HYPNOTIC ACTIVITY OF 3-HYDROXY, N-DESMETHYLDIAZEPAM (OXAZEPAM)

Diazepam (5–10 mg) and its hydroxylated metabolites, temazepam (10–20 mg) and oxazepam (15–30 mg), have limited effects on performance in man (Clarke & Nicholson, 1978), and these drugs in the doses indicated may be appropriate to the management of sleep difficulties for those involved with skilled work. However, although the hypnotic activity of diazepam and temazepam have been described (Nicholson, Stone & Clarke, 1976; Nicholson & Stone, 1976), there would appear to be little information available on the effect of oxazepam in this dose range on sleep in man.

The subjects were six healthy male volunteers aged between 20 and 31 years. They were familiar with the laboratory, and with the techniques used in recording sleep activity. They were required to refrain from napping and undue exercise, and to abstain from caffeine and alcohol after mid-day on the days which involved sleep recordings. The subjects reported to the sleep laboratory for two consecutive nights at weekly intervals for 6 weeks, and retired to bed at a set time between 23.00 and 23.30 h. On the first night the subjects ingested a placebo. The analysis was concerned with the second night only, when they ingested either an active compound (15, 30 or 45 mg oxazepam or 10 mg diazepam) or on two occasions a placebo. There were no differences between the sleep measures of the nights with ingestion of placebo, and so the measures were combined to give the control values. The order of ingestion of the drugs and placebos was random, and the study was double blind. On each occasion the subjects ingested two identical capsules.

Details of recording techniques, scoring of the electroencephalographic records, statistical analysis of the sleep measures and analogue scales were the same as those given in a previous paper, except that the F1–F7 derivation was replaced by C4–A1 (Nicholson, Stone, Clarke & Ferres, 1976). The sleep laboratory was sound attenuated and temperature and humidity were controlled.

At 0.5 h before 'lights out' the subjects completed assessments of their well-being related to a 100 mm analogue scale. The assessments were: How did you feel during the day? and How do you feel now? The extremes of the scale were *Tired* (00) and *Fresh* (100), and *Very Sleepy* (00) and *Wide Awake* (100) respectively. The subjects were woken at 07.30 h the next day, and 0.5 h after awakening completed four assessments. The assessments and the extremes of the 100 mm analogue scales were, C: I slept, *very poorly—very well*, D: Now I feel, *very tired—wide awake*, E: I fell asleep, *never—immediately* and F:

After I fell asleep I slept, *very badly—very well*. In each case a favourable response tended toward the 100 extreme of the scale. The only change in subjective assessments of sleep and well-being was impaired wakefulness ($P < 0.001$) on awakening after overnight ingestion of 45 mg oxazepam. This would be consistent with the residual effects of oxazepam on performance (Clarke & Nicholson, 1978).

Oxazepam had a marked effect on sleep (Tables 1, 2, 3, 4 and 5). It increased total sleep time, reduced the duration of awake activity and of drowsy (stage 1) sleep, and increased the duration of stage 2 sleep. There was no evidence, even with the 45 mg dose, of change in slow wave or rapid eye movement sleep. However, it was not possible to establish an effect on sleep onset latency, and this finding is consistent with pharmacokinetic data which suggest slow absorption of the drug (Wyeth—Internal Report) and performance data which show a delayed appearance of impairment (Molander & Duvhök, 1973; Clarke & Nicholson, 1978). The effect of a single dose of diazepam, which was included as an active control, was similar to that described previously (Nicholson, Stone & Clarke, 1976).

It is evident that in the dose range free from residual effects on performance, oxazepam (15–30 mg) is a useful hypnotic, though further studies are required to establish its effectiveness in the clinical situation. The effect of 30 mg oxazepam on the sleep period time (sleep onset to final awakening) is more pronounced than that of 10 mg diazepam. Though oxazepam does not reduce sleep onset latencies, the effect persists well into the night without affecting the normal structure of sleep.

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Table 1 Effect of oxazepam (15, 30 and 45 mg) and diazepam (10 mg) on various sleep measures compared with placebo (means for six subjects)

<i>Measure</i>	<i>C/V</i>	<i>Placebo</i>	<i>15</i>	<i>Oxazepam (mg)</i> <i>30</i>	<i>45</i>	<i>Diazepam (mg)</i> <i>10</i>
Total sleep time (min)	5.70	433.96	446.17	469.42**	485.42***	456.00
Stage shifts in first 6 h	10.50	118.42	115.50	93.8***	107.17*	106.50
Sleep onset latency (min)	37.20	15.83	14.92	24.33	17.83	13.83
Latency (min) to stage 3	30.70	13.17	13.67	11.75	13.17	15.08
Latency (min) to stage REM	42.10	72.42	82.42	70.75	66.83	97.75
REM/NREM ratio	17.50	0.33	0.33	0.36	0.30	0.32

C/V = Coefficient of variability (s.d. $\times$ 100/mean) of each measure
 Significance levels * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 2 Effect of oxazepam (15, 30 and 45 mg) and diazepam (10 mg) compared with placebo on duration (min) of sleep stages in first 6 h of sleep (means for six subjects)

<i>Sleep stage</i>	<i>C/V</i>	<i>Placebo</i>	<i>15</i>	<i>Oxazepam (mg)</i>		<i>Diazepam (mg)</i>
				30	45	10
0†	65.40		NS	(*)	*	*
1	24.30	31.38	26.17	15.00 ***	14.17 ***	26.50
2	9.00	223.92	235.83	255.08 **	282.58 ***	255.50 **
3	30.20	35.67	46.33	41.83	45.83	45.92
3+4	19.20	77.71	78.33	77.50	77.03	69.75
REM	15.20	111.25	112.75	122.42	112.33	113.42

C/V=Coefficient of variability (s.d. × 100/mean) of each measure

Significance levels **P*<0.05; ** *P*<0.01; *** *P*<0.001

† Non-parametric analysis.

Table 3 Effect of oxazepam (15, 30 and 45 mg) and diazepam (10 mg) compared with placebo on percentage of total sleep time occupied by each sleep stage (means for six subjects)

<i>Sleep stage</i>	<i>C/V</i>	<i>Placebo</i>	<i>15</i>	<i>Oxazepam (mg)</i>		<i>Diazepam (mg)</i>
				30	45	10
1	26.80	7.06	5.83	3.17***	2.92***	5.82
2	7.40	50.01	51.72	54.02*	57.68***	54.53*
3	29.50	8.08	10.32	8.87	9.45	9.35
4	42.70	9.43	6.93	7.60	6.28	5.58 *
3+4	19.90	17.53	17.23	16.43	15.73	14.92
REM	13.30	24.90	24.55	25.98	22.92	24.32

C/V=Coefficient of variability (s.d. × 100/mean) of each measure

Significance levels **P*<0.05; ** *P*<0.01; *** *P*<0.001.**Table 4** Effect of oxazepam (15, 30 and 45 mg) and diazepam (10 mg) compared with placebo on 2 hourly distribution (min) of stages 1 and 2 (means for six subjects)

<i>Sleep stage</i>	<i>Interval (h)</i>	<i>C/V</i>	<i>Placebo</i>	<i>15</i>	<i>Oxazepam (mg)</i>		<i>Diazepam (mg)</i>
					30	45	10
1	0–2†	109.00		NS	NS	NS	NS
	2–4†	74.60		NS	*	*	NS
	4–6	43.70	9.75	6.00 *	3.17 ***	3.67 **	6.00 *
2	0–2	16.60	50.00	42.25	47.92	58.17	56.58
	2–4	15.00	64.43	65.92	71.83	70.33	69.33
	4–6	24.10	61.63	71.25	79.75	78.92	72.25

C/V=Coefficient of variability (s.d. × 100/mean) of each measure

Significance levels **P*<0.05; ** *P*<0.01; *** *P*<0.001

† Non-parametric analysis.

Table 5 Effect of oxazepam (15, 30 and 45 mg) and diazepam (10 mg) compared with placebo on awakenings (means for six subjects)

Awakening (sleep stage)	Measure	C/V	Placebo	15	Oxazepam (mg) 30	45	Diazepam (mg) 10
0	Number	81.8	1.42	0.67	1.50	1.17	1.00
	†Duration (min)	95.0		NS	NS	NS	NS
1	Number	36.1	13.17	10.67	6.50 ***	9.00 *	9.83
	Duration (min)	46.0	10.88	10.50	4.58	5.83	7.33
0-1	Number	34.6	10.50	7.17	5.33 **	6.83 *	7.17
	†Duration (min)	51.1		NS	NS	NS	NS

C/V= Coefficient of variability (s.d. $\times$ 100/mean) of each measureSignificance levels * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

† Non-parametric analysis.

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