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STUDIES ON SLEEP AND PERFORMANCE WITH A TRIAZOLO-1, 4-THIENODIAZEPINE (BROTIZOLAM)

A.N. NICHOLSON, BARBARA M. STONE & PETA A. PASCOE

Royal Air Force Institute of Aviation Medicine, Farnborough, Hampshire

1 Brotizolam, a triazolo-1,4-thienodiazepine, was studied in healthy young adults. Electroencephalographic sleep variables and subjective effects, and performance on a visuo-motor coordination task were measured.

2 In the sleep studies six males each ingested 0.2, 0.4 and 0.6 mg brotizolam overnight. All doses increased total sleep time, improved the sleep efficiency index, and reduced drowsy sleep and number of awakenings. Brotizolam 0.4 and 0.6 mg also reduced awake activity and increased stage 2 sleep. There was some evidence of a delay to the first REM period, but only 0.6 mg reduced the total duration of REM sleep. There were no changes in slow wave sleep.

3 In the performance studies six females each ingested 0.4 mg in the morning and 0.2, 0.4 and 0.6 mg brotizolam at night. After morning ingestion of 0.4 mg there was impaired performance from 0.5 to 5.5 h. There were no residual effects after 0.2 mg brotizolam, but with 0.4 mg there was a residual effect at 9.5 h, and 0.6 mg led to impairments up to 15.0 h after ingestion.

4 Brotizolam is a short-acting hypnotic. In doses around 0.2 mg it has useful hypnotic activity free of adverse effects on sleep and residual effects on performance. With 0.4 mg the hypnotic effect is enhanced with only minimal residual effects.

Introduction

Over the past few years several new benzodiazepines have been developed to provide hypnotics with improved profiles which lack residual effects on performance. Fosazepam in which a dimethyl-phosphinylmethyl group replaced the methyl radical of diazepam was an early example. The parent compound had a very short half-life, but it was the principal metabolite, nordiazepam, which was responsible for its activity, and so the sleep-wakefulness cycle was modified from 24 to 30 h after ingestion (Nicholson, Stone & Clarke, 1976). Other innovations have included nitro and halogen radicals as with flunitrazepam, and the replacement of the benzo ring with a thieno group as with clotiazepam, but more recently heterocyclic ring structures resistant to metabolic breakdown have been introduced across the methyl position. One such compound, triazolam-a triazolo-1, 4-benzodiazepine with an orthochlorophenyl group, has proved to be a useful hypnotic with a short duration of action (Roth, Kramer & Lutz, 1976; Nicholson & Stone, 1980).

Several of these variations have now been combined in the triazolo-thieno-1, 4-diazepines of which brotizolam (2-bromo-4-(2-chlorophenyl)-9-methyl-6H-thieno-[3, 2-*f*]-1, 2, 4-triazolo-[4, 3-a]-1, 4 diazepine) is an example (Figure 1). Results of animal studies and early human investigations indicate that it is a potent drug, with the advantage of low toxicity and little propensity for coma in overdose. The mean elimination half-life of the compound is estimated at 4.4 h. Brotizolam may be useful in the management of insomnia when residual sequelae must be avoided, and so we have studied its effect both on sleep and on performance in healthy young adults.

Methods

Sleep studies

Six healthy males familiar with sleep recording techniques were studied. They were aged between 18 and 27 (mean 22) years, and weighed between 66.0 and 78.5 (mean 71.3) kg. They were required to refrain from napping and undue exercise, and to abstain from alcohol during the day preceding the experimental nights. Only decaffeinated coffee was used from a week before the study. Subjects reported 1.5 h before bedtime. The individual rooms were light proofed, sound attenuated and temperature

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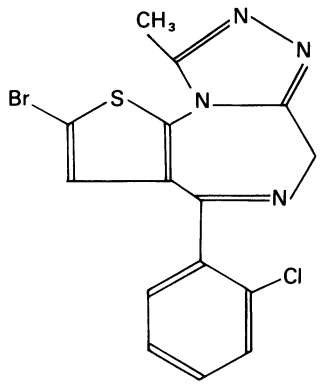

Figure 1 Structural formula of brotizolam: 2-Bromo-4-(2-chlorophenyl)-9-methyl-6H-thieno-[3, 2–7]-1, 2, 4-triazolo-[4, 3-a]-1, 4 diazepine.

(18 ± 1°C) and humidity (55 ± 1%) controlled. In an adjoining room three channels of electroencephalographic activity were recorded (C_4-A_1, P_1-T_5 and O_zP_z-O_3), together with the electromyogram and the electro-oculograms. The methods are described in detail elsewhere (Nicholson & Stone, 1979).

Two adaptation nights with ingestion of placebo, separated by 1 week, preceded the study. Afterwards each subject ingested 0.2, 0.4 and 0.6 mg brotizolam, 10 mg diazepam and on two further occasions placebo. All medication was identical in appearance and the experimental stage of the study was double-blind. Treatments were presented in random order and a week separated each assessment. Subjective assessment of sleep and well-being were measured using visual analogue scales. Half an hour after awakening each subject completed four assessments. The assessments and extremes of the 100 mm analogue scales were — A: I slept, *Very poorly — Very well;* B: Now I Feel, *Very sleepy — Wide awake;* C: I fell asleep, *Never — Immediately* and D: After I fell asleep I slept, *Very badly — Very well.* In each case a favourable response tended towards the 100 extreme of the scale.

Each sleep record was scored independently into 30 s epochs by two analysts according to the criteria of Rechtschaffen & Kales (1968). Differences in the annotation of sleep stages between the scorers were resolved, but did not occur in more than 5% of the epochs. These data and subjective assessments 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 if the value exceeded 50% a non-parametric method was used (Friedmann two-way analysis of variance).

Performance

The subjects were six healthy females aged between 19 and 32 (mean 24) years, weighing between 49.0 and 72.0 (mean 57.2) kg. They were required to avoid napping and undue exercise, and to abstain from alcohol from 19.00h on the day before overnight ingestion of tablets, and during the experimental day. They ate a light breakfast, and no coffee or other beverages containing caffeine were consumed on experimental days when subjects were provided with decaffeinated coffee. Subjects were trained on a visuo-motor coordination task (Borland & Nicholson, 1974) until they had reached steady performance. They were required to position a spot inside a randomly moving circle displayed on an oscilloscope, using a hand-held stick, and 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. The subjects reached a plateau performance within 100 s, after which scoring began. The laboratory was sound attenuated and air conditioned.

Overnight ingestion of 0.2, 0.4 and 0.6 mg brotizolam and morning ingestion of 0.4 mg brotizolam allowed the measurement of immediate and residual effects on performance. Subjects took matched drugs and/or placebos at 'lights out' (23.00 h) and at 08.00 h, and were therefore unaware whether the immediate or residual consequences were being studied. Performance was measured at 08.30, 09.30, 11.30, 13.30 and 16.00 h, and so immediate effects were recorded at 0.5, 1.5, 3.5, 5.5 and 8.0 h, and residual sequelae were recorded at 9.5, 10.5, 12.5, 14.5 and 17.0 h after ingestion. The trial was double-blind with treatments arranged in random order separated by 1 week. After each performance session the subject completed assessments of performance and well-being related to a 100 mm line. The extremes of the 100 mm analogue scale were — How well did you perform? *Useless* (00) — *Perfect* (100). Other assessments have included questions on concentration, lethargy and well-being. Comparisons between post- drug and post-placebo measures were made using analysis of variance.

Results

Sleep

Effects of diazepam and brotizolam on sleep are given in Table 1, 2, 3, 4, 5 and 6. Effects of 10 mg diazepam were comparable with previous studies (Nicholson *et al.*, 1976) except that stage 1 (drowsy)

Table 1 Effect of brotizolam on various sleep measures (means for six subjects)

Measures (*min*)	*c/v*	*Placebo*	*Diazepam (mg)* 10	*Brotizolam (mg)* 0.2	0.4	0.6
Total sleep time	2	457.0	475.9 **	471.8 **	472.8 **	469.1 *
Sleep onset latency	25	16.5	17.3	15.1	18.7	20.0
Latency to stage 3 sleep	78	11.6	13.7	22.7	13.6	12.6
Latency to REM sleep[1]	35	74.5	75.8	100.2	124.3 *	99.0
Stage shifts (6 h)	14	113.8	102.2	110.2	104.7	110.7
REM/NREM	14	0.33	0.37	0.34	0.32	0.27 *
Sleep efficiency index[2]	2	0.925	0.953 **	0.950 *(*)	0.953 **	0.944 *

C/V Coefficient of variability (s.d. × 100/mean) for each measure
Significance levels $*P < 0.05$; $**P < 0.01$.
[1]Latency to REM sleep for 0.2, 0.4 and 0.6 mg brotizolam were not increased individually compared with placebo but when combined (mean − 107.8 min) the increase was significant ($P < 0.05$).
[2]Sleep efficiency index — Total sleep time/Time in bed.

Table 2 Effect of brotizolam on duration (min) of sleep stages in first 6 h from sleep onset latency (means for six subjects)

Stage	*c/v*	*Placebo*	*Diazepam (mg)* 10	*Brotizolam (mg)* 0.2	0.4	0.6
Awake[1]	56	5.1	2.3	3.0	1.8[2] *	2.6
1[3]	31	20.6	12.5 **	14.0 *	12.8 **	13.0 **
2	6	180.6	194.0	190.5	197.9 *	208.6 ***
3	24	37.0	37.6	42.8	38.7	40.3
4	24	42.9	38.8	46.7	46.1	39.8
3+4	15	79.9	76.3	89.5	84.8	80.1
REM[4]	14	73.2	74.4	62.0 *	61.0 *	55.0 **

C/V Coefficient of variability (s.d. × 100/mean) for each measure
Significance levels $*P < 0.05$; $**P < 0.01$; $***P < 0.001$
[1]Non-parametric analysis. Duration of awake activity for 0.4 and 0.6 mg brotizolam combined was less than placebo ($P < 0.05$).
[2]Effect of 0.4 mg brotizolam on awake activity was related to the second 2 hourly (2–4 h) interval of sleep ($P < 0.05$).
[3]Effects of 10 mg diazepam ($P < 0.001$) and 0.2, 0.4 and 0.6 mg brotizolam ($P < 0.05, < 0.01, < 0.01$ respectively) were related to the third 2 hourly (4–6 h) interval of sleep.
[4]Effect on REM sleep was related to the first 2 hourly (0–2 h) interval of sleep ($P < 0.05$).

sleep was reduced in the present study. Over the dose range 0.2–0.6 mg, brotizolam increased total sleep time, reduced stage 1 sleep and improved the sleep efficiency index, and 0.4 and 0.6 mg also reduced awake activity. There were no changes in slow wave sleep. An effect of individual doses on latency to rapid eye movement (REM) sleep was not established, but by pooling results it appeared that the latency was increased over the dose range. However, the effect was not consistent. It was not observed at any dose in two subjects, and only in one subject was it observed at all three doses. The mean duration and percentage of REM sleep were reduced at all three doses during the first 6 h of sleep, particularly in the first 2 hourly interval, but over the whole night REM sleep and the REM/NREM ratio were reduced with the highest dose only. The subjects as a group assessed that their sleep was improved over the whole dose range; they fell asleep quicker and after they had fallen asleep, they slept better. Assessments of well-being the next morning suggested that a residual effect may have been detected after the highest dose, but this did not reach statistical significance (Table 7).

Table 3 Effect of brotizolam on percentage distribution of sleep stages in first 6 h after sleep onset latency (means for six subjects)

Stage	*C/V*	*Placebo*	*Diazepam (mg)* *10*	*Brotizolam (mg)* *0.2*	*0.4*	*0.6*
Awake[1]	57	1.4	0.7	0.8	0.5	0.7
			*		*	
1	31	5.8	3.5	3.9	3.6	3.7
			**	*	**	**
2	6	50.9	54.2	53.3	55.3	58.4
					*	**(*)
3	24	10.5	10.5	12.0	10.8	11.3
4	24	12.0	10.8	13.0	12.8	11.1
3+4	16	22.5	21.3	25.1	23.6	22.4
REM	14	20.6	20.8	17.4	17.1	15.4
				*	*	**

C/V Coefficient of variability (s.d. × 100/mean) for each measure
Significance levels $*P < 0.05$; $**P < 0.01$; $***P < 0.001$
[1]Non-parametric analysis. Percentage of awake activity for 10 mg diazepam and for 0.4 and 0.6 mg brotizolam combined were less than placebo ($P < 0.05$).

Table 4 Effect of brotizolam on duration (min) of sleep stages over the whole night from sleep onset latency (means for six subjects)

Stage	*C/V*	*Placebo*	*Diazepam (mg)* *10*	*Brotizolam (mg)* *0.2*	*0.4*	*0.6*
Awake[1]	57	7.7	3.3	4.8	2.8	3.4
			*		*	
1	29	32.5	20.4	22.7	20.6	20.8
			**	*	**	**
2	7	236.5	252.7	242.4	252.3	271.5
						**
3	24	40.3	37.7	42.9	40.1	40.7
4	24	43.0	38.8	46.7	46.1	39.8
3+4	16	83.3	76.4	89.6	86.2	80.4
REM	11	116.5	128.9	120.8	113.7	100.1
						*

C/V Coefficient of variability (s.d. × 100/mean) for each measure
Significance levels $*P < 0.05$; $**P < 0.01$
[1]Non-parametric analysis. Durations of awake activity for 10 mg diazepam and for 0.4 and 0.6 mg brotizolam combined were less than placebo ($P < 0.05$).

Table 5 Effect of brotizolam on percentage distribution of sleep stages over the whole night from sleep onset latency (means for six subjects)

Stage	*C/V*	*Placebo*	*Diazepam (mg)* *10*	*Brotizolam (mg)* *0.2*	*0.4*	*0.6*
Awake[1]	58	1.7	0.7	1.0	0.6	0.7
			*		*	
1	29	6.9	4.3	4.8	4.3	4.3
			**	*	**	**
2	7	50.4	52.7	50.8	53.2	57.2
						**
3	24	8.6	7.9	9.1	8.5	8.6
4	24	9.1	8.1	9.8	9.7	8.5
3+4	16	17.8	15.9	18.9	18.2	17.1
REM	10	24.8	27.0	25.3	23.9	21.1
						*

C/V Coefficient of variability (s.d. × 100/mean) for each measure
Significance levels $*P < 0.05$; $**P < 0.01$
[1]Non-parametric analysis. Percentage awake activity for 10 mg diazepam and for 0.4 and 0.6 mg brotizolam combined were less than placebo ($P < 0.05$).

Table 6 Effect of brotizolam on awakenings (0+1) over whole night (means for six subjects)

	Placebo	*Diazepam (mg)*	*Brotizolam (mg)*		
		10	*0.2*	*0.4*	*0.6*
Number	7.7	3.8 *	4.3	3.3 *	4.7
Duration (min)	20.1 *	6.2 * *	9.3	4.5 *	7.9 *

Significance level $*P < 0.05$ (non-parametric analysis)

Table 7 Effect of brotizolam on subjective assessments of sleep and well-being (means for six subjects)

		Diazepam (mg)	*Brotizolam (mg)*		
Assessments	Placebo	*10*	*0.2*	*0.4*	*0.6*
A	70	82 *	86 **	87 **	87 **
B	57	56	58	53	44
C	77	84	87	84 *	82
D	73	85 *	91 **	86 **	88 **

Significance levels $*P < 0.05$; $**P < 0.01$
Assessments were: A: I slept, *Very poorly — Very well;* B: Now I feel, *Very sleepy — Wide awake;* C: I fell asleep, *Never — Immediately;* D: After I fell asleep I slept, *Very badly — Very well.*

Performance

Effects of the drug on visuo-motor coordination are given in Table 8 and illustrated in Figure 2. After morning ingestion of 0.4 mg, impaired performance was observed from 0.5 h to 5.5 h. There were no residual effects with 0.2 mg brotizolam, but there was a residual effect with 0.4 mg at 9.5 h ($P < 0.05$) and with 0.6 mg at 9.5 ($P < 0.001$), 10.5 ($P < 0.01$) and 15.0 h ($P < 0.05$). Impaired performance over the dose range 0.2–0.6 mg was a linear effect at 10.5 h ($P < 0.001$). The subjects did not assess their performance as impaired, although as a group they considered that their ability to concentrate after the morning ingestion of 0.4 mg had deteriorated.

Discussion

The effect of brotizolam on performance has been studied previously by Grünberger, Saletu, Linzmayer, Kalk & Berner (1978). Normal subjects received 0.1, 0.3 and 0.5 mg brotizolam, and measurements of performance were made 2.0, 4.0, 6.0 and 8.0 h after ingestion. Effects were dose dependent. Brotizolam 0.1 and 0.3 mg impaired attention for at least 2 h after ingestion, while 0.5 mg impaired attention and decreased motor activity for at least 6 h and reduced concentration for at least 8 h. These observations are comparable with the present data, though we also observed performance after

Table 8 Analysis of variance and significance levels for change in performance (compared with placebo) on visuo motor coordination (arbitrary units) (means for six subjects)

Source	*Degrees of freedom*	*Mean squares*	*F*	*Significance levels*
Subject (S)	5			
Drug (D)	3	37.0102	7.49	**
SxD	15	4.9445		
Total (a)	23			
Time (T)	4	11.0499	2.30 (SxT)	
DxT	12	4.5211	2.95	**
SxT	20	4.8025	3.13	***
SxDxT	60	1.5340		
Total	119			

	Approximate time of performance measure (h)				
Brotizolam	*08.30*	*09.30*	*11.30*	*13.30*	*16.00*
0.2 mg night	−0.13	0.02	−0.12	0.08	0.01
0.4 mg night	−0.48 *	−0.35	−0.08	−0.13	−0.05
0.6 mg night	−0.96 ***	−0.70 **	−0.30	−0.46 *	−0.09
0.4 mg morning	−0.66 **	−1.40 ***	−1.31 ***	−0.58 **	−0.22

Least significant differences from placebo for means of 6 are $*P < 0.05 = 0.42$; $**P < 0.01 = 0.57$; $***P < 0.001 = 0.76$

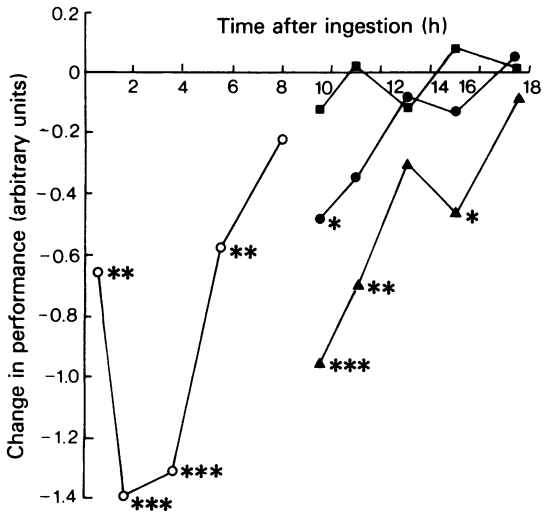

Figure 2 Immediate and residual effects of brotizolam on visuo-motor coordination (arbitrary units). Open symbols-morning ingestion. Filled symbols-overnight ingestion ■ 0.2 mg; ○, ● 0.4 mg; ▲ 0.6 mg. Significance levels $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

overnight ingestion and with 0.4 mg it was impaired for about 10 h, and so a time of day effect may exist. Performance may recover quicker on a task being practised throughout the period of a drug effect, or impairment may be greater in the early morning because of a synergistic effect with the relatively low level of performance. Rates of metabolism may also differ with time of day, and so the residual effects of a drug to be taken at night may not be accurately defined by day-time studies.

Over the dose range 0.2–0.6 mg there was a marked improvement in the sleep efficiency index, and so there is broad agreement with Saletu, Grünberger, Volavka & Berner (1979), who, using the spectral density of the electroencephalogram, predicted hypnotic activity over the dose range 0.3–0.5 mg. In our studies 0.4 mg brotizolam increased total sleep time and reduced awake activity and drowsy sleep without adverse changes in REM and slow wave sleep. The effect of 0.2 mg was equally useful, and this dose increased total sleep time, and reduced drowsy sleep and number of awakenings.

It is clear that brotizolam over the dose range 0.2–0.4 mg has distinct advantages over other well established hypnotics. In comparable studies with visuo-motor coordination, overnight ingestion of 30 mg flurazepam impaired performance well into the next afternoon, while that of 10 mg nitrazepam was followed by decrements throughout the next working day (Borland & Nicholson, 1975). The place of brotizolam in therapeutics must therefore be considered in relation to short-acting hypnotics, such as temazepam (10–20 mg), and triazolam (0.125–0.25 mg), which are also without adverse effects on sleep and residual effects on performance. Temazepam (20 mg) and triazolam (0.25 mg) increase total sleep time, reduce awake activity and drowsy sleep and markedly reduce awakenings, and this profile is similar to that observed with brotizolam. Temazepam and triazolam in the doses cited are free of residual sequelae though with higher doses residual effects are likely. Essentially, brotizolam (0.2–0.4 mg), temazepam (10–40 mg) and triazolam (0.25–0.50 mg) are similar in terms of effectiveness as hypnotics and time course of residual sequelae. 0.6 mg brotizolam would appear to have no advantage over a lower dose in terms of efficacy. Indeed, it reduces the duration of REM sleep and has persistent effects on performance, although it is possible that, as the present studies were carried out in females with lower body weight, severity and persistence of effects may be exaggerated compared with those in men.

It remains to be seen whether further clinical studies support the promise of these early investigations in healthy man, but brotizolam, in doses around 0.2 mg is likely to be useful in the initial management of sleep difficulties especially when residual effects the next day are to be avoided. Brotizolam is a potent hypnotic, and so careful attention must be given to the most appropriate dose range, and in this context a dose between 0.2 and 0.4 mg — nearer to 0.4 mg — is likely to have only minimal, if any, effects on performance and could prove particularly appropriate in the management of the more severe insomniac.

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