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Effects of lormetazepam and of flurazepam on sleep

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1 Nine poor sleepers of mean age 61 years took part in a double-blind, balanced order study in which, during three periods of 3 weeks, each took lormetazepam 1 mg, lormetazepam 2.5 mg, and flurazepam 30 mg.

2 Using electrophysiological measures, sleep was found to increase by 0.75 h with each treatment condition, mainly through more of stage 2 sleep. The treatments reduced the delay to sleep and led to fewer and shorter awakenings, with little difference among the three treatments. Slow-wave sleep was reduced by flurazepam and by lormetazepam 2.5 mg.

3 After flurazepam intake ceased, there was evidence of persisting drug effects for as long as 7 nights. In contrast, when lormetazepam 2.5 mg ceased, there was significant rebound reduction of sleep duration below baseline for up to 3 withdrawal nights, and there was a similar though non-significant trend after lormetazepam 1 mg had ceased.

4 Wakefulness in the final 2 h of nocturnal recording during the third week of drug intake was significantly reduced below baseline by flurazepam, but was little affected by lormetazepam.

5 The differences among the treatment conditions could be attributed to the long-persistence of flurazepam *vs* the more rapid elimination of lormetazepam.

Keywords lormetazepam flurazepam sleep

Introduction

Lormetazepam and flurazepam are benzodiazepine derivatives in use as hypnotics, and differing sharply in their persistence in the body. Lormetazepam has an elimination half-life of about 10 h in young adults, and 20 h in the elderly (Humpel *et al.*, 1979, 1980). Flurazepam, through its principal active metabolite, has an elimination half-life of the order of 100 h even in young adults (Breimer & Jochemsen, 1983). We sought to measure and to compare their effects on sleep.

It may be assumed that an hypnotic should increase the time spent asleep, and reduce the amount of wakefulness interrupting sleep, though it is uncertain to what degree there is a correlation between duration of sleep, its subjective quality and its presumptive restorative value (Adam, 1979). Hypnotic drugs are commonly taken for weeks or more and so the design included 3 weeks of regular intake, to see if tolerance and withdrawal effects could be measured.

Seven women (aged 54, 54, 60, 60, 63, 65, 66 years) and two men (57, 62 years), mean age 61 years, chosen because they considered themselves to be poor sleepers, and to be of the age and sex distribution of those who commonly take hypnotic drugs, took part. They had taken no CNS drugs in the preceding months, they were asked not to take other drugs or alcohol. The study was approved by the Royal Edinburgh Hospital Ethics Committee and each subject gave informed consent.

Each subject participated in three sequences, each of 6 weeks, with 4-week intervals between the first and second and between the second and third. Throughout each sequence the subjects took matching capsules every night at bedtime

and during the first 2 weeks these were placebo capsules, during the next 3 weeks they contained active drug, and in the sixth week placebos again were taken. During each 3-week period of active drug, the same preparation was taken each night, and during one 3-week period the subject took lormetazepam 1 mg, in another 3-week period the subject took lormetazepam 2.5 mg and during the other 3-week period the subject took flurazepam 30 mg. The order of administration of drug was by a latin square design, with 'single-blind' conditions for the placebo periods and 'double-blind' conditions for the active drug periods. Subjects attended the sleep laboratory on a total of 14 nights during each 6 weeks. In the first week of placebos there were 2 nights at the sleep laboratory for adaptation and in the second week 2 nights for the recording of baseline values. The first and fourth nights of the subsequent week gave 'early drug' data. At the end of the fourth week there was a further adaptation night and in the fifth week (the third week of active drug) the nineteenth and twenty-first nights on the drug gave 'late drug' data. In the final week the first, second, third, fifth and seventh nights provided withdrawal data.

On all nights the electroencephalogram, eye movements and submental muscle tone were recorded. Lights-out was at approximately 22.30 h, and 8 h 45 min was recorded each night. Subjects slept in comfortable, air-conditioned bedrooms. Ultimately the records were coded and scored 'blind' into the different stages of sleep and wakefulness (Rechtschaffen & Kales 1968). Thereafter the code was broken, and the raw data analyzed by a computer programme, and finally by use of the BMDP statistical packages of the Health Sciences Computing Facility, University of California.

In the statistical analysis, the mean of the 2 baseline nights, the mean of the 2 early drug nights, and the mean of the 2 late drug nights were determined for each individual for each of 33 different sleep measures and these means have been used in the analysis of results, together with the individual values for each of the 5 withdrawal nights. In the first place, each of the three drug sequences was treated separately by an analysis of variance with repeated measures to determine whether any of the individual drugs had an effect on the particular measure of sleep. Here the degrees of freedom were always 7,56. The individual withdrawal nights were used rather than the means because mean values could conceal systematic changes with time following the withdrawal. Where, for any measure, the co-efficient of variation was consistently above 0.50, the non-parametric Friedman's analysis of variance by ranks was used, and this was used for sleep latency, measures of wakefulness and amounts of slow wave sleep. Where analysis of variance proved significant, correlated *t*-tests or the Wilcoxon signed-ranks test were used. In the *t*-tests degrees of freedom were 8, and in the Wilcoxon generally 9, depending on the number of non-zero differences. A further analysis of variance was carried out to determine whether there were any differences among the drugs during drug-taking periods. The data used in these analyses were the differences from the baseline means. A drug term (df = 2,16) referred to differences among the three drugs, additionally a night term (df = 1,8), indicated any consistent difference between the early and late drug periods irrespective of the drug being taken and a drug x night interaction term revealed any difference among the treatments in the pattern of change between the early and late drug periods. Thereafter, correlated *t*-tests between pairs of conditions were carried out to compare the drugs, particularly during the early and late drug periods, using the differences from the baseline means.

To see if the withdrawal of any one of the drugs led to greater disturbance of sleep, further analysis of variance was carried out in which three different withdrawal periods (drug term) at five levels (night term) were compared, using differences from the baseline means. The drug term could thereby reveal differences among the drugs upon withdrawal. The night term could show if there was a significant change across the 5 individual nights following withdrawal and the drug x night interaction term could reveal any inter-dependence. When appropriate, correlated *t*-tests were subsequently employed using differences from baseline means to compare, for example, the effect of withdrawal of flurazepam 30 mg with the effect of withdrawal of one of the doses of lormetazepam on a specified night.

Results

In Tables 1, 2 and 3 are summarized the data of principal interest and we elaborate below the main findings.

Sleep duration increased

Subjects slept about 0.75 h longer with any of the three treatments, mainly through increased duration of stage 2 sleep. Making comparisons with the baseline means for total sleep, and using *t*-tests, for all three treatments the early drug mean and the late drug mean were both significantly lengthened at the $P < 0.05$ criterion or better. The same was true when sleep duration

Table 1 Lormetazepam 1 mg: features of sleep (means and s.d. where appropriate)

	Base-line	*Early drug*	*Late drug*	*Withdrawal 1*	*2*	*3*	*5*	*7*	*Analysis of variance* (Parametric, df = 7, 56; non-parametric, df = 7)
Total sleep (min)	435.7 ±38.0	478.8 ±21.5	470.6 ±27.2	396.1 ±59.7	387.0 ±61.7	413.8 ±62.9	424.6 ±45.2	444.2 ±43.3	$F =$ 5.84 $P <$ 0.001
Sleep onset latency (min)	30.8	21.5	26.7	41.1	69.8	48.8	29.9	42.6	$\chi r^2 =$ 13.0, $P =$ 0.07
REM latency (min)	71.9	84.6	86.3	69.0	80.9	76.0	80.0	61.7	$\chi r^2 =$ 9.6, NS
Total stage 1 (min)	50.6 ±26.4	43.9 ±12.3	44.6 ±13.6	44.1 ±15.9	48.4 ±23.2	46.2 ±19.3	60.2 ±18.0	46.5 ±18.9	$F =$ 1.7, NS
Total stage 2 (min)	241.2 ±21.6	301.0 ±38.0	276.9 ±40.5	224.0 ±50.0	217.6 ±44.5	224.3 ±55.6	246.4 ±49.5	248.2 ±39.0	$F =$ 5.3 $P <$ 0.001
Total stages 3 + 4 (min)	53.4	44.4	55.3	39.1	51.7	50.1	36.3	54.3	$\chi r^2 =$ 5.2 NS
Total REM sleep (min)	90.5 ±19.6	89.5 ±19.4	93.7 ±19.2	88.8 ±26.7	69.2 ±20.7	93.2 ±21.4	81.6 ±19.8	95.2 ±12.8	$F =$ 1.8 NS
Awakenings in first 4 h cumulative sleep	2.00	1.22	0.89	2.67	2.89	2.22	3.11	2.33	$\chi r^2 =$ 16.5 $P =$ 0.02
Intervening wake, first 4 h (min)	31.2	5.6	4.4	44.4	41.2	31.0	35.3	14.0	$\chi r^2 =$ 17.1 $P =$ 0.017
Total recording duration (min)	522.4 ±2.7	522.9 ±2.2	525.2 ±0.7	523.0 ±2.2	528.0 ±3.2	524.3 ±2.3	523.0 ±5.3	524.0 ±2.7	$F =$ 3.32 $P =$ 0.005

Table 2 Lormetazepam 2.5 mg: features of sleep (means and s.d. where appropriate)

	Base-line	*Early drug*	*Late drug*	*Withdrawal 1*	*2*	*3*	*5*	*7*	*Analysis of variance* (Parametric, df = 7, 56; non-parametric, df = 7)
Total sleep (min)	448.6 ±36.8	496.4 ±6.1	481.2 ±22.0	382.0 ±55.6	401.2 ±69.1	386.1 ±51.7	421.5 ±38.5	429.1 ±52.0	F = 11.4 $P <$ 0.001
Sleep onset latency (min)	31.1	20.9	21.6	54.8	50.8	64.0	47.0	37.1	χr^2 = 23.0 P = 0.002
REM latency (min)	84.4	117.6	97.2	84.3	65.9	75.7	83.4	72.4	χr^2 = 23.2 P = 0.002
Total stage 1 (min)	50.9 ±17.8	36.2 ±10.8	49.0 ±26.7	44.6 ±23.9	45.3 ±16.6	40.6 ±16.7	46.0 ±24.7	39.5 ±14.6	F = 1.6 NS
Total stage 2 (min)	246.0 ±31.9	321.3 ±41.6	307.8 ±39.2	228.0 ±48.1	220.8 ±54.6	210.6 ±35.2	216.7 ±28.6	237.0 ±26.8	F = 13.4 $P <$ 0.001
Total stages 3 + 4 (min)	54.6	49.1	38.9	28.9	46.9	53.8	73.2	56.1	χr^2 = 22.2 P = 0.002
Total REM sleep (min)	97.0 ±19.1	89.8 ±14.8	85.4 ±18.4	80.5 ±33.7	88.1 ±19.3	81.0 ±24.5	85.5 ±22.3	96.5 ±25.2	F = 1.2 NS
Awakenings in first 4 h cumulative sleep	2.22	0.78	1.00	3.11	3.22	3.22	3.00	1.67	χr^2 = 19.0 P = 0.008
Intervening wake, first 4 h (min)	21.6	1.4	4.2	55.2	38.9	33.1	8.5	6.8	χr^2 = 27.4 P = 0.001
Total recording duration (min)	525.4 ±1.1	525.5 ±1.5	526.3 ±2.7	524.6 ±1.2	526.7 ±2.6	526.4 ±1.7	527.0 ±1.5	525.1 ±4.6	F = 1.41 NS

Table 3 Flurazepam 30 mg: features of sleep (means and s.d. where appropriate)

	Base-line	*Early drug*	*Late drug*	*Withdrawal 1*	*2*	*3*	*5*	*7*	*Analysis of variance* (Parametric, df = 7, 56; non-parametric, df = 7)
Total sleep (min)	449.9 ±30.7	489.2 ±9.5	498.2 ±11.4	479.2 ±28.0	468.1 ±47.4	465.2 ±47.7	451.1 ±35.5	443.1 ±59.6	$F =$ 3.56 $P <$ 0.003
Sleep onset latency (min)	33.2	26.1	18.6	21.3	23.4	27.7	41.7	28.0	$\chi r^2 =$ 14.9 $P =$ 0.038
REM latency (min)	83.8	93.7	104.7	103.4	92.2	114.2	93.2	98.9	$\chi r^2 =$ 5.1 NS
Total stage 1 (min)	46.2 ±18.7	29.8 ±7.5	34.6 ±11.2	44.3 ±11.6	48.7 ±20.7	51.9 ±13.4	47.8 ±18.0	46.0 ±23.1	$F =$ 4.6 $P <$ 0.001
Total stage 2 (min)	267.3 ±31.0	331.1 ±32.4	348.3 ±44.7	327.3 ±52.1	309.6 ±53.5	288.4 ±43.5	272.4 ±34.1	269.2 ±53.9	$F =$ 8.9 $P <$ 0.001
Total stages 3 + 4 (min)	47.4	39.2	30.2	18.0	21.7	40.2	36.8	42.7	$\chi r^2 =$ 20.3 $P =$ 0.005
Total REM sleep (min)	88.9 ±19.0	89.1 ±20.5	85.2 ±18.0	89.6 ±25.1	88.0 ±25.2	84.7 ±20.8	94.1 ±18.9	85.2 ±29.9	$F =$ 0.3 NS
Awakenings in first 4 h cumulative sleep	2.17	0.78	0.28	1.22	1.78	1.44	1.11	1.44	$\chi r^2 =$ 15.0 $P =$ 0.036
Intervening wake, first 4 h (min)	21.7	2.3	1.1	4.5	6.7	12.0	8.2	6.6	$\chi r^2 =$ 15.5 $P =$ 0.03
Total recording duration (min)	526.1 ±1.4	524.4 ±1.3	524.9 ±2.5	524.8 ±1.6	526.0 ±2.7	526.7 ±2.2	527.3 ±1.7	527.8 ±4.4	$F =$ 2.88 $P =$ 0.012

was treated as a proportion of the total duration of nocturnal recording time. When the three treatment conditions were themselves compared, using differences from the baseline means, there were no significant differences among the treatments.

Quicker to fall asleep

The latency to the onset of sleep, always showing a high degree of scatter among poor sleepers, was reduced on average by about 10 min under each of the three drug conditions. In the case of lormetazepam 1 mg, non-parametric analysis of variance just missed significance, but for lormetazepam 2.5 mg analysis of variance was significant and subsequent Wilcoxon tests, making comparison with the baseline mean, revealed significance during early drug intake ($P = 0.01$), but a non-significant difference ($P = 0.07$) for late drug intake. The effect of flurazepam was non-significant during early drug ($P = 0.09$) but significant during late drug intake ($P = 0.03$). Using differences from baseline means, there were no significant differences among the three treatments.

Less frequent awakenings

Throughout the study no subject slept less than a cumulative total of 4 h on any one night (though sometimes less than 5 h) and so, keeping total sleep constant, we considered how often subjects awakened in the course of accumulating their first 4 h of sleep. Analysis of variance was significant for each treatment and inspection of the Tables reveals a reduction in the frequency of awakenings associated with all three active treatments. Wilcoxon tests confirmed that with lormetazepam 1 mg subjects wakened less often during both early drug ($P = 0.025$) and late drug ($P = 0.04$). The lesser frequency of awakenings did not reach significance with the larger dose of lormetazepam, nor during early intake of flurazepam, though it did during late flurazepam intake ($P = 0.01$). There were no significant differences among the three treatments.

Less intervening wakefulness

The cumulative duration of wakefulness that intervened in the course of accumulating the first 4 h of sleep was reduced by all three treatments. Using Wilcoxon tests the reduction was significant with lormetazepam 1 mg, both early ($P = 0.01$) and late ($P = 0.02$); with lormetazepam 2.5 mg for early drug only ($P = 0.03$); and with flurazepam both early ($P = 0.04$) and late ($P = 0.01$). There were no significant differences among the treatments.

Sleep stages

Administration of all three treatments, as mentioned, increased total stage 2 sleep. The duration of REM sleep in the whole night was little affected, though in the first 4 h of cumulative sleep, REM sleep tended to be reduced by flurazepam and by lormetazepam 2.5 mg, with which latter the reduction was significant on *t*-test, both for early and late drug periods at the $P = 0.001$ criterion.

Slow-wave sleep (stages 3 + 4) was little affected by lormetazepam 1 mg, but was reduced by flurazepam during early drug ($P = 0.04$) and late drug ($P = 0.02$) and during late intake of lormetazepam 2.5 mg ($P = 0.02$). The amount of time spent in stage 1 (drowsiness) was reduced significantly only by flurazepam: early drug, $P = 0.02$; late drug, $P = 0.01$. There were no significant differences among the treatments in effects on slow wave sleep or on stage 1.

The final 2 h

We examined the final two recorded hours of each night during baseline and during late drug. The number of minutes of wakefulness was highly variable from night to night and subject to subject. We took the mean of the two nights for each subject and then the group means were used and revealed: lormetazepam 1 mg, baseline 21.5 min, late drug 18.1 min; lormetazepam 2.5 mg, baseline 20.9 min, late drug 14.0 min; flurazepam 30 mg, baseline 18.2 min, late drug 5.5 min. Thus the only substantial difference was for flurazepam and, on the Wilcoxon test, only this reduction was significant, $P = 0.03$.

Changes during drug administration

There were a few trends to increasing effect of flurazepam within the two early drug nights, and between the early and the late drug periods in, for example, slow wave sleep, but these did not reach significance.

Tolerance, evidenced as a lesser effect of drug administration during late drug intake compared with that seen in the early days of intake, was suggested by a number of measures in the case of lormetazepam 2.5 mg; for example, mean total sleep duration decreased by 15 min ($P = 0.06$).

Drug persistence

After flurazepam intake had ceased there was evidence of persisting drug. Thus, on the first withdrawal night, total sleep duration was still significantly elevated ($P = 0.01$) and the mean figures suggested a continuing effect for another two nights. Stage 2 sleep continued significantly elevated compared with baseline into the second

withdrawal night ($P = 0.02$). Persistence was even clearer in the reduced frequency of awakenings in the first 4 h of accumulated sleep, which effect continued as long as the fifth withdrawal night ($P = 0.03$), while intervening wakefulness in the first 4 h of sleep was still low compared with baseline on the seventh withdrawal night ($P = 0.05$). In contrast, when either dose of lormetazepam ceased to be taken, withdrawal phenomena tended to appear.

Withdrawal effects

Withdrawal of lormetazepam 1 mg was associated with shorter sleep and greater variability of duration among subjects, but on no measure did comparisons of baseline mean values with individual withdrawal nights reach significance, though for total sleep on the second withdrawal night, $P = 0.07$.

Withdrawal of lormetazepam 2.5 mg was associated with diminished total sleep and greater variability compared with baseline; for total sleep on the first withdrawal night, $P = 0.004$ and on the third withdrawal night, $P = 0.007$.

Comparisons were made among the treatments using differences from baseline for the five withdrawal nights and analysis of variance provided a significant drug term ($F = 5.30$, $P = 0.017$) and a significant drug x night interaction term ($F = 2.38$, $P = 0.026$). Correlated t-tests revealed no significant differences between the two doses of lormetazepam, but sleep was significantly shortened on the first withdrawal night after lormetazepam 1 mg when comparison was made with the first night after flurazepam intake ceased, ($t = 3.30$, $P = 0.01$). The same was true of the first withdrawal night of lormetazepam 2.5 mg, compared with flurazepam ($t = 4.74$, $P = 0.002$) and on the third withdrawal night there was still a difference between flurazepam and lormetazepam 2.5 mg, ($t = 4.25$, $P = 0.003$).

Discussion

Both lormetazepam and flurazepam in the doses used were effective hypnotics. The Tables indicate that in, for example, augmenting sleep duration and diminishing awakenings, there was little advantage in the larger dose of lormetazepam compared with the smaller dose, and indeed the larger dose was associated with significant rebound phenomena. Using a population 20 years younger, Kales *et al.*, (1982a) gave doses of lormetazepam 0.5 mg, 1 mg, 1.5 mg and 2 mg to different groups of poor sleepers. There were only six subjects in each group and inter-group comparisons were constrained by the variability among groups, but, like ourselves, the authors concluded that there was little greater efficacy to be achieved from the higher dosages. In their data, too, there was a suggestion that higher doses of lormetazepam were associated with some tolerance by a second week of intake, though, as in our study, such trends were not significant.

Rebound phenomena upon withdrawal of hypnotics are to be expected and we have, for example, found rebound reduction of sleep duration below baseline subsequent to regular intake of nitrazepam 5 mg or lormetazepam 2 mg (Adam *et al.*, 1976; Oswald *et al.*, 1982). Such rebound phenomena were not manifest in the present study after flurazepam intake, and Kales *et al.* (1982b) have similarly reported absence of rebound following flurazepam. Presumably this is because it is impossible abruptly to withdraw flurazepam. What we find are effects that must be attributed to prolonged persistence of active metabolite for as many as 7 days. Kales *et al.* (1982b) imply that it is a good feature of flurazepam that there is no rebound, but we have to emphasize the corollary of flurazepam's persistence, namely drug accumulation and impairment of social judgement and of psychomotor skill by day, as we have found to be associated with regular flurazepam intake by the middle-aged, in contrast to the absence of measured impairments with lormetazepam 1 mg, and only minimal, if any, daytime impairments from lormetazepam 2.5 mg (Oswald *et al.* 1979). The clinical choice is thus: daytime dopiness and no rebound, or daytime clear-headedness but bad sleep for some nights when the drug stops following regular intake. In our view the second of these options offers the lesser disadvantage, particularly as a small dose of the more rapidly-eliminated lormetazepam is an effective hypnotic.

Although lormetazepam is an example of a fairly short-life hypnotic, others are more rapidly eliminated, for example, triazolam, which has an elimination half-life of about 3 h (Jochemsen *et al.*, 1983). There may be disadvantages from a drug that can lead to abruptly-varying tissue concentrations, and withdrawal effects during the day. Morgan & Oswald (1982) reported increasing daytime anxiety from regular triazolam 0.5 mg at night, a finding since confirmed by Kales *et al.* (1983), and consistent with more extreme psychological symptoms associated with larger doses (Van Der Kroef, 1979). On the other hand, 24 weeks of intake of lormetazepam 2 mg nightly had no effect on daytime anxiety (Oswald *et al.*, 1982). The critical factor is presumably the difference in elimination time and it was with this in mind that we examined the

last 2 h of the night to see if any withdrawal rebound effects could be discerned as the day was about to begin. Kales *et al.* (1983) had reported 'early morning insomnia' as a late-night withdrawal phenomenon during the second week of intake of 'rapidly eliminated benzodiazepines' and similar late-night broken sleep from accustomed sodium amylobarbitone had previously been reported from our laboratory (Ogunremi *et al.*, 1973). Although lormetazepam is fairly rapidly eliminated, there was no evidence in our data of the early morning insomnia (Kales *et al.*, 1983) reported for triazolam. The amount of wakefulness was similar to baseline, and would suggest relative freedom from residual drug effects as the time for rising approached. In contrast, because flurazepam was still having strong effects just before the time for rising, freedom from residual effects at breakfast time could not be expected. If a very rapidly-eliminated drug such as triazolam may bring disadvantages of one kind, and the long-acting flurazepam bring disadvantages of an opposite nature, an optimal compromise may perhaps be found in an hypnotic, such as lormetazepam, which avoids either extreme.

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