SINTAMIL IN THE TREATMENT OF DEPRESSION: A COMPARISON OF SINGLE VS. DIVIDED DOSE ADMINISTRATION

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Sintamil *(nitroxazepin hydrochloride)* is a new antidepressant with the following chemical structure—10 (3-Dimethylaminopropyl)-2-nitro dibenz (b,f) -1,4-oxazepin 11 (10 H)—one hydrochloride. This compound has been investigated in both animals and humans for its antidepressant activity with impressive results. The overall positive response to Sintamil therapy was observed in 73.1% in a combined group of patients with all types of depressions. (Gupta and Mankodi, 1972). It has been reported to be equally effective as Imipramine and Trimipramine in the treatment of depression. Furthermore, it is extremely well tolerated with a lesser number of patients experiencing a lesser number of side effects in comparison to both Imipramine and Trimipramine.

A common practice in the pharmacotherapy of depressive illness is to prescribe the antidepressant drug in three divided doses. However, in recent years pharmacological and clinical studies have shown that prescribing a single daily dose of antidepressants is scientifically sound. Absorption of these drugs after oral administration is remarkably prompt—maximum absorption taking place in the first 30 to 60 minutes. However, since they have a long biological half life (Dimascio and Schader, 1969) the drug accumulates in the body tissues from where it is released slowly.

Furthermore, since it is now known that a considerable number of Psychiatric patients (both in-patients and out-patients) fail to take their medication in the prescribed dose (Park and Lipman, 1964, Willcox et al. 1965, Hare and Willcox, 1967), a single daily dose regimen is more likely to be taken reliably than the thrice daily dosage (General practitioners clinical trial, 1970, Hussain and Choudhary, 1973, Blackwell, 1976). Other reported advantages of the single daily dose are—increased convenience for both the patients and nursing staff, avoidance of certain side effects such as the transient drowsiness occurring after oral intake which is troublesome during the day, but is useful in promoting sleep when given in a single bedtime dose. Finally a single dose is also more economical than its equal amount dispensed in divided doses.

In view of these reports it was decided to carry out a double blind study to compare the efficacy and tolerability of a single bedtime dose of Sintamil with that of an equal amount of drug given in three divided doses, in the treatment of depression.

MATERIAL AND METHOD

The total sample consisted of 57 patients attending the Psychiatric department of Rajendra Hospital, Patiala and diagnosed as suffering from a depressive illness. This include cases of (a) Endogenous depression, i.e. Manic-depressive psychosis-depressed and Involutional Mancholia. (I.C.D. No. 296) and (b) Reactive depressions, i.e. Depressive Nervous (I.C.D. No. 300.4). 8 subjects failed to complete the minimum 4 week trial period, so that the present report is based on a total of 49 cases. There were 28 males 21 females ranging in age from 16 to 64 years with a mean age of 39.2 years. Patients with a history of other psychiatric illness including alcohol and

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*Clinical trials were conducted under the code number CIBA 2330 - Go.*
drug dependence, evidence of organic disease, or with a history of intake of drugs known to produce depression and pregnant women were excluded from the study.

The patients were randomly assigned on a double blind basis to the two treatment groups, i.e. (a) The single daily dose (S.D.) group (25 subjects) who received 75 mgm. of Sintamil at bedtime, and matching placebo tablets in the morning and afternoon, and (b) the divided dose (D.D.) group (24 subjects) who received 25 mgm Sintamil t.i.d. during the first four weeks of the trial. In case of those who were not recovered at the end of the 4 week trial, the dose was increased to 150 mgm. daily either as a single bedtime dose or in three divided doses after opening the code. They were followed up for a minimum of two weeks on this dose.

No other drug was given during the trial period, however if considered necessary a day time tranquilizer (diazepam) or a hypnotic (nitrazepam) was added. All adverse effects reported by the patient were recorded, with their day of onset and severity. Psychiatric assessments in the form of Hamilton Rating Scale for depression (Hamilton, 1960) and a Clinical Global Impression was recorded at weekly intervals throughout the period of study.

RESULTS

The distribution of patients in the S.D. group and the D.D. group according to age, sex, duration and type of illness is shown in Table 1.

Therapeutic Effects

Table 2 shows the group Hamilton Rating Scale scores (HRS) for the two groups separately, starting with the initial (pretreatment) score and at weekly intervals thereafter. Improvement was assessed as the percentage reduction in the global score from the initial score. It is seen that by the end of the 4th week there was a 71.2% reduction in the HRS score in the S.D. group as compared to a reduction of 68.9% in the D.D. group. The reduction in the group HRS score thus being almost the same in both the groups.

Table 3 shows the individual response of patients in the S.D. and D.D. groups at 4 weeks and 6 weeks, as measured in terms of percentage reduction in the HRS scores and on clinical global assessment. At the end of 4 weeks on a fixed daily dose of 75

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**TABLE 1—Characteristics of the Single daily dose (S. D.) group and the divided dose (D.D.) group**

| Characteristics | S.D. group (N=25) | D.D. group (N=24) |
|-----------------|-------------------|-------------------|
| Age             |                   |                   |
| Range           | 16—64 yrs.        | 18+60 yrs.        |
| Mean and S.D.   | 39.7±13.2         | 38.6±11.6         |
| Sex             |                   |                   |
| Males           | 15                | 13                |
| Females         | 10                | 11                |
| Type of illness |                   |                   |
| Endogenous      | 16                | 18                |
| Reactive        | 9                 | 6                 |
| Duration of illness |          |                   |
| Mean and S.D.   | 8.4 months±7.2    | 6.8 months±6.2    |

**TABLE 2—Comparison of the group scores on the Hamilton Rating Scales for the initial 4 week trial period.**

| Period            | S.D. group | D.D. group |
|-------------------|------------|------------|
| Total %age score reduction | N=25 | N=24 |
| Initial (pretreatment) | 427 | 373 |
| First week        | 283 | 286 | 23.3 |
| Second week       | 196 | 216 | 42.1 |
| Third week        | 163 | 160 | 57.1 |
| Fourth week       | 123 | 116 | 68.9 |
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TABLE 3—Showing the individual patient response in the S. D. and D. D. groups measured as percentage reduction in H. R. S. score and on clinical global assessment

| Percentage reduction in HRS score at 4 weeks on 75 mgm./day | Clinical assessment at 4 weeks* on 75 mgm/day | clinically recovered | Clinical assessment at 6 weeks** on 150 mgm/day | clinically recovered |
|----------------------------------------------------------|------------------------------------------------|--------------------|----------------------------------------------|---------------------|
| EXPERIMENTAL GROUP | | | | |
| Single daily | | | | |
| N = 25 | | | | |
| 1. | 2 | 4 | 18 | 11 | 22 |
| 2. | 3 | 3 | 7 | 11 | 9 | 19 |
| 3. | 13% | 13% | 29% | 46% | 37.5% | 79.1% |
| Divided dose | | | | | | |
| N = 24 | | | | | | |
| *At 4 weeks; $X^2 = 0.21$, d.f. = 1, N.S. | | | | | | |
| ** At 6 weeks: $X^2 = 0.69$, d.f. = 1, N.S. | | | | | | |

mgn. a day the number of patients who were clinically recovered was 11 (44%), in the S. D. group, and 9 (37.5%) in the D. D. group. This difference is not statistically significant. After a further two weeks treatment on an increased dose of 150 mgm. a day the number clinically recovered rose to 22 (88%) in the S. D. group, and 19 (79%) in the D. D. group. Here again the response rate is slightly better in the S. D. group, but the difference is not statistically significant.

**Adverse Effects**

9 out of the 25 subjects in the S.D. group (36%), reported a total of 16 side effects, whereas in the D.D. group 7 out of 24 (29%) complained of a total of 13 side effects related to the use of the drug during the trial period. A list of all the adverse effects reported is given in Table 4. It is apparent that dryness of mouth and constipation are the only two common complaints, reported by 9 (18.3%) and 7 (14.3%) subjects respectively. Although the total number of side effects observed in the two groups is similar, there does seem to be a difference in the frequency of occurrence of specific symptoms, e.g. dryness of mouth and dizziness is observed more commonly among the divided dose group, while palpitation, restlessness and blurred vision are marginally more among the single daily dose group.

**Concomitant therapy**

Concomitant therapy in the form of tranquilizers and/or hypnotics had to be given to 10 patients in the S.D. group (40%), and to 9 patients in the D.D. group (37.5%). In the S.D. group, 7 patients were given additional tranquilizers alone, 2 hypnotics alone and 1 was given both a daytime tranquilizer as well as a hypnotic. In the D.D. group 5 were given tranquilizers only, 3 hypnotics only and 1 both a tran-

TABLE 4—Showing number of patients reporting side effects in the two treatment groups

| Side effects | S.D. Group | D.D. Group |
|-------------|------------|------------|
| Dryness of mouth | 3 | 6 |
| Constipation | 5 | 2 |
| Dizziness | 0 | 3 |
| Heaviness of head | 1 | 1 |
| Palpitation | 2 | 0 |
| Irritability | 0 | 1 |
| Blurred vision, Vomiting, Tinnitus, Burning in abdomen, Restlessness | 1 each | Nil |
quillizer plus a hypnotic. Thus 3 patients in the S.D. group needed a bed-time hypnotic as compared to 4 in the D.D. group. Apparently, Sintamil does not have much sedative activity as in the case of some other tricyclic antidepressants which, when given in a single bed-time dose are reported to promote sleep and thus render the prescription of a hypnotic unnecessary (Hussain and Chaudhary, 1973).

DISCUSSION

The findings of the present study support the hypothesis that a single daily dose of an antidepressant is as effective as the same amount of the drug given in divided doses. These results are similar to those of Kramer (1962), Hussain and Chaudhary (1973). Being a new drug which had not previously been given in large single doses, it was decided to put all patients on a fixed daily dose of 75 mgm. of Sintamil for the first 4 weeks of the trial, at which time in the absence of any serious side effects the dose could be increased to 150 mgm daily in those patients who failed to respond to the smaller dose. At the end of the 4 week trial period we obtained almost identical reductions in the group Hamilton Rating Scale scores—the percentage reduction being 71.2% in the S.D. group, and 68.9% in the D.D. group. On clinical global assessment also the response rates in the two groups are almost the same—44% in S.D. group and 37.5% in the D.D. group. At the end of 6 weeks the recovery rates had increased to 88% in the S.D. group and 79% in the D.D. group. The overall response rate to Sintamil therapy in the present study is found to be 82%—which is somewhat higher than the rate of 71.1% reported by Gupta and Mankodi (1972) for a mixed group of patients treated with Sintamil.

Adverse side effects from Sintamil intake were complained of by less than a third of all the subjects in the present study. (36% in the S.D. group, and 29% in the D.D. group) and the side effects were generally mild and did not necessitate stoppage of treatment in any case. This is again in conformity with earlier reports of a lower frequency of adverse effects on Sintamil as compared to other tricyclic anti-depressants. (Gupta and Mankodi, 1972). The findings that dryness of mouth and dizziness were more common in the divided dose subjects is of interest since it tends to occur within the first two or three hours after oral ingestion of the drug. On the other hand constipation was more common with the single bed-time dose administration.

In conclusion, it can be stated that Sintamil appears to be equally effective as an antidepressant both when given in a single bed-time dose or in the traditional three divided doses. Furthermore, it has relatively few side effects, and the more troublesome ones of dryness of mouth and dizziness are considerably less with the single night time dosage schedule. Finally, a single daily dose given at bed time is more convenient and likely to increase patient compliance as compared to the thrice a day schedule.

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