EVALUATION OF THE EFFECTS OF CLOBAZAM, A 1,5 BENZODIAZEPINE, ON MOOD AND PSYCHOMOTOR PERFORMANCE IN CLINICALLY ANXIOUS PATIENTS IN GENERAL PRACTICE

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1 The methodology of clinical trials of anxiolytic drugs carried out in general practice conditions is discussed. Particular problems include: the selection of suitable patients; placebo effects; the influence of non-specific variables such as life-events; and patient compliance.

2 Clobazam, a novel 1,5 benzodiazepine, and diazepam were compared with placebo in a double-blind group comparative trial in general practice, which was designed to avoid as many confounding variables as possible. Anxiety-reducing effects were evaluated and at the same time the effects of the drugs on psychomotor performance were examined.

3 Both clobazam and diazepam produced significant improvements in anxiety ratings on the Hamilton Anxiety Scale and the Morbid Anxiety Inventory, whereas placebo did not.

4 The placebo group demonstrated a significant improvement in performance on a pursuit rotor and digit symbol substitution test (DSST), whereas the diazepam group's performance did not change. The clobazam group showed improvement in both tests, significantly so in the DSST. This suggests that diazepam produces impairment in performance, which had negated the practice effect seen in the placebo group, whereas clobazam did not seem to produce similar impairment.

Introduction

DURING the past decade anxiolytic/sedative drugs of the benzodiazepine group have been prescribed in ever-increasing quantities, both in hospitals and in general practice (Silverstone & Turner, 1978).

As it is in general practice that such drugs are most widely used, it is obviously desirable to examine their efficacy under general practice conditions. However, clinical assessment of benzodiazepines in a general practice setting presents special difficulties, as a host of non-specific events can occur which influence the patient's emotional state and thus obscure differences between active drugs, and between active drug and placebo. When such non-specific variables are not considered, and when no placebo group is used, it is frequently reported that there is no difference between the reference drug, usually diazepam, and the new drug under test. The unwarranted conclusion is then all too frequently drawn that, as no difference was found between the two drugs, the new drug must be an effective anxiety-reducing agent. This ignores the probability that much of the improvement observed

may well have been due to the non-specific events or to a placebo response.

The appearance of a novel benzodiazepine, clobazam, provided an opportunity to set up a trial in general practice which attempted to minimize the influence of non-drug variables.

Clobazam is a new 1,5-benzodiazepine which differs structurally from currently available 1,4-benzodiazepines; the numbering referring to the position of the nitrogen atom in the heterocyclic ring. Although the animal pharmacological profile of clobazam is generally similar to that of the other benzodiazepines (Barzaghi *et al.*, 1973), there are some differences in that clobazam has a relatively greater 'anxiolytic' effect when compared with its action on motor function. In man, clobazam exhibits effective anti-anxiety activity (Hunt *et al.*, 1974; Coste-Simonin & Krantz, 1975; Cottin *et al.*, 1975; Martin, 1975; Koeppen, 1979) without significant deleterious effects on psychomotor performance (Berry *et al.*, 1974; Borland & Nicholson, 1974; Hindmarch, 1979).

The present study was designed to evaluate, in

general practice conditions, the efficacy of clobazam as an anxiety-reducing agent in clinically anxious patients, and at the same time to monitor the effects of the drug on psychomotor function in these patients.

Methods

Patients who presented to their general practitioner with symptoms suggesting primary anxiety were admitted to the study, with the exception of those patients whose anxiety was short-lived and who were likely to experience a spontaneous remission during the course of the trial. Also excluded were patients known to be chronic sufferers from neurotic anxiety states who were presumed unlikely to respond in any degree to a psychoactive drug (Salkind, 1972).

Patients fulfilling the diagnostic criteria were admitted to the study if they scored 14 or more on the Morbid Anxiety Inventory (MAI) (Salkind, 1973). The MAI is a self-rating questionnaire in which scores of 14 and above have been shown to correlate highly with the clinical diagnosis of morbid anxiety.

The patients were of either sex, aged 15–65 yr. Pregnant patients were excluded, as were patients with renal or hepatic disease, known alcoholics, patients with psychotic illness or any patients already receiving any CNS-active drugs.

The patients were seen every two weeks, when their clinical state was assessed by means of the MAI, the Hamilton Anxiety Scale (HAS) (Hamilton, 1959), and a clinical global rating. Following the initial visit, data were collected on the number of capsules that had been taken and an open-ended question concerning adverse effects was asked. In addition any significant life events which may have occurred were enquired about.

The design of the trial was somewhat unusual; the study plan is shown in Table 1.

clinical experience with clobazam has established a dose relationship to diazepam of 2:1, that is, clobazam 10 mg is equivalent to diazepam 5 mg. Patients started on a dose of three capsules a day but were allowed to take up to a maximum of six capsules a day, that is clobazam 60 mg or diazepam 30 mg. Patients were dispensed 84 capsules to last the 14 d between visits (visits 2–3) and capsules not taken were returned by the patients and counted.

All patients were finally re-assessed after a further 2 weeks without drugs.

Psychomotor function

At visits 2 and 3, that is, before and after the active treatment period, psychomotor performance was assessed using a pursuit rotor which involves tracing a moving light spot on a screen with a light-sensitive probe. The total length of time 'on-target' during six timed intervals is used as the test criterion. A digit symbol substitution test (DSST) derived from the Wechsler Adult Intelligence Scale (Wechsler, 1955) was also given. In this test ten symbols are taken to represent ten numbers (0–9). The numbers are randomly tabulated and repeated in different sequences many times. The patient has to match as many symbols to the numbers as he can over a timed period (4 minutes).

Results

Sixty-six patients entered the study; of these, 59 qualified for entry to the double-blind phase, whereas seven patients showed a remission of their anxiety during the 2 weeks' non-specific treatment period. Four patients were subsequently withdrawn from the analysis. Of these, three (two in the clobazam group and one in the diazepam group) did not return after

Table 1 Study plan

<i>Treatment group</i>	<i>1 (14d)</i>	<i>2 (14 d)</i>	<i>3 (14 d)</i>	<i>4</i>
Clobazam	Vitamin C	Clobazam	No treatment	
Diazepam	Vitamin C	Diazepam	No treatment	
Placebo	Vitamin C	Placebo	No treatment	

All patients were initially given non-specific drug treatment (ascorbic acid 25 mg three times daily) in order to eliminate any concurrent drug therapy effects, and to identify placebo responders. After 2 weeks patients were re-assessed and those who still scored 14 or more on the MAI, that is, only those with continuing anxiety, were admitted to the double-blind, comparative part of the trial. Patients entering the double-blind phase of the study were randomly allocated to treatment with either clobazam (10-mg capsules), diazepam (5-mg capsules) or placebo. Extensive

visit 2, for reasons which are not known. The fourth patient (in the diazepam group) was informed at hospital, during the active treatment phase, that he had had a myocardial infarction. His anxiety increased dramatically.

The age and sex distribution of the remaining 55 patients is shown in Table 2. Tables 3 and 4 show the distribution by diagnosis and the duration of patients' anxiety. Overall the groups can be seen to be broadly comparable. There are some differences in age and sex distribution between the groups but these are not

Table 2 Age and sex distribution (age range 17–62 years)

		Male	Female
Placebo	Mean age	28 ± 5.4	40.2 ± 15.7
	<i>n</i>	4	16
Clobazam	Mean age	44 ± 18.3	36.8 ± 13.2
	<i>n</i>	4	13
Diazepam	Mean age	37.9 ± 12.5	30 ± 5.4
	<i>n</i>	9	9

Table 3 Distribution by diagnosis

	Placebo	Clobazam	Diazepam
Acute anxiety	10	10	12
Chronic anxiety	5	3	4
Mixed anxiety/ depression	4	2	1
Phobic anxiety	0	1	1
Other	1	1	0
	20	17	18

Table 4 Duration of patients' anxiety (weeks)

	Clobazam (<i>n</i> = 14)	Diazepam (<i>n</i> = 8)	Placebo (<i>n</i> = 14)
Median	8	11	9
Range	6–70	6–52	4–52

significant.

Table 5 shows the mean total number of capsules taken over the treatment period for each treatment group, and from this has been calculated the mean

Table 5 Capsule count and dosage

	Total no. of capsules taken	Average no. of capsules taken per day	Average daily dose (mg)
Placebo	50 ± 21	3.9 ± 1.5	0
Clobazam	45 ± 22	3.5 ± 1.7	35
Diazepam	50 ± 20	3.4 ± 1.3	17

Table 6 Mean (± s.d.) MAI scores

	Visit				Significance of change between visit 2 and 3
	1	2	3	4	
Placebo (<i>n</i> = 20)	28.2 ± 6.9	23.7 ± 7.4	22.1 ± 9.1	18.5 ± 6.7	NS
Clobazam (<i>n</i> = 17)	29.7 ± 7.7	28.7 ± 8.6	25.5 ± 9.8	22.5 ± 7.5	<i>P</i> < 0.002
Diazepam (<i>n</i> = 18)	26.1 ± 7.5	26.1 ± 9.2	21.5 ± 11.1	23.7 ± 7.8	<i>P</i> < 0.03

average daily dose of clobazam and diazepam. As can be seen, patients stayed more or less at the starting dosage level.

The evaluation of anxiety reduction was based on the MAI and HAS assessments at visit 2 (baseline) and visit 3 (after 2 weeks' active treatment). Mean scores on the MAI are shown in Table 6.

There was a significant reduction in scores between visits 2 and 3 in both the clobazam and diazepam groups but not in the placebo group. However, there was no significant difference between the three treatment groups at visit 3.

The results from the HAS were similar and are shown in Table 7 and Figure 1. Again there was a significant reduction in scores for clobazam and diazepam but not for placebo, but no significant difference between groups.

After stopping the medication at visit 3, patients who had been receiving active drugs tended to show a rebound worsening in anxiety according to the HAS (Table 7, Figure 1), whereas patients who had been taking placebo showed no such rebound effect.

Figure 1 HAS scores. ■, Clobazam; ●, diazepam, ▲, placebo.

Table 7 Mean ($\pm$ s.d.) HAS scores

	Visit				Significance of change between visit 2 and 3
	1	2	3	4	
Placebo ($n = 20$)	21.7 $\pm$ 4.2	15.6 $\pm$ 6.5	14.3 $\pm$ 7.7	14.0 $\pm$ 5.1	NS
Clobazam ($n = 17$)	24.4 $\pm$ 6.8	20.4 $\pm$ 8.2	14.7 $\pm$ 9.5	17.0 $\pm$ 7.0	$P < 0.02$
Diazepam ($n = 18$)	21.9 $\pm$ 6.3	18.4 $\pm$ 6.6	14.1 $\pm$ 9.4	18.1 $\pm$ 6.7	$P < 0.05$

The results of the performance tests are shown in Tables 8 and 9. In the DSST the number of correct substitutions has been used as the test criterion and the mean scores for the three groups are shown. There was a general increase in scores due to the practice effect of repeating the test after a short interval. However, there was a difference between the groups in that the clobazam and placebo groups showed a

highly significant improvement in scores, whereas the diazepam group demonstrated little change. With the pursuit rotor there was an improvement in scores in both the placebo and clobazam groups but not in the diazepam group, though here only the changes in the placebo group achieved significance (Table 9).

Adverse effects

Patients were asked a general question about the occurrence of adverse reactions. There were few positive replies and the only side-effect of any note was drowsiness which occurred in the placebo group as well as the active drug groups. There was no significant difference between the groups. Two patients (one in the clobazam group and one in the placebo group) stopped taking the capsules because of drowsiness.

Table 8 Mean ($\pm$ s.d.) DSST scores

	Before treatment	After treatment	
Placebo ($n = 20$)	124 $\pm$ 34	154 $\pm$ 29	$P < 0.001$
Clobazam ($n = 16$)	99 $\pm$ 35	125 $\pm$ 38	$P < 0.005$
Diazepam ($n = 18$)	113 $\pm$ 43	117 $\pm$ 42	NS

Table 9 Mean ($\pm$ s.d.) Pursuit rotor times (secs)

	Before treatment	After treatment	
Placebo ($n = 20$)	35.5 $\pm$ 18.4	45.5 $\pm$ 22.4	$P < 0.02$
Clobazam ($n = 16$)	31.5 $\pm$ 19.7	34.6 $\pm$ 21.7	NS
Diazepam ($n = 16$)	34.3 $\pm$ 25.5	33.7 $\pm$ 20.9	NS

Life-events

The occurrence of important life events, their nature and whether they were 'positive' or 'negative' were recorded. There was little difference between the three groups; during the active treatment phase there was a tendency for the clobazam group to be more adversely affected than the other groups.

Discussion

Placebo effects

A major objective of this study was to attempt, by using a novel methodological approach, to exclude as many confounding variables as possible in order to derive an objective evaluation of clobazam as an anxiolytic agent. The initial 2-week period without specific anxiety-reducing drugs was designed to exclude, as far as possible, placebo responders or patients who were going to remit spontaneously. Seven patients who fell into this category and whose MAI score had fallen below 14 were excluded at visit 2.

Scrutiny of the results reveals that the group of patients eventually allotted to placebo had had a considerable reduction in scores from visit 1 to visit 2 on both the MAI and the HAS. Although illustrating very clearly the value of the initial 'no-treatment' phase,

this has unfortunately influenced the results during the period of active treatment. The baseline for the drug comparison was visit 2 but, because the placebo group by chance had shown the most pronounced 'placebo effect', the scores on the MAI and HAS for this group at visit 2 are lower than for both the clobazam and diazepam groups.

Both active drug groups subsequently showed a significant reduction in mean scores between visits 2 and 3, but the placebo group did not.

Selection of patients

In a study of this sort it is reasonable to test a drug on a selected group of patients likely to exhibit sensitivity to drug effects, since one of the objectives of a trial is to assess the effectiveness of the particular drug. It has been postulated that patients presenting with anxiety in general practice may be divided into three

groups (Salkind, 1972): those with basal MAI levels of below 14 whose anxiety will spontaneously remit within 4–6 weeks, and who are previously well adjusted; those with basal levels of about 30 (the chronic anxiety patients), who are unlikely to respond in any significant degree to active treatment; and an intermediate group who are likely to be the ones most sensitive to drug effects. It was this last group that we attempted to select for this study.

Elimination of defaulters

Unease about not following instructions to maintain a fixed dosage regimen is a common reason for patients defaulting. Only 3 out of 59 patients in the present study defaulted; this low rate may be ascribed to the special relationships existing in general practice, and also to the flexible dosage scheme. An additional benefit is that such a scheme allows a more accurate capsule count, since there is no point in falsification of the number of capsules taken.

Effects of life-events

In a previous trial (Bonn *et al.*, 1971) life-events were shown to be an important factor in studies of this type. Downing & Rickels (1978) have stressed that to disregard important life-events occurring during the course of a trial may result in bias. They suggest that, although improved circumstances generally lead to no change in those taking active anti-anxiety drugs, they do cause positive change in placebo takers. In contrast, a deterioration in a patient's life situation is associated with a deterioration in patients in the active drug groups, but no change in placebo takers. In the present study the occurrence of significant life-events, whether positive or negative, was low and does not seem to have influenced the results.

Conclusions

No between-group differences in MAI and HAS scores at visits 2 and 3 have been shown. However, both clobazam and diazepam produced a significant reduction in scores from visit 2 to visit 3, whereas placebo did not. We believe that this finding provides

evidence of clobazam and diazepam having a true anti-anxiety effect.

Further evidence pointing to a real drug effect with both clobazam and diazepam was the rebound in an anxiety scores shown at the follow-up visit. Both active drug groups showed an increase in scores on the HAS and MAI on withdrawal.

Reported side-effects were few, with no specific problems emerging. Special enquiry was made about subjective experience of drowsiness and again the incidence was generally low.

The results of the psychomotor testing were more interesting. The placebo group demonstrated significant practice effects with improvement in both the pursuit rotor and digit symbol substitution tests, whereas the diazepam group showed no learning effects at all. This suggests that diazepam produces an impairment in motor coordination which has negated the practice effect.

The results with clobazam are similar to those with placebo in that there is a clear improvement in performance on both tests, which is highly significant in the DSST. Thus clobazam does not seem to produce the same impairment in performance as diazepam, and this is consistent with the published work on this aspect of clobazam.

In general it may be observed that the special selection of patients for anxiolytic trials in general practice, together with the elimination of placebo responders, resulted in a drug trial of increased sensitivity. It is sometimes argued that to include placebo groups when dealing with patients suffering from psychoneurotic conditions is unwarranted. However, in general practice patients may be monitored much more closely than is possible with hospital out-patient practice. There is increased contact between clinician and patient, and easy access so that patients may contact the physician at any time if their symptoms deteriorate. We feel that the inclusion of placebo groups enables more valid conclusions to be drawn when evaluating the activity of anxiolytic drugs in general practice conditions.

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Discussion

PROFESSOR D. LAWSON (Glasgow) commented on the considerable differences between the treatment groups in the mean HAS and MAI scores at visit 2, before entry to the double-blind phase of the study. He asked whether this was allowed for in the assessment of the drug effects between visits 2 and 3.

DR T. SILVERSTONE (London) replied that in spite of random allocation of the patients to each treatment group, the placebo group by chance ended up with a preponderance of placebo responders, as shown by the much larger reduction in scores in this group from visit 1 to visit 2. There was no way in which this could have been allowed for. He had discussed in the paper the evaluation of the effects of the active drugs in the light of the difference in baseline scores (at visit 2). He felt that the conclusions were valid.

PROFESSOR J.R. WITTENBORN (New Jersey)

added a comment that there is a difference between the significance of a change and the significance of a difference between changes. One may have one change that was not significantly greater than zero, and another one that was significantly greater than zero, but there could still be no significant difference between these changes. This problem is particularly relevant to placebo comparisons.

DR K. TAEUBER (Frankfurt) commented on the description of the DSST as a test of psychomotor performance. The DSST is a test of attention and the ability to concentrate, and is not strictly a test of psychomotor performance. Having shown no impairment of psychomotor performance by means of the pursuit rotor, this study also demonstrated that clobazam produced no detrimental effects on attention.