Br. J. clin. Pharmac. (1979), **7**, 69S–76S

PSYCHOMOTOR CHANGES DURING INITIAL DAY OF BENZODIAZEPINE MEDICATION

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1 The detracting psychomotor effects of diazepam (5 mg three times daily) and clobazam (an investigational 1,5-benzodiazepine) were compared with placebo effects over the course of the initial day of medication. Tests were administered at hourly intervals and the data were analyzed from the standpoint of contrasts at each session and from the standpoint of trends that accrued during the course of the day.

2 It is concluded that among normal volunteers diazepam 5 mg three times daily may be near the threshold for detracting psychomotor consequences during the initial day and that clobazam seems to be without detracting consequences and may have some enhancing effects.

Introduction

As benzodiazepines and other minor tranquillizers find their principal use in the outpatient management of anxiety, the possible detracting effects of these medications on various psychomotor aspects of everyday behaviour are a matter of practical interest. In approaching this problem it is important to distinguish between the immediate effects during the initial day of medication and cumulative effects which accrue in the course of continuing treatment. It is believed that the greatest potential risk lies in the initial experience where the patient is unfamiliar with possible detracting effects of the medication. For this reason, specific knowledge of any initial psychomotor concomitants should be made known to out-patients, particularly those involved in the operation of machinery, appliances, or other equipment which could involve hazard to the patient or others. There are accounts, both public and private, of out-patients who have been involved in accidents possibly as a consequence of impaired function associated with psychotropic medication (Murray, 1960; 1962).

The present inquiry compares the psychomotor response to placebo medication with the response to two other medications, diazepam (a 1,4-benzodiazepine widely used as an anxiolytic) and clobazam, an investigational 1,5-benzodiazepine believed to have a high therapeutic index and a low incidence of side-effects (Hunt *et al.*, 1974). This investigation is one of a series based on the assumption that out-patients have a much greater exposure to accidents as a result of psychomotor impairment than in-patients and that the initial day of medication may be the most critical period. It is believed, moreover, that differences between normal volunteers and psychiatric out-patients tend to be more of degree than of kind and that normal volunteers are preferable subjects for these investigations because any impairment in consequence of medication would not be obscured by the confounding therapeutic gains expected in patients.

Methods

The sample comprised 90 male volunteers who were over 21 years of age and had been screened in order to eliminate individuals who were ill or otherwise unfit. The screening procedure included a psychiatric interview, a physical examination, and various blood and urine tests, including the SMA-12.

The paid volunteer subjects were required to appear at the laboratory at 08.00 without having had any food, alcohol, or stimulating beverage, such as coffee, tea, or Coca-Cola. They were required to remain in the laboratory through an 11-h sequence which involved ten 30-min testing sessions. These test sessions were separated by free intervals of about 25 min each.

The alternative medications were assigned on a predetermined double blind randomized basis with 30 subjects in each treatment group; double-blind conditions were maintained throughout the study. Each

subject was administered his medication in an indistinguishable capsule (clobazam 10 mg, diazepam 5 mg, or placebo) after the first, fourth, and seventh testing sessions. Thus by mid-afternoon the subjects had received a usual daily dosage (clobazam 30 mg or diazepam 15 mg).

The initial, premedication testing session occurred shortly after 08.00. This was followed by the first dosage unit of medication. A light breakfast was then offered. A lunch of sandwiches and milk or other non-stimulating beverage was offered after the second dosage unit. Light refreshments were available during the day which ended by 19.00.

The testing session was repeated at hourly intervals and included the following sequence: (1) A Digit Symbol Substitution Test, similar to that found in the Wechsler Adult Intelligence Scale. (2) The Numerical Ability test from the Differential Aptitude Test. Because of the burdensome testing schedule, the Numerical Ability test was given at only three of the hourly sessions, the first, fifth and tenth. (3) The number of spontaneous perceptual reversals reported as the subject looked at the Necker cube for 1 minute. (4) Balance beam procedure. The possible effect of medication on equilibrium was tested by a procedure at the first, fifth and tenth sessions in which the subject was required to walk the length of a 14-foot 2 inch × 4 inch beam and return. The wider surface of the beam rested on the floor, and the subject carried a light 4-foot stick across his shoulders. Mercury switches were placed at both ends of the stick so that any significant lateral deflection of the subject's normal upright posture was recorded electronically. In addition, a count was made of the number of times the subject stepped from the beam to the floor. (5) Time Estimation Test (Falk & Bindra, 1954; von Sturmer, 1966; Lehmann, 1967). In this test the subject provided his estimation of the duration of a 15-s interval. Each estimation was produced by depressing a button switch; no objective standard interval was available to the subject for comparison. Each session comprised a block of five independent estimations of a 15-s interval.

(6) Simple Vigilance (continuous performance). In this procedure the subject was presented with a random sequence of 600 letters. Each letter was illuminated for 0.1 s and successive letters were separated by an interval of 0.8 second. Thus, the test involved a total of 9 min, and the subject's task was to signal the appearance of the letter 'X' when it appeared. The various letter stimuli were presented automatically, and the subject's responses were also recorded automatically. On the basis of this recording, it was possible to determine the number of correct responses per session, the number of incorrect responses per session, and the latencies of both the correct and the incorrect responses.

(7) Complex Vigilance (continuous performance). This test, which was begun 30 s after the end of the previous test, involved the same situation as the simple vigilance test. The response requirements however, were different. The complex test required the subject to identify only those 'Xs' which were preceded by the letter 'A', and in addition to identify any letter 'C' that was preceded by an 'X'. Thus, in this complex task, the letter 'X' sometimes served as a target stimulus, sometimes as a signal identifying a target, and sometimes as neither. The conditional recognition of 'Xs' and 'Cs' in this complex test was scored according to the same programme followed for the Simple Vigilance test. The number of correct responses and the number of incorrect responses were determined, as well as their latencies.

Stimuli for the simple and complex vigilance tasks, as well as cues for the time estimation test, were presented to the subject by In-line projectors (Industrial Electronics Engineering) mounted in a black wooden box (11″ × 12″ × 12″) located on a table directly in front of the subject. The projectors were mounted at a 60° angle to the horizontal. A push-button switch centred before the box about 6 inches above the table surface was used for responses on all automated tasks. Stimulus presentation and response monitoring were controlled by a NOVA 2 mini-computer (Data General Corporation) interfaced through standard 28 V relays. Both paper tape and printed (teletype) copies of the data were generated at each test session.

Each of the various scoring alternatives was analyzed independently. The significance of inter-group contrasts at each testing session was provided by an analysis of variance of residual scores (that is,

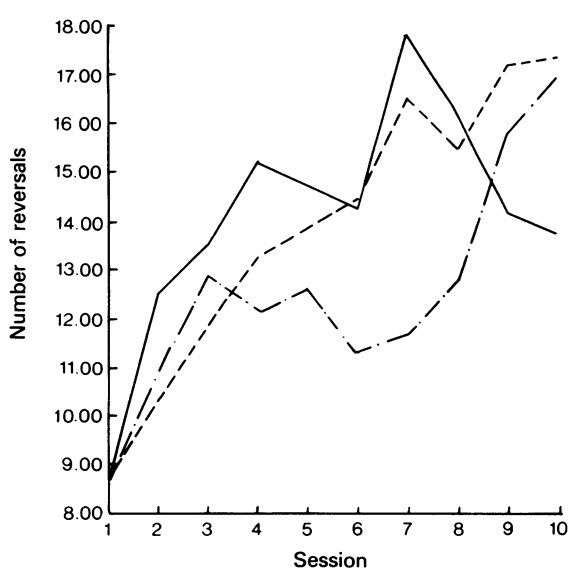

Figure 1 Necker cube (corrected for premedication differences). ——, Placebo; –·–·–·–, diazepam; – – –, clobazam.

scores that have been corrected for initial premedication differences on the basis of the regression of these scores on their respective premedication scores). The average of residual scores for the seventh to tenth sessions was similarly examined. In addition, for the cube reversal, the time estimation and for both the Simple and Complex Vigilance tests, the significance of intergroup differences in trend patterns throughout the course of the day, were examined on a linear, quadratic and cubic basis. The medication groups were compared in terms of the incidence of individuals whose response was atypical, for example, individuals whose performance involved virtually no errors or whose performance was so deficient as to imply a qualitative distinction. The incidence of individuals whose performance varied greatly from session to session was also of interest. Individuals with the most erratic performances and individuals with the least erratic performances were compared from the standpoint of the 'depression' and 'psychasthenia' scores from the Minnesota Multiphasic Personality Inventory (MMPI).

Results

Digit symbol substitution test (DSST)

The DSST was carried out each hour throughout the day, but performance on this test provided no significant distinction among the three medication groups. The average initial premedication total score for all groups combined was 38.8, and the final total score was 47.0. The increments in total score were large during the morning but diminished throughout the day, generating a typical learning curve.

Differential aptitude test (DAT) (numerical ability)

At the initial pretreatment administration of the DAT, the average score for the three treatment groups was 15. At midday, the score had risen to 18, and for the third and last administration the average score was 22. There were no significant differences among the average scores of the three treatment groups. Alternative scoring, such as number of items completed correctly, failed also to distinguish between the treatments at any time.

In addition, the subjects were asked to estimate the amount of time allowed for the DAT (the actual time allowed was 8 minutes). This estimation increased from a pretreatment mean of 8.9 min to a mean of 9.5 at midday and 9.7 at the end of the day. There were no significant differences among the groups for this estimation.

Necker cube

Spontaneous perceptual reversals reported by the subjects while gazing at the Necker cube for 1 min were counted for each of the ten hourly sessions comprising the daily sequence. The initial mean was 8.7 (all groups combined) and the final mean was 16. The general acquisition curve followed a quadratic function which distinguished significantly between the diazepam and clobazam groups ($P<0.02$). Although the pattern of acquisition was impaired for the diazepam group (Figure 1), this differential effect was not significant at any one session.

Balance beam procedure

Two scores were derived from the balance beam procedure: the number of times the subject stepped off the beam on to the laboratory floor and the number of seconds that the subject's posture was sufficiently inclined to register on the apparatus for showing lateral departures from vertical posture.

At the time of the initial premedication test, the subjects stepped off the beam an average of 1.8 times for all groups combined. At the time of the midday testing, however, the average frequency of stepping off the beam was increased somewhat for the placebo and diazepam groups, but reduced to 1.0 for the clobazam group; the differences among the groups were barely significant ($P<0.10$). At the third testing at the end of the day, there was a further reduction in the frequency with which the clobazam group stepped off the beam; the average was 0.8 (Figure 2). At this time, the distinction was significant ($P<0.05$).

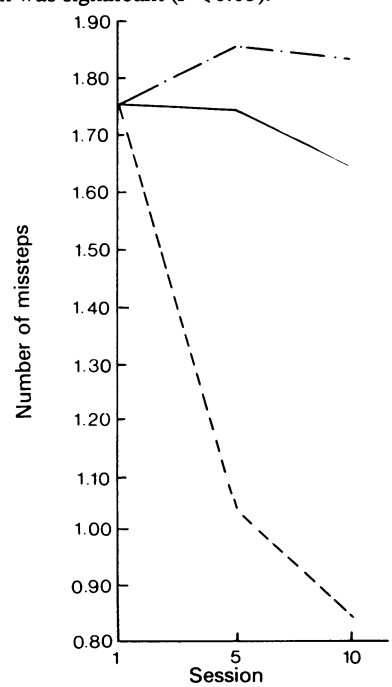

Figure 2 Number of missteps on balance beam (corrected for premedication differences). ——, Placebo; – · – · –, diazepam; – – –, clobazam.

For all groups combined, the average cumulative time the subject's body was laterally inclined was 8.1 s on the pretest and 8.3 s at the midday testing; there was little difference between the mean scores for the three groups. At the third testing the average for the total group remained at 8.3, but there was a slight increase in the time the clobazam subjects were inclined and a decrease in the time the diazepam subjects were inclined. These differences however, did not approach statistical significance. It is possible that the slight increase in the time the clobazam group was inclined was associated with their remaining on the beam with fewer steps to the floor than the other treatment groups.

Time Estimation Test

This test comprised a block of five separate productions of a 15-s interval. The data for each of these five estimations were analyzed independently, that is, for each of the ten sessions the three medications were compared for each of the five independent estimations. It has been found in other investigations that subjects tend to overestimate the duration of a temporal interval (Eson & Kafka, 1952; Falk & Bindra, 1954; Treisman, 1963). If they are asked to depress a button switch for a given period of time, the duration of the period produced by pressing the button tends to exceed the duration requested. This is most evident when (as in the present procedure) no objective standard is available. In a previous study Wittenborn *et al.* (1976) found that imipramine tends to suppress this overestimation.

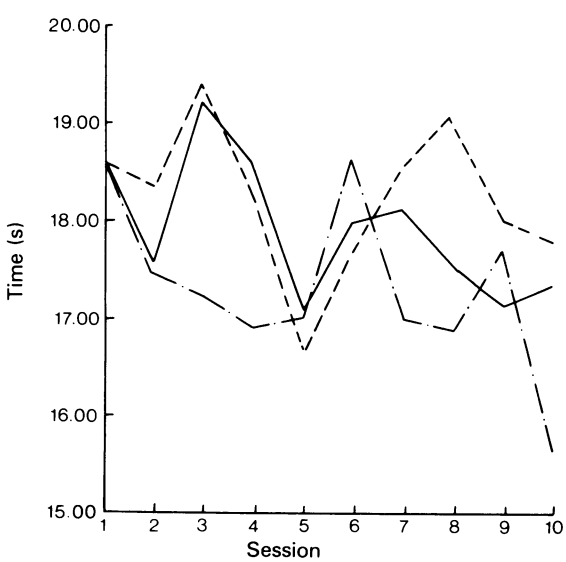

Figure 3 Estimation of 15-s interval (corrected for premedication differences). ——, Placebo; –.–.–, diazepam; – – –, clobazam. Estimation number 4 in block of 5. All premedication estimations below 4 s omitted.

Figure 3 summarizes the response pattern in the present data for the fourth estimation in the respective blocks of trials. The values in Figure 3 are residual scores which were corrected for differences in the initial premedication session. All three medication groups tended to overestimate the duration of the 15-s interval. The overestimation tended to be less for the diazepam group than for the placebo and clobazam groups. Nevertheless, the estimations did not provide a significant intergroup contrast.

Simple Vigilance (continuous performance)

The test yielded several scores. Two sets of analyses were carried out for each of these scores; one analysis included all individuals who generated a scorable response for a given session, and a second analysis excluded those individuals who may have failed to follow the directions, for example, those whose response was 3.5 or more standard deviations above or below the mean for that session. Regardless of the mode of analysis, however, none of these various scores provided a significant discrimination among the medication groups.

For each session the number of persons whose score deviated 3.5 or more standard deviations from the group was considered, but the incidence of this degree of deviance failed to indicate a significant or consistent drug difference.

Complex Vigilance (continuous performance)

Two sets of analyses were carried out for each of these scores; one analysis included all individuals who generated a scorable response for a given session, and a second analysis excluded those individuals who may have failed to follow the directions, for example, those whose response was 3.5 or more standard deviations above or below the mean for that session. The elimination of grossly deviant responses had no appreciable consequence.

Number of correct responses. The number of correct responses tended to increase for all three medication groups during the first 3 h, but there were no important increments thereafter.

In the afternoon there was a diminution in the number of correct responses for the diazepam group (figure 4). As a consequence the difference in linear trends between the diazepam and clobazam groups is significant ($P<0.05$).

The standard deviation of the latency of the correct responses, as well as the mean latency of correct responses, was examined, but no appreciable differences among the medication groups were apparent.

Number of incorrect responses. Two different ways of

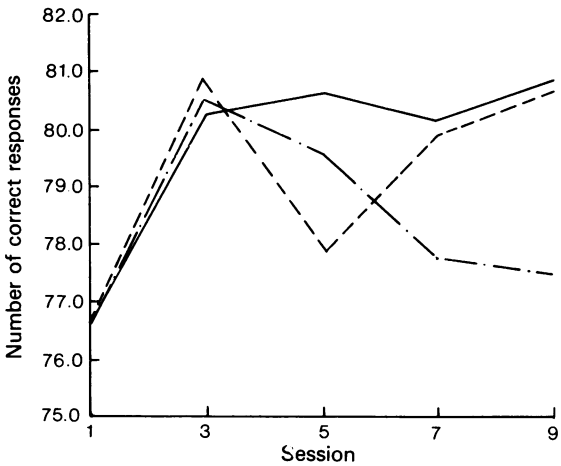

Figure 4 Number of correct responses to complex vigilance (continuous performance) (corrected for premedication differences). All values more than 3.5 s.d. from $\bar{X}$ omitted. —— Placebo; _.-.-._, diazepam; ---, clobazam.

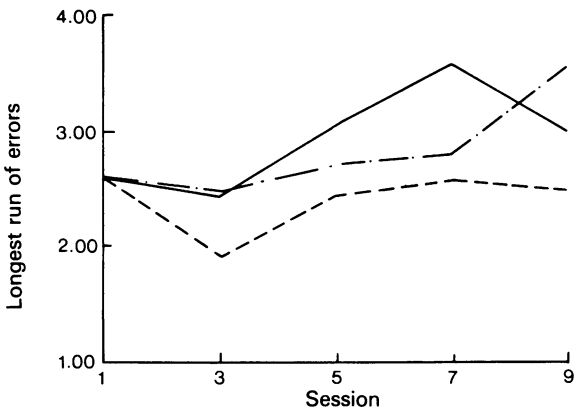

Figure 5 Longest run of errors to complex vigilance (continuous performance) (corrected for premedication differences). ——, Placebo; –.–.–, diazepam; ---, clobazam.

scoring the number of incorrect responses were applied on alternate sessions, but neither of these generated a significant contrast among the medication groups at any one session. When corrections for initial differences among the groups were made, the general trend showed the fewest incorrect responses to have been made by the clobazam group at all sessions except the tenth session, in which the differences among the groups were small. No one session generated a significant contrast, but the divergence in group trends approached significance ($P<0.11$).

The latency of incorrect responses was also examined. Although the clobazam group showed a somewhat shorter latency for their incorrect responses than the other groups, no significant differences were found.

Longest run of errors. When the longest run or sequence of incorrect responses was examined, it was found at all sessions that the length of error sequences was shorter for the clobazam group than for the other groups (Figure 5). These contrasts were highly significant at the fourth and ninth sessions. When the averages for trials 3–10 were compared, it was found that the average length of an error sequence was significantly shorter ($P<0.01$) in the clobazam group than in either the placebo or the diazepam group. Thus, persisting or continuing periods of impaired vigilance were much less characteristic of the clobazam subjects than of the other subjects. Quadratic trends also showed the significant contrast in favour of clobazam.

Erratic responses. Erratic responders may be identified in terms of intra-individual differences in number of correct responses during the nine successive sessions following the premedication session. For this purpose individuals whose number of correct responses varied from session to session by 15 or more were arbitrarily identified as erratic responders. Six subjects in the placebo group, 13 in the diazepam group, and 11 in the clobazam group met this criterion. On this basis diazepam was found to produce somewhat more erratic responders than placebo ($P<0.10$), but the difference between the other groups did not approach significance (χ^2). When the statistical significance of each individual's intersession variability was considered, it was found that both diazepam and clobazam produced significantly more subjects with intersession variability than did placebo.

It was thought that erratic responders might be characterized by their MMPI scores, particularly their 'psychasthenia' and 'depression' scores. An association between low manifest anxiety and disturbed functioning in response to diazepam has been noted in normal volunteers (Frostad *et al.*, 1966). In order to examine this possibility, the eight most erratic and the eight least erratic subjects were identified for each medication group. For each medication group the most and the least erratic subgroups were compared on the basis of their MMPI scores. No appreciable MMPI differences were noted in either the placebo group or the clobazam group. In the diazepam group, however, the most erratic subjects had low 'depression' scores ($\bar{X} = 16.8$). A comparable contrast was found for the 'psychasthenia' scores with the most erratic subjects having low scores on 'psychasthenia' (most erratic $\bar{X} = 8.1$ and least erratic $\bar{X} = 12.5$). These contrasts however, were not significant at the 5% level.

Conclusions

Before 1970, almost all of the literature describing the effect of diazepam on the psychomotor performance

of normal volunteers was based on studies of the effect of medication over several days or more and provided no indication of the psychomotor consequences during the first day of treatment.

Frostad *et al.* (1966) assigned 30 normal male volunteers to diazepam and 30 to placebo. The dosage was 10 mg the first day, 20 mg on both the second and third days and 10 mg before testing on the fourth day. Relative to the placebo group, the diazepam subjects were found to have developed significantly higher skin resistance and significantly lower performance on a written mathematics test. Lawton & Cahn (1963) used a crossover design with a sample of 20 normal male volunteers and compared diazepam 5 mg three times daily with placebo and with combinations of diazepam and alcohol over a 3-d period. In the diazepam trial, diazepam 5 mg was given also before criterion testing on the morning of the fourth day. Cancellation and peg board performances of the subjects receiving diazepam were significantly inferior to that of subjects receiving placebo. Hughes *et al.* (1965) used a crossover design to compare diazepam 6 mg with chlordiazepoxide 15 mg and placebo in a sample of 18 student volunteers. Subjects received medication 2 d before assessment. No detracting effects for either drug were reported, but the procedure did reveal significant detraction in consequence of alcohol.

Since 1970, there have been several reports describing psychomotor consequences during the initial day of diazepam medication. Linnoila & Mattila (1973) used 20 groups of 20 volunteers each in a comparative examination of the effects of diazepam 5 mg, diazepam 10 mg, no drug, placebo, and several other groups not relevant to the present interest. The testing equipment included a complex reaction time test and a complex coordination test having some features found in driving simulation test equipment. The results of this inquiry are remarkable in the sense that a 10 mg dose of diazepam resulted in improved performance; the diazepam subjects made significantly fewer errors than the control group, and their reaction time was shorter.

Jaattela *et al.* (1971) described the response of healthy volunteers to a single oral dose of diazepam 10 mg. Each group included 65 men and 25 women. Double-blind placebo controls were available for comparison, and assessments were made before medication and at 1 and 2 h after medication. Relative to placebo, the impairment in the DSST performance was significant for both men and women; number span was significant in men only. The most significant effects relative to placebo were found 1 h after medication.

Ghoneim *et al.* (1975) reported a comparison of dosage units of 10 and of 20 mg diazepam (injected) with placebo. Assessments were made before medication and at 2, 6 and 8 h later. Both of these single doses of diazepam were accompanied by a significant impairment relative to placebo in digit span, tapping, serial learning and delayed recall. Short-term memory and simple reaction time showed no drug effect. Choice reaction time showed an increased variability. For the most part, the results were apparent at the 2-h post-medication testing. Six hours after medication the psychomotor functions were completely restored except delayed recall following the high dosage medication. A secondary biphasic response due to the emergence of diazepam metabolites (Baird & Hailey, 1972) was not revealed by the later testing sessions.

Although Linnoila & Mattila (1973) have reported paradoxical improvements in various aspects of psychomotor performance after diazepam in 10 mg units, other studies have established the fact that 10 mg dosage units of diazepam, whether administered repeatedly over a period of several days or as a single unit on the day of assessment, can result in psychomotor impairments. Whether the usual dose of diazepam 5 mg three times daily adversely affects psychomotor performance on the initial day may not be inferred from the available literature. The present inquiry suggests, however, that diazepam 5 mg three times daily could impair perceptual fluidity as indicated by the Necker cube and perceptual accuracy in a complex continuous vigilance procedure. The present effect was cumulative, however, and became apparent after the administration of the second 5 mg unit when trend lines began to diverge sufficiently to generate the significantly differentiating patterns of response. Failure to find an indication of significant impairment after the initial morning 5 mg dosage unit of diazepam in the present study corresponds with the Linnoila & Mattila report (1973) which indicated no significant change after diazepam 5 mg and the Holgate report (1973) which indicated that diazepam 5 mg intravenously did not alter operant response rates.

There are only a few publications which describe the psychomotor effects of clobazam. Berry *et al.* (1974) briefly described a study involving six male volunteers. The results of medication in two conditions were assessed. The first was after a single dose where the alternatives were clobazam 10 mg alone, clobazam 10 mg plus alcohol, alcohol alone, placebo, and diazepam 10 mg (a high initial dose); this single-dose regimen was repeated at weekly intervals for a total of six testings per subject. At hourly intervals the subject was tested for braking reaction time (simulated driving), pursuit rotor, addition, and various subjectively reported aspects of mood. Clobazam did not increase braking reaction time when compared with placebo, but diazepam 10 mg did produce a significant increase at 1–3 h after ingestion. Clobazam in combination with alcohol also produced a significant change. The pursuit rotor proved more sensitive to clobazam with significant loss after clobazam alone, clobazam and alcohol, and after alcohol alone. Whether all these changes on the pursuit rotor were relative to placebo

was not indicated. Mental arithmetic was not affected, but there were mood changes in response to both drugs and alcohol with elevation of mood, relaxation, and a shortened perception of the passage of time.

In a second part of the inquiry, four subjects received clobazam 10 mg three times daily for 2 weeks and two subjects received diazepam 5 mg three times daily for the same period. Assessments were made before and continued after the final dosage on day 14. After a drug-free interval of 1 week, this 2-week sequence of medication and assessments was repeated. After this period of continuing treatment, there was a generally improved psychomotor performance, particularly with clobazam. There was also some diminution in the quality of mood ratings. Thus, the immediate detracting effect of diazepam observed in the first part of the study was not sustained in the continuing medication. As no placebo control was involved in the continuing medication trial, it is possible that the enhanced psychomotor performance was in part an unidentified practice effect.

Borland & Nicholson (1974) described a comparative study involving clobazam, diazepam and chlordiazepoxide. Five normal male subjects were involved in 2-d regimen of testing and medication. This regimen was repeated on four different occasions, each separated by 4 weeks. The first day of the 2-d regimen examined the subject's performance on a pursuit rotor, a subjective assessment of his pursuit rotor performance, and a choice reaction time test. These tests were repeated at four different intervals during the day. On the second day of the 2-d regimen, the testing was preceded by medication in the form of chlordiazepoxide 20 mg, clobazam 20 mg, diazepam 10 mg, or placebo. The medication was administered to each subject on each of the four occasions in a random order and the procedures were carried out using double-blind conventions. Neither clobazam nor chlordiazepoxide generated a significant difference from the placebo control. With diazepam, there was an immediate significant decrement in pursuit rotor and diazepam subjects could correctly identify their deteriorated performance on the pursuit rotor. This loss was recovered by the end of the day in a manner which suggests either a disappearance of diazepam effects or a learning effect which counterbalanced the medication effect. The writers suggest that the clobazam group may have experienced a slight improvement in pursuit rotor, but the contrasts were not statistically significant. Thus, the Borland & Nicholson study (1976), like the second part of the Berry *et al.* study (1974), shows no consistent detraction in response to clobazam; and they suggest that clobazam could have an enhancing effect.

Despite differences in research design and specific criteria used, the results of the present investigation are in reasonable correspondence with the relevant reports of controlled studies by other investigators.

It seems that psychomotor detraction accompanying initial diazepam medication is dose-related. The effect of an initial dose of 10 mg has been detected (Jaattela *et al.*, 1971; Ghoneim *et al.*, 1975) 1 or 2 h after administration, but no certain effect of an initial dose of 5 mg was shown. The effect of diazepam 5 mg repeated at intervals of approximately 3 h in the present procedure seemed to be cumulative through the course of the initial day and was reflected in significant divergences in trend lines. Diazepam has been described as disappearing from the circulation about 1.5 h after administration and re-appearing as metabolites about 6 h after administration (Baird & Hailey, 1972). This biphasic pattern would suggest for the present inquiry that the primary effect of the third 5 mg unit administered in the early afternoon and the secondary effect of the inital 5 mg unit administered between 08.00 and 09.00 could have been cumulative and thereby account for the emergence of group contrasts later in the day (see Figures 3 and 4).

Clobazam, in contrast to diazepam, may have an enhancing effect on certain aspects of psychomotor function. In the present procedure, clobazam was associated with relatively few missteps using the balance beam procedure and relatively short sequences of errors in a procedure calling for continuous vigilance. Whether the effect is indicative of a heightened vigilance or of an increased motivational level is a subject for further inquiry, but these enhancing effects correspond with the possible improvement suggested in the reports of Berry *et al.* (1974) and of Borland & Nicholson (1974).

In conclusion, it is suggested that 5 mg three times daily may be near the threshold for psychomotor detraction during the initial day of diazepam medication and that clobazam 10 mg three times daily has no appreciable detracting, and may have some enhancing effects.

The research reported here was supported by Hoechst-Roussel Pharmaceuticals, Inc., Somerville, New Jersey, and is a part of the continuing programme of the Rutgers Interdisciplinary Research Center.

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Discussion

DR P. NICHOLSON (Frankfurt) asked what were the effects of fluctuations in the severity of anxiety on psychomotor performance tests, in the absence of drug therapy.

DR M. LADER (London) in reply described the results of some longitudinal studies in anxious patients in whom the severity of their anxiety was mirrored by impairment in psychomotor tests. It was also known that anxious patients may show an impairment of up to 20% in IQ tests.

PROFESSOR J. R. WITTENBORN (New Jersey) added a comment that the relationship between affective level and drug level, particularly psychomotor effects, is far from clear. A number of studies have shown that, when you consider people who are initially high and low in anxiety, the subjects who are high in anxiety usually change in a more favourable direction than those who are relatively low in anxiety. It is necessary to point out that such changes as these can, to some degree at least, be statistical artifacts, for example, the regression of extremes toward the mean that always occurs with the subsequent application of the same or highly correlated measures.

Despite this statistical quality of fallible data, Frostad *et al.* (1966) have observed that in response to diazepam patients with initially low manifest anxiety were patients who really had more disturbed functioning than those who had a high anxiety. In Professor Wittenborn's own study there was an association in the diazepam group between intraserially erratic responses and a low score on the psychasthenia portion of the MMPI and a low score on the depression portion of the MMPI. This would seem contradictory in its implications to what has been found in comparative studies of individuals with high or low extreme levels of anxiety.

Professor Wittenborn felt that this whole relationship between drug effects, mood changes and other variables is worth exploring because if, as indicated here, clobazam does modify the mood, then the mood effect itself might very well potentiate or suppress the psychomotor consequences.