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HYPNOTIC ACTIVITY AND EFFECTS ON PERFORMANCE OF LORMETAZEPAM AND CAMAZEPAM—ANALOGUES OF TEMAZEPAM

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1 The effects of lormetazepam and camazepam on sleep electroencephalography, visuo-motor coordination, digit symbol substitution and subjective assessments of mood and sleep quality were compared with placebo in six young adult males (18–27 years). The study was double blind.

2 Over the dose range 0.5, 1.0 and 2.0 mg, lormetazepam increased total sleep time ($P < 0.05$), reduced wakefulness ($P < 0.05$) and drowsy sleep (linear effect $P < 0.05$). With 2.0 mg there were increases in stage 3 ($P < 0.05$) and reduction in rapid eye movement sleep ($P < 0.01$). Overnight ingestion of 2.0 mg, was followed by impaired visuo-motor coordination and fewer substitutions with the digit symbol test.

3 The hypnotic effect of 10–20 mg camazepam was limited to reduced awake activity ($P < 0.05$), and with 20 mg there were increased substitutions on the digit symbol test. After 40 mg overnight stage 4 sleep was reduced ($P < 0.001$) and performance at the digit symbol test was impaired ($P < 0.05$ at 9.75 h). Morning ingestion of 20 mg camazepam did not alter performance, and the subjects assessed themselves to be more relaxed.

4 Lormetazepam is not specially indicated for those involved in skilled activity, but may prove useful for patients with insomnia resistant to other drugs. Camazepam would appear to be a promising anxiolytic with minimal effects on performance.

Introduction

In the use of hypnotics a favourable balance is sought between sedative activity and residual effects on performance, and pharmacokinetics give some indication whether a drug is likely to be suitable. With single dose ingestion the half-life of the distribution phase of the parent compound or of its metabolites relates closely to the appearance of residual sequelae, while the elimination half-life not only determines whether accumulation will occur with repeated ingestions, but may also decide whether residual effects can be expected at higher doses, and whether they will persist.

In the context of the use of hypnotics by those who carry out skilled work, one of the metabolites of diazepam, 3-hydroxydiazepam (temazepam), has proved to be useful. Plasma concentration falls rapidly during the distribution phase, and its relatively short elimination half-life makes accumulation less likely than with its parent drug diazepam. Further, unlike diazepam, there is no long-acting metabolite, and so with the dose range 10–20 mg residual sequelae are unlikely even with daily ingestion. However, its usefulness may be limited (Nicholson & Stone, 1979a,b), and so we have studied the activity of two analogues, lormetazepam with an orthochlorophenyl group and camazepam in which the 3-position is substituted, to establish whether such minimal changes in the molecule can improve hypnotic activity without increasing residual sequelae (Figure 1).

Methods

Six healthy males, familiar with sleep recording techniques, aged between 18 and 27 (mean 22) years, and weighing between 66.0 and 78.5 (mean 71.3) kg were studied. They were required to refrain from napping and undue exercise, and to abstain from alcohol on the day before and the day of each experiment. Beverages containing caffeine were not used from a week before and throughout the study.

Sleep

Two adaptation nights when placebos were ingested at night and in the morning were separated by 1 week.

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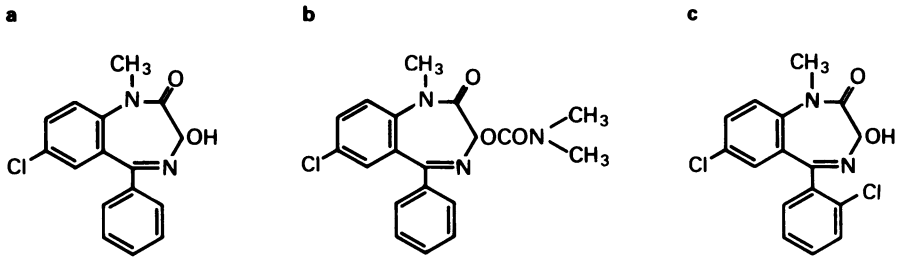

Figure 1 Structural formulae of (a) temazepam (b) camazepam and (c) lormetazepam. With camazepam the 3-hydroxy is replaced by a dimethylaminocarbonyl radical, and with lormetazepam there is an orthochlorophenyl group.

Afterwards, each subject took 10, 20 and 40 mg camazepam or 0.5, 1.0 and 2.0 mg lormetazepam overnight with matching placebos in the morning, 20 mg camazepam and 1.0 mg lormetazepam in the morning after matching placebos at night, and on two occasions placebos night and morning. A multiple dummy technique was used, and the subjects were unaware whether residual or immediate effects were being evaluated. Treatments were arranged double blind in a random order, a week separating each assessment.

Two groups of three subjects reported 1.5 h before bedtime. Tablets were ingested under supervision at 'lights out' (23.00, 23.15 or 23.30 h) and exactly 9 h later (08.00, 08.15 or 08.30 h). The individual bedrooms were light-proofed and sound attenuated. Temperature (18 ± 1°C) and humidity (55 ± 1%) were controlled. In an adjoining room, using a paper speed of 10 mm s^{-1}, three channels of electroencephalographic (EEG) activity were recorded (C_4–A_1, P_1–T_5 and O_zP_z–O_3), together with the electromyogram and the electro-oculogram. Further details of recording techniques are given elsewhere (Nicholson & Stone, 1979c). Each sleep record was scored independently into 30 s epochs by two analysts according to the criteria of Rechtschaffen & Kales (1968). Disagreements between the analysts were resolved, but did not occur in more than 4% of the epochs.

Half an hour after awakening, each subject completed four assessments of sleep and well-being using 100 mm analogue scales. The assessments and extremes of the scales were I slept, *Very poorly – Very well*; Now I feel, *Very sleepy – Wide awake*; I fell asleep, *Never – Immediately* and 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 EEG and subjective data were analysed statistically. The coefficient of variability (s.d. × 100/mean) of each measure (C/V) was examined to decide whether an analysis of variance was appropriate. The arbitrary level was 50%, and a non-parametric method (Friedman two-way analysis of variance) was used when values exceeded 50%.

Performance

Overnight ingestion of three doses of each drug and the morning ingestion of the middle dose of each drug allowed measurements of residual and immediate effects on performance. Residual sequelae were recorded at 9.5, 10.5, 12.5, 14.5 and 17.0 h and immediate effects at 0.5, 1.5, 3.5 5.5 and 8.0 h after ingestion.

The subjects were trained on a visuo-motor coordination task (Borland & Nicholson, 1974) until they reached steady performance. Using a hand-held stick they were required to position a spot inside a randomly moving circle displayed on an oscilloscope. An error signal proportional to the distance between the spot and the centre of the circle controlled the difficulty of the task by modulating the mean amplitude of the movement of the circle. The position of the circle and spot, and so the radial error, were recorded. Each experimental run lasted 10 min, and trained subjects reached a plateau performance within 100 s after which time scoring began. The laboratory was sound attenuated and air-conditioned. After each performance session the subjects completed assessments of performance related to a 100 mm line. The extremes of the scale were: How well did you perform? *Useless* (00) – *Perfect* (100).

Digit symbol substitution (DSS) was also tested. A series of 100 different sheets each with 200 randomised digits (0–9) arranged in 10 rows was presented. Under each digit there was a space where the subjects were required to write the appropriate symbol indicated by a code at the top of each page. The code was different for each of the 100 sheets. In each session subjects were given two sheets, and 2 min, timed separately, to complete as many spaces as possible for each sheet. In all tests and for all subjects errors were extremely rare, and so only the number attempted was analysed. Subjects were trained on the test until they reached steady performance and DSS was measured immediately after the first three visuo-motor coordination sessions. Immediate effects were recorded at 0.75, 1.75 and 3.75 h and residual sequelae at 9.75, 10.75 and 12.75 h after ingestion.

Table 1 Effect of lormetazepam and camazepam on various sleep measures (means for six subjects)

Measures	*C/V*	*Placebo*	*Lormetazepam (mg)* 0.5	1.0	2.0	*Camazepam (mg)* 10	20	40
Total sleep time (min)	2	489.3	499.3*	498.4*	495.4*	489.3	494.0	493.1
Sleep onset latency (min)	16	15.8	13.2	13.6	14.1	16.3	16.8	16.8
Latency (min) to stage 3	7	13.2	13.8	13.7	13.3	13.0	12.9	12.4
Latency (min) to REM sleep	8	91.4	74.8	103.4	127.4	78.7	92.5	92.3
Stage shifts (6 h)	14	104.9	85.7**	96.5	98.5	103.0	113.3	93.3
†REM/NREM	16	0.36	0.35*	0.33*	0.27*	0.30*	0.32*	0.33*
Sleep efficiency index	13	0.96	0.97	0.97	0.97	0.97	0.96	0.96

Significance level: * $P < 0.05$, ** $P < 0.01$
†REM/NREM: Linear decrease with lormetazepam over the dose range ($P < 0.05$).
C/V = Coefficient of variation (s.d. × 100/mean)

Mood

Subjective assessments of mood on 100 mm lines were completed on five occasions during the day at the same time as the assessments of performance. The statements and extremes of the scales were: I am, *Extremely wide awake – Extremely sleepy*, I am, *Very tense – Very relaxed*, I am, *Very calm – Extremely anxious*, I am, *Very energetic – Very lethargic*, I am, *Very dull – Very alert*, I have, *No ability to concentrate – Complete ability to concentrate* and I am, *Highly efficient – Completely useless*. Comparisons between the post-drug and post-placebo measures were made using analysis of variance, and the data were also averaged over all test sessions.

Results

Effects on sleep are given in Tables 1, 2, 3, 4 and 5. Over the dose range (0.5, 1.0 and 2.0 mg) lormetazepam increased total sleep time ($P < 0.05$), reduced wakefulness ($P < 0.05$) and reduced drowsy sleep—a linear effect ($P < 0.05$). After the highest dose stage 3 sleep was increased ($P < 0.05$) and rapid eye movement (REM) sleep reduced ($P < 0.01$), and these changes were linear ($P < 0.05$ and < 0.01 respectively). With camazepam the only hypnotic effect was reduced awake activity ($P < 0.05$), but with the highest dose (40 mg) stage 4 sleep was reduced—a linear effect over the dose range ($P < 0.05$). The subjects as a group assessed their sleep as improved with lormetazepam—particularly at the highest dose, and considered their wakefulness the next day elevated with 0.5 and 1.0 mg. Some improvements in sleep were also reported with camazepam.

The overnight ingestion of 0.5 and 1.0 mg lormetazepam were free of residual effects the next day, though with 2.0 mg overnight there was a marked performance decrement which tended to persist (Tables 6, 7 and Figure 2). 10 and 20 mg camazepam ingested overnight were free of residual sequelae. Indeed with 20 mg the number of substitutions on the digit symbol test was increased, though with 40 mg overnight there was evidence of a minimal residual effect (Figure 3). An immediate effect of 1.0 mg lormetazepam on performance was evident, though it was not possible to establish any immediate

Table 2 Effect of lormetazepam and camazepam on duration (min) of sleep stages (means for six subjects)

Stage	*C/V*	*Placebo*	*Lormetazepam (mg)* 0.5	1.0	2.0	*Camazepam (mg)* 10	20	40
†Awake	64	4.3	1.5*	0.4*	0.8*	2.3*	2.1*	1.2*
††1	29	27.3	24.1	20.8	17.1**	22.8	26.1	20.3*
2	7	241.0	252.8	250.4	268.6**	258.1	252.6	275.0***
3	24	42.8	45.3	51.7	56.1*	50.4	50.3	48.2
4	28	50.4	49.8	52.4	48.1	45.2	44.5	28.8***
3+4	15	93.2	95.1	104.1	104.2	95.6	94.8	77.0*
†REM	13	128.6	126.8	122.8	105.3**	112.8	119.8	120.4

Significance levels: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$
†Transformed data with non-parametric analysis.
††Linear decrease ($P < 0.05$) with lormetazepam over the dose range for stages 1 and REM.
C/V = Coefficient of variation (s.d. × 100/mean).

Table 3 Effect of lormetazepam and camazepam on percentage of sleep stages (means for six subjects)

			Lormetazepam (mg)			*Camazepam (mg)*		
Stage	*C/V*	*Placebo*	*0.5*	*1.0*	*2.0*	*10*	*20*	*40*
†Awake	127	0.86	0.30*	0.08*	0.17*	0.47*	0.42*	0.24*
1	30	5.5	4.8*	4.2*	3.4*	4.7	5.3	4.1
††2	7	48.7	50.4	50.1	54.1**	52.4*	51.0	55.6***
3	23	8.7	9.1	10.4	11.4*	10.3	10.1	9.8
4	27	10.1	9.9	10.5	9.6	9.2	8.9	5.8**
3+4	14	18.8	19.0	20.9	21.0	19.4	19.0	15.6*
REM	13	26.0	25.4	24.7	21.2**	23.0	24.2	24.4

Significance levels: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$
†Transformed data with non-parametric analysis.
††Linear increase with lormetazepam and camazepam over the dose ranges ($P < 0.05$).
C/V = Coefficient of variation (s.d. × 100/mean).

Table 4 Effect of lormetazepam and camazepam on duration of sleep stages (min) in first 6 h of sleep (means for six subjects)

			Lormetazepam (mg)			*Camazepam (mg)*		
Stage	*C/V*	*Placebo*	*0.5*	*1.0*	*2.0*	*10*	*20*	*40*
†Awake	82	2.9	1.2*	0.3*	0.6*	1.8*	1.6*	0.6*
††1	39	16.9	11.9	12.4	7.9**	17.0	17.1	12.2
2	7	180.2	187.8	182.7	201.2**	185.6	191.4	210.5***
††3	24	41.3	38.7	49.7	55.5*	44.0	43.5	47.9
††4	26	48.5	47.4	52.4	48.1	44.9	44.4	28.8
3+4	14	89.8	86.1	102.1*	103.6*	88.9	87.9	76.8*
††REM	20	69.9	72.4	62.3	46.3***	66.4	61.3	59.7

Significance levels: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$
†Transformed data with non-parametric analysis.
††Linear change with lormetazepam over the dose range on stages 1 and 3 ($P < 0.05$) and REM ($P < 0.01$) sleep, and also with camazepam on stage 4 ($P < 0.05$). Effects of lormetazepam on stages 2 and 3+4 are related to the 2–4 h interval.
C/V = Coefficient of variation (s.d. × 100/mean).

Table 5 Effect of lormetazepam and camazepam on number of awakenings (means for six subjects)

			Lormetazepam (mg)			*Camazepam (mg)*		
	C/V	*Placebo*	*0.5*	*1.0*	*2.0*	*10*	*20*	*40*
Over whole night	53	4.3	2.5**	0.8**	1.5**	3.5	3.7	2.2
First 6 h	70	2.8	1.8	0.5	1.0	2.7	2.8	1.2

Analysis on transformed data.
Significance levels: **$P < 0.01$.
C/V = Coefficient of variation (s.d. × 100/mean).

Table 6 Analysis of variance and significance levels for change in performance (compared with placebo) on visuo-motor coordination (arbitrary units) after drugs (means for six subjects)

Source	*Degrees of freedom*	*Mean squares*	F	*Significance levels*
Subject (S)	5	1831.28		
Drug (D)	8	192.82	1.54	
SxD	40	125.1		
Time (T)	4	190.77	3.76	*
SxT	20	50.77		
DxT	32	34.38	1.49	($P = 0.58$)
SxDxT	160	23.09		
Total	269			

	Time (h) after ingestion (overnight/morning)				
Lormetazepam	*9.5/0.5*	*10.5/1.5*	*12.5/3.5*	*14.5/5.5*	*17.0/8.0*
0.5 mg overnight	−0.38	−0.33	−0.18	0.19	0.24
1.0 mg overnight	−0.44	−0.35	−0.30	−0.33	−0.43
2.0 mg overnight	−1.16**	−0.93*	−0.43	−0.45	−0.41
1.0 mg morning	−1.47***	−1.18**	−0.35	−0.43	−0.14
Camazepam					
10 mg overnight	−0.13	−0.34	−0.12	−0.53	−0.21
20 mg overnight	−0.35	−0.42	−0.29	−0.47	0.30
40 mg overnight	−0.72(*)	−0.53	−0.09	−0.44	−0.45
20 mg morning	−0.12	−0.07	−0.32	−0.05	0.15

Least significant differences from placebo (LSD) for means of 6 are: *$P < 0.05 = 0.75$, **$P < 0.01 = 1.0$, ***$P < 0.001 = 1.24$

Table 7 Change in the number of substititions on digit symbol substitution after drugs compared with placebo (means for six subjects)

		Overnight ingestion (mg)						*Morning ingestion (mg)*	
Time (h) after ingestion		*Lormetazepam*			*Camazepam*			*Lormetazepam*	*Camazepam*
overnight	*/ morning*	*0.5*	*1.0*	*2.0*	*10*	*20*	*40*	*1.0*	*20*
9.75	0.75	−7.00	−0.16	−12.33**	−1.16	−4.00	−9.50*	−28.33***	−3.00
10.75	1.75	−1.17	−0.67	−2.34	+1.16	+7.66*	−3.50	−19.67***	+0.33
12.75	3.75	−6.33	−3.67	−3.67	+6.17	+9.50*	−7.00	−10.50**	−0.83

Least significant differences compared with placebo (LSD) for means of 6 are: *$P < 0.05 = 7.47$, **$P < 0.01 = 9.91$, ***$P < 0.001 = 12.83$

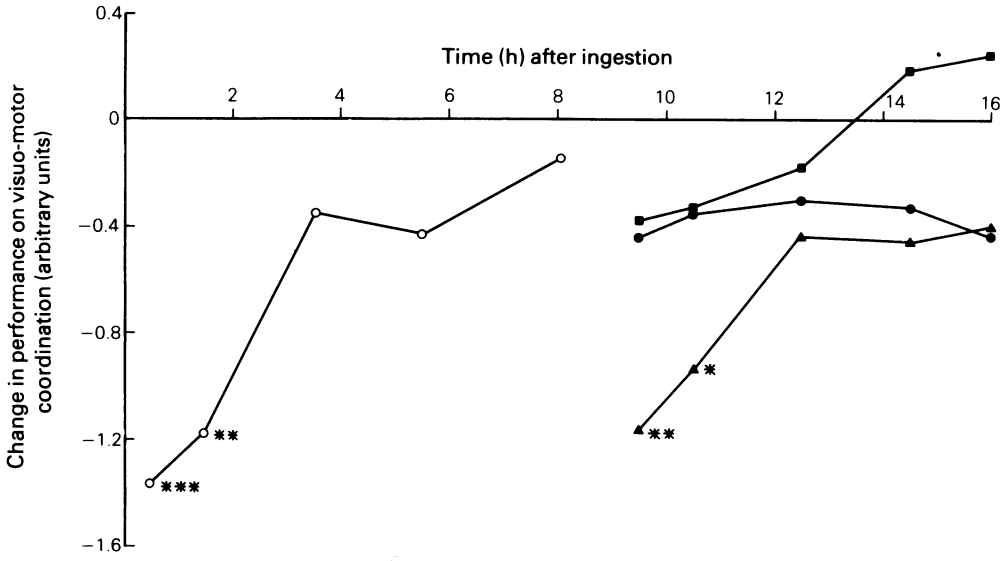

Figure 2 Immediate and residual effects of lormetazepam on visuo-motor coordination compared with placebo (means for six subjects). ■ 0.5 mg overnight, ● 1.0 mg overnight, ○ 1.0 mg morning, ▲ 2.0 mg overnight. Significance levels: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

deleterious effect on performance with 20 mg camazepam.

The subjects as a group assessed their performance as impaired after the morning ingestion of 1.0 mg lormetazepam ($P < 0.05$ at 09.30, 11.30 & 13.30 h), and after the overnight ingestion of 2.0 mg lormetazepam ($P < 0.05$ at 09.30 h). During the day they considered themselves more relaxed and/or more calm with 10 mg camazepam ($P < 0.01$) overnight, and with 20 mg camazepam ($P < 0.05$) and 1.0 mg lormetazepam ($P < 0.001$) ingested in the morning. With 1.0 mg lormetazepam both overnight and in the morning ($P < 0.001$) and 40 mg camazepam overnight ($P < 0.05$) assessments of ability to concentrate were lowered.

Discussion

Lormetazepam (0.5, 1.0 and 2.0 mg) has useful hypnotic activity, but its use may be associated with alterations in sleep patterns. REM sleep is reduced linearly over the dose range, and similar observations as well as rebound effects on withdrawal have been reported by Oswald *et al.* (1979) in a chronic study in subjects with sleep difficulties. However, we have observed impaired visuo-motor coordination and reduced substitutions on the digit symbol test after overnight ingestion of 2.0 mg, whereas they concluded that, even with 2.5 mg overnight, there were no residual effects the next day. They did, however observe impaired manual dexterity ($P < 0.05$) early in

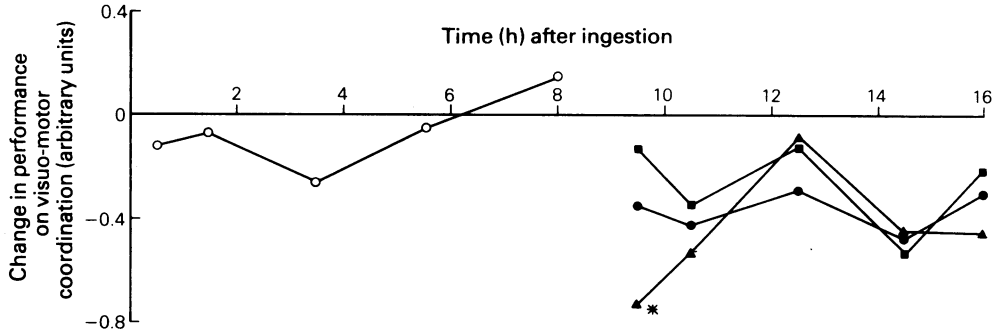

Figure 3 Immediate and residual effects of camazepam on visuo-motor coordination compared with placebo (means for six subjects). ■ 10 mg overnight, ● 20 mg overnight, ○ 20 mg morning, ▲ 40 mg overnight. Significance levels: $*P < 0.05$: $**P < 0.001$: $***P < 0.001$.

the morning after the initial overnight ingestion of 2.5 mg lormetazepam, though this was considered a chance result. Further, rebound of REM sleep on withdrawal was reported after repeated ingestion of 1.0 mg, but not after 2.5 mg. Both these observations suggest a persistent effect of the 2.5 mg dose.

Although studies related to the occasional use of hypnotics in healthy individuals may not apply directly to repeated ingestion in insomniacs, they are a useful approach to the initial investigation of the action of a drug in man. Trials related to the projected clinical use of a drug may lack sensitivity, and so the information should be interpreted with caution particularly if it conflicts with data obtained under more easily controlled conditions. Adequate supervision over the circumstances and behaviour of subjects is desirable, and this is particularly important immediately preceding measurements of performance. Smoking, alcohol and caffeine consumption are difficult to control over many months, and these factors in groups with wide ranges and educational attainment may provide variable data, and drug effects may be undetected. Further, compliance over several months cannot be assumed. Subjects may conform to the daily ingestion of a drug and high patient acceptability, but may be less compliant with a drug with adverse effects.

Lormetazepam may prove to be useful and may have advantages over other hypnotics, but, at least, in doses above 1.0 mg it is not specially indicated when impaired performance the next day is to be avoided. The pharmacokinetics of the drug (Humpel *et al.*, 1979) are consistent with this conclusion. Drugs such as lormetazepam with multicompartment model kinetics have an initial rapid fall in plasma concentration, but residual effects are likely to be prolonged if the plasma concentration early the next morning, presumably related to the slower elimination phase, is above that of the threshold for impaired performance.

Changes in sleep with 10 and 20 mg camazepam were minimal. However, non-anxious subjects reported being more relaxed the next day, and there were increased substitutions on the digit symbol test after 20 mg. With 40 mg camazepam the normal sleep pattern was distorted, and there was an impairment of performance in the morning. Camazepam over the dose range 10–20 mg may be useful as an anxiolytic, but higher doses may have undesirable effects.

It would appear that though substitution of the temazepam molecule with an orthochlorophenyl group produced a more potent drug, substitution in the 3-position with a dimethylaminocarbonyl radical led to a diminution of the hypnotic activity seen with the hydroxylated metabolites of diazepam, oxazepam and temazepam (Nicholson & Stone, 1976, 1978). However, the increased potency of lormetazepam does not provide a more advantageous balance between sedative activity and residual effects. In the clinical context, though lormetazepam is not specially indicated for those involved in skilled activity, it may prove to be useful for patients with insomnia resistant to other drugs, while camazepam has promise as an anxiolytic with minimal effects on performance.

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