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PLASMA LEVELS OF LORMETAZEPAM AFTER SUBLINGUAL AND ORAL ADMINISTRATION OF 1 MG TO HUMANS

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ABSTRACT

A new galenical formulation containing 1 mg lormetazepam (LMZ) for sublingual administration ("sleeping wafer", see Figure 1) has been developed. In an open-cross over design the plasma lormetazepam levels were monitored radioimmunologically in 16 volunteers. Subjects received the sublingual formulation and an oral tablet (Noctamid^{R}-1) in a randomized sequence at weekly intervals. After sublingual administration the mean plasma lormetazepam levels were significantly higher between 7.5 and 25 minutes than after administration of the tablet. The earlier rise in plasma LMZ levels is also reflected in partial areas under the plasma level curve up to 45 minutes. LMZ was completely absorbed from both formulations as shown in total AUCs.

It is anticipated that sublingual administration of the new formulation will lead to a 40 - 50 % reduction of sleep latency. Possibilities for therapeutic application of the new formulation are discussed.

INTRODUCTION

From a pharmacokinetic point of view a modern hypnotic should fulfill two essential requirements: The

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plasma levels of the active ingredient should increase immediately after administration to guarantee that the patient will rapidly fall asleep. After induction of sleep the plasma level of pharmacologically active substances should decay rapidly in order to reduce the possibility of hangover effects, drug accumulation and possible late interactions, e. g., with alcohol.

Lormetazepam (7-chloro-5-(2-chlorophenyl)-3-hydroxy-1-methyl-2,3-dihydro-1 H-1,4-benzodiazepin-2-one) is a modern, low-dose benzodiazepine which has been characterized as a potent hypnotic (1). Like other 3-hydroxy-benzodiazepines it has a comparatively short terminal plasma half-life of approximately 10 hours and no pharmacologically active metabolite with a half-life longer than that of the parent compound has been found (2, 3). Absorption half-life after oral administration of a tablet is short (0.67 $\pm$ 0.53 hours) but varies widely between subjects (2). With the aim to increase absorption rate of lormetazepam a special sublingual formulation was developed. The time course of plasma lormetazepam levels was measured after oral administration of the sublingual formulation and after oral administration of a tablet in a randomized cross-over design.

SUBJECTS, MATERIAL AND METHODS

Sixteen healthy volunteers (8 males and 8 females) whose biological data are given in Table 1 participated in the study. All volunteers were shown to be healthy by clinical examination and routine tests of renal and hepatic function. None of the subjects received medication within 2 weeks prior to the study and no drugs other than lormetazepam were given during the study.

Drugs

Subjects were given 2 treatments at weekly intervals: 1 mg lormetazepam as sublingual "sleeping wafer" and as

tablet[1]. The sublingual formulation contained 1 mg lormetazepam as a solid solution in a mixture of cellulose and a soluble cellulose derivative. The sleeping wafer looks like a small paper square (12 x 12 mm) similar to a postage stamp, separated by perforations (Fig. 1). The cellulose carrier is odorless and tasteless, and dissolves within a few minutes.

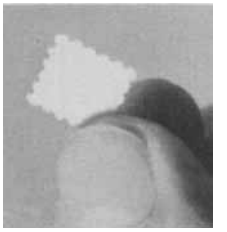

Fig. 1: Photo of "sleeping wafer"

Experimental design

The trial corresponded to an open, cross-over design. Subjects received the two treatments in a randomized sequence at 8.00 a.m. at weekly intervals.

Blood sampling

Venous blood (5 ml) was sampled immediately before and at specified time points up to 30 hours after both drug administrations. Plasma from heparinized blood samples was stored at - 20°C until analysis.

Analysis

0.1-ml portions of plasma samples were extracted with diethyl ether, dissolved in BSA buffer and analysed by a specific radioimmunoassay described by Hümpel et al. (2). Instead of N-methyl-^{3}H-diazepam, ^{3}H-lormetazepam with a specific activity of 6.1 Ci/mmole (= 225.7 MBq/mmole) was used as tracer.

Pharmacokinetic and statistical evaluation

Total (AUC_{tot}) and partial areas ($AUC_{0.25}$, $AUC_{0.5}$, $AUC_{0.75}$) under the plasma lormetazepam level curve were calculated by means of the trapezoidal rule. Partial and total areas under the curve, the quotients of partial areas and total area and the plasma concentrations at corresponding time points were statistically tested by the paired t-test.

Terminal half-lives were determined from mean

(1) Noctamid^{R}-1: manufacturer Schering AG Berlin/Bergkamen.

Table 1: Subject characteristics
m = male, f = female

No.	Initial	Sex	Age (years)	Weight (kg)	Height (cm)
1	M. H.	m	26	69	187
2	B. B.	m	21	75	173
3	M. C.	m	20	67	183
4	L. A.	f	21	52	169
5	O. R.	m	19	70	178
6	T. U.	f	34	58	172
7	B. M.	m	33	62	179
8	F. S.	f	22	59	165
9	R. U.	f	32	60	170
10	G. R.	m	34	70	178
11	N. H.-J.	m	28	84	190
12	S. S.	f	38	71	170
13	L. I.	f	36	50	162
14	S. U.	m	30	80	181
15	J. M.	f	30	65	170
16	B. D.	f	32	59	171
			x 28.5 s 6.2	x 61.9 s 16.9	x 174.9 s 7.8

values by regression analysis (time points 15 - 30 hours). Blank levels were not subtracted from plasma concentrations.

RESULTS AND DISCUSSION

Tables 2 and 3 show the individual, Figure 2 the mean values of the time course of the plasma lormetazepam concentration after sublingual and oral administration of 1 mg to 16 subjects. On an average, there is an earlier rise in the lormetazepam levels after sublingual administration as compared to oral administration.

The sublingual dosage form produced statistically significant, higher (approx. 2-fold) lormetazepam levels between 7.5 and 25 minutes than did the oral tablet. Absorption was complete from both dosage forms as shown by the total areas under the plasma curve. The total area after the sublingual dose amounted to 59.8 $\pm$ 18.2 ng h/ml and after the oral dose to 73.5 $\pm$ 20.8 ng h/ml. These figures were not statistically different from the AUC values for young volunteers (61 $\pm$ 21 ng h/ml) reported previously (2).

Terminal half-lives of 11.6 hours (sublingual) and 11.2 hours (oral) were in agreement with half-lives determined for young subjects (9.9 $\pm$ 2.4 hours) (2). Calculations of the partial areas and of the quotients of partial area and total area are presented in Table 4.

A comparison of all partial areas up to 45 minutes and also of the quotients of partial area and total area under the plasma LMA level curve shows that LMZ is more rapidly available after administration of the sublingual dosage form. The quotients are regarded as a more precise parameter for changes in the time course of the plasma level curves than partial areas since interindividual differences in the absolute, total area are eliminated. All differences in Table 4 were statistically

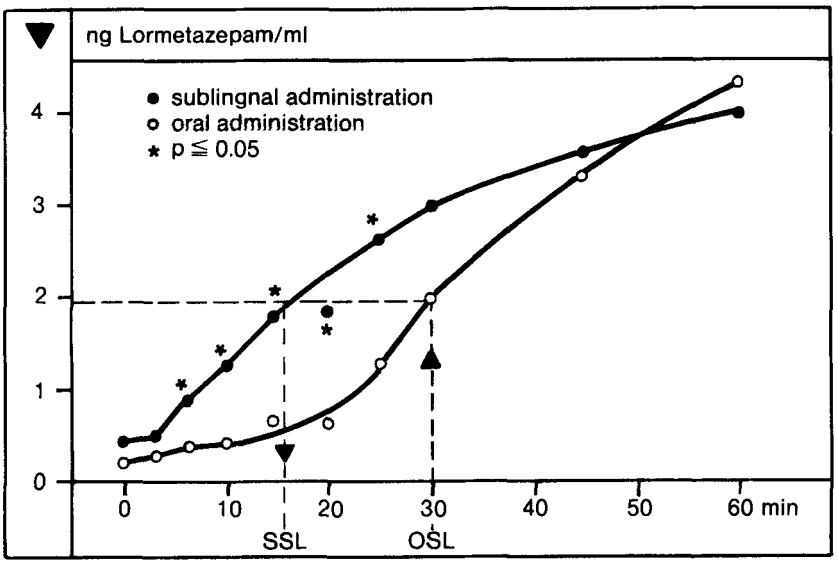

Fig. 2: Mean Lormetazepam plasma levels after sublingual (●) and oral (o) administration of 1 mg Lormetazepam to 16 subjects, SSL = sublingual sleep latency, OSL = oral sleep latency

* difference is statistically significant at $p \leq 0.05$ (paired t-test)

significant at a level of p = 0.01 except the $AUC_{0.75}$, which was significant at a p = 0.05 level.

After oral administration of 1 mg lormetazepam a mean sleep latency of 30 minutes has been reported (5). In the present investigation and in earlier reports (2) mean plasma levels of 2 ng/ml were determined 30 minutes after oral ingestion. Considering this concentration as threshold level for the induction of sleep, the present figures show that after sublingual administration of the new formulation this level was already reached at approximately 17 minutes. Therefore a 40 to 50 % reduction of sleep latency can be expected in subsequent clinical trials.

Table 2: Individual Lormetazepam plasma levels after sublingual administration of 1 mg as "sleeping wafer" to 16 subjects. Individual blank (0 h) levels (mean 0.51 ± 0.78 ng/ml) have not been subtracted.

time	TS 1	TS 2	TS 3	TS 4	TS 5	TS 6	TS 7	TS 8	TS 9	TS 10	TS 11	TS 12	TS 13	TS 14	TS 15	TS 16
2.5 min	0	0.59	0.0	0	0	0.19	1.74	0	0.06	0	0.12	0.03	0.10	1.34	0.02	0
5	0	*	0.43	0.36	0	0.41	1.75	0	0.81	0.04	0.37	0.63	0.11	0.76	0.14	0
7.5	0	*	1.21	0.58	0.46	0.93	2.19	0	1.56	0.24	0.81	1.10	0.26	0.33	0.62	0.83
10	0	0.76	2.39	0.80	1.60	1.32	2.03	0.01	2.08	0.37	1.41	2.22	0.41	0.27	0.94	1.24
15	0.25	0.85	4.14	0.93	2.06	1.93	2.14	0	2.86	0.99	1.60	3.72	1.02	1.36	1.43	1.58
20	0.50	1.00	2.05	1.10	*	3.73	2.82	0.17	2.23	1.24	*	2.35	1.75	2.00	1.92	3.21
25	1.40	1.38	2.97	1.90	2.00	4.07	3.38	0.53	4.03	2.63	2.5	4.50	2.72	0.95	2.63	3.87
30	1.52	1.18	4.01	1.62	1.85	5.91	3.50	0.83	4.56	3.78	2.44	*	2.84	1.28	2.62	5.44
45	1.69	1.68	5.70	1.96	1.83	5.09	4.45	1.46	4.04	3.58	2.67	4.33	5.45	2.25	3.90	5.83
1 h	2.95	2.37	5.36	4.07	1.97	5.09	5.55	2.93	4.27	3.93	3.01	4.44	5.83	1.63	4.49	5.95
1.5	3.30	5.10	5.16	3.68	2.51	5.66	7.56	5.11	4.68	5.09	3.06	5.25	6.83	1.62	4.91	5.74
2	3.79	4.39	4.75	4.39	3.68	5.17	6.02	3.38	4.53	4.11	2.83	3.23	6.31	2.17	4.27	4.30
3	2.96	2.86	3.63	5.18	2.11	3.63	6.61	1.99	3.99	3.95	2.69	2.86	6.04	4.44	3.84	3.61
4	*	3.31	4.23	4.25	2.80	3.70	5.67	2.00	3.16	3.66	2.51	1.92	5.51	4.24	3.84	3.01
5	1.57	2.73	4.01	3.38	2.11	2.94	7.11	1.84	3.23	3.15	2.59	2.19	5.23	3.30	3.24	3.84
6	1.41	3.07	4.91	3.83	2.34	2.45	4.23	1.70	2.87	2.89	2.33	2.09	4.25	2.69	2.77	2.25
8	1.06	3.14	3.55	3.55	2.37	2.70	3.16	1.11	2.04	2.81	2.00	1.58	3.64	2.45	2.46	2.14
10	1.26	2.65	3.91	3.11	3.74	2.49	2.76	1.22	0.79	2.56	1.92	1.35	3.47	2.10	2.44	1.63
24	0.04	1.60	2.01	1.29	2.30	1.54	1.46	0.08	0.80	1.21	0.78	0.99	0.61	1.13	1.13	0.33
30	0.02	1.42	0.95	0.75	0.98	0.89	0	0.08	0.47	0.81	0.53	0.82	0.66	0.96	0.83	0.13

* values not available

Table 3: Individual Lormetazepam plasma levels after peroral administration of 1 mg as Noctamid®-1 tablet to 16 subjects. Indiviual blank (0 h) levels (mean 0.32 ± 0.32 ng/ml)

time	TS 1	TS 2	TS 3	TS 4	TS 5	TS 6	TS 7	TS 8	TS 9	TS 10	TS 11	TS 12	TS 13	TS 14	TS 15	TS 16
2.5 min	0.15	0.88	0.15	0	0.20	0.10	0	0.75	0.01	*	0.09	0.29	0.23	0.45	0.18	0
5	0.18	0.90	0.27	0	0.11	0.22	0	0.67	0.23	0	0.28	0.19	0.19	0.45	0.20	0
7.5	0.11	1.04	0.45	0	0.17	0.15	0	0.87	0.34	*	0.61	0.30	0.21	0.40	0.20	0
10	0.30	1.10	*	0.07	0.17	0.40	0.30	0.91	0.33	0.09	0.69	0.49	0.29	0.35	0.30	0
15	*	1.37	0.20	*	0.84	0.51	0.65	0.98	0.30	0.09	1.59	0.89	0.37	0.71	0.49	0
20	0.62	1.39	0.53	0.18	0.16	1.37	0.61	1.05	0.24	0.22	1.50	0.61	0.29	0.87	1.03	0.20
25	0.54	1.42	2.72	1.29	0.38	*	0.99	1.05	0.56	0.44	2.36	1.10	0.74	1.41	2.26	0.42
30	0.58	1.64	4.25	0.34	0.43	2.46	1.62	1.65	0.79	1.65	2.39	1.51	2.56	1.66	6.26	1.21
45	1.52	4.94	4.08	3.87	1.41	5.02	3.55	2.15	1.26	3.71	3.26	3.30	3.80	1.99	7.16	2.47
1 h	2.05	8.02	7.48	3.18	3.66	5.10	5.42	2.00	1.57	4.29	4.11	2.27	5.18	2.18	7.07	5.68
1.5	7.30	8.98	12.96	7.63	5.51	9.97	3.98	5.21	5.64	*	4.28	5.82	6.86	2.37	6.35	6.48
2	7.39	5.57	7.96	5.77	4.82	8.42	4.67	6.49	5.51	8.22	6.16	3.56	6.18	3.02	5.50	5.13
3	6.53	4.72	6.05	5.83	3.52	*	3.75	5.36	5.00	6.15	4.33	3.52	5.51	3.48	4.99	3.48
4	4.54	4.35	5.67	4.93	3.83	5.83	2.76	4.00	4.47	5.89	3.74	3.69	4.38	3.84	4.32	2.83
5	4.03	3.19	4.70	6.08	3.03	5.44	2.32	3.76	4.17	4.73	3.74	3.35	4.07	4.80	4.04	2.97
6	3.61	3.09	4.64	5.12	2.90	6.77	2.32	3.09	3.13	3.94	3.03	2.99	3.46	5.18	3.26	2.51
8	2.33	2.52	4.02	4.11	2.79	4.81	2.47	2.05	2.42	3.86	3.07	2.44	2.93	4.96	2.80	2.13
10	2.53	2.54	3.78	3.39	2.74	4.23	2.34	1.70	2.11	3.33	2.63	2.38	2.89	5.88	2.45	1.83
24	1.28	1.76	1.47	1.69	1.25	1.53	0.50	0.37	0.61	1.67	1.10	1.24	1.05	2.42	1.28	0.24
30	0.06	1.26	0.95	0.71	0.89	0.90	0.09		0.39	1.24	0.78	0.86	0.69	2.67	0.97	0.13

* values not available

Table 4: Pharmacokinetic and statistical evaluation of plasma level curves after sublingual and oral administration of 1 mg lormetazepam to human subjects

	AREAS (ng x h/ml)				QUOTIENTS		
	$AUC_{0.25}$	$AUC_{0.5}$	$AUC_{0.75}$	AUC_{tot} $(0 \leq 30)$	$\frac{AUC_{0.25}}{AUC_{tot}}$	$\frac{AUC_{0.5}}{AUC_{tot}}$	$\frac{AUC_{0.75}}{AUC_{tot}}$
SUBLINGUAL	0.21 ± 0.13	0.72 ± 0.34	1.57 ± 0.71	59.8 ± 18.2	0.35 ± 0.21	1.27 ± 0.62	2.74 ± 1.35
PERORAL	0.09 ± 0.07	0.34 ± 0.20	1.00 ± 0.51	73.5 ± 20.8	0.13 ± 0.12	0.48 ± 0.30	1.40 ± 0.70
statistical significance $p \leq$	0.01	0.01	0.05	0.01	0.01	0.01	0.01

The new sublingual formulation offers a variety of practical and clinical advantages as compared to conventional tablets:
Administration is convenient for the patient and may avoid the automatism of daily (nightly) tablet-taking. No glass of water is necessary. The sleeping wafer is easily and completely dissolved in the mouth without leaving behind undissolved material. At least a part of the dose is rapidly absorbed via the oral mucosa, thus avoiding first-pass metabolism in the liver and resulting in a prompt onset of drug action.

The sublingual lormetazepam formulation may be well-suited in pre-operative sedation, when no gastric contents are required as well as in post-operative and geriatric patients who have difficulties in swallowing solid material. It also represents a comfortable, non-invasive alternative to injections.

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