THE EFFECT OF CLOBAZAM AND LORAZEPAM ON THE PSYCHOMOTOR PERFORMANCE OF ANXIOUS PATIENTS

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1 Psychomotor performance and anxiety were measured in 70 anxious outpatients in a randomized double-blind, placebo-controlled trial comparing the 1,5-benzodiazepine clobazam (10 mg twice a day) to lorazepam (1 mg twice a day). Carefully selected tests were administered pre-treatment and at 2 and 9 days after treatment. Compliance was checked by blood assays.

2 All three treatment groups (clobazam, lorazepam and placebo) showed a significant improvement in anxiety over the course of the trial. There were no significant differences between the groups in terms of anxiety reduction.

3 All three groups improved over the course of the trial in choice reaction time, digit symbol substitution test, Purdue pegboard test (both hands) and in the Inglis paired-associate learning test: there were no significant differences between the groups with regard to these tests. There was no change in critical flicker fusion threshold over the trial period in any of the three groups.

4 The placebo and clobazam groups showed a significant improvement in two of the Purdue pegboard tests (preferred hand and assembly) from pre-treatment to 2 days but no further improvement at 9 days. The lorazepam group, however, showed no improvement in these two tests from pre-treatment to 2 days; a significant improvement only emerged between the 2-day and 9-day assessments. This might reflect an initial, transient sedation in the lorazepam-treated patients.

5 Generally, we failed to demonstrate any consistent impairment in psychomotor performance with either clobazam or lorazepam in our anxious patients. These findings contrast with those obtained after administration of 1,4-benzodiazepines (e.g., lorazepam) to normal volunteers and they suggest that data from the latter cannot necessarily be extrapolated to anxious patients.

Key words clobazam lorazepam psychomotor performance anxious patients

Introduction

The benzodiazepines are among the most widely prescribed group of medicines. One of their major problems is sedation and particularly impairment of psychomotor performance. The 1,4-benzodiazepines (e.g., diazepam and lorazepam) have been consistently found to impair performance on various tasks in normal volunteers (Hindmarch, 1980). However, an analysis of the review of patient studies by Wittels & Stonier (1981) revealed that the benzodiazepine-induced psychomotor impairment occurred less frequently in patients than in volunteers.

Clobazam, a 1,5-benzodiazepine, has caused less psychomotor impairment than the 1,4-benzodiazepines in volunteers (Hindmarch & Gudgeon, 1980). This trend also emerged in patients (Doongaji *et al.*, 1979; Salkind *et al.*, 1979; Hill *et al.*, 1981) although these latter studies can be criticized for using only a limited range of psychomotor measures.

We have investigated the effects of clobazam, lorazepam and placebo on the psychomotor performance of anxious outpatients by using a randomized double-blind design. The performance variables were

selected on the basis of their sensitivity in detecting 1,4-benzodiazepine-placebo differences (Hindmarch, 1980; Wittenborn, 1980) and so that the total battery assessed the various components of psychomotor performance.

Methods

Patients

The patients were general outpatients attending the Retreat Day Hospital, Cape Town who were judged by the attending general practitioner to require a minor tranquillizer for anxiety. Patients were excluded on the following criteria:

- i. age under 18 or over 65 years;
- ii. treatment with psychotropic agents in the previous 3 weeks;
- iii. alcoholic problems.

Informed consent was obtained from all patients and the trial was approved by the Ethical Review Com-

mittee of the University of Cape Town Medical Faculty.

Treatment conditions

The trial patients were allocated according to a randomized block design, double-blind code to one of the following three groups:

- i. placebo 1 capsule twice a day.
- ii. clobazam 1 capsule (10 mg) twice a day.
- iii. lorazepam 1 capsule (1 mg) twice a day.

Patients were continued on this regimen for 9 days. Psychological assessments were undertaken before treatment commenced, after 2 days and after 9 days. Patients were always tested at the same time of day and they were instructed to abstain from alcohol and from cigarettes for 24 h prior to the assessments. One hundred and twenty patients were started on the trial medication.

Tests

The following tests were applied:

- (a) Hamilton anxiety scale (HAS) (Hamilton, 1959)
- (b) Digit symbol substitution test (DSST) (Matarazzo, 1972)
- (c) Purdue pegboard tests (PPT) using preferred hand, both hands and assembly tasks (Tiffin, 1968)
- (d) Choice reaction time (CRT) (Hindmarch, 1979)
- (e) Critical flicker fusion threshold (CFFT) (Hindmarch, 1979)
- (f) Inglis paired-associate learning test (IPALT) (Inglis, 1959).

Assay

In order to check on compliance, 5 ml of blood was drawn from all patients at the Day 9 visit and assayed for clobazam and lorazepam by means of electron capture gas chromatography as adapted from the methods of Peat & Kopjak (1979).

Results were analyzed by a two-way analysis of variance (Anova) with repeated measures on factor B, i.e., time of assessment.

Results

Patients

Table 1 gives details of patient numbers in each group and ages. There was a 39.2% drop-out rate (i.e., patients who did not complete the trial): chi-square analysis revealed no differences between this rate in the three treatment groups. Three patients were excluded from the trial on account of aberrant drug assay results.

Drug levels

The clobazam group had a median clobazam concentration of 460 ng/ml (range 114–1000) and the lorazepam group a median lorazepam concentration of 20 ng/ml (range 9.0–35.8). The placebo group had zero concentrations of benzodiazepines.

Anxiety

The anxiety scores are shown in Table 2. The two-way Anova revealed a significant difference between the three treatment groups at the pretreatment assessment: the placebo patients had significantly lower scores than both the clobazam ($P < 0.05$) and the lorazepam ($P < 0.01$) groups.

Therefore, all the anxiety data were reanalyzed using a two-way analysis of covariance with repeated measures on factor B. This disclosed that the three treatment groups improved significantly over time. There were no significant differences between the placebo, clobazam and lorazepam groups in terms of anxiety reduction at either 2 days or 9 days.

Table 1 Number of patients and age distribution

	Placebo	Clobazam	Lorazepam
Initial number of patients	40	40	40
Number of patients who completed treatment	21	29	23
Number of patients where blood assays indicated non-compliance	1*	2**	0
Number of patients finally analyzed in trial	20	27	23
Median age	35	38	32
Range	(18–63)	(18–51)	(20–57)

* Blood assay in this patient revealed benzodiazepines.

** Blood assays in these patients revealed benzodiazepines other than clobazam.

Table 2 Hamilton anxiety scale scores (mean $\pm$ s.d.)

	Pre-treatment	After 2 days	After 9 days
Placebo	20.7 ($\pm$ 3.9)	14.3 ($\pm$ 3.8)	13.2 ($\pm$ 4.4)
Clobazam	22.7* ($\pm$ 4.7)	15.1 ($\pm$ 4.8)	12.1 ($\pm$ 5.0)
Lorazepam	23.9** ($\pm$ 4.3)	14.8 ($\pm$ 3.5)	11.4 ($\pm$ 3.0)

* $P < 0.05$ clobazam vs placebo** $P < 0.01$ lorazepam vs placebo

Psychomotor performance

Table 3 shows that for the DSST, PPT (both hands), CRT and IPALT there was no interaction effect on the two-way Anova but there were significant B main effects (changes over time), i.e., improvement occurred in all three treatment groups during the course of the trial.

There was no significant change in the CFFT over the trial period in any of the three groups.

Table 4 shows that different trends were found in two of the Purdue pegboard tests (preferred hand and assembly). The two-way Anova revealed an interaction (AB) effect in these two tests and therefore the simple main effects were analyzed. In both these pegboard tests the three B simple main effects (changes over time for a specific treatment group) were significant. Subsequent Tukey *t*-test analysis demonstrated that the clobazam and placebo groups showed a significant improvement from pre-treatment to 2 days but no change from 2 days to 9 days. In the lorazepam group, however, there was no change from pre-treatment to 2 days but a significant improvement from the 2-day to 9-day assessments. The only significant A simple main effect (difference between treatment groups at a specific time) emerged in the pegboard assembly test at the 2-day assessment when the lorazepam was significantly lower ($P < 0.01$) than both the placebo and the clobazam groups (Table 4).

Discussion

The drop-out rate of 39.2% in our trial compares favourably with that found in other studies, where default is reported in between 25% and 50% of out-patients (Blackwell, 1976). Of the 73 patients who completed the trial, three were deemed non-compliant owing to irregular blood assays and were excluded from the trial.

From the standpoint of efficacy, there were no significant differences between the clobazam, lorazepam and placebo groups: all of these showed a significant reduction in anxiety over the course of the trial. This was not surprising as substantial placebo effects are generally observed with anxious patients. Bellantuono *et al.* (1980) reported that, out of a total of 85 studies which assessed the anxiolytic efficacy of the benzodiazepines, 44 showed the drug to be much better and 26 showed it to be slightly better than placebo. In 14 studies there was no difference between drug and placebo, and one trial found the drug to be worse than placebo.

Except for the CFFT, which showed no change during the course of the trial in any of the groups, there was an overall trend for performance to improve on all the other tests over time in the clobazam, lorazepam and placebo groups. This can probably be attributed both to a lowering of anxiety and to practice effects.

There was thus no evidence of impaired psycho-

Table 3 Changes in scores over time (B main effects)

Test	Pre-treatment (B1 mean)*	P (B1 vs B2)	After 2 days (B2 mean)*	P (B2 vs B3)	After 9 days (B3 mean)*	P (B1 vs B3)
DSST	23.5	< 0.01	28.8	< 0.01	31.1	< 0.01
PPT (both hands)	9.9	NS	10.2	< 0.05	10.6	< 0.01
CRT	0.67	< 0.01	0.65	< 0.01	0.62	< 0.01
IPALT	12.4	< 0.01	9.1	NS	8.9	< 0.01

* This represents the mean for the clobazam, lorazepam and placebo groups combined. This was done as the analysis of variance had revealed no interaction effect.

Table 4 Purdue pegboard test scores (preferred hand, assembly) (mean $\pm$ s.d.)

	Pre-treatment (B1)	P (B1 vs B2)	After 2 days (B2)	P (B2 vs B3)	After 9 days (B3)	P (B1 vs B3)
<i>Preferred hand</i>						
Placebo (A1)	13.1 ($\pm$ 1.8)	< 0.01	14.6 ($\pm$ 1.7)	NS	15.1 ($\pm$ 1.9)	< 0.01
Clobazam (A2)	13.3 ($\pm$ 1.9)	< 0.01	14.2 ($\pm$ 1.8)	NS	14.1 ($\pm$ 1.8)	< 0.05
Lorazepam (A3)	13.5 ($\pm$ 2.0)	NS	13.6 ($\pm$ 1.7)	< 0.01	14.6 ($\pm$ 1.6)	< 0.01
<i>Assembly</i>						
Placebo (A1)	43.6 ($\pm$ 8.0)	< 0.05	47.1 ($\pm$ 8.9)	NS	48.3 ($\pm$ 6.8)	< 0.01
Clobazam (A2)	42.2 ($\pm$ 7.9)	< 0.01	46.5 ($\pm$ 6.2)	NS	46.0 ($\pm$ 7.8)	< 0.01
Lorazepam (A3)	40.7 ($\pm$ 7.4)	NS	41.4* ($\pm$ 8.0)	< 0.01	46.0 ($\pm$ 9.4)	< 0.01

* $P < 0.01$ A1 vs A3, $P < 0.01$ A2 vs A3

motor performance due to clobazam in either 2 days or 9 days. With lorazepam, however, there was evidence of impaired performance (i.e., impairment relative to placebo) in two pegboard tests at the 2-day assessment only. This impairment possibly reflected an initial sedation in the lorazepam group which had disappeared by 9 days. This is interesting because the volunteer studies of lorazepam assessed performance after 1–3 days (Wittenborn, 1980), and it was during this period that impairment was found. Our findings strongly suggest the need for assessments at later as well as early stages.

Our selection of psychomotor tests was based on reviews of volunteer studies with 1,4-benzodiazepines (Hindmarch, 1980; Wittenborn, 1980). We chose only those tests which these reviews had identified as being the most sensitive in detecting psychomotor impairment with 1,4-benzodiazepines (including lorazepam) relative to placebo. The lorazepam-

treated volunteers had generally shown impairment in all of the tests we selected; yet, in our lorazepam group, we observed impairment in the pegboard test only. This discrepancy is important clinically because it highlights the differential effect of benzodiazepines on volunteers and anxious patients. One of the major reasons is that anxiety itself may adversely affect psychomotor functions in patients and that the reduction of anxiety *per se* may enhance performance. Data based on volunteer studies, therefore, cannot necessarily be extrapolated to the clinical situation.

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