EFFECT OF A METABOLITE OF DIAZEPAM, 3-HYDROXYDIAZEPAM (TEMAZEPAM), ON SLEEP IN MAN

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- 1 The effect of 3-hydroxydiazepam (temazepam, 10 mg and 20 mg) on sleep was studied in six healthy adult males using electroencephalography for sleep measures, and analogue scales for subjective assessments of well-being and sleep quality. The effects were compared with diazepam (5 mg and 10 mg).
- 2 Effect on total sleep time was restricted to the night of ingestion. There was no change in total sleep time after temazepam (10 mg), but with 20 mg total sleep time was increased ($P = 0.01$). Sleep onset latencies and awakenings were markedly reduced.
- 3 Temazepam reduced the duration (min) of stage 0 ($P = 0.05$) and stage 1 ($P = 0.01$) sleep, and the effect on stage 1 was seen during each two hourly interval of sleep ($P = 0.05$). No effects were observed with stage 3, 3+4 and REM sleep, except that the appearance of the first REM period was delayed with temazepam (20 mg) ($P = 0.001$).
- 4 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

The effectiveness and residual sequelae of a hypnotic are related to the pharmacokinetic and behavioural properties of its metabolites, as well as to the parent drug. This is particularly true of diazepam. Diazepam in the dose range 5-10 mg has limited effects on sleep (Nicholson, Stone & Clarke, 1976a) and on performance (Borland & Nicholson, 1975) in man, but, though a higher dose may prove to be more effective as an hypnotic, the increased formation of its principal metabolite, nordiazepam, is likely to lead to more persistent behavioural effects. Nordiazepam has residual effects on performance (Tansella, Zimmermann Tansella & Lader, 1974), and modifies sleep for about 30 h after ingestion (Nicholson, Stone, Clarke & Ferres, 1976b).

Another metabolite of diazepam is of particular interest as a hypnotic. An additional pathway is initiated by hydroxylation. 3-hydroxydiazepam (temazepam), like diazepam (Figure 1), possesses hypnotic qualities (Fuccella, Tosolini, Moro & Tamassia, 1972; Maggini, Murri & Sacchetti, 1969), but its metabolism is not complicated by an active metabolite with a long half time. It could prove to be a useful hypnotic for persons involved in skilled activity, and so we have studied the effect of temazepam (10 mg and 20 mg) on sleep in healthy man.

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 each treatment (placebo or dose of drug) involved 4 days. For two nights the subjects slept at home and retired at a set time between 23.00 and 23.30 h, and for the next two 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). The drug or placebo was ingested on the third night only i.e. first night in the sleep laboratory. 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

Figure 1. Structural formulae of (a) diazepam and (b) 3-hydroxydiazepam (Temazepam).

laboratory, and this night (recovery night) was used to observe any residual effects of the drugs. 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.

Four ingestions of placebo, each a separate 4 day assessment, were included to determine whether any trend in sleep measures occurred during the study. Each subject ingested a placebo identical to the formulation of temazepam, temazepam (10 mg and 20 mg), three placebos identical to the formulation of diazepam, and

diazepam (5 mg and 10 mg). Temazepam was ingested as soft gelatine capsules (Scherer formulation), and diazepam was ingested as capsules. On each occasion the subject ingested two identical capsules. The study was double blind.

Details of recording techniques, scoring of the electroencephalographic (EEG) records into sleep stages, and statistical analysis of the sleep measures and analogue scales are given in a previous paper (Nicholson *et al.*, 1976b).

Results

Studies with the first three ingestions of placebo (capsules) were related in time to the studies with diazepam, and, as no difference could be established between the sleep measures, they were combined to form the control values for diazepam. The third (capsules) and fourth (soft gelatine capsules) ingestions of placebo were related to the studies with temazepam. No differences could be established between the respective sleep measures for these different forms of placebo, and so they were combined to form the control values for temazepam.

The effects of temazepam compared with those of diazepam on total sleep time, number of stage shifts in the first 6 h, latency to stage 3 and the first REM period, and the REM/NREM ratio are given in Table 1. No effects were observed with temazepam (10 mg) and diazepam (5 mg). With temazepam (20 mg) total sleep time was increased to 486.3 min ($P=0.01$), and with diazepam

Table 1 Effect of diazepam (5 mg and 10 mg) and temazepam (10 mg and 20 mg) on various sleep measures (means for six subjects)

Measure	C/V	Night of	Diazepam (mg)			Temazepam (mg)		
			Placebo	5	10	Placebo	10	20
Total sleep	8	Ingestion	413.2	443.0	457.8	430.4	461.8	486.3
Time (min)		Recovery	402.5	429.3	423.4	420.5	428.7	397.8
Stage shifts in	18	Ingestion	88.8	84.8	85.3	97.7	92.5	82.5
first 6 h		Recovery	82.5	112.5	86.8	96.6	93.0	85.2
Sleep onset	39	Ingestion	30.7	19.7	23.5	21.9	16.7	16.8
Latency (min)		Recovery	27.8	22.6	17.3	20.4	15.3	28.5
Latency (min)	81	Ingestion	40.2	34.3	31.6	37.4	28.5	28.0
to stage 3		Recovery	33.5	18.2	41.5	16.5	31.9	27.3
Latency (min)	33	Ingestion	85.6	102.0	98.7	70.8	90.1	139.5
to stage REM		Recovery	83.8	88.1	66.9	71.0	85.0	98.5
REM/NREM	23	Ingestion	0.25	0.26	0.22	0.29	0.32	0.27
ratio		Recovery	0.25	0.28	0.24	0.27	0.27	0.25

Coefficient of variability (C/V) = s.d. $\times$ 100/mean.

(10 mg) total sleep time was increased to 457.8 min ($P = 0.05$). There was no effect on total sleep time of the recovery night. A regression equation ($P = 0.05$) was fitted to the temazepam data—total sleep time = $431.6 + 2.795$ dose (mg), and using this equation the dose of temazepam equivalent to the effect of diazepam (10 mg) on total sleep time was 9.4 mg. There were no effects of the drugs on stage shifts or on latency to stage 3, but with temazepam (20 mg) there was an increase in the latency to the appearance of the first REM period ($P = 0.001$). The REM/NREM ratios were not altered.

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 the observations 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, and with diazepam it was rejected at the 30 min ($P = 0.01$) latency for the night of ingestion. The effect of temazepam was marked. For the night of ingestion the hypothesis was rejected at the 30 min ($P = 0.001$), 25 min ($P = 0.01$) and 20 min ($P = 0.02$) latencies, but there were no carry over effects to the next 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. There was no effect of diazepam on number of awakenings to 0 and 1 activity for the night of ingestion, though temazepam reduced the number of awakenings to 0. Temazepam and diazepam reduced the duration (min) of awakenings to 0 activity. There was no effect of diazepam on duration (min) of awakenings to 1, but the effect of temazepam was marked. With both drugs there was some evidence of carry over effects to the recovery night. With temazepam this was related to awakenings to 1 activity only.

The effect of temazepam and diazepam 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 diazepam (5 mg and 10 mg), or of temazepam (10 mg). With temazepam (20 mg) the value of stage 1 just failed to reach significance for the night of ingestion, though there were compensatory increases in stage 2 on the first night ($P = 0.01$), and reduced stage 1 during the recovery night ($P = 0.05$). These changes suggested reduced stage 1 during the night

Table 2 Effect of diazepam and temazepam on number and duration (min) of awakenings during first 6 h of sleep (means for six subjects)

Awakening (sleep stage)	Measure	C/V	Night of ingestion				Recovery night			
			Placebo	Diazepam	Placebo	Temazepam	Placebo	Diazepam	Placebo	Temazepam
0	Number	39	12.4	6.7	10.2	5.6	9.0	7.3	9.8	9.0
	Duration	65	17.2	5.1	10.7	4.1	12.2	7.2	10.1	9.5
0+1	Number	29	8.3	6.0	8.2	5.4	6.5	5.3	8.3	7.5
	Duration	63	34.9	15.1	24.0	7.2	26.6	23.6	21.5	21.0
1	Number	31	7.0	9.0	6.5	5.3	8.0	7.7	6.3	5.9
	Duration	37	8.8	11.5	5.7	3.8	11.7	8.0	6.9	5.8

Coefficient of variability (C/V) = s.d. $\times$ 100/mean.

Table 3 Levels of significance for deviations from equal distributions around critical values for number of awakenings with placebo, diazepam and temazepam

<i>Awakening (sleep stage)</i>	<i>Treatment</i>	<i>Night of ingestion</i>			<i>Recovery night</i>		
		<9	<12	<15	<9	<12	<15
0	Placebo	NS	NS	**	NS	**	***
	Diazepam	NS	NS	***	NS	*	*
	Temazepam	*	**	***	NS	*	**
		<6	<9	<12	<6	<9	<12
1	Placebo	NS	**	***	NS	NS	NS
	Diazepam	NS	NS	*	NS	NS	**
	Temazepam	NS	**	***	NS	**	**
		<9	<12	< 5	<9	<12	<15
0+1	Placebo	NS	NS	*	NS	NS	***
	Diazepam	NS	*	***	**	**	**
	Temazepam	*	**	***	NS	***	***

Significance Levels: * $P = 0.05$; ** $P = 0.01$; *** $P = 0.001$.**Table 4** Levels of significance for deviations from equal distributions around critical values for duration (min) of awakenings with placebo, diazepam and temazepam

<i>Awakening (sleep stage)</i>	<i>Treatment</i>	<i>Night of ingestion</i>			<i>Recovery night</i>		
		<6	<9	<12	<6	<9	<12
0	Placebo	NS	NS	NS	NS	NS	*
	Diazepam	NS	*	***	NS	NS	*
	Temazepam	NS	**	***	NS	NS	NS
		<6	<9	<12	<6	<9	<12
1	Placebo	NS	NS	***	NS	NS	NS
	Diazepam	NS	NS	NS	NS	NS	*
	Temazepam	**	***	***	NS	*	*
		<15	<20	<25	<15	<20	<25
0+1	Placebo	NS	NS	NS	NS	NS	NS
	Diazepam	NS	NS	NS	NS	NS	NS
	Temazepam	**	***	***	NS	NS	NS

Significance levels: * $P = 0.05$; ** $P = 0.01$; *** $P = 0.001$.**Table 5** Effect of diazepam (5 mg and 10 mg) and temazepam (10 mg and 20 mg) on percentage of total sleep time occupied by each sleep stage (means for six subjects)

<i>Stage</i>	<i>C/V</i>	<i>Night of</i>	<i>Diazepam (mg)</i>			<i>Temazepam (mg)</i>		
			<i>Placebo</i>	<i>5</i>	<i>10</i>	<i>Placebo</i>	<i>10</i>	<i>20</i>
1	17	Ingestion	13.1	12.3	10.8	9.2	7.6	6.3
		Recovery	12.8	11.3	14.4	10.3	9.7	6.4
2	6	Ingestion	59.0	59.1	62.2	60.9	62.5	66.2
		Recovery	58.6	58.8	59.2	61.5	61.6	66.9
3	37	Ingestion	6.1	6.6	7.8	6.8	5.3	5.4
		Recovery	7.5	7.5	6.7	6.3	6.1	5.8
3+4	30	Ingestion	7.9	9.3	9.2	8.0	5.9	6.4
		Recovery	9.1	9.0	6.9	7.2	7.6	7.0
REM	17	Ingestion	20.1	20.4	17.9	22.0	24.0	21.1
		Recovery	19.6	21.0	19.5	21.1	21.3	19.8

Coefficient of variability (C/V) = s.d. $\times$ 100/mean.

of ingestion, though it was not possible to show statistical significance because the placebo value was low.

The effect of the drugs on the duration (min) of sleep stages is given in Table 6. The effects of diazepam (5 mg and 10 mg) were limited to reduced stage 0 ($P = 0.05$), but with temazepam (10 mg and 20 mg) there was a similar reduction of stage 0 ($P = 0.05$), and there was also reduced stage 1 ($P = 0.01$) with evidence of compensatory increases in stage 2 (ingestion night, $P = 0.05$; recovery night, $P = 0.001$). There were no other effects on NREM or REM sleep. Sleep stages were analysed further into 2-hourly intervals from sleep onset latency. With stage 0 a non-parametric analysis of the 2-hourly distributions was carried out because of the high variability of the data. There was an overall reduction of stage 0 during the first interval ($P = 0.05$). The distributions of stages 1, 2 and REM are given in Table 7, but the variability of the 2-hourly distributions of 3 and 3+4 were too high for means to have any relevance. With stage 1 a non-parametric analysis of the first 2-hour interval revealed a reduction with temazepam ($P = 0.05$), and analysis of variance for the second and third intervals showed that the effect was maintained ($P = 0.05$). No other effects were observed with the 2-hourly distribution data, and there was no evidence of effects on the distribution of REM sleep.

The assessments of the subjects are given in Table 8. For the night of ingestion changes in subjective assessments were limited to an overall assessment of improved sleep with temazepam ($P = 0.05$). No other changes in assessments were

observed with temazepam. Correlation of sleep measures and subjective assessments proved to be of more value. A feeling of freshness during the day was associated with an increased total sleep time ($P = 0.05$), reduced sleep onset latency ($P = 0.01$), reduced stage 1 sleep ($P = 0.001$) and REM sleep ($P = 0.05$). Increased wakefulness was related to reduced sleep onset latency ($P = 0.05$), reduced stage 1 ($P = 0.05$), increased stage 3+4 ($P = 0.05$) and reduced REM ($P = 0.01$) sleep. Improved sleep was related to increased total sleep time ($P = 0.001$) and reduced stage 0 ($P = 0.001$), while falling asleep quickly was related to reduction of stage 1 sleep ($P = 0.01$).

Discussion

It is evident from the present studies that there are important differences between the effects of temazepam and diazepam on sleep in man. Though 10 mg of both temazepam and diazepam reduce the duration (min) of stage 0 (awake) activity, only temazepam reduces the duration of stage 1 (drowsy) sleep. This particular effect is also shown by less awakening to stage 1, and by the analysis of the 2-hourly distributions which reveal reduced stage 1 activity throughout the first 6 h of sleep. It is important to emphasize that with temazepam (10 mg) there is little or no increase in total sleep time, and that, except for a compensatory increase in stage 2, the reductions in awake and drowsy sleep are without changes in the duration of other stages. Further, that with temazepam (20 mg), though there is a marked increase in total sleep

Table 6 Effect of diazepam (5 mg and 10 mg) and temazepam (10 mg and 20 mg) on duration (min) of sleep stages in first 6 h of sleep (means for six subjects)

Stage	C/V	Night of	Diazepam (mg)			Temazepam (mg)		
			Placebo	5	10	Placebo	10	20
0	56	Ingestion	18.3	5.8	5.4	12.2	6.5	4.5
		Recovery	13.1	5.8	11.1	12.2	8.3	14.6
1	25	Ingestion	34.1	31.6	27.3	25.4	14.9	11.7
		Recovery	33.5	26.3	40.3	25.6	25.0	18.9
2	7	Ingestion	214.4	227.2	231.9	222.4	242.3	257.1
		Recovery	214.0	220.1	223.0	222.8	226.0	242.5
3	29	Ingestion	34.7	43.5	46.0	36.5	27.8	31.1
		Recovery	38.2	40.7	30.7	33.2	33.0	26.0
3+4	36	Ingestion	26.0	29.8	38.5	28.7	24.8	26.0
		Recovery	31.1	33.7	29.9	28.6	26.2	22.8
REM	20	Ingestion	58.5	52.0	49.3	63.7	68.5	55.7
		Recovery	61.3	67.2	54.9	66.3	67.8	57.9

Coefficient of variability (C/V) = s.d. $\times$ 100/mean.

Table 7 Effect of diazepam and temazepam on the 2-hourly distributions (min) of sleep stages 1, 2 and REM from sleep onset latency (means for six subjects)

Stage	Interval (h)	C/V	Night of ingestion			Recovery night		
			Placebo	Diazepam	Placebo	Placebo	Diazepam	Temazepam
1	0-2	73	6.5	4.4	3.9	1.5	5.0	3.4
	2-4	38	10.0	8.5	7.9	4.4	10.4	8.8
	4-6	35	17.6	16.6	13.6	7.4	18.2	13.4
2	0-2	13	78.7	79.0	82.1	93.7	81.8	81.2
	2-4	16	77.4	81.1	77.7	83.2	71.2	73.2
	4-6	19	58.3	69.4	62.7	72.8	61.0	66.9
REM	0-2	75	6.7	3.3	6.9	3.4	8.4	10.2
	2-4	44	20.5	18.5	22.9	26.4	23.4	25.6
	4-6	36	31.3	28.9	34.0	32.3	29.6	27.9

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

Table 8 Effects of diazepam and temazepam on assessments of well-being and sleep quality (means for six subjects). (The data refer to mm of a 100 mm scale)

Assessment	C/V	Night of ingestion			Recovery night		
		Placebo	Diazepam	Placebo	Placebo	Diazepam	Temazepam
A	16	56.7	61.6	60.7	63.4	50.7	66.5
B	26	Morning after ingestion			Morning after recovery night		
		53.8	69.2	58.5	79.1	68.2	61.1
		54.5	63.9	64.7	70.2	68.3	60.1
		66.8	75.2	70.3	81.1	73.3	73.2
C	15						
D	15						
E	20	58.2	72.5	69.0	80.5	71.3	70.0
							68.3

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

time, the only evidence of carry over effects to the recovery night is reduced awakenings to 1 activity. Another important effect of temazepam is a marked reduction in sleep onset latency.

These findings are important when temazepam and diazepam are compared for their usefulness as hypnotics for healthy persons involved in skilled activity. The effect of diazepam (10 mg) on performance and on sleep is limited, but, though doses of diazepam exceeding 10 mg may be more effective as a hypnotic, it is likely that the increased hypnotic action would be complicated by the persistent activity of its principal metabolite. Nordiazepam has an elimination half time of about 2 days (Tansella, Siciliani, Burti, Schiavon, Zimmermann Tansella, Gerna, Tognoni & Morselli, 1975; Tognoni, Gomeni, Maio, Alberti, Franciosi & Scieghi, 1975). It leads to residual effects on performance (Tansella *et al.*, 1974), and modifies sleep for about 30 h after ingestion (Nicholson *et al.*, 1976b). Temazepam does not have the potential disadvantage of a metabolite with a long half time. With 10 mg there is no prolongation of total sleep time, and with 20 mg carry over effects to the recovery night are limited to reduced awakenings to stage 1 activity.

Though the effects of temazepam on sleep onset latencies and on awake and drowsy activity are without changes in the durations (min) of stage 3, stage 3+4 and REM sleep, there is a delay in the appearance of the first REM period. This finding is of interest as it was also observed with potassium clorazepate (15 mg), an anxiolytic with nordiazepam as its principal metabolite, but it was not observed with nordiazepam (10 mg) itself (Nicholson *et al.*, 1976b). On the other hand, though nordiazepam (10 mg) reduces the latency to stage 3, clorazepate (15 mg), diazepam (10 mg) and temazepam (20 mg) have no effect on the latency to this sleep stage.

These findings, together with the present observation that temazepam shortens markedly the latency to stage 2, suggest that benzodiazepines have differential effects on the various sleep stage latencies. The significance of these

observations is not clear, but it is evident that reduced latency to stages 2 and 3 and increased latency to the first REM period all decrease desynchronized EEG activity during the first part of the night. In previous studies correlations between subjective assessments of well-being and EEG measures of sleep after benzodiazepines suggested that an improved sense of well-being (increased freshness) after overnight ingestion may be related to more synchronized and less desynchronized EEG activity (Nicholson *et al.*, 1976a, b). Similar observations have been made in the present studies. Increased freshness during the day after ingestion was associated with increased total sleep time, reduced sleep onset latency, reduced stage 1 and REM sleep, while increased wakefulness was related to reduced sleep onset latency, reduced stage 1 and REM sleep and increased stage 3+4. It would appear that subjective assessments of well-being, as well as quality of sleep, may have some value in indicating the EEG effects of drugs on sleep, and this possibility is worthy of further study.

It is evident that temazepam has useful properties related to its hypnotic activity. It has a short half time (Fuccella *et al.*, 1975), and its metabolism is not complicated by an active metabolite with a long half time. Temazepam shortens markedly sleep onset latencies and reduces both stage 0 (awake) and stage 1 (drowsy) sleep. Its effects are restricted, for all practical purposes, to the night of ingestion. Though the effects of the drug on performance in man have yet to be studied, these observations suggest that they are unlikely to be pronounced. Temazepam may prove to be of value for persons who need a hypnotic and are involved in skilled activity during the day after overnight ingestion.

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