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CLOBAZAM, A 1,5-BENZODIAZEPINE, AND CAR-DRIVING ABILITY

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1 The effects of clobazam, a new anxiolytic agent (a 1,5-benzodiazepine) on car-driving ability and other tests of psychomotor performance were investigated in a double-blind, cross-over study *v.* placebo in normal volunteers.

2 Clobazam (20 mg) or placebo was given nightly for six nights to ten volunteers and subjective ratings of sleep and subjective and objective assessments of behaviour and psychomotor performance on the morning following drug ingestion were recorded.

3 Clobazam significantly improved the subjective ratings of sleep induction and quality of induced sleep.

4 Clobazam did not significantly impair performance in a variety of psychomotor tests and car-driving ability.

5 The validity of the measures used and the relevance of the findings to real life car-driving situations are discussed.

Introduction

Impairment of mental functioning and psychomotor performance has been demonstrated in laboratory studies of a wide range of benzodiazepine derivatives including nitrazepam (Malpas & Joyce, 1969); diazepam (Korttila & Linnoila, 1975); flurazepam (Bond & Lader, 1973); N-desmethyldiazepam (Tansella, Zimmerman-Tansella & Lader, 1974) and chlordiazepoxide (Hughes, Forney & Richards, 1965). Any impairment of psychomotor skills is of obvious importance, in view of the widespread use of these drugs, for patients driving motor vehicles.

Clobazam is a new 1,5-benzodiazepine which differs structurally from currently available 1,4-benzodiazepines: the nomenclature referring to the position of the nitrogen atom in the heterocyclic ring (Figure 1). However, while the animal pharmacological profile of clobazam is similar to that of other benzodiazepines (Barzaghi, Fournex & Mantegazza, 1973), the drug does appear to be significantly different in its effects on human psychomotor performance. Clobazam exhibits effective anti-anxiety activity (Hunt, George & Ridges, 1974; Coste-Simonin & Krantz, 1975; Cottin, Dachary, Marie, Pagot, Ramant & Sales, 1975; Martin, 1975) without significant deleterious effects on psychomotor performance (Berry, Burtles, Grubb & Hoare, 1974; Borland & Nicholson, 1974). The present study investigates the effects of clobazam on car-driving ability and related tests of psychomotor performance.

Methods

Subjects

The subjects were ten volunteers (five male and five female) with a mean age of 27 years, who were regular drivers and had held full driving licences for an average of 6.5 years.

Tests and assessments

Tests of driving ability were devised in conjunction with the Institute of Advanced Motorists whose officers were responsible for the marshalling and the awarding of error scores. The driving tasks were timed and subjects were instructed to complete the manoeuvres as quickly as possible so as to approximate to real life car-driving situations. Each subject used the same test car throughout the study. Errors and penalty points were given when a subject's car

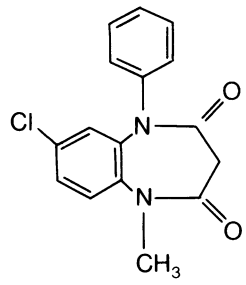

Figure 1 The structural formula of clobazam.

touched marker beacons, or stalled or stopped or failed to complete the test to a predetermined criterion level, or when subjects made other infringements of the instructions given to them. Each test situation ('garage', 'parked car') was represented in this present instance by markers, beacons and bollards.

Driving ability

The four tests of driving ability comprised

Estimation of width at a distance. Subjects seated in their car instructed marshals to adjust two markers placed 25 feet in front of the car until sufficient room was available to enable the car to be driven forward and through the markers, allowing 4 inches each side of the car. This task was completed four times for each assessment, twice with the markers initially together and twice with the markers wide apart.

Reverse parking. Subjects were allowed three movements of their car to reverse into a space between two parked cars. This procedure was completed three times for one assessment, the response measure being the mean error score and the mean time taken to complete the three trials.

Garaging a car. Subjects had to garage their car by one forward and one reverse movement into a garage set at right angles to their initial direction of travel. When garaged it had to be possible for the nearside door to be opened fully without touching the garage wall. This task was completed three times for one assessment, the performance measure being the mean time taken and the mean number of errors scored.

Manoeuvring ability (slalom). This test involved full left and right steering locks being applied as subjects had to manoeuvre round six beacons, passing each on alternate sides. At the final beacon subjects turned and slalomed back to the start line. This task was completed three times for one assessment, error points being awarded for touching beacons, stalling, missing a turning sequence, etc.

Personality and subjective assessments of sleep

The Middlesex Hospital Questionnaire (MHQ) (Crown & Crisp, 1970) was used as a measure of trait personality states, and Spielberger's State Anxiety Inventory (Spielberger, Gorsuch & Lushene, 1968) was used to measure transient changes in perceived anxiety. The subjective quality of sleep and early morning behaviour was assessed using a 10 cm line analogue scale sleep evaluation questionnaire (Hindmarch, 1975).

Psychomotor performance

The choice reaction time apparatus is described fully elsewhere (Hindmarch, 1975) and utilizes a display of five coloured lights, one of which is illuminated at random and extinguished by the subject pressing the appropriate response key. The mean latency of response to twenty presentations of the light stimulus is the performance measure utilized. A digit symbol substitution task (DSST) based on the Wechsler Adult Intelligence scale subtest (Wechsler, 1955) was also used: the time taken to complete the substitution was recorded along with the number of errors made.

Medications

Clobazam was administered as a single night-time dose of 20 mg at which level it has been shown to have beneficial effects on sleep (Nicholson, Stone & Clarke, 1977). Clobazam (20 mg) or placebo was taken nightly 30 min before retiring, for six nights. The basic design of the study was a double-blind cross-over but since clobazam has been shown to have a long half-life (Hoechst, AG, internal report), a wash-out period of seven nights on placebo was interposed between the active treatment conditions.

Results

Driving ability

Figure 2 shows the mean error scores obtained on all driving tests for both drug and placebo conditions while Figure 3 shows the mean time taken to complete the paced driving tasks. Table 1 shows the results of a cross-over analysis of variance between the two test days. The only significant treatment effect occurred with the reverse parking test where times were significantly slower under the drug condition ($P < 0.05$). Table 1 also indicates the pronounced difference between subjects with respect to the time taken to complete the driving tests. These inter-subject differences are mirrored only in the error scores for the reverse parking test ($P < 0.05$).

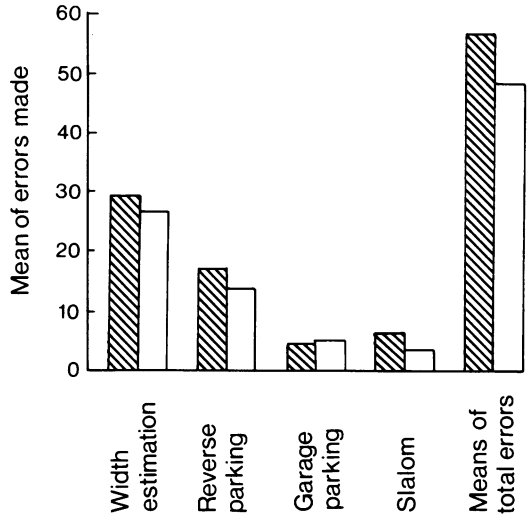

Figure 2 Means of error scores obtained on driving tests. Mean of total errors on clobazam 57.8, s.e. mean 9.8, s.d. 31.0. Mean of total errors on placebo 48.3, s.e. mean 6.9, s.d. 22.0. (▨) clobazam; (□) placebo.

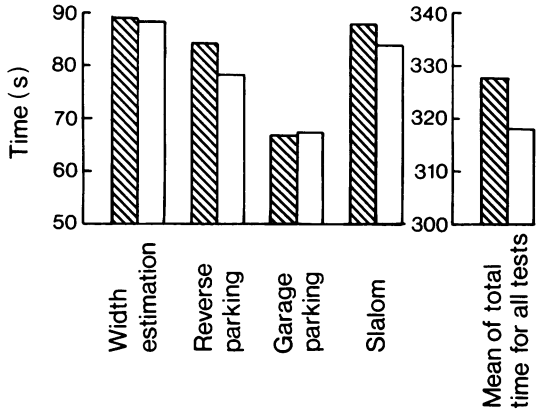

Figure 3 Mean times taken to complete driving tests. Mean of total time for all tests on clobazam 372.2 s, s.e. mean 12.5, s.d. 39.6. Mean of total time for all tests on placebo 317.7 s, s.e. mean 13.5, s.d. 42.6. (▨) clobazam; (□) placebo.

Personality and 'subjective feeling' scores

Figure 4 shows the mean score obtained on the sleep evaluation questionnaire for both drug and placebo. The total sleep inducement scores and the total 'hangover' scores were computed for every subject in two 1-week periods, i.e. the six nights on which subjects received clobazam (20 mg) at night and the six nights they received matching placebo.

Table 1 Table of *F*-values arising from the application of a cross-over analysis of variance using two test days

	Psychomotor tests		*Tests of driving ability*									
			Width estimation		*Reverse parking*		*Garaging*		*Slalom*		*Total*	
Significance between	*CRT*	*DSST time*	*Time*	*Errors*	*Time*	*Errors*	*Time*	*Errors*	*Time*	*Errors*	*Time*	*Errors*
Treatment	0.51	1.75	0.01	0.28	6.37§	0.26	0.33	0.89	2.91	5.10	2.02	0.83
Periods	3.81	0.91	1.32	4.18	1.26	1.37	0.74	2.93	0.63	1.20	0.04	1.44
Subjects	28.11*	5.82†	5.17‡	1.67	12.87*	4.38§	21.54*	2.93	5.25§	3.05	13.23*	3.21

Differences between treatments are tested using the *F*-distribution and 1, 8 degrees of freedom.
Differences between periods are tested using the *F*-distribution and 1, 9 degrees of freedom.
Differences between subjects are tested using the *F*-distribution and 9, 9 degrees of freedom. Significance levels indicated: $P < 0.001 = *$; $P < 0.01 = †$; $P < 0.025 = ‡$; $P < 0.05 = §$.
CRT, choice reaction time; DSST, digit symbol substitution task.

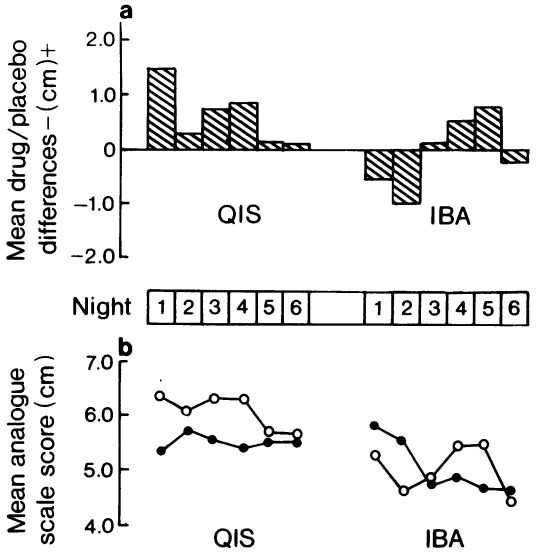

Figure 4 Mean changes in subjective ratings of sleep. (a) Mean drug/placebo differences for the subjective ratings of the quality of induced sleep (QIS) and the integrity of behaviour following awakening (IBA). (b) Clobazam (O) and placebo (●) compared on the mean nightly ratings for the subjective quality of induced sleep (QIS) and integrity of early morning behaviour (IBA).

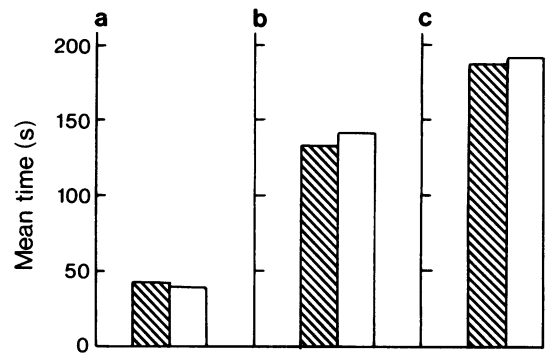

Figure 5 Mean times for psychomotor performance tasks (a) choice reaction time (CRT) (×100), (b) digit substitution time (DSST); (c) mean time for both CRT and DSST. Mean time for CRT and DSST on clobazam 175.2 s, s.e. mean 10.1, s.d. 31.8; on placebo 182.6 s, s.e. mean 8.9, s.d. 28.0. (▨) clobazam; (□) placebo.

The scores obtained on the MHQ and Spielberger Anxiety Scales showed that the subjects were within the normal range and there were no consistent effects or changes evident.

Psychomotor performance

Figure 5 shows the mean response latencies for both choice reaction time and digit symbol substitution tasks under drug and placebo conditions. There were not sufficient errors made on the DSST task to warrant a statistical analysis of the results and so these figures are not presented.

Discussion

A consideration of Figures 2, 3 and 5 indicates that a repeated dose of clobazam (20 mg) at night for six nights does not produce a significant effect, when compared to placebo values, on any of the car-driving or psychomotor performance parameters utilized in this study.

An examination of the raw data from two subjects showed a marked decrement in both car-driving ability and psychomotor performance as a result of drug administration. This noticeable interference with car-driving performance in individual cases was not associated with lengths of car-driving experience, or personality or any other easily identifiable factor, and can only be attributed to a specific 'sensitivity' of certain individuals to the drug administered, since the impairment of car-driving ability and of psychomotor performance was not generally found.

Figure 4 shows that the subjective ratings of sleep induction and the quality of induced sleep were consistently in favour of clobazam. The subjective ratings of 'the integrity of early morning behaviour', i.e. hangover, showed no consistent trend and indicate that clobazam does not produce any significant impairment of early morning behaviour. The period effect is also not significant but there are important ($P < 0.01$) inter-subject differences.

There are, however, certain riders to be added to these general conclusions.

(i) Most experiments conducted to investigate the interaction between benzodiazepines and car-driving behaviour have utilized laboratory analogues of car-driving tasks, or car-driving simulators, with acute doses of the drug being administered (e.g. Landauer, Milner & Patman, 1969; Linnoila & Mattila, 1973). However, the results from such studies are inconclusive and the validity of the tests used questionable (Silverstone, 1974) since the real life car-driving situation demands a totally different set and levels of response from the laboratory or simulator situation (Betts, Clayton & MacKay, 1972). Parrott & Hindmarch (1975a) have also shown that the change induced in psychomotor performance measures by a range of psychoactive drugs is a function of the task

situation, and specifically that the effect on arousal and performance parameters of an acute dose of clobazam (10 mg) is a function of the level of reinforcement inherent in the psychomotor task used to measure performance (Parrott & Hindmarch, 1975b). Since most car-driving simulators are complex machines with a high level of intrinsic interest, then it could be argued that the measures of performance obtained on such machines are more likely to be due to the interaction between drug effects and intrinsic reinforcement levels than to drug effects alone; although the car-driving situation used here is arguably free from intrinsic reinforcement especially with experienced drivers. The effect of the motivational component of the competitive spirit engendered between subjects could be an important variable.

(ii) The tests used here to measure car-driving ability are useful assessments of car handling at low speeds; and while they may not represent the range and complexity of the skills involved in car-driving on public highways they do provide a close and more valid approximation to real life driving conditions (Clayton, 1976) than laboratory or simulator situations. Nevertheless, the lack of drug induced impairment could be due to the insensitivity of the present car-driving tasks (Silverstone, 1974) or to the relatively simple driving skills required to complete them. However, similar tasks have been used in studies (Betts *et al.*, 1972; Hindmarch, 1976) when drug induced impairments of slow speed driving performance have been shown.

(iii) The present volunteer subjects were all physically healthy and psychologically normal individuals and it could be argued that they are not representative of the patient population likely to be prescribed clobazam in clinical practice. However, benzodiazepine derivatives are often prescribed as adjunct therapy and they could easily be given to psychologically normal, car-driving patients. The potential risks to car-driving patients from the effects of psychotropic drugs are unclear but Kibrick & Smart (1970) suggested that up to 50% of the general population do drive after drug use at least once a year and up to 15% of accident-involved drivers have taken a psychotropic compound prior to their accident. In view of these factors it appears that the results of this present study are not too inappropriate or lacking in relevance.

When the mean results of the group were considered, a repeated dose of clobazam (20 mg) significantly improved subjective ratings of sleep induction and quality of sleep. It did not impair performance in either subjective or objective tests of psychomotor behaviour or car-driving ability. However, when the individual results were considered, car driving and psychomotor function were impaired in two of the ten subjects.

Our experiment was not designed to detect drug effects before the sixth day of treatment, and we cannot draw conclusions from this study about acute effects.

It is clear that the repeated administration of clobazam does not produce adverse effects on performance in the majority of persons but there is, as yet, no way of detecting those who may be more sensitive to its action.

We gratefully acknowledge the assistance given in marshalling and scoring the tests of driving skill by the officials of the Institute of Advanced Motorists. Our thanks are due also to Dr Barbara Hunt for her encouragement and help in the early organization of the studies.

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