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Repeated dose effects of lormetazepam and flurazepam upon driving performance

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Summary. The residual effects of lormetazepam 1 mg and 2 mg in soft gelatine capsules on driving performance were assessed and compared to those of flurazepam 30 mg, which is also a powerful hypnotic, but possesses a far less favourable pharmacokinetic profile with a long-acting sedative metabolite.

Driving performance was tested 10 to 11 h and 16 to 17 h post administration, after 2 days on placebo (baseline), and 2, 4 and 7 days of drug treatment (active), and after 1 and 3 days following the resumption of placebo (washout).

The driving test consisted of operating an instrumented motor-vehicle over a 72 km highway circuit in light traffic. Flurazepam 30 mg significantly impaired the ability to control the lateral position of the vehicle compared to placebo baseline measurements. The degree of impairment was substantial in the female subjects and was greater in the morning than in the afternoon. Lormetazepam 1 mg showed no residual effect on driving performance. Lormetazepam 2 mg impaired driving performance to some extent on the following morning, 10 to 11 h post administration, but no residual effect was found in the afternoon.

All drugs improved sleep quality and prolonged sleep duration to more or less the same extent.

Key words: lormetazepam, flurazepam; hypnotics, driving performance

Benzodiazepine hypnotics differ greatly in their achievement of an ideal pharmacodynamic profile, i.e. possessing a favourable balance between hypnotic efficacy and residual sedative effect. Some, mainly older benzodiazepines are either so slowly eliminated, or form metabolites which are so slowly eliminated, that they produce substantial impairment of performance on the following day. This was found with respect to driving performance after, for instance, flurazepam 30 mg and 15 mg, nitrazepam 10 mg, loprazolam 2 mg, and flunitrazepam 2 mg (O'Hanlon, 1984). In a subchronic study, temazepam 20 mg (in soft gelatine capsules) had no significant effect on driving performance at any time in the day during a week of nocturnal medication (Volkerts and O'Hanlon, 1986). This confirmed previous laboratory findings (e.g. Hindmarch, 1976; Lader et al., 1978). A closely related compound lormetazepam is also a 3-hydroxy benzodiazepine. The pharmacokinetic profile of temazepam and lormetazepam after single oral doses in a soft gelatine capsule formulation is similar (Pierce et al., 1984). Lormetazepam 1 mg is generally comparable to temazepam 20 mg with respect to efficacy (Nicholson, 1986). The pharmacokinetic profile of lormetazepam suggests that residual sedation resulting in deterioration of performance will be minimal. The suggestion was confirmed by several investigators for the 1 mg dose (e.g., Nicholson and Stone, 1982; Subhan and Hindmarch, 1983; Griffith et al., 1986).

However, lormetazepam is recommended by its manufacturer in a 2 mg dose for the treatment of more "resistant" insomnia. There is no evidence that the residual effects of lormetazepam 2 mg on performance are also minimal. Nicholson and Stone (1982) reported a substantial residual effect of a 2.5 mg dose, whereas Oswald et al. (1979), using a different subject population and testing procedure, failed to find such an effect of the same dosage. It remains unclear whether lormetazepam 2 mg should be considered as a safe hypnotic with respect to residual effects on normal daily routine performance in potentially hazardous situations.

A good example of a normal daily routine task that might well be hazardous if performance were deficient, is driving a motor vehicle in traffic. It has been repeatedly asked whether any laboratory test is a valid predictor of practical performance effects (Silverstone, 1974; Clayton, 1976; O'Hanlon, 1984). For the purpose of testing drug ef-

fects on driving performance O'Hanlon et al. (1982) developed a realistic on-the-road test. The same standard method has often been applied in studies of the residual effects of hypnotics (Volkerts and O'Hanlon, 1986), antidepressants (Louwerens et al., 1986) and anxiolytics (Brookhuis and Borgman, 1988). In some cases particular drugs/dosages appeared as if they might be unsafe if used by drivers. In other cases, the degree of impairment did not warrant such a severe judgement, but rather the advice to exercise more caution than normal.

Lormetazepam may be safer for use by drivers than certain other benzodiazepine hypnotics. So far, however, laboratory tests of the residual effects of lormetazepam on performance provide no clear evidence for its safety with respect to driving. The need to assess the residual effect of lormetazepam on driving performance led to the investigation reported here, in which its residual effects after repeated 1 mg and 2 mg doses were compared with those of flurazepam 30 mg administered in the same way.

Materials and methods

Subjects

Sixteen subjects, 6 males and 10 females (26 to 41 years old) were selected on the basis of the following criteria. All subjects had been diagnosed by their physicians as suffering from insomnia and were treated with benzodiazepine hypnotics sometime during the 2-year period preceding the study. They had held a driver's licence for at least 4 years and had driven at least 5,000 km. They had no history of psychotic, neurological, cardiovascular, respiratory, hepatic or renal disorders.

The subjects gave written informed consent and were treated in accordance with the Declaration of Helsinki. This included approval of the protocol by the standing Ethical Review Committee of the University, medical screening of the subjects and optimal care for safety in the driving test, i.e. redundant controls in the test vehicle and a licenced driving instructor to take control when necessary. The subjects were paid for their participation.

Design

The study was conducted according to a 3-way cross-over design, double-blind with respect to drug administration. Lormetazepam 1 mg and 2 mg and flurazepam 30 mg were each administered for eight consecutive nights in separate treatment series. Placebo was administered on the preceding 2 nights, and on the following 3 nights, of each active medication period. Driving tests were given twice on the days after 2 nights on placebo, after 2, 4 and 7 nights of active medication (drug days d2, d4 and d7) and after 1 and 3 additional nights of placebo (washout day w1 and w3). Each subject took part in a total of 36 driving test trials over a period of 12 weeks.

Owing to the subchronic treatment cross-over design, the loss of data from a single trial would remove that subject from the simultaneous overall comparison of all experimental factor effects. In fact, occasional adverse weather conditions precluded the measurement of driving performance by 9 subjects in 1 or 2 scheduled trials. Although the overall rate of data loss was low, the only analyses possible were comparisons of the complete data sets obtained from all available subjects within the three treatment series.

Treatment and activity schedule

At the start of each treatment series, the subject received a package containing 13 separate sealed units, labeled in progression by day. A double-dummy technique was used, so each unit contained 2 soft gelatin capsules and 1 tablet. Ten h before beginning the first driving test the subject ingested the contents of the appropriate unit and retired to bed within half an hour. Nine h after ingestion the subject was instructed to arise and to eat a light meal. Thereafter the subject was transported to the beginning of the test circuit to assume control of the instrumented vehicle and to begin the driving test. A clinical sleep questionnaire was completed on each test day before the first test ride.

After the driving test each subject gave a blood sample. They were then transported to their homes. There they were allowed to consume another light meal with one cup of tea or coffee. In the afternoon, beginning 16 h after ingestion, the same procedure was repeated.

Driving test

The driving tests were conducted over a 72 km circuit on a primary highway. The highway consisted of two traffic lanes (3.6 m wide) in each direction. The test vehicle was an extensively modified station wagon. Structural modifications included duplicated controls for the front passenger for use, if necessary, by one of the accompanying experimenters (a licensed driving instructor) to control the car in case of sudden or extreme deterioration in the subject's performance. This was not necessary during the study.

External modifications consisted of a doppler radar, mounted under the rear bumper, for measuring forward velocity, and an electro-optical device ("lane-tracker") for measuring the lateral position of the vehicle relative to the painted stripe delineating the road.

The analogue signals from lateral position and speed sensors were A/D converted and sampled on-line at 1 Hz by an LSI 11/23

Table 1. Mean SD lateral position during active treatment for males and females in the morning and afternoon

	Plac	Day 2	Day 4	Day 7	Was 1	Was 3	
male (a.m.)	19.7	19.6	21.8	21.8	19.1	14.8	flurazepam
male (p.m.)	18.3	18.9	19.1	18.0	19.1	16.3	30 mg
female (a.m.)	18.1	24.1	24.6	25.5	21.6	17.9	
female (p.m.)	18.0	21.0	22.5	22.1	20.0	17.5	
male (a.m.)	18.9	17.6	17.4	18.5	16.9	18.1	lormetazepam
male (p.m.)	18.1	17.7	17.7	18.1	17.1	17.9	1 mg
female (a.m.)	19.1	20.0	21.4	21.4	19.9	20.9	
female (p.m.)	19.5	20.0	18.9	21.4	19.9	20.0	
male (a.m.)	15.2	18.0	17.3	18.1	15.0	15.0	lormetazepam
male (p.m.)	17.1	16.8	14.5	15.9	15.5	16.2	2 mg
female (a.m.)	18.5	21.4	21.5	20.4	19.9	18.9	
female (p.m.)	20.8	21.0	18.8	19.7	20.0	19.9	

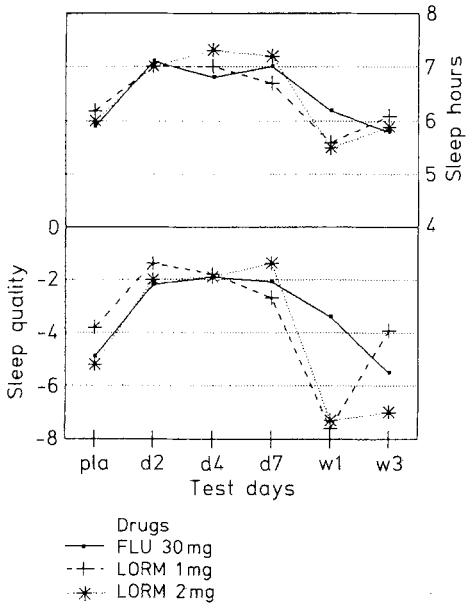

Fig. 1. Mean sleep quality scores *(bottom)* and estimated total sleep duration *(top)* as a function of successive treatment nights for all 3 conditions

mini-computer system installed in the test vehicle. Digital pulse codes were registered by the computer to indicate the beginning and end of each successive circuit segment and passing manoeuvres.

Each subjects was informed beforehand of her/his legal responsibility to drive safely at all times. The subjects were informed of the possibility that some of the treatments might impair their ability to do so. They were encouraged to tell the onboard experimenter immediately if they ever doubted their ability to continue driving in a safe manner.

The subjects were instructed to maintain a constant speed (95 km/h) and a steady lateral position within the right traffic lane, preferably in the middle of it. They were to deviate from these instructions in order to pass a slower vehicle.

Results

Lateral position

Group mean standard deviation (SD) for lateral position, a measure of weaving, is shown in Table 1 for each test day, separately for the mornings and afternoons. Average placebo baseline values were practically identical for all conditions, except for the afternoon value in the lormetazepam 2 mg phase. No reasonable explanation for this disparity can be offered.

Six males and 7 females yielded a complete data set for the flurazepam 30 mg treatment series. Manova revealed a significant effect of treatment of flurazepam 30 mg relative to placebo baseline in the SD lateral position parameter: $F(3,9) = 5.0$, $P < 0.029$. However, there was also a significant overall effect of daytime: $F(1,11) = 10.9$, $P < 0.007$. Residual drug effects were most apparent in the morning. The factor sex showed no significant overall effect, nor any interaction with the other factors.

Five males and 6 females gave a complete data set for the lormetazepam 1 mg treatment series. Manova revealed no significant effect of treatment with lormetazepam 1 mg relative to placebo, nor an interaction of drug and daytime. Lormetazepam 1 mg had no effects on SD lateral position, neither for males or females.

Four males and 6 females yielded a complete data set for the lormetazepam 2 mg treatment. Manova revealed no significant effect of treatment relative to placebo, but there was a suggestion of a multivariate interaction of drugs and daytime ($F(3,6) = 3.1$, $P < 0.11$). Pairwise comparisons of placebo and each of the three treatment days showed significant interactions of drugs and daytime on all three drug days. Probably the high afternoon placebo baseline value was partly responsible for this result. In this condition, too, sex had no significant effect, nor did it show a significant interaction with any other factor.

Other statistical descriptors of lateral position (mean, skew and kurtosis) were not significantly different between or within treatment conditions.

Speed

In the flurazepam 30 mg treatment series subjects drove faster after medication than after placebo. Although the increase in speed only averaged about 2 to 3 km/h, the effect was significant ($F(3,9) = 4.5$, $P < 0.027$). No elevation in average speed was found after lormetazepam 1 mg or 2 mg.

Sleep parameters

Subjects indicated the quality and duration of sleep on the previous night before the morning ride on each test day. Subjective sleep quality scores and estimates of total sleep duration on all test days were obtained from 14 subjects. One subject was not involved in the flurazepam 30 mg treatment series and another did not fill in her form after 7 nights of lormetazepam 1 mg. The mean group sleep quality and estimated total sleep duration are displayed as a function of successive treatment nights in Fig. 1.

Sleep by the group was mildly disturbed on placebo baseline nights, in a similar way under every condition.

Table 2. Serum drug concentration (ng/ml) correlated with SD lateral position across subjects

		N-desalkyl F		Lormet 1 mg		Lormet 2 mg	
		ng/ml	r	ng/ml	r	ng/ml	r
Day 2	(AM)	46.9	0.31	3.8	0.16	7.3	0.44
Day 2	(PM)	43.1	0.37	2.7	0.17	5.0	0.24
Day 4	(AM)	81.0	0.12	3.8	0.22	7.9	0.01
Day 4	(PM)	91.6	0.64	3.3	0.32	6.0	0.27
Day 7	(AM)	117.3	0.48	4.3	0.38	7.1	0.12
Day 7	(PM)	113.2	0.02	3.0	0.12	5.7	0.09
Was 1	(AM)	103.7	0.30	1.3	0.12	2.2	0.64
Was 1	(PM)	99.4	0.20	0.9	0.12	1.9	0.66
Was 3	(AM)	75.9	0.48	0.3	0.18	0.4	0.40
Was 3	(PM)	74.6	0.16	0.2	0.11	0.3	0.22

Mean sleep quality was between −4 and −5 (best 0, worst −14) and mean sleep duration was about 6 h. Subjects reported improved sleep quality after 2, 4 and 7 nights of medication with flurazepam 30 mg and lormetazepam 1 and 2 mg, accompanied by an increase in estimated sleep duration of about 60 min. MANOVA revealed effects of treatment with all drugs on sleep quality. After flurazepam 30 mg ($F(3,11) = 3.3$, $P < 0.063$), after lormetazepam 1 mg ($F(3,11) = 2.7$, $P < 0.099$), and after lormetazepam 2 mg ($F(3,11) = 3.4$, $P < 0.05$). The effects on estimated sleep duration were: flurazepam 30 mg: ($F(3,11) = 2.2$, $P < 0.15$), after lormetazepam 1 mg ($F(3,11) = 1.8$, $P < 0.21$), and after lormetazepam 2 mg ($F(3,11) = 8.8$, $P < 0.002$). Significant improvements were maintained throughout active medication with lormetazepam 2 mg. Cessation of medication caused a deterioration in sleep quality and shortening of sleep duration in all three conditions, most marked in the lormetazepam 1 and 2 mg series, where the subjects reported poor sleep quality and duration. However, MANOVA revealed no significant effect of cessation of active treatment in any of the three medication periods relative to placebo.

Serum drug concentrations

Serum concentrations of lormetazepam and the active metabolite of flurazepam N-desalkylflurazepam were measured in blood samples taken on all test days after the driving tests. The serum drug concentrations are given in Table 2 together with Pearson correlations (r) of the concentrations with SD lateral position scores across subjects.

Discussion

Driving performance

Flurazepam 30 mg had an adverse effect on the driving performance of the subjects in so far as their ability precisely to control the lateral position of the test vehicle was concerned. No sign of developing tolerance over test days was found with flurazepam 30 mg, even after a week of continuous use. The driving test on the 7th day after medication showed that the group mean SD lateral position remained elevated relative to the placebo baseline level.

In the flurazepam 30 mg test series major driving impairment occasionally appeared. One (female) subject, with a normal, "average" placebo baseline level, recorded an increase of 22.4 cm in the morning test on the second day after 2 nights of medication, and 14.3 cm in the afternoon.

Lormetazepam 1 mg did not seem to affect the group ability precisely to control the lateral position of the test vehicle. No meaningful elevation in SD lateral position relative to placebo baseline was found. The largest impairment measured was an elevation for a (male) subject of 4.6 cm in the morning of the third test day, i.e. after 4 days of medication, and one other (male) subject recorded an impairment of 5.6 cm in the afternoon of the same test day. The results reported here could justify a claim of safety in use of lormetazepam 1 mg by motor vehicle drivers.

Driving test performance after lormetazepam 2 mg was not so clearly unaffected as after the 1 mg dose. MANOVA showed no significant impairment, but in the morning tests mean SD lateral position elevations of 2–3 cm relative to placebo baseline levels were found on every test day during the active medication period. Some individual reactions were sufficient to forestall a claim that the drug was free of residual effects. One subject had an elevation of 10.3 cm in the morning after 4 nights of medication relative to a normal placebo baseline level. Another subject recorded a 6.4 cm elevation in the afternoon after 2 nights of medication. These changes were not exceptional in the group, so a conclusion regarding lormetazepam 2 mg is that a warning to drive cautiously in the morning should be conveyed to anyone taking this drug.

Sleep parameters

The group as a whole suffered from mild sleep disturbance. Nonetheless, all three hypnotics had a beneficial effect on sleep quality and duration in the active medication test period. For this subject sample, the hypnotics were all efficacious over a week of medication, i.e., there appeared to be no tendency for sleep quality or duration to return to baseline over the days of active medication. Following cessation of flurazepam treatment, sleep quality of the group had recovered to baseline or only slightly below if by the third placebo washout night. Cessation of lormetazepam medication had more a immediate and dramatic effects. A significant deterioration of sleep quality immediately followed withdrawal of lormetazepam 1 mg on the first night although not on the third night. Following withdrawal of lormetazepam 2 mg sleep quality dropped below baseline on the first and third night (not significant). Signs of rebound insomnia after cessation of lormetazepam medication have been reported by others (eg., Kales et al., 1982, Kales et al., 1983).

Conclusions

Flurazepam 30 mg and lormetazepam 1 mg and 2 mg (soft gelatine capsules) are potent hypnotics, as confirmed by the limited data of the present experiment. Lormetazepam 2 mg seemed to show greater hypnotic efficacy. Withdrawal of lormetazepam 1 and 2 mg caused rebound insomnia. Flurazepam 30 mg had a deleterious residual effect on driving performance by the female subjects. The results repeat a previous study employing the same method (O'Hanlon et al., 1984). From the driving test and blood serum levels it seems that accumulation of N-desalkylflurazepam in the blood, although not the only factor (cf Volkerts and O'Hanlon, 1986), is accompanied by a decrease in lateral position control. Such effects were totally absent after lormetazepam 1 mg, making it a strong candidate for use by patients who operate motor vehicles.

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