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IMMEDIATE EFFECTS ON HUMAN PERFORMANCE OF A 1,5-BENZODIAZEPINE (CLOBAZAM) COMPARED WITH THE 1,4-BENZODIAZEPINES, CHLORDIAZEPOXIDE HYDROCHLORIDE AND DIAZEPAM

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1 The immediate effects on human performance of the 1,5-benzodiazepine, clobazam (20 mg), and the 1,4-benzodiazepines, chlordiazepoxide hydrochloride (20 mg) and diazepam (10 mg), were studied by adaptive tracking and measurement of reaction time. Each drug was ingested at 09.00 h and performance was measured at 09 h 30 min (0.5 h), 11 h 30 min (2.5 h), 14 h 30 min (5.5 h) and 18 h 30 min (9.5 h after ingestion).

2 With diazepam decrements in performance on adaptive tracking were observed at 0.5 h and 2.5 h and performance was enhanced at 9.5 h after ingestion. With clobazam performance at individual times did not differ significantly from control, but there was evidence of an improvement in performance during the day. There was no evidence of impaired performance on adaptive tracking after chlordiazepoxide hydrochloride.

3 Reaction time was slowed at 0.5 h and 2.5 h after diazepam and chlordiazepoxide hydrochloride. A decrease in reaction time was observed at 9.5 h after diazepam. No changes in reaction time were observed after clobazam.

4 The subjects as a group differentiated correctly between performance decrements on adaptive tracking after diazepam and the absence of performance decrements after clobazam and chlordiazepoxide hydrochloride. The persistence of the decrement in performance after diazepam was accurately assessed.

5 It is evident that the nature and persistence of impaired performance and the ability to appreciate impaired performance vary considerably between the benzodiazepines, and that the choice of a benzodiazepine should include careful consideration of performance sequelae.

Introduction

In previous studies (Borland & Nicholson, 1974, 1975; Borland, Nicholson & Wright, 1975) we examined the residual effects of hypnotics on human performance. The studies included observations on 1,4-benzodiazepines and it was shown that, as with many other hypnotics, impaired performance may persist well into the next day after overnight ingestion. Residual effects on performance may not be an essential property of an effective drug, and there are differences in the severity and persistence of performance decrements between hypnotics. Studies with methaqualone hydrochloride (400 mg) have failed to reveal effects on performance from 10 h after overnight ingestion, while with flurazepam hydrochloride (30 mg) recovery of function is delayed to the early part of the afternoon and with nitrazepam (10 mg) impaired performance persists to the early evening.

It is evident that drugs within a group, such as the benzodiazepines, may have different effects on performance as well as different therapeutic activity. In this context there is interest in benzodiazepines with the nitrogen atoms of the heterocyclic ring in the 1,5 position instead of the 1,4 position. An example is clobazam (1-phenyl-5-methyl-8-chloro-1,2,4,5-tetrahydro-2,4-diketo-3H-1,5-benzodiazepine, Hoechst Pharmaceuticals, Figure 1) which has been shown to be more active as a sedative in animals than chlordiazepoxide hydrochloride (Barzaghi, Fournex & Mantegazza, 1973), but which has been reported to have limited effects on human performance (Berry, Burtles, Grubb & Hoare, 1974). Both clobazam and chlordiazepoxide hydrochloride would appear to have a shorter duration of action than that of the 1,4-benzodiazepines used primarily as hypnotics, and so we have looked for immediate rather than residual effects. We have compared these drugs with diazepam, which is known to lead

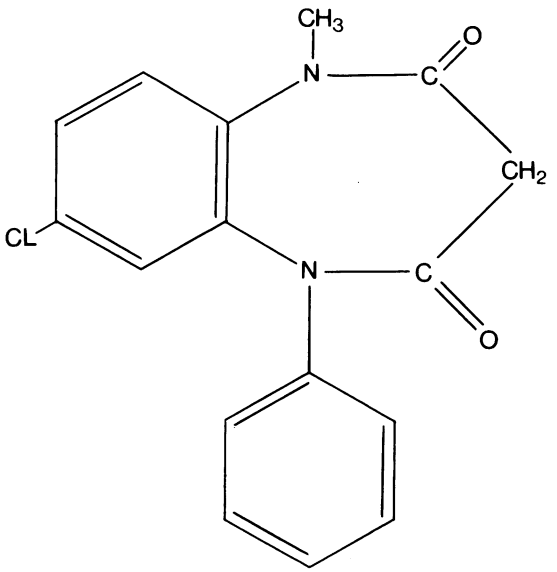


Figure 1 The structural formula of clobazam.

to performance decrements in man (Jäättelä Mannistö, Paatero & Tuomisto, 1971; Linnoila & Mattila, 1973).

Methods

The adaptive tracking task used as the measure of performance required the subject to position a spot inside a randomly moving circle displayed on an oscilloscope. The movement of the spot was controlled by a handheld 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. This technique provided the adaptive component of the task. The movement of the circle on the oscilloscope was produced by two independent maximum length binary sequences. Low pass filtering smoothed the output of the binary sequences and the movement of the circle was statistically random. Independent x and y signals derived from high grade potentiometers mounted on the control stick were fed via an 'aerodynamic loop' to the inputs of the oscilloscope. The loop avoided an artificial one to one relationship between the control stick and spot movement and smoothed out any small steps caused by the potentiometer windings.

The oscilloscope (Airmec 383) had a distortion-free, medium persistence tube and displayed the task over an area of 20 x 20 cm. It was modified by the addition of x axis beam switching and allowed two independent signals to be displayed in each axis. A voltage proportional to the distance between the spot and the centre of the target circle was generated and the radial error signal was computed. A voltage proportional to the square of the circle radius was subtracted from the square of the radial error signal. The output from the scoring circuit was fed to a voltage integrator and the output of the integrator, scaled from zero to 10, controlled the mean amplitude of the task.

At the start of each experiment the output from the integrator was set at zero and the circle was stationary. The subject positioned the spot inside the circle and the negative error signal made the integrator output increase. The circle tended to move away from the spot and, when the spot could no longer be maintained inside the target circle due to the increasing difficulty of the task, the polarity of the voltage to the integrator reversed and the task became less demanding. The integrator had a long time constant which allowed each subject to 'warm up' gradually. With zero error the task required about 25 s to reach maximum difficulty. A constant displacement of 4 cm between the spot and the centre of the circle would reduce the task to zero difficulty within 6 s. As the subjects became aware of the penalty of error signals they tried to avoid all errors, but the task did not permit maximum performance to be reached. An 8 channel pen recorder monitored the tracking equipment and the performance of each subject.

Experiments were carried out in a sound attenuated and air-conditioned room. Subjects were required to reach steady performance on the task before studies commenced. In subjects familiar with this type of performance task, such as pilots, steady performance would have been reached within a few days, but with scientific personnel it was reached with daily practice only after 2-3 weeks. Practice sessions were made available between experiments.

Assessment of performance on adaptive tracking

The positions of the circle and spot and the radial error signal were recorded for the x axis only together with the output from the task integrator. Each tracking run lasted 10 min and the subjects reached steady performance within the first 100 s of each run. The mean amplitude of the task over the final 500 s was computed using a voltage to frequency converter and digital counter. This was the performance measure.

Subjective assessment of performance on adaptive tracking

Each subject was presented after each task with a line 100 mm in length. The question 'What standard of performance did you reach' was asked and the subject made the assessment by crossing the line with a pencil between the extremes of Zero and Perfect. The assessment was quantified by measuring in mm the displacement of the mark from the Zero extremity.

Measurement of reaction time

Reaction time was measured 2 min after the completion of each tracking run. Subjects pressed a handheld morse key to cancel a group of red lights switched on at random intervals. The light signal was produced by 5 light emitting diodes (650 nm: 2.0×10^{-3} candela) arranged within a 5 x 5 cm square. The group of lights was viewed at a distance of 1 m and was illuminated for 1 second. The inter-trial time varied between 1 and 8 seconds. Twenty-five trials were presented to each subject and the mean of the last twenty trials was recorded as the reaction time. Reaction time was measured in 10 ms intervals accurate to the nearest 2 ms.

Experimental procedure

Five healthy male subjects were used. Their ages ranged from 24 to 39 (mean 32) years and their weights ranged from 67 to 83 (mean 72) kg. Instructions were given to all subjects to avoid alcohol within 24 h of the experiment and they were not involved in any other form of drug therapy. There were no restrictions on the consumption of non-alcoholic beverages. The subjects ate a light breakfast about an hour before ingestion of the placebo or drug.

The assessment of the effect of placebo or of drug was carried out over 2 days. On the first day four assessments of each subject's performance were made at 09 h 30 min, 11 h 30 min, 14 h 30 min and 18 h 30 min. This pattern of performance assessment was repeated on the second day, after the placebo or drug had been given at 09.00 hours. Each subject carried out an assessment just before 09.00 h on each of the two experimental days, but the results were not used in the analyses. Each subject completed four 2-day sessions separated by 4 weeks. The capsules contained chlordiazepoxide hydrochloride (20 mg), clobazam (20 mg), diazepam (10 mg) or placebo and were given in a separate random order for each subject. The trial was double blind and placebo and drugs were presented in identical capsules.

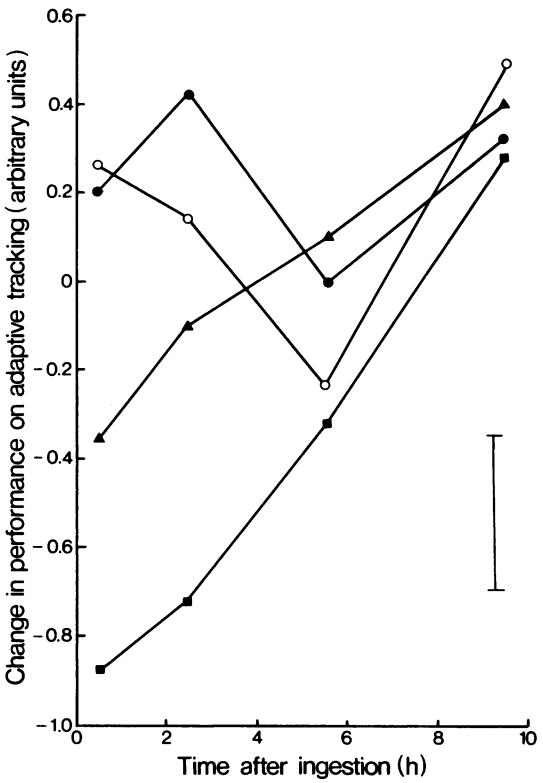
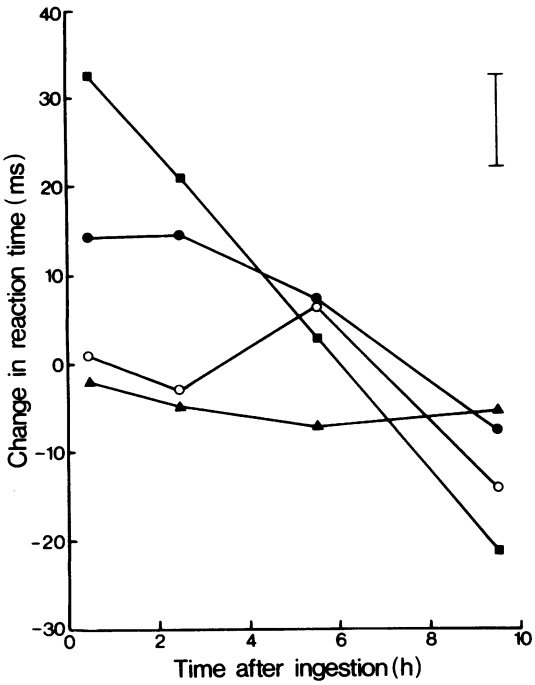


Figure 2 Change in performance on adaptive tracking (arbitrary units) for all subjects ($n = 5$) after placebo (○), clobazam (20 mg) (▲), chlordiazepoxide hydrochloride (20 mg) (●); and diazepam (10 mg) (■). Standard error (0.34 arbitrary units) is given as a vertical bar.

Results

Changes in performance on adaptive tracking, in assessments of performance and in reaction time were analysed by analysis of variance. The analyses were concerned with the performance measures and assessments of performance at 09 h 30 min, 11 h 30 min, 14 h 30 min and 18 h 30 min on each of the 2 days. For the subjects as a group there were no significant differences between performance measures or between assessments of performance during day 1 and so, in each case, the four values were combined to give the appropriate mean. Performance on adaptive tracking and on reaction time, and assessment of performance on adaptive tracking, during the day after administration of the drug or placebo, were each subtracted from the appropriate mean for analysis. The results are given in Tables 1, 2 and 3 and illustrated in Figures 2 and 3.



Performance on adaptive tracking was significantly impaired only after diazepam, at 0.5 h and 2.5 h after ingestion. The subjects as a group differentiated correctly between the effect of diazepam and the absence of effects after placebo, clobazam and chlordiazepoxide hydrochloride, and they assessed the duration of impaired performance after diazepam accurately. After placebo there was an enhanced performance on adaptive tracking at 18 h 30 min compared with the previous day. This difference was significant at the 5% level, but the enhanced performance did not differ significantly from performance after each drug at this time.

With diazepam and chlordiazepoxide hydrochloride reaction time was increased at 0.5 h and 2.5 h, and with diazepam there was a decrease in reaction time at 9.5 hours. There were no changes

Figure 3 Change in reaction time (ms) for all subjects ($n = 5$) after placebo (○); clobazam (20 mg) (▲); chlordiazepoxide hydrochloride (20 mg) (●); and diazepam (10 mg) (■). Standard error (9.6 ms) is given as a vertical bar.

Table 1 Analysis of variance and significance levels for performance change on adaptive tracking (arbitrary units) after drugs

Source	*Degrees of freedom*	*Mean squares*	F	*Significance levels*
Subjects (S)	4	1.361911	4.59	**
Drug (D)	3	1.678505 (SxD)	1.83	
Time (T)	3	1.313938	4.43	**
SxD	12	0.917326	3.09	**
SxT	12	0.380235	1.28	
DxT	9	0.407297	1.37	
SxDxT	36	0.296901		
Total	79			

	Time after ingestion			
Placebo or drug	*09 h 30 min (+0.5 h)*	*11 h 30 min (+2.5 h)*	*14 h 30 min (+5.5 h)*	*18 h 30 min (+9.5 h)*
Placebo	0.26	0.14	−0.24	0.49 *
Clobazam (20 mg)	−0.36	−0.14	0.10	0.40
Diazepam (10 mg)	−0.88 ***	−0.73 **	−0.33	0.29
Chlordiazepoxide (20 mg)	0.20	0.42	−0.01	0.31

Least significant differences from zero for means of 5 were 5% = 0.49; 1% = 0.66; 0.1% = 0.87; (* = 5%; ** = 1%; *** = 0.1%)
Least significant differences between means of 5 were 5% = 0.70; 1% = 0.94; 0.1% = 1.24.

Table 2 Analysis of variance and significance levels for change in assessment of performance on adaptive tracking (arbitrary units) by subjects after drugs

Source	*Degrees of freedom*	*Mean squares*	F	*Significance levels*
Subjects (S)	4	1.5897	3.30	*
Drugs (D)	3	1.9175	3.98	*
Time (T)	3	2.9865	6.20	**
SxD	12	0.6851		
SxT	12	0.5595		
DxT	9	0.6976	1.45	
SxDxT	36	0.4814		
Total	79			

	Time after ingestion			
Placebo or drug	*09 h 30 min (+0.5 h)*	*11 h 30 min (+2.5 h)*	*14 h 30 min (+5.5 h)*	*18 h 30 min (+9.5 h)*
Placebo	−0.10	0.46	0.04	0.38
Clobazam (20 mg)	−1.04	−0.44	0.28	0.10
Diazepam (10 mg)	−1.26 ***	−0.66 *	−0.28	0.38
Chlordiazepoxide (20 mg)	−0.04	0.02	0.08	0.38

Least significant differences from zero for means of 5 were 5% = 0.63; 1% = 0.84; 0.1% = 1.11. (* = 5%; ** = 1%; *** = 0.1%)

Table 3 Analysis of variance for change in reaction time (ms) by subjects after drugs

Source	*Degrees of freedom*	*Mean squares*	F	*Significance levels*
Subjects (S)	4	286.8416	1.24	
Drug (D)	3	864.6737 (SxD)	1.83	
Time (T)	3	2169.5110	9.36	***
SxD	12	471.8106	2.03	*
SxT	12	186.4896		
DxT	9	546.4082	2.36	*
SxDxT	36	231.8734		
Total	79			

	Time after ingestion			
Placebo or drug	*09 h 30 min (+0.5 h)*	*11 h 30 min (+2.5 h)*	*14 h 30 min (+5.5 h)*	*18 h 30 min (+9.5 h)*
Placebo	1.2	−3.0	8.8	−14.2 *
Clobazam (20 mg)	−1.9	−4.3	−6.6	−5.6
Diazepam (10 mg)	32.5 ***	20.6 **	3.0	−21.2 **
Chlordiazepoxide (20 mg)	14.2 *	14.5 *	8.6	−8.7

Least significant differences from zero for means of 5 were 5% = 13.8; 1% = 18.5; 0.1% = 24.4. (* = 5%; ** = 1%; *** = 0.1%).
Least significant differences between means of 5 were 5% = 19.5: 1% = 26.2; 0.1% = 34.5.

in reaction time after clobazam. With placebo there was a decrease in reaction time significant at the 5% level at 18 h 30 min, but there were no significant differences in reaction time between placebo and drugs at this time.

Though there was no evidence that performance was impaired at any individual time interval after clobazam, inspection of Figure 2 suggests that an improvement in performance on adaptive tracking had occurred with time. This possibility was examined by comparing the change in performance at 0.5 h and 2.5 h with the change in performance at 5.5 h and 9.5 hours. The analyses showed that an improvement in performance on adaptive tracking significant at the 5% level had occurred. With diazepam the improvement in performance was significant at the 1% level. A similar analysis revealed an improvement in reaction time during the day with diazepam (significant at the 0.1% level) and with chlordiazepoxide hydrochloride (significant at the 5% level). There was no evidence of any change in performance during the day with chlordiazepoxide hydrochloride on adaptive tracking and with clobazam on reaction time.

Discussion

The present studies have shown that benzodiazepines with established therapeutic activity, such as diazepam and chlordiazepoxide hydrochloride, may have very different effects on performance. Diazepam (10 mg) leads to impairment on adaptive tracking and increased reaction time for at least 2.5 h after ingestion, whereas chlordiazepoxide hydrochloride, ingested as a single 20 mg dose, leads to slowing of reaction time over a similar period, but with no impairment on adaptive tracking. On the other hand clobazam (20 mg) did not have an effect either on adaptive tracking or on reaction time.

It is of interest that placebo led to enhanced performance on both adaptive tracking and reaction time at the end of the day. Ingestion of a capsule may increase the motivation of subjects to overcome the possible deleterious effects of its contents, and, though this may not lead to improved performance during the early part of the day, it may modify performance as the end of the experiment is reached. In this sense the absence of an 'end of day' effect after a drug could be considered as an impairment of function, but, if performance at the end of the day after a drug does not differ significantly from that after placebo and there is no other evidence of modified performance, it would be unreasonable to ascribe any significance to the absence of an 'end of day' effect.

With clobazam there was evidence of a trend of improved performance during the day and an absence of enhanced performance on adaptive tracking at the end of the day. These findings may suggest an effect of the drug on performance, but it is considered that they provide little support for the observation that performance is impaired after this drug (Berry, *et al.*, 1974). With diazepam there was an enhancement of performance at the end of the day on both adaptive tracking and reaction time. This phenomenon may be either an 'end of day' effect related to the motivation of subjects after the ingestion of a capsule, or a rebound in performance related to increased nervous arousal after the effect of the drug had worn off. The latter, which is seen as a residual effect of some hypnotics, is discussed elsewhere (Borland *et al.*, 1975), but, as in the present experiments the phenomenon was observed at the end of the day, it is not possible to differentiate between these possible mechanisms.

In the present studies with diazepam performance decrements were assessed accurately, though in studies on the residual effects of hypnotics (Borland & Nicholson, 1975) subjects were often unable to assess their impaired performance and their return to control activity. Such effects were observed with pentobarbitone sodium (200 mg) and particularly after nitrazepam (10 mg), but with flurazepam hydrochloride (30 mg) subjects were able to assess accurately their improvement in performance during the day and when they had returned to control performance. These observations suggest that the nature and duration of impairment may vary considerably between drugs.

Though different drugs may have different effects on performance the rate of excretion will influence the persistence of impairment as well as the duration of therapeutic activity. Diazepam has pronounced initial effects on performance, but with a half life of between two and three hours (de Silva, Koechlin & Bader, 1966) there is a rapid recovery of function. In the present experiments the curves of recovery of function for reaction time and adaptive tracking respectively intersected the zero axes at 6 h and 7.5 h after ingestion. With chlordiazepoxide hydrochloride (10 mg) the initial effect on performance is limited, but it tends to persist, and this may be related to a half life which varies between 6 and at least 15.5 h (Schwartz, Postma & Gaut, 1971). With this drug the curve of recovery for reaction time intersected the zero axis at 7.5 h after ingestion. In a previous study (Borland & Nicholson, 1975) a slow recovery in performance, greater than 19 h, was observed after

nitrazepam which has a long effective half life (Rieder, 1973). The short half life of diazepam with rapid recovery from impaired performance and the ability of subjects to assess their impaired performance accurately would suggest that diazepam may have a greater potential for use as an hypnotic than hitherto considered (Montagu, 1972).

The present experiments emphasize the complexity of impaired performance after ingestion of drugs. It is evident that drugs, even within a broadly similar group, may have very different effects on performance. No definite effects on performance were observed after the 1,5-benzodiazepine, clobazam, but obvious performance deficits were observed after diazepam and chlordiazepoxide hydrochloride. On the other hand with the overnight ingestion of the 1,4-benzodiazepines, nitrazepam and flurazepam hydrochloride, residual effects on performance persisted well into the next day (Borland & Nicholson, 1975). Within the benzodiazepines the nature and persistence of impaired performance and the ability to appreciate impaired performance vary considerably and need careful consideration. It would appear that therapeutic activity and deleterious effects on performance can be dissociated, at least to some extent.

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