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THE EFFECTS OF REPEATED NOCTURNAL DOSES OF CLOBAZAM, DIPOTASSIUM CHLORAZEPATE AND PLACEBO ON SUBJECTIVE RATINGS OF SLEEP AND EARLY MORNING BEHAVIOUR AND OBJECTIVE MEASURES OF AROUSAL, PSYCHOMOTOR PERFORMANCE AND ANXIETY

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1 Repeated nocturnal doses of 30 mg clobazam and dipotassium chlorazepate 15 mg showed no significant effects compared to matching placebo on tests of psychomotor performance and serial subtraction of numbers given in the morning and afternoon of the day following treatment.

2 Both active preparations improved the perceived quality of sleep compared to placebo.

3 A reduction in rated anxiety scores was found with clobazam on the afternoon of the day following treatment together with an elevation of critical flicker fusion thresholds.

4 Dipotassium chlorazepate was found to impair performance of a low level conceptual task but not to influence performance at a more difficult level.

Introduction

Nocturnal treatment with anti-anxiety agents with long pharmacologically active half lives has advantages in allowing unwanted side-effects to dissipate during sleep and in providing a residual anti-anxiety activity the day following medication (Nicholson, Stone, Clarke & Ferres, 1976). Sedation and drowsiness are common side-effects of benzodiazepine derivatives used as anti-anxiety agents, and while these are unwanted in ambulatory patients operating machinery or driving motor vehicles they are useful concomitants of nocturnal administration in assisting the induction of sleep.

However, Bixler, Scharf & Kales (1972) have shown that drugs which improve sleep have a tendency to produce a hangover of detrimental effects the morning following medication and this has been shown for a variety of benzodiazepine derivatives (Hindmarch, 1975, 1976; Hindmarch, Parrott & Arenillas, 1977).

Dipotassium chlorazepate, a precursor of diazepam, is used clinically for the treatment of anxiety on a nocturnal regimen. Clobazam, a 1,5 benzodiazepine derivative has been shown to be effective in the clinical treatment of anxiety (Hunt, George & Ridges, 1974; Cottin, Dachary, Marie, Pagot, Ramant & Sales, 1975; Villard, 1976; Sandler, Brunswick, Digiacomo & Mendels, 1977; Charalampous, 1977). However, clobazam, like dipotassium chlorazepate, has a long active half life and also produces metabolites which could exert some pharmacological effect (Barzaghi, Fourneaux & Mantegazza, 1973; Rupp, Badian, Christ, Hadjú, Kulkarni, Taeuber, Uihlein, Bender & Vanderbeke, 1979). It seems reasonable then that the nocturnal administration of clobazam might provide a residual anxiolytic activity the day following medication.

This study compares the effects of clobazam and dipotassium chlorazepate against placebo on subjective ratings of sleep, early morning behaviour and anxiety and objective assessments of psychomotor performance and cognitive processing ability during the morning and afternoon of the day following repeated nocturnal doses.

Methods

Experimental design

Three treatment conditions were used, viz. clobazam 30 mg, dipotassium chlorazepate 15 mg and placebo, all presented in identical hard gelatin capsules. One capsule was taken 0.5 h before retiring to bed, on each of 3 consecutive nights. Testing, on the measures detailed below, took place on the morning and/or afternoon of the fourth day. Each subject acted as his own control, and at least 1 week 'washout' period was

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allowed between treatments. Prior to the experiment all subjects received practice on the test measures. The procedure was double blind: data was collected under a sealed code, and the order of treatments was randomized.

Assessments

The subject's evaluations of sleep and early morning behaviour were reported on the Leeds Sleep Evaluation Questionnaire (Hindmarch, 1975, 1976; Hindmarch *et al.*, 1977; Parrott & Hindmarch, 1978a). This self-completion set of 10 cm line analogue rating scales measures four subjective aspects of sleep and early morning behaviour, viz. the perceived ease of getting to sleep, the quality of induced sleep, the ease of awakening from sleep and the integrity of behaviour following wakening. The questionnaire was administered on the morning of the test day.

Psychomotor performance was assessed using a complex choice reaction time apparatus (Hindmarch, Parrott & Lanza, 1978; Parrott & Hindmarch, 1978b) in which subjects had to respond to a colour-position stimulus by pressing the appropriate response button. This assessment was made in the morning and the afternoon of the test day when the response measure taken was the mean latency of response to twenty-four stimulus presentations.

Central nervous system arousal and integrative ability was measured using critical flicker fusion thresholds for four light emitting diodes in foveal fixation at 1 metre (Hindmarch, 1975). Individual thresholds were determined using the psychophysical method of limits for three ascending and three descending scales (Woodworth & Schlosberg, 1958).

Cognitive processing ability was assessed using a concept identification task (Hindmarch & Parrott, 1978; Hindmarch *et al.*, 1978). Subjects were required to abstract the common element from sets of line drawings. The concepts to be identified were of two levels of difficulty, and presented in several parallel forms to preclude learning. The response measure recorded was the time taken to complete the correct identification. Assessment on this measure took place on the afternoon of the test day.

State anxiety was measured on the Spielberger rating scales (Spielberger, Gorusch & Lushene, 1968) and subjects also completed 10 cm line analogue rating scales for perceived anxiety and alertness on the afternoon of the test day.

Mental arithmetic ability was measured on the

Table 1 The mean scores obtained on all measures for each treatment condition together with s.d. and significant changes from placebo values indicated from paired *t*-tests performed between the conditions

		Placebo	*Clobazam 30 mg*	*Dipotassium chlorazepate 15 mg*
Psychomotor performance task (s)	a.m.	0.65± 0.08	0.68± 0.12	0.65± 0.11
	p.m.	0.62± 0.14	0.64± 0.10	0.63± 0.10
Critical flicker fusion Threshold (Hz)	a.m.	30.2 ± 2.6	31.9 ± 1.7 **	30.0 ± 2.1
	p.m.	30.8 ± 2.3	31.0 ± 2.6	30.3 ± 2.4
Spielberger rating scale	p.m.	18.7 ± 2.8	16.3 ± 1.7***	18.6 ± 2.8
Analogue rating scales (cm) (p.m.)	Anxiety	6.1 ± 2.6	7.2 ± 2.6	7.1 ± 2.2
	Alertness	5.3 ± 2.1	6.7 ± 1.6	6.6 ± 2.9
Concept identification task (s) (a.m.)	Easy	69.9 ± 3.8	77.4 ± 4.8	89.6 ± 5.2*
	Hard	96.3 ± 6.0	102.0 ± 6.1	82.9 ± 4.7
Sleep evaluation questionnaire (cm) (a.m.)	GTS	58.1 ±14.4	61.8 ±16.7	61.4 ± 9.9
	QOS	43.8 ±17.0	57.6 ±23.0*	54.2 ±20.0*
	AFS	32.9 ±17.0	29.5 ±10.0	30.6 ±16.6
	BFW	41.3 ±17.7	40.9 ±23.0	40.5 ±24.0
Serial subtraction of numbers (s) (p.m.)	3s	25.0 ± 7.2	26.7 ± 6.9	24.5 ± 6.2
	7s	42.2 ±17.9	41.0 ±14.3	40.9 ±19.8
	17s	64.5 ±24.4	66.4 ±28.6	55.7 ±16.5
Serial subtraction errors	3s	3	1	7
	7s	7	5	5
	17s	14	8	10

GTS ease of getting to sleep; QOS quality of sleep; AFS ease of awakening; BFW behaviour following awakening.
*$P < 0.05$, **$P < 0.02$, ***$P < 0.01$.

afternoon of test days using the serial subtraction of numbers technique. Subjects were required to subtract either 3, 7, or 17 from a three figure number and continue with ten sequential subtractions from the remainder. The time taken to complete the subtractions and the number of erroneous answers given were the response measures taken.

Subjects

Twelve consenting volunteers were admitted to the study (3 female and 9 male) with a mean age of 27 years. All were in normal physical and mental health without a history of renal, hepatic or cardiac disorder. Actual or possible pregnancy and concurrent medication or medical treatment also precluded participation. Subjects used public transport and refrained from excessive alcohol use for the duration of the study and consumed no alcohol on the evening preceding the test day. No restrictions were imposed on diet, beverage or nicotine consumption: each subject acted as his own control.

Results

Two subjects were withdrawn from the study (one needed treatment for bronchitis, the other failed to attend all test sessions) leaving complete data for ten individuals. The mean response scores for each treatment condition on the assessment measures are presented in Table 1 together with confidence levels (two tailed) for significant changes with respect to placebo: values obtained from paired *t*-tests performed between the treatment conditions.

Discussion

The changes produced by both active preparations on the psychomotor performance task were not significant, either on the morning of the test day, or on the afternoon.

Clobazam can be seen to significantly ($P < 0.02$) increase the early morning levels of central nervous system arousal and integration measured via critical flicker fusion thresholds. Dipotassium chlorazepate produces a slight depression of thresholds obtained in the morning and afternoon when compared to placebo, but the results are not significant. The data obtained following the treatment with clobazam is entirely consistent with the view that this drug exerts its anxiolytic activity by elevating arousal and central integrating mechanisms (Hindmarch, 1978). The tendency of dipotassium chlorazepate to reduce the critical flicker fusion threshold with respect to placebo is in accord with Marjerrison, Neufeldt, Holmes & Ho (1973) findings that the drug impaired attentiveness, decreased ratings of mood and produced sedation.

The results from the objective measures of arousal are concordant with the subjective reports of alertness obtained on the line analogue scales. Clobazam is seen to significantly increase ($P < 0.05$) the afternoon ratings of alertness compared to placebo, and the Spielberger ratings for 'state' anxiety are seen to be significantly improved, i.e. reduced, ($P < 0.01$) following repeated doses of clobazam. Dipotassium chlorazepate is not noticeably different from placebo on the Spielberger assessments: a paradoxical finding considering the effectiveness of the drug in the clinical treatment of anxiety (Wiersum, 1972; Feurst, 1973; Kasich, 1973; Lapierre, 1975). However, both active treatments increased the subjective ratings of anti-anxiety activity, but neither were significant when compared to placebo.

The concept identification task given in the morning of the test days shows that dipotassium chlorazepate significantly ($P < 0.05$) increased the response latency for the correct solution of the easy concepts. This impairment of a low level, low interest task relates to everyday activities where the behaviour is habitual and the response requirements not demanding of cognitive or attentional systems. However, when the task requirements are more demanding of attentional systems (hard conceptual level) dipotassium chlorazepate shows no impairment of response times when compared to placebo. Clobazam has been previously shown to behave similarly (Parrott & Hindmarch, 1975b) but in this instance there are no significant changes produced by the drug on the concept identification task when compared to placebo.

Table 1 shows the mean times taken to complete the serial subtraction of numbers. None of the drug treatments produced a significant change from placebo values. The errors produced on the serial subtraction task for 7s and 17s (Table 1) are not significantly changed by the active treatments. However, chlorazepate produces noticeably more errors than either placebo or clobazam on the serial subtraction of 3s. This effect reaches significance against clobazam, $P = 0.035$, using the binomial comparison and illustrates again the interference of low level performance produced by dipotassium chlorazepate (Marjerrison *et al.*, 1973).

The impairment of low level performance found here has also been shown for a variety of stimulant and sedative preparations (Parrott & Hindmarch, 1975a, 1977, 1978b). Such results suggest that a lowered task performance following administration of sedative drugs will be observed in those patients who are more likely to be performing tasks requiring little attention than in those whose performance demands varied attentional and cognitive skills.

The results from the sleep evaluation questionnaire show that both active compounds significantly improve ($P < 0.05$) the perceived quality of sleep. There is also a tendency for both to improve the rated ease of getting to sleep, with respect to placebo, and to reduce the ratings of early morning behaviour. These findings are in accordance with a recent nocturnal dose ranging study of clobazam (Hindmarch & Parrott, 1978) on subjective aspects of sleep and early morning behaviour and Nicholson *et al.* (1977) showed that subjective reports of less wakefulness followed the morning after acute ingestion of 10 and 20 mg clobazam.

There were no significant differences shown between the three treatment conditions on a test of psychomotor performance and integration.

Inasmuch as both drugs behave similarly with respect to the rated aspects of sleep and early morning behaviour, we note that clobazam is distinguished from dipotassium chlorazepate by significantly improving both objective and subjective measures of central nervous system arousal and integration. This finding corroborated previous research with clobazam (Hindmarch, 1978) and suggests that the mechanisms by which this drug alleviates anxiety are not via sedation or tranquillization, but by way of direct action on mechanisms of arousal and sensory integration.

The anxiolytic activity of clobazam is shown as a significant reduction in the Spielberger rating scores administered the afternoon following nocturnal treatment with the drug. This reduction in anxiety coincides with a significant increase in the perceived feelings of alertness, again relating the anxiety-reducing properties of the drug to its activity on central arousal mechanisms.

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