

## EFFECT OF N-DESMETHYLDIAZEPAM (NORDIAZEPAM) AND A PRECURSOR, POTASSIUM CLORAZEPATE, ON SLEEP IN MAN

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1 The effect of N-desmethyldiazepam (nordiazepam, 5 and 10 mg) and potassium clorazepate (15 mg, a precursor of nordiazepam) on sleep was studied in six healthy adult males. Electroencephalography (EEG) was used for sleep measures, and analogue scales were used for subjective assessments of well-being and sleep quality.

2 Effects on total sleep time were limited to the night of ingestion. There were increases with nordiazepam (5 and 10 mg) ( $P = 0.05$  and  $0.001$  respectively), and with clorazepate (15 mg) ( $P = 0.01$ ). Sleep onset latencies were shortened, particularly with nordiazepam, and awakening to stage 0 activity was reduced, by both drugs. The latency to stage 3 was reduced by nordiazepam (5 and 10 mg) ( $P = 0.05$ ).

3 There were no effects of nordiazepam (5 mg) on the duration (min) of sleep stages. Nordiazepam (10 mg) and clorazepate (15 mg) reduced the duration of stage 0 and stage 1, and there were increases in stage 2. Reduced stage 1 and increased stage 2 sleep were observed during the recovery night. No effects were observed with stage 3, but there was evidence that stage 4 activity was depressed on the recovery night only. No effects were observed on REM sleep, except that the appearance of the first REM period was delayed with clorazepate (15 mg) ( $P = 0.01$ ). The effect of nordiazepam (10 mg) and clorazepate (15 mg) were comparable, and each modified sleep for about 28-30 h after ingestion.

4 With nordiazepam (10 mg) and clorazepate (15 mg) the subjects, as a group, reported improved sleep, but subjective assessments of well-being were not altered. Correlations were calculated for sleep measures and subjective assessments.

### Introduction

In previous studies we have been concerned with the effect of hypnotics on performance using adaptive tracking as an occupation orientated task. With barbiturates and the 1,4-benzodiazepines, nitrazepam (10 mg) and flurazepam hydrochloride (30 mg), performance was impaired 16 h or more after overnight ingestion (Borland & Nicholson, 1974, 1975a), and these observations suggested that residual effects on performance may be an inevitable sequel of an effective hypnotic. However, further studies have shown that impaired performance does not persist beyond 10 h with the overnight ingestion of methaqualone hydrochloride (400 mg) (Borland, Nicholson & Wright, 1975), and that, with the morning ingestion of diazepam (10 mg), performance returns to control values within 7.5 h (Borland & Nicholson, 1975b). The restricted effects of diazepam on performance, together with its limited potential for

misuse, suggest that it could prove to be a useful hypnotic for persons involved in skilled activity.

Like many other benzodiazepines the behavioural activity of diazepam is related, not only to the pharmacokinetic and behavioural properties of the parent drug, but also to its metabolites. N-desmethyldiazepam is the principal metabolite of diazepam, and, in view of our interest in the possible use of diazepam or a closely related drug as an hypnotic for persons involved in skilled activity, we have studied the effect of this metabolite on sleep in man. We have also studied potassium clorazepate (dipotassium-7-chloro-2,3-dihydro-2,2-dihydroxy-5-phenyl-1H-1,4-benzodiazepine-3-carboxylic acid) which is believed to be absorbed largely as N-desmethyldiazepam after decarboxylation by the gastric juices (Itil, Saletu & Marasa, 1972). The formulae of the two drugs are shown in Figure 1.

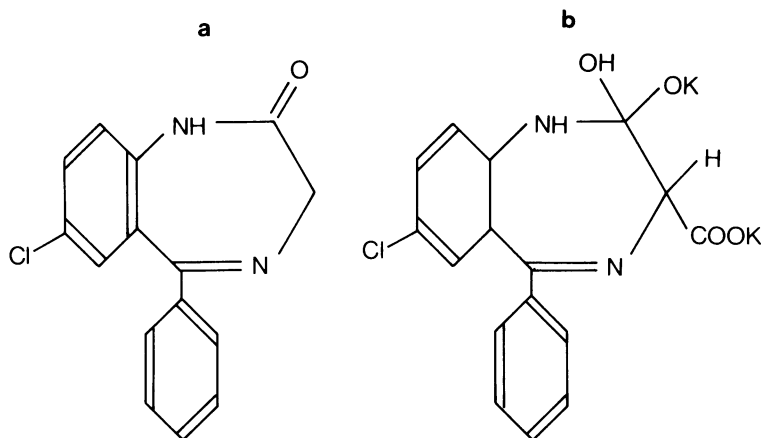


Figure 1 Structural formulae of N-desmethyldiazepam (a) and potassium clorazepate (b).

## Methods

The subjects were six healthy male volunteers aged between 19 and 43 years. They were familiar with the laboratory, and with the techniques used in recording sleep activity. The assessment of the effect of each treatment (placebo or dose of a drug) involved 4 days. For 2 nights the subjects slept at home and retired at a set time between 23.00 and 23.30 h, and for the next 2 nights the subjects slept in the sleep laboratory. 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 sleep laboratory was sound attenuated, and the temperature ( $18 \pm 1^\circ\text{C}$ ) and humidity ( $55 \pm 2\%$ ) were controlled. Nine to twelve days separated each assessment. The subjects reported at the sleep laboratory 1.5 h before their set time to retire. At 0.5 h before 'lights out' the subjects completed an assessment of their well-being related to a 100 mm analogue scale. The assessment (A) was: How did you feel during the day? The extremes of the scale were *Tired* (00) and *Fresh* (100). In the morning the subjects were allowed to wake naturally, and 0.5 h after awakening completed four assessments. The assessments and the extremes of the 100 mm analogue scales were, B: I slept, *very poorly-very well*, C: Now I feel, *very sleepy-wide awake*, D: I fell asleep, *never-immediately* and E: After I fell asleep I slept, *very badly-very well*. In each case a favourable response tended toward the 100 extreme of the scale.

Drug or placebo was ingested on the third night only, i.e. first night in the sleep laboratory. On each occasion the subject ingested two identical capsules. They were taken with water at the set time between 23.00 and 23.30 h (lights out). No capsules were ingested on the fourth night, i.e. second night in the sleep laboratory, and this night (recovery night) was used to observe residual effects of the drug on sleep. Three ingestions of placebo were used to determine whether any trend in sleep measures occurred during the study. Each subject received three ingestions of placebo, N-desmethyldiazepam (nordiazepam, 5 mg and 10 mg) and potassium clorazepate (clorazepate, 15 mg). The study was double blind.

Recordings were made with silver-silver chloride electrodes filled with electrode jelly, and applied to the skin with colloidin. The scalp was abraded to improve electrical contact, and a resistance of less than  $10\text{ k}\Omega$  was maintained throughout each night. The three electroencephalographic (EEG) channels were recorded from the frontal ( $F_1$ - $F_7$ ), parieto-temporal ( $P_1$ - $T_5$ ) and parieto-occipital ( $O_zP_z$ - $O_3$ ) regions. The electrodes were placed according to the 10-20 system (Jasper, 1958), and the intervening site was selected to reduce subject discomfort and to ensure an artifact free recording (Williams, Karacan & Hirsch, 1974). The electromyogram (EMG) was recorded from the submental musculature, and electro-oculograms (EOG) were recorded from the right eye-nasion and the left eye-nasion. A grass 8-10 EEG machine was used. It was situated in an adjoining room, and the recording paper was run at 10 mm/s

throughout the night. The half amplitude frequency response for the EEG recordings was 0.07 to 40 Hz; for the EMG recordings it was 2.5 to 90 Hz with a selective 50 Hz notch filter, and for the EOG recordings it was 0.5 to 30 Hz.

Each sleep record was scored independently into 30 s epochs by two analysts. The analysis of the sleep stages was carried out according to the scheme of Rechtschaffen & Kales (1968), with the recommendations of Williams *et al.* (1974) for epochs between obvious sleep stages. Differences in the annotation of sleep stages between the analysts were resolved, but did not occur in more than 3% of the epochs analysed. Using the sleep stage epochs, each night's sleep was analysed for various measures (Williams *et al.*, 1974). The coefficient of variability (s.d. x 100/mean) of each measure (C/V) was used as a preliminary criterion to decide whether an analysis of variance was appropriate. The arbitrary level was 50%, and if the value was above 50% a non-parametric method was used. The Friedmann two-way analysis of variance was the initial approach, and with a general effect of the drugs the Wilcoxon Signed-Ranks Matched-Pairs test was used. If an effect was not shown by the Friedmann test, but any effect of the drugs was in the same direction, the data for the drugs were combined to reduce variability and a differential t test carried out for the first night only. Sleep onset latencies and awakenings were tested against the hypothesis that the distribution about certain critical values was equal using the binomial test. With this approach it was possible to show whether the drugs reduced individual values. The subjective assessments were analysed by analysis of variance, and a correlation matrix between the EEG measures and subjective assessments calculated.

**Results**

No trends in the various sleep measures were observed with the three separate ingestions of placebo, and so they were combined to give the placebo values.

The effect of nordiazepam and clorazepate on total sleep time, number of stage shifts in the first 6 h, latency to stage 3 and to the first REM period, and the REM/NREM ratio are given in Table 1. Effects on total sleep time were restricted to the night of ingestion. With nordiazepam (5 mg) total sleep time increased to 460.4 min ( $P = 0.05$ ), and with nordiazepam (10 mg) and clorazepate (15 mg) the total sleep times were 505.3 min ( $P = 0.001$ ) and 480.2 min ( $P = 0.01$ ) respectively. A regression equation ( $P = 0.05$ ) was fitted to the

**Table 1** Mean effect of nordiazepam (5 and 10 mg) and clorazepate (15 mg) on various sleep measures in six subjects

Measure	C/V	Night of ingestion			Recovery night				
		Placebo	Nordiazepam (mg) 5	Nordiazepam (mg) 10	Clorazepate (mg) 15	Placebo	Nordiazepam (mg) 5	Nordiazepam (mg) 10	Clorazepate (mg) 15
Total sleep time (min)	8	413.2	460.4	505.3	480.2	402.5	418.1	428.2	439.6
Stage shifts in first 6 h	18	88.8	99.0	93.8	86.8	82.5	99.0	83.5	95.3
Sleep onset latency (min)	60	30.7	15.3	17.8	17.4	27.8	19.1	15.3	15.0
Latency (min) to stage 3	123	40.2	16.7	13.4	51.3	33.5	35.8	65.3	21.7
Latency (min) to stage REM	39	85.6	81.9	99.1	142.0	83.8	59.3	77.3	95.2
REM/NREM ratio	21	0.25	0.26	0.26	0.21	0.24	0.28	0.29	0.26

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

Table 2 Mean effect of nordiazepam and clorazepate on number and duration (min) of awakenings during first 6 h of sleep in six subjects.

Awakening (sleep stage)	Measure	C/V	Night of ingestion			Recovery night		
			Placebo	Nordiazepam	Clorazepate	Placebo	Nordiazepam	Clorazepate
0	Number	53	12.4	6.8	6.3	9.0	6.1	8.3
	Duration	77	17.2	7.7	4.4	12.3	5.0	8.7
0+1	Number	45	8.3	6.1	6.0	6.5	4.8	7.5
	Duration	72	34.9	13.1	10.3	26.6	12.2	21.3
1	Number	28	7.0	7.4	7.2	8.0	8.0	8.2
	Duration	21	8.8	7.6	6.9	11.7	9.7	7.4

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

nordiazepam data—total sleep time = 413.6 min + 9.210 dose (mg). The dose of nordiazepam equivalent to the effect of clorazepate (15 mg) on total sleep time was 7.2 mg. There were no effects on stage shifts, but there was an increase ( $P = 0.01$ ) in the latency to the first REM sleep period with clorazepate (15 mg) though the REM/NREM ratio was not changed. As the coefficient of variability (C/V) for latency to stage 3 was greater than 50% a non-parametric analysis was used. For the night of ingestion the latency to stage 3 was reduced with both nordiazepam (5 and 10 mg) ( $P = 0.05$ ).

The means for sleep onset latency and number and duration (min) of awakenings are given in Tables 1 and 2, but the data were tested against the hypothesis that individual subject values were distributed equally around critical values. For sleep onset latency the values chosen were 20, 25 and 30 min. With placebo the hypothesis was supported for each value, but with nordiazepam it was rejected at the 30 min ( $P = 0.001$ ) and 25 min ( $P = 0.02$ ) latency for the night of ingestion, and at the 30 min ( $P = 0.02$ ) latency for the recovery night. With clorazepate the hypothesis was rejected at the 30 min ( $P = 0.05$ ) latency for the night of ingestion and for the recovery night.

The analysis for awakenings is given in Tables 3 and 4. For number of awakenings to stage 0 and stage 0 + 1 activity the critical values were 9, 12 and 15, and for the number of awakenings to stage 1 activity the values were 6, 9 and 12. For duration (min) of awakenings to 0 and 1 the values were 6, 9 and 12 min and for 0 + 1 activity the values were 15, 20 and 25 min. Nordiazepam reduced the number of awakenings to 0 and 0 + 1, but did not reduce the number of awakenings to 1. Clorazepate had no effect on awakenings to 0 or 1, though it had an effect on the number of awakenings to 0 + 1. There was some evidence of carry over effects. No effect of nordiazepam on duration of awakenings could be established during the night of ingestion, but clorazepate reduce the duration of awakenings to 0 and 0 + 1. There were effects during the recovery night with both nordiazepam and clorazepate.

The effect of nordiazepam and clorazepate on the percentage of total sleep time occupied by each sleep stage is given in Table 5. It was not possible to establish an effect of nordiazepam (5 mg). The percentage of stage 1 was reduced with nordiazepam (10 mg) ( $P = 0.01$ ). The percentage of stage 2 was increased after both nordiazepam (10 mg) ( $P = 0.05$ ) and clorazepate ( $P = 0.001$ ), and this effect was carried over to the recovery night with each drug ( $P = 0.05$ ). No effects were observed on stage 3, but analysis of the combined stages 3 + 4 showed a reduction

during the recovery night after nordiazepam (10 mg) ( $P = 0.01$ ) and clorazepate (15 mg) ( $P = 0.05$ ). The means of stage 4 relate to the three youngest subjects only, and have not been tabulated because of the high variability of the values.

The effect of the drugs on the duration (min) of the sleep stages is given in Table 6. No effects could be demonstrated with nordiazepam (5 mg).

The high variability of the stage 0 activity precluded an analysis of variance, but non-parametric analysis revealed an effect with clorazepate ( $P = 0.05$ ). With stage 1 there was a reduction after both nordiazepam (10 mg) ( $P = 0.001$ ) and clorazepate (15 mg) ( $P = 0.01$ ), and these effects were limited to the first night. Stage 2 was increased after both drugs on the night of ingestion (nordiazepam,  $P = 0.05$ ; clorazepate,

**Table 3** Levels of significance for deviations from equal distribution around critical values for number of awakenings with placebo, nordiazepam and clorazepate.

Awakening (sleep stage)	Treatment	Night of ingestion			Recovery night		
		<9	<12	<15	<9	<12	<15
0	Placebo	NS	NS	**	NS	**	***
	Nordiazepam	NS	*	**	NS	*	**
	Clorazepate	NS	NS	*	NS	NS	*
1	Placebo	NS	**	***	NS	NS	NS
	Nordiazepam	NS	NS	*	NS	NS	*
	Clorazepate	NS	NS	*	NS	NS	*
0 + 1	Placebo	NS	NS	*	NS	NS	***
	Nordiazepam	NS	*	**	NS	*	***
	Clorazepate	NS	*	*	NS	*	*

Significance levels: \*  $P = 0.05$ ; \*\*  $P = 0.01$ ; \*\*\*  $P = 0.001$

**Table 4** Levels of significance for deviations from equal distribution around critical values for duration (min) of awakenings with placebo, nordiazepam and clorazepate.

Awakening (sleep stage)	Treatment	Night of ingestion			Recovery night		
		<6	<9	<12	<6	<9	<12
0	Placebo	NS	NS	NS	NS	NS	NS
	Nordiazepam	NS	NS	NS	NS	**	**
	Clorazepate	NS	*	*	NS	NS	NS
1	Placebo	NS	NS	***	NS	NS	NS
	Nordiazepam	NS	NS	**	NS	NS	NS
	Clorazepate	NS	NS	*	NS	NS	*
0 + 1	Placebo	NS	NS	NS	NS	NS	NS
	Nordiazepam	NS	NS	NS	NS	NS	*
	Clorazepate	NS	NS	*	NS	NS	*

Significance levels: \*  $P = 0.05$ ; \*\*  $P = 0.01$ ; \*\*\*  $P = 0.001$ .

**Table 5** Mean effect of nordiazepam (5 and 10 mg) and clorazepate (15 mg) on percentage of total sleep time occupied by each sleep stage in six subjects

Sleep stage	C/V	Night of ingestion			Recovery night		
		Placebo	Nordiazepam (mg) 5 10	Clorazepate (mg) 15	Placebo	Nordiazepam (mg) 5 10	Clorazepate (mg) 15
1	21	13.1	10.5	9.8	12.8	10.6	9.7
2	6	59.0	63.2	66.8	58.6	60.1	64.0
3	46	6.1	5.3	5.4	7.5	5.2	3.7
3+4	39	7.9	8.6	6.2	9.1	7.5	4.3
REM	16	20.1	20.4	17.3	19.6	21.8	22.0

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

**Table 6** Mean effect of nordiazepam (5 and 10 mg) and clorazepate (15 mg) on duration (min) of sleep stages in first 6 h of sleep in six subjects

Sleep stage	C/V	Night of ingestion			Recovery night		
		Placebo	Nordiazepam (mg) 5 10	Clorazepate (mg) 15	Placebo	Nordiazepam (mg) 5 10	Clorazepate (mg) 15
0	64	18.3	10.5	5.3	13.1	7.8	5.8
1	30	34.1	25.3	21.5	33.5	26.6	24.8
2	7	214	222	255	214	229	242
3	46	26.0	21.9	26.5	31.1	22.9	16.1
3+4	37	34.7	37.4	30.7	38.2	34.4	18.6
REM	19	58.5	64.5	47.8	61.3	61.9	69.4

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

$P = 0.01$ ) and on the night of recovery ( $P = 0.01$ ). No effects could be established on stage 3, though an analysis of the combined stages 3 + 4 showed a reduction during the recovery night (nordiazepam,  $P = 0.01$ : clorazepate,  $P = 0.05$ ). The means for stage 4 were not included in the table as they referred to the three youngest subjects only, and the variability of the data was high.

Sleep stages were analysed into two hourly intervals from sleep onset latency. With stage 0 a non-parametric analysis of the two hourly distributions was carried out because of the variability of the data. There was an overall reduction of stage 0 during the first interval ( $P = 0.05$ ). Clorazepate also reduced the duration of stage 0 in the second interval ( $P = 0.05$ ), but no other effects were observed. The two hourly distributions of stages 1, 2 and REM are given in Table 7. The variability of the two hourly distributions of 3 and 3 + 4 were too high for means to have any relevance. With stage 1 an analysis of variance showed a reduction ( $P = 0.01$ ) during the second and third intervals with clorazepate, and a reduction ( $P = 0.01$ ) during the third interval with nordiazepam. The effect of nordiazepam was carried over to the third interval of the recovery night ( $P = 0.05$ ) and the effect of clorazepate was carried over to the second interval of the recovery night ( $P = 0.01$ ). Increases were observed in stage 2 and these reached significance during the second and third intervals with clorazepate, and the third interval with nordiazepam ( $P = 0.05$ ). There was no evidence of any effects of the drugs on the two hourly distributions of REM sleep.

The means of the assessments by the subjects are given in Table 8. For the night of ingestion changes in subjective assessments were limited to sleep quality, and were seen only with nordiazepam (10 mg) and clorazepate (15 mg). The subjects reported improved sleep. They fell asleep quicker and slept better, but no consistent changes were related to the recovery night. Correlation showed that subjectively improved sleep was related to an increased total sleep time ( $P = 0.001$ ), reduced sleep onset latencies ( $P = 0.01$ ), less stage 0 ( $P = 0.001$ ) and stage 1 ( $P = 0.01$ ) with increased stage 3 + 4 ( $P = 0.05$ ). A sense of freshness during the day (assessment A) was associated with increased latency to the first REM period ( $P = 0.01$ ), and reduced REM sleep ( $P = 0.01$ ), and a feeling of wakefulness in the morning (assessment C) was associated with increased total sleep time ( $P = 0.05$ ), reduced sleep onset latency ( $P = 0.01$ ), increased latency to first REM period ( $P = 0.05$ ), depressed stage 1 and REM sleep ( $P = 0.05$ ).

Table 7 Mean effect of nordiazepam and clorazepate on the two hourly distributions (min) of sleep stages 1, 2 and REM from sleep onset latency in six subjects.

Sleep stage	Interval (h)	C/V	Night of ingestion			Recovery night		
			Placebo	Nordiazepam	Clorazepate	Placebo	Nordiazepam	Clorazepate
1	0-2	64	6.5	4.8	5.1	5.0	5.1	8.5
	2-4	42	10.0	7.7	5.5	10.4	8.3	4.8
	4-6	38	17.6	9.8	10.9	18.2	12.4	13.4
2	0-2	14	78.7	79.7	94.1	81.8	90.3	87.2
	2-4	15	77.4	74.6	89.3	71.2	76.7	90.9
	4-6	16	58.3	70.6	71.4	61.0	68.6	65.4
REM	0-2	62	6.7	6.2	3.8	8.4	5.6	4.7
	2-4	40	20.5	18.0	16.7	23.4	24.3	18.7
	4-6	37	31.3	34.5	27.3	29.6	35.8	33.8

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

**Table 8** Mean effects of nordiazepam (5 and 10 mg) and clorazepate (15 mg) on assessments of well-being and sleep quality in six subjects. The assessments are mm on a 100 mm analogue scale.

Assessment	C/V	Placebo		Nordiazepam (mg)		Clorazepate (mg)	
		5	10	5	10	15	15
A	18	56.8	59.8	52.3	59.8	62.2	59.8
B	25	53.8	77.3	69.5	77.3	80.7	59.8
C	18	54.7	63.8	58.2	63.8	60.2	73.0
D	13	66.6	78.5	77.2	78.5	80.3	74.2
E	20	58.0	76.0	68.5	76.0	82.2	67.3

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

## Discussion

The present experiment was designed to explore the effectiveness of a single dose of an hypnotic in circumstances which may have produced slightly disturbed sleep. Placebo or hypnotics were studied during the first night in the sleep laboratory using subjects who, though familiar with the recording techniques and the sleep laboratory, had slept at home for the two previous nights. Two questions arise from such an experimental design. Would the sleep patterns of the first night in the laboratory of each 4 day assessment have remained comparable throughout the experiment, and would the sleep patterns of the 2 nights in the laboratory of each assessment have been comparable if drugs had not been ingested? As far as the first question is concerned no trends in the sleep measures could be shown between the assessments of placebo spread over many weeks, and so it is reasonable to assume that the drugs were evaluated on a steady state. With regard to the second question, comparison of sleep measures on the night of ingestion of each placebo and of the three corresponding recovery nights did not reveal any statistically significant changes.

Though no consistent changes in sleep measures could be established between the night in the sleep laboratory with ingestion of placebo and the corresponding recovery night, inspection of the data shows differences in values for some means between the night of ingestion and the recovery night which could influence the value of the measure after a drug required to reach statistical significance. This is so with awakenings to 0, where the number and duration (min) of awakenings for the recovery night after placebo were less than for the night of ingestion. For this reason an analysis related to change (increase or decrease) of values was more appropriate. Using this analysis it was possible to show that nordiazepam reduced awakenings to 0 during the night of ingestion and that nordiazepam and clorazepate reduced awakenings to 0 + 1 during the night of ingestion and the recovery night. The duration (min) of awakenings to 0 and 0 + 1 was reduced by clorazepate during the night of ingestion, though nordiazepam had a marked effect on the duration of awakenings to 0 during the recovery night. These data show that both nordiazepam and clorazepate have an effect on stage 0 activity during the night of ingestion, with some residual effects during the recovery night.

With clorazepate (15 mg) there was a reduction in the duration (min) of stage 0, but with nordiazepam (10 mg) and clorazepate (15 mg) there was a reduction in the duration (min) of stage 1 with compensatory increases in stage 2



carried over to the next night. The two hourly analyses showed that the effect of nordiazepam on stage 1 was related to the last interval, while that of clorazepate was spread over the second and third interval. There was also evidence from the two hourly analyses of carry over effects on stage 1 to the next night with both drugs. These studies show that the effect of nordiazepam and clorazepate on stage 0 and 1 activity extends well into the recovery night after ingestion of each drug.

Though no changes were detected in stage 3 after both nordiazepam and clorazepate, the analysis of stages 3 + 4 revealed a reduction during the recovery night with both drugs. The effect of the drugs seen during the recovery night with the combined states 3 + 4 arose from three subjects only, and it was not reasonable to carry out a separate analysis of stage 4. But it would appear possible that, though low doses of benzodiazepines such as nordiazepam (5 mg) have little or no effect on stage 4, the effect of high doses may be related to compensatory increases in stage 4 secondary to the effects of the drug on reducing stage 0 and 1 activity, as well as to the direct effect of the drug in reducing stage 4 itself. These influences would lead to different effects on stage 4 between the ingestion and night of recovery. The residual effect of the drugs during the recovery night may lead only to a reduction of stage 4, whereas the need to compensate for reductions in other activity brought about by the immediate ingestion of the drug may lead to little or no change in stage 4, even though a depressant effect of the drug on this activity may have been present.

Sleep onset latencies and total sleep times are important measures of an hypnotic effect. Both nordiazepam and clorazepate reduced the latencies of sleep onset with some shortening during the recovery night. This phenomenon, together with other effects of these drugs during the recovery night, is probably related to the long half life (circa 2 days) of nordiazepam (Tansella, Siciliani, Burti, Schiavon, Zimmermann-Tansella, Gerna, Tognoni & Morselli, 1975; Tognoni, Gomeni, Maio, Alberti, Franciosi & Scieghi, 1975) which is also the principal metabolite of clorazepate. On the other hand an increase in total sleep time was not observed during the recovery night and this would suggest that, though there are carry over effects of these drugs such as reductions of stage 0 and stage 1 activity, they are likely to be limited to the first few hours of the next night's sleep.

The hypnotic effects of nordiazepam and clorazepate are in many ways similar. Using the regression data based on the effect of nordiazepam on total sleep time the effect of clorazepate (15 mg) was equal to that of nordiazepam

(7.2 mg). But overall, it would appear more likely that the effect of clorazepate (15 mg) is equivalent to that of nordiazepam (10 mg). However, there are some differences between these drugs. There was no effect of nordiazepam on REM sleep, but with clorazepate there was a delay in the appearance of the first REM period. There is no obvious explanation for this finding, but it raises the question whether clorazepate is absorbed after administration, and whether it may have effects on sleep separate from those of its principal metabolite. Delay in the appearance of the first REM period may be of particular interest as this effect was shown to be related to subjective assessments of freshness during the day. Another difference between the drugs was their effect on latency to stage 3. This was reduced with both dose levels of nordiazepam, but there was no effect with clorazepate. No specific relation with subjective assessments of well-being or sleep quality could be established with this measure.

The subjective assessments provided useful information on the effect of both nordiazepam and clorazepate. The assessments related to well-being during the day after ingestion of each drug did not differ from those of the day after ingestion of placebo, but the assessments related to sleep were changed. With nordiazepam (10 mg) and clorazepate (15 mg) the subjects, as a group, reported falling asleep quicker and sleeping better. The subjects did not report increased sleepiness the morning after ingestion of either drug, but such assessments which relate to the residual effects of a drug, may not be reliable (Borland & Nicholson 1975a). Indeed, residual effects of nordiazepam on performance have been reported by Tansella, Zimmermann-Tansella & Lader (1974). It is of interest that subjectively improved sleep was related only to the high dose of nordiazepam and clorazepate (15 mg), even though with nordiazepam (5 mg) there was some increase in total sleep time and reduction in sleep stage latencies. This may suggest that a subjective assessment of improved sleep is associated only with marked changes in sleep patterns, and that a useful improvement in sleep may not be easily appreciated.

In the context of subjective assessments of sleep the correlation proved more sensitive. An improved sense of well-being (increased freshness) during the day after administration of the drugs was related to reduction of REM sleep during the first 2 h of the night, i.e. increased latency and reduced duration (min), and a feeling of increased wakefulness in the morning was associated particularly with reduced sleep onset latency. The EEG correlates of getting to sleep and better sleep during the night could not be separated. They

involved an increase in total sleep time, reduced sleep onset latency, and less stage 0 and stage 1. It would appear that the feeling of freshness during the day and of increased wakefulness in the morning were associated with fairly specific changes in sleep during the night, but that the correlates of subjective improvements of sleep quality involved marked and widespread effects.

The present study defines the sleep induced by nordiazepam, the principal metabolite of diazepam, in the range 5-10 mg. It is characterized by a marked increase in total sleep time, reduction in sleep onset latencies, reduced latency to stage 3, less stage 0 and stage 1 activity with compensatory increases in stage 2. These effects are without changes in the latency to the first REM period, the percentage distribution of REM sleep, the duration of REM sleep in the first 6 h of the night or the REM/NREM ratio, but there may be changes in stage 4 related to other effects on sleep stages as well as to direct effects of the drug. The effect of clorazepate (15 mg) would appear to be broadly equivalent to that of 10 mg nordiazepam, except that there is a delay in the appearance of the first

REM period, though there is no change in the latency to stage 3.

It would appear that nordiazepam and clorazepate modify the sleep of man for 28-30 h after ingestion. With overnight ingestion, nordiazepam (10 mg) and clorazepate (15 mg) modify the sleep of the subsequent night, and so are likely to have anxiolytic effects during the intervening day. These observations would accord with the long half time of nordiazepam, and the present therapeutic use of clorazepate. Our interest is in the use of benzodiazepines as hypnotics by healthy persons involved in skilled activity. The present studies, together with the studies of Tansella *et al.* (1974), suggest that nordiazepam, or drugs which give rise to significant plasma levels of nordiazepam, may be more appropriate in the treatment of anxiety and of insomnia secondary to psychopathology.

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