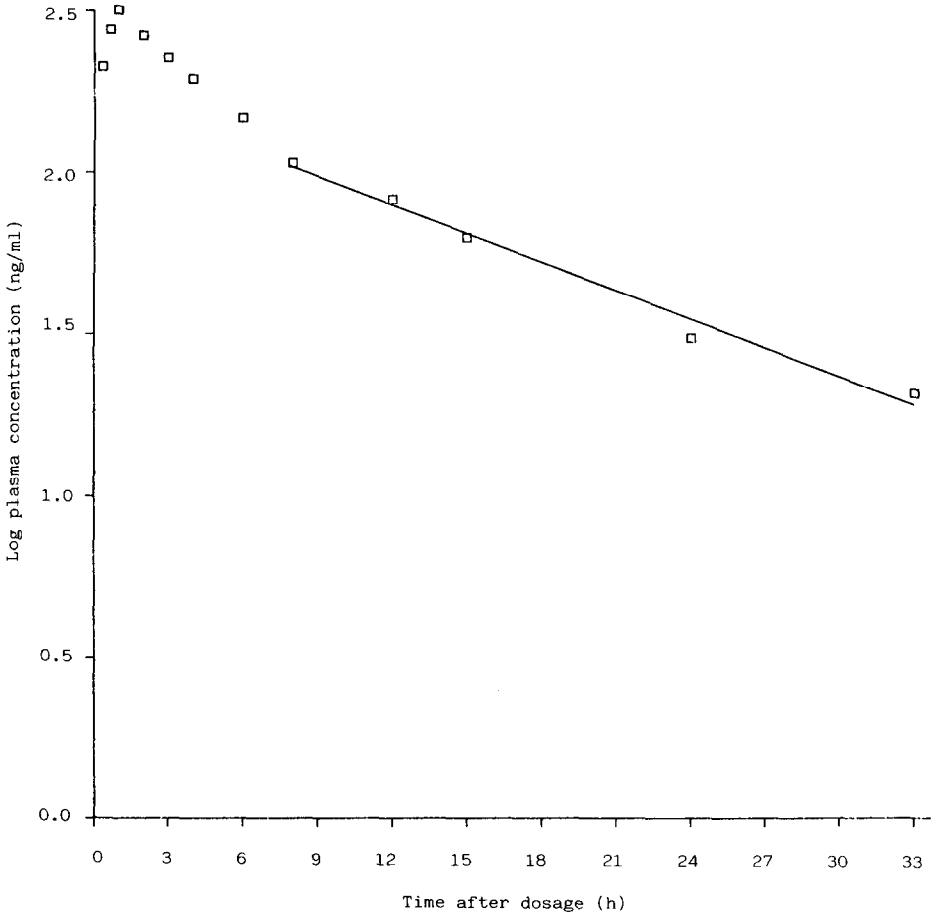

Fig. 3. Log plasma concentration data from Volunteer 1 following 20 mg temazepam as the elixir formulation.

This study was carried out primarily during sleeping hours. Pharmacokinetic parameters derived from such a study are perhaps therefore more relevant than those from a daytime study for a drug with established hypnotic effects. Calculated figures, however, showed little difference when compared with those derived from daytime studies. The terminal phase half-life, for example, ranging from 5 to 15 h (mean 9 h) was comparable with that reported by Fucella (1979) and Bittencourt et al. (1979). The shorter half-life reported by Fucella (1979) in 6 subjects given temazepam capsules in the evening was not confirmed in the present study. The terminal phase half-life of temazepam is nevertheless short compared with many benzodiazepines. Although it may be argued that the 'distribution phase' may be more relevant over the period of sleep, the relatively low sub-therapeutic plasma drug levels and shorter half-life beyond about 8 hours confirm the usefulness of this drug as a hypnotic without a prolonged residual sedating effect (Hindmarch, 1979). In addition, the use of temazepam formulated as the elixir will provide the rapid sleep induction demanded of this short-acting benzodiazepine.

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