A CONTROL CLINICAL TRIAL OF A NEW ANXIOLYTIC 'CLOBAZAM'

GURMEET SINGH, M. B. B. S., M. R. C. Psychiat., D. P. M. (Lond.),
Dip. Psychiat. (McGill), Dip. Am. Board of Psychiat. and Neurology,
VIJAY KUMAR, M. B. B. S., M. D. (Psych.), P. C. M. S.
RUPINDER KAPUR, M. B. B. S., M. D. (Psych.), P. C. M. S.

SUMMARY

Clobazam as a twice-a-day dosage (10 mg-20 mg) regimen and Diazepam in a thrice-a-day schedule (5 mg-5 mg-5 mg) were both effective in controlling moderate to severe anxiety neurosis. 83 patients were studied in a controlled, randomised, double-blind trial. Patients received active drug for the first six-weeks and placebo for the next two weeks. Weekly evaluation was performed clinically for anxiolytic effect as well as effect on motor coordination studied on the Pursuit Rotor.

Clobazam did not significantly differ from Diazepam in the dosage schedules studied. At the end of the two-week placebo treatment period, patients on Clobazam showed more improvement. Motor coordination was not impaired in both treatment groups. Clobazam treated patients had better motor performance at the end of the 14-day post-treatment placebo period. Side effects were reported with equal frequency in both the populations.

Newer benzodiazepines are being introduced for the treatment of anxiety neurosis. The effort to establish more than "me too" drugs is always present. In clinical practice an achievement in less-side effects or better patient compliance would be a significant contribution to therapeutics.

Clobazam is unique in its structural relationship to the general class of benzodiazepines. It has a nitrogen atom in the '5' position, instead of the '4' position, which may contribute to the differential effects on the desired tranquilising, or taming behaviour and the undesired effects on motor coordination.

Clobazam is a relatively new benzodiazepine, which is being investigated in India. Previous studies (de Figueiredo et al., 1981; Doongaji et al., 1978) have shown the drug has good anxiolytic effect even during withdrawal from treatment. In these studies a dose of 30 mg in equally divided doses per day has been studied. In view of its prolonged efficacy, we were interested to study the anxiolytic efficacy of 30 mg Clobazam as two divided doses of 10 mg and 20 mg per day. It was also important to determine if the administration of 20 mg Clobazam at night, could have any effect on motor coordination.

The trial was specially designed to study the efficacy of the twice-a-day regimen of Clobazam, any effects on motor coordination, and the anxiolytic activity during drug withdrawal.

METHODOLOGY

Eighty-three adult outpatients diagnosed as anxious neurotics entered the study. By random allocation, patients received either Clobazam as 10 mg at morning and 20 mg at night or Diazepam as 5 mg three times a day. To maintain double-blind conditions, the double-dummy technique of drug administration was used. Each patient

---

1Professor and Head, Department of Psychiatry, Medical College, Patiala.
2Psychiatrist, Civil Hospital, Jalandhar.
3Psychiatrist, Civil Hospital, Hoshiarpur.
therefore received numerically two capsules three times a day, corresponding to the respective doses of Clobazam and Diazepam.

Patients with clinical evidence of severe hepatic, renal or cardiovascular pathology, or organic brain damage, were excluded. A history of drug abuse, affective psychosis or benzodiazepine sensitivity also excluded patients from entry. Pregnancy or its possibility did not permit inclusion of such females into study. Patients who were already on anxiolytic therapy underwent a one week wash out on placebo.

For inclusion, a patient had to be diagnosed as an anxious neurotic, with a score of at least 14 on the Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959), as well as at least two on the items of anxious mood and general somatic (muscular and sensory). Treatment was administered by randomisation in packets specially packed for each patient for the 7-days of the week. Active drug treatment was for six weeks followed by two-weeks treatment on placebo.

Efficacy evaluation was done at the end of each week on the HARS, by the Research Worker, as well as on the Clinical Global Impression Scale (CGI) (ECDEU Assessment Manual, 1970) by the principal investigator.

At each evaluation period, motor coordination was tested on the Koerth's Pursuit Rotor. Patients underwent each time a familiarisation trial run (30 secs). Subsequently, the mean of 3 trials was considered as an assessment.

RESULTS

Demography

Out of 83 patients who entered the study, 40 received Clobazam, and 43 received Diazepam. Groups were comparable for demographic variables as seen in Table I. Seven patients (5 in Clobazam group and 2 in Diazepam group) had duration of illness less than 1 month while 18 patients (8 in Clobazam group and 10 in Diazepam group) had duration more than 2 years. These patients were also included in the analysis.

| TABLE 1—Demographic Variables |
|-------------------------------|
| Clobazam | Diazepam |
|-----------------|---------|
| Patients entered in study    | 40      | 43      |
| Drop-outs          | 8       | 15      |
| Available for analysis  | 32      | 28      |
| Sex               |         |         |
| Male              | 17      | 17      |
| Female            | 15      | 11      |
| Age (years)       | 30.56 ± 1.64 | 34.78 ± 2.41 |
| Weight (kgs)      | 53.3 ± 1.51 | 56.38 ± 2.16 |

Clinical Assessment

Both drugs significantly reduced the basal score of anxiety on the HARS at the end of 6 weeks treatment. The onset of activity was seen for both drugs at the end of 8 days. At the end of 6 weeks of treatment, patients on Clobazam showed 71 per cent improvement and those on Diazepam improved by 67 per cent (Table 2).

At the end of further 2 weeks during which patients received placebo, the Clobazam treated group continued to improve by 11 per cent. Further improvement in the Diazepam series was 4 per cent.

The HARS was subjected to further analysis on the clusters of psychic and somatic anxiety. By Wilcoxon's Signed Rank Test, significant improvement was seen for both groups (starting with week 1 till the end of 6 weeks treatment).
A CONTROLLED CLINICAL TRIAL OF A NEW ANXIOLYTIC

TABLE 2—Percentage improvement on total scores of HARS

| Treatment period | Placebo period |
|------------------|---------------|
|                  | Day 8 | Day 15 | Day 22 | Day 29 | Day 36 | Day 43 | Day 50 | Day 57 |
| Clobazam         | 38.20 | 52.23  | 61.00  | 64.00  | 68.50  | 71.00  | 2.68   | 11.00  |
| Diazepam         | 41.45 | 49.48  | 51.50  | 61.00  | 63.08  | 67.00  | 2.75   | 4.00   |

Differences were not significant at any evaluation period. Onset of activity seen on Day 8 for both drugs (p<0.001). Percentage reduction in placebo period is with respect to Day 43.

On the cluster of somatic anxiety, Clobazam produced an improvement of 70 per cent and Diazepam an improvement of 67 per cent (Table 3).

TABLE 3—Percentage improvement on psychic and somatic anxiety clusters

|                | Clobazam | Diazepam |
|----------------|----------|----------|
|                | Psychic  | Somatic  | Psychic | Somatic |
| Day 8          | 39.74    | 35.97    | 41.36   | 41.99   |
| Day 15         | 52.90    | 51.23    | 48.58   | 51.00   |
| Day 22         | 61.33    | 59.40    | 52.52   | 57.46   |
| Day 29         | 64.03    | 64.00    | 59.52   | 62.54   |
| Day 36         | 69.00    | 68.00    | 63.00   | 63.49   |
| Day 43         | 72.00    | 70.00    | 67.00   | 67.30   |
| Day 50         | -0.67    | 4.72     | +0.66   | +5.8    |
| Day 57         | +8.57    | +14      | +4.93   | -2.25   |

* Differences not significant at any evaluation. Percentage reduction in placebo period is with respect to Day 43.

On the psychic anxiety cluster, the percentage improvement after Clobazam treatment was 72 per cent, and following Diazepam 67 per cent (Table 3).

The anxiolytic effect of Clobazam was better than Diazepam during the 2 week drug withdrawal period. The cluster of somatic anxiety continued to improve by 14 per cent after Clobazam and by 2 per cent after Diazepam. Psychic anxiety was further reduced by 8 per cent with Clobazam and by 4 per cent with Diazepam, at the end of the post-drug placebo treatment (Table 3).

On the HARS, significant (p<0.05) improvement was observed in Clobazam treated patients for the symptoms insomnia, general somatic (muscular) on Day 22, and for depressed mood on Days 22 and 29. Patients who received Diazepam improved significantly (p<0.05) on Days 8 and 15, for respiratory and gastrointestinal symptoms.

To assess continuing drug effect during the 2 week period on placebo, the Sum of Improvement Scores (SIS) was calculated on the principle of Sum of Reduction Scores used by Doongaji et al. (1978).

Clobazam treated patients had a higher sum of improvement on the total HARS, as well as in the clusters of psychic and somatic anxiety (Table 4). During this period, six variables of the HARS—fear, intellect, depressed mood, general somatic (sensory), cardiovascular and respiratory continued to respond to Clobazam. Against this, only two symptoms, gastrointestinal and behaviour at interview (general) showed improvement in patients on Diazepam.

In both the treatment groups, continued therapeutic effect was seen for insomnia and general somatic (muscular).
TABLE 4—Sum of improvement scores during post-treatment placebo period

|                  | Clobazam (N=30) | Diazepam (N=24) |
|------------------|-----------------|-----------------|
| Total HARS       | 32              | 16              |
| Anxiety psychic  | 9               | 8               |
| Anxiety somatic  | 23              | 8               |

On the Clinical Global Improvement (CGI) Scale, more patients showed moderate and marked improvement on Clobazam. On Days 50 and 57, significantly more patients showed moderate and marked improvement after receiving Clobazam ($p<0.06$) (Table 5).

TABLE 5—Clinical Global Impression Scale (CGIS) (Patients who showed moderate and marked improvement)

| Day  | Clobazam (N=28) | Diazepam (N=28) |
|------|-----------------|-----------------|
| 8    | 20              | 17              |
| 13   | 26              | 20              |
| 22   | 27              | 21              |
| 29   | 29              | 23              |
| 36   | 30              | 22              |
| 43   | 30              | 22              |
| 50   | 31              | 22*             |
| 57   | 30/30           | 18/24**         |

* $p=0.0686$ (by Fisher's Test)
** $p=0.0104$ (by Fisher's Test)

Motor performance

Performance was assessed as 10 per cent if contact on target could be made for 30 seconds. The percentage of total time was calculated and tested by Wilcoxon’s Sum of Rank Test for both populations. Both the treatments significantly improved performance.

The Sum of Improvement Scores of motor performance on the Pursuit Rotor was calculated for both drug treated groups during withdrawal based on average for the populations. The Sum of Improvement Scores in patients on Clobazam was 78 and in the Diazepam treated patients was 33, at the end of the 2 week drug free period (Table 6). Thus motor performance continues to improve in both Clobazam and Diazepam groups after stopping the anxiolytic medication, the improvement being relatively more in subjects who were on Clobazam.

TABLE 6—Status of patients on Pursuit Rotor during placebo period (Day 43-57)

|                  | Clobazam | Diazepam |
|------------------|----------|----------|
| Total            | 28       | 23       |
| Patients who improved | (9)     | (2)      |
| (Improvement above 75%) |        |          |
| Patients who worsened | 3       | 5        |
| Patients with no change | 1       | 2        |
| Sum of Improvement Score | 78.27   | 33.23    |

SIDE EFFECTS

Drowsiness was the commonest side effect reported. 22 out of 32 patients on Clobazam and 19 out of 28 patients on Diazepam complained of drowsiness as side effect (Table 7). Both drugs did not adversely affect any clinical chemistry parameters.
**Table 7—Patients who reported side effects**

|              | Clobazam (n=32) | Diazepam (n=28) |
|--------------|-----------------|-----------------|
| C. N. S.     |                 |                 |
| Drowsiness   | 22 (68.75%)     | 19 (67.86%)     |
| Giddiness    | 4 (12.5%)       | 3 (10.71%)      |
| Heaviness in eyes | 1 (3.1%)   | 0 (0%)          |
| Trembling    | 1 (3.1%)        | 0 (0%)          |
| G. I. T.     |                 |                 |
| Constipation | 0 (0%)          | 3 (10.71%)      |
| Bad taste in mouth | 9 (28.1%) | 9 (32.14%) |
| Increased thirst | 1 (3.1%)   | 1 (3.57%)       |
| Dryness of mouth | 1 (3.1%)   | 0 (0%)          |
| SKIN         |                 |                 |
| Itching      | — (0%)          | 1 (3.5%)        |
| MISCELLANEOUS|                 |                 |
| Heavy voice  | 1 (3.1%)        |                 |
| Disinterest in work | 1 (3.1%) |                  |
| Falling down on walking | 1 (3.1%) | (7.14%)         |

**DISCUSSION**

Data from the study on both the clinical as well as the motor performance testing show Clobazam is an effective agent, with good maintenance of anxiety in the twice-a-day dosage regimen. On the HARS as well as on the two clusters of psychic and somatic anxiety, both drugs show good anxiolytic effect by Day 8. Patients who received Clobazam showed a trend for better maintenance of therapeutic effect till the end of the two-week post-treatment period on placebo.

Both de Figueiredo et al. (1981) and Doongaji and associates (1978) observed this phenomenon after 4 weeks treatment with Clobazam followed by one week on placebo. Our study demonstrates that the drug has prolonged anxiolytic activity long after treatment is stopped. This action ensures the smooth transition to the non-drug state, when treatment requires to be stopped or as is encountered in common practice when patients forget to take their medication. Clobazam apparently has a strong carry over effect which is observed clinically on the HARS and both clusters of psychic and somatic anxiety.

On motor performance testing, the better trend for improving function is observed during the post treatment period in patients who received Clobazam. This could be attributed to the good anxiolysis with Clobazam affecting especially somatic symptoms like tremor. The corresponding somatic variable, general somatic (muscular) also showed significant improvement after treatment with Clobazam, and continued to improve during withdrawal.

The good carry over effect of Clobazam may be due to its active metabolite. The parent compound itself has a long-life of 18 hours. Pharmacological studies have shown the metabolite N-desmethyl Clobazam is active in animal experimentation (Fielding and Hoffman, 1979) and has receptor binding potency similar to the parent compound (Hunt, 1979).

From pharmacokinetic studies, the half-life of the metabolite is 36-36 hours, and it accumulates to a steady-state level about 8 times higher than the parent compound (Rupp et al., 1979). This data explains good maintenance anxiolytic effect of Clobazam and also the improvement which was seen during the withdrawal stage.

Throughout evaluation, higher trends have been observed on anxiolytic effect, motor coordination and maintenance of therapeutic response after treatment was stopped in patients who have received Clobazam. The results are clinically significant, especially in the light of comparisons made between two active
drugs than between active drug and placebo.

Drowsiness occurred with equal frequency in both the treatment groups. It seemed worthwhile to study the reasons for drop-outs where available to ascertain any cause-effect relation to the drugs under study. Out of the 8 drop-outs who received Clobazam, only one complained of severe drowsiness. 5 patients out of 15 on Diazepam dropped out due to drowsiness.

This trial suggests a dose of Clobazam as 10 mg at morning and 20 mg at night does not produce any detrimental effect on motor coordination with respect of Diazepam (15 mg) in 3 equally divided doses. The effect of Clobazam is well maintained after treatment is discontinued, so that there is no risk of a worsening of anxiety, in the event of a patient forgetting to take medication. The twice-a-day schedule is a forward step in improving patient compliance.

Perhaps Clobazam can be called a “better” anxiolytic, since it meets the conditions for “better” as defined by Vinar (1973). “It affects some symptoms in a more intensive way, its therapeutic effects endure longer, it has fewer side-effects, and is simpler to administer.”

ACKNOWLEDGEMENTS

The study was supported by Hoechst Pharmaceuticals Limited, Bombay, India. Acknowledgement is made to Mr V. A. Deshpande for statistical assistance.

BIBLIOGRAPHY

de Figueiredo, R., Franchini, A., Martinho, A., Hindmarsh, I. (1981). Differences in the effect of two benzodiazepines in the treatment of anxious outpatients. Int. Pharmacopsychiat., 16, 57.

Doongaji, D. R., Sheth, A., Apte, J. S., Lekhawalla, P. D., Khare, C. B., Thatts, S. S. (1978). Clobazam versus Diazepam: A double-blind study in anxiety neurosis. J. Clin. Pharmac., 18, 358.

Eddeu Assessment Manual (1970). 2nd Revision, Washington DC: U.S. Department of Health, Education and Welfare, Govt. Printing Office.

Fielding, S., Hoffman, I. (1979). Pharmacology of anti-anxiety drugs with special reference to Clobazam. Brit. J. Clin. Pharmac., 7, 7S.

Hamilton, M. (1959). The assessment of anxiety states by rating. Brit. J. Med. Psychol., 33, 50.

Hunt, P. (1979). Assay of Clobazam in human serum by a radio-receptor technique. Brit. J. Clin. Pharmac., 7, 37S.

Rupp, W., Badian, M., Christ, O., Hajdu, P., Kulkarni, R. D., Taeuber, K., Uhlenh, M., Bender, R., Vanderbeke, O. (1979). Pharmacokinetics of single and multiple doses of Clobazam in humans. Brit. J. Clin. Pharmac., 7, 51S.

Vinar, O. (1973). Introductory remarks. New agents in Psychiatry. Curr. Therap. Res., 15, 105, 749.