

CLOBAZAM SINGLE OR DIVIDED DOSE AGAINST DIAZEPAM IN ANXIETY NEUROSIS

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SUMMARY

One-hundred-and-fifteen patients diagnosed as anxiety neurotics randomly received in a double blind study 20 mg clobazam (Frisium) as a single nightly dose (37 patients) or 10 mg b.d. (38 patients) or diazepam 5 mg t.i.d. (40 patients) for six weeks, followed by two weeks on placebo. Both the single and divided doses of clobazam were therapeutically equivalent to diazepam. After drug withdrawal, all three treatment groups continued to improve. Patients on clobazam showed better motor performance than the diazepam series. Patients on clobazam divided dose performed significantly better than those on diazepam. Minor side-effects occurred in all patients. From the results clobazam as a single dose of 20 mg has good anxiolysis without any hangover effect.

The objective of this study was a comparison of anxiolytic efficacy of clobazam as either a single or equally divided 20mg daily dosage with that of 5 mg diazepam thrice daily. Earlier studies have suggested that clobazam may have a prolonged anxiolytic effect, and have drawn attention to the need to investigate the drug at doses lower than 30 mg/day (Doongaji et al 1978).

Material and Methods

Of 115 patients available for analysis, 38 received clobazam (Frisium) in two equally divided doses of 10 mg at morning and 10 mg at night, 37 patients received a single 20 mg dose at night and 40 patients received 5 mg of diazepam three times a day. Treatment distribution was randomized and administered by a double-dummy technique such that at each dosing patients always received numerically two identical capsules. Identical placebo capsules were substituted for clobazam or diazepam whenever required.

All patients scored at least 14 on the Hamilton Anxiety Rating Scale (1959) and at least 2 on the symptoms of General Somatic (muscular, sensory and anxious mood).

Patients with clinical evidence of any pathology affecting absorption, metabolism or excretion were excluded from the study. Pregnancy or its possibility did not permit the entry of females to the study. For the first six weeks all patients received active treatment and for the next two weeks placebo therapy was given. This phase of placebo treatment was single-blind, the patients being unaware of the treatment they were receiving.

Evaluation was done at weekly intervals on the HARS by an experienced research worker and on the Clinical Global Impression (CGI) Scale (Guy 1976) by the principal investigator.

At the evaluation, motor coordination was tested on the pursuit rotor. After the familiarization run, the average of three runs (each of 30 sec) was taken as the efficacy criterion.

Results

Patient characteristics are presented in Table 1. The percentage reduction on the initial HARS scores for the three groups is shown in Table 2. Both the single and divided doses of clobazam were comparable to diazepam in therapeutic efficacy at the

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Table 1
Demographic Characteristics of the 155 Patients

Treatment	No. of Patients	Male	Female (Years)	Mean Age \pm SE (kg)	Mean Weight \pm SE	Mean Duration of Illness (months)
Clobazam	38	28	10	28.18 \pm 0.99	55.45 \pm 1.24	13.66 \pm 1.44
Clobazam (20 mg)	37	26	11 (35)	27.77 \pm 0.97	54.41 \pm 11.11	14.39 \pm 1.77 (36)
Diazepam (5 mg t.i.d.)	40	28	12	27.56 \pm 1.05 (39)	56.63 \pm 1.54	13.60 \pm 1.63

Table 2
Percentage Reduction in Initial HARS Scores

Treatment	Active Treatment						Placebo	
	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57
Clobazam (10-10 mg)	21.58	33.22	47.57	56.10	64.68	68.85	23.76	35.97
Clobazam (20 mg)	23.41	32.77	48.38	57.66	66.72	71.48	21.22	35.37
Diazepam (5 mg t.i.d.)	22.79	35.16	47.83	54.91	63.71	69.77	21.08	32.96

Percentage reduction in placebo period is with reference to Day 43.

end of the six-week treatment period. During the next two weeks on placebo, further reduction in the anxiety scores were observed in equal measure for all three treatment groups.

On the clusters of psychic and somatic anxiety, statistical comparison revealed that diazepam did not differ from either the single or the divided dosage schedule of clobazam.

At the end of the six weeks' active drug treatment, five variables in each of the series of clobazam single dose and diazepam, responded with over 75% improvement (Table 3). In the clobazam divided dose group only two variables showed more than 75% improvement.

In the post treatment period on placebo, the percentage reduction for the psychic anxiety cluster was highest (39%) in the

Table 3
Hars Variables Showing at least 75% improvement on Day 43

Clobazam (10-10 mg)	Clobazam (20 mg)	Diazepam (5 mg t.i.d.)
Respiration Genito-urinary	Depressed mood General somatic, sensory Respiration Gastrointestinal Genito-urinary	Fears Depressed mood General somatic, sensory Genito-urinary Behaviour at interview

single dose series compared with 35% in the divided dose series and 30% in the diazepam series.

On the somatic anxiety cluster, during post-treatment placebo therapy, the divided dose group showed further percentage reduction of 36%. In the single dose group 34% further reduction was seen and diazepam treated patients responded with a further improvement of 35%.

On the CGI evaluation, the percentage of responders who showed at least marked improvement were analysed (Table 4). Patients on clobazam single dose responded better than the remainder two groups at the end of both treatments and the placebo periods.

Table 4
Percentage of patients showing at least marked improvements

Day	Clobazam (20 mg)	Clobazam (10-10 mg)	Diazepam (5 mg t.i.d.)
8	2.7	2.7	10.3
15	5.4	13.5	10.3
22	17.2	15.6	17.1
29	29.6	28.1	22.9
36	50.0	38.7	48.6
43	60.0	51.6	55.6
50	70.8	61.3	68.6
57	79.2	72.0	74.3

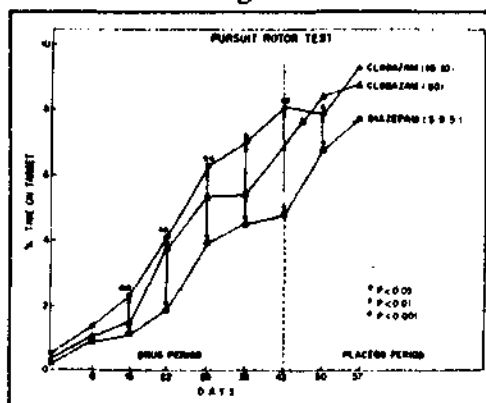
No significant difference by the Chi square test.

Motor Coordination

All three groups of patients (Figure) showed significant improvement in motor performance as early as the end of the first week of treatment. Improvement continued till the end of the six weeks' drug treatment period and the trend was maintained even during the subsequent two weeks on placebo therapy.

Both the clobazam single and divided dose series showed better motor performance than the diazepam group throughout the study. From Day 15 until Day 50, patients who received clobazam divided dosage performed significantly better than the diazepam group of patients.

Figure



Side effects:

Minor side effects were present in all three treatment groups. Under Clobazam conditions two patients complained of an itching sensation and one developed a rash on the arm and back. Two other complaints volunteered were abdominal pain and apprehension from the clobazam divided dose and diazepam series.

Pain in the limbs was reported by two patients one of whom had received clobazam and the other diazepam. These reported side-effects were transient. No treatments was administered and they regressed spontaneously.

Discussion

This study was designed to investigate the anxiolytic activity of clobazam either as a 20 mg single or divided dose, compared to diazepam in a 5 mg thrice daily schedule. Clobazam has already been investigated as an anxiolytic at a 30 mg divided dosage, (Salkind et al 1979, Wallis et al 1979, de Figueiredo et al 1981).

Data from these earlier studies indicated that clobazam has a good maintenance of anxiolytic effect and could therefore be effective in a smaller dose and perhaps as a single dose schedule.

In this study all three treatment groups showed considerable improvement. A marked reduction in scores was also observed during the post-treatment placebo period.

Clobazam as 20 mg in a single or divided dose showed therapeutic effect comparable to diazepam 5 mg t.i.d. A trend for better anxiolysis was seen with the single dose regimen.

All three treatment groups showed encouraging results on the somatic cluster of anxiety. It might therefore be interesting to study clobazam also in the treatment of depression, especially since somatization is a common presentation in Indian patients suffering from both anxiety neurosis and depression.

The single dose of clobazam 20 mg was free from detrimental effects on motor performance and these patients performed better than those on diazepam. With the 20 mg divided dose, clobazam patients had significantly better motor performance than the diazepam series. Side-effects were generally low with all three treatment schedules, and could not be attributed to the drugs under study. The study suggests further investigation with the single dose of 20 mg especially since it offers convenience of therapy with good anxiolysis and no hangover effect.

Though in the doses studied, clobazam and diazepam have superiority in lack of sedative effect evidenced in psychomotor performance, the single dose regimen of clobazam and its maintained anxiolysis after stopping treatment are of importance in assisting the gradual withdrawal from drug

treatment thereby reducing the risk of benzodiazepine dependence in patient populations, as suggested by Marks (1978).

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References

1. DOONGAJI, D. R., SHETH, A., APTE, J. S., LAKDAWALLA, P. D., KHARE, C. B., and THATTE, S. S. (1978), Clobazam versus diazepam - a double blind study in anxiety neurosis. *Journal of Clinical Pharmacology* 18, 358-364.
2. de FIGUEIREDO R., FRANCHINI, A., MARTINHO, A. and HINDMARCH, I. (1981), Differences in the effect of two benzodiazepines in the treatment of anxious outpatients. *International Pharmacopsychiatry* 16, 57-65.
3. GUY, W. (1976), Clinical Global Impressions. In: ECDEU Assessment Manual for Psychopharmacology, pp.217-222. Editor: W. Guy. Rockville: NIMH.
4. HAMILTON, M. (1959), The assessment of anxiety states by rating. *British Journal of Medical Psychology*, 32, 50-55.
5. MARKS, J. (1978), The Benzodiazepines: Use, Overuse, Misuse, Abuse. P. 36, MTP Press, Lancaster, England.
6. SALKIND, M. R., HANKS, G. W., and SILVERSTONE, T. (1979), Evaluation of the effects of clobazam, a 1, 5-benzodiazepine, on mood and psychomotor performance in clinically anxious patients in general practice. *British Journal of Clinical Pharmacology* 7, 113-118.
7. WALLIS, T. D., VALLE-JONES, J. C., CRAVEN, J. R., HANKS, G. W. and STONIER, P. D. (1979), Single daily dose treatment of anxiety with clobazam of dipotassium chlorazepate. *British Journal of Clinical Pharmacology* 7, 123-128.