A COMPARISON OF A DIVIDED AND A SINGLE DOSE REGIME OF DOTHIEPIN AND ITS THERAPEUTIC EFFICACY

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SUMMARY

In a double-blind study the advantages of a once-a-day dosage of a tricyclic antidepressant as against a thrice daily dosage regimen was evaluated using dothiepin (Prothiaden) and matching placebo tablets. Twenty eight adult patients of both sexes participated in the study and were randomly allocated to drug treatment. Out of 28 patients who received dothiepin, 17 showed good improvement, in 6 improvement was fair and in 5 there was no improvement. These findings show that the response to dothiepin was satisfactory. Further, both treatments were equally effective in relieving symptoms of depression.

Dothiepin hydrochloride (Prothiaden) is a tricyclic anti-depressant. Chemically, it is 11-(3-dimethylaminopropylidene)-6, 11-dihydrodibenz (b, e) thiepin hydrochloride. Dothiepin possesses pharmacological properties similar to imipramine, amitriptyline and related drugs (Lipsedge et al., 1971; Sim et al., 1975; Herridge, 1975).

Recently it has been reported by some workers that steady state plasma levels of a tricyclic antidepressant can be maintained by administering the drug as a single dose at night (Kramer, 1962; Dimascio and Shader, 1969; Marshall, 1971) and clinical experience suggests that this method of administration is effective in relieving symptoms of depression. Dothiepin has a relatively long half-life which makes it suitable for a single dose administration (Horesovsky et al., 1967).

Therefore, the present study was planned to assess the antidepressant properties of dothiepin and also to compare the efficacy and tolerability of two dosage regimens, viz. three times daily dose and single nocturnal dose of dothiepin in patients with depression.

METHODOLOGY

The study was conducted at the Department of Psychiatry, Goa Medical College, Panaji, Goa. In this double-blind trial, 30 patients suffering from depression as a primary illness and not a secondary manifestation of any other illness, and in whom treatment with antidepressants was thought suitable, were selected. All patients were admitted initially for two weeks as inpatients. The duration of the trial was four weeks.

The patients admitted into the trial were randomly allocated to either Group D (three times daily dose) or Group N (single nocturnal dose). The group receiving three times daily dose of dothiepin was given equal total number of placebo tablets as a single dose at night and the group receiving single dose of dothiepin at night received identical placebo tablets three times daily in order to ensure that the trial remained strictly double-blind.

Initially, in the first week, patients belonging to group D received one tablet of dothiepin three times daily and patients in group N were given single nocturnal dose of three dothiepin tablets. Thereafter, depending on the patient’s response, dose was increased every week, the maximum number of dothiepin tablets being six daily. To any change in the daytime dose, there was a corresponding change in the number of tablets given as a single dose at night and vice versa. Dothiepin was supplied as 25 mg tablets, and placebo as identical looking tablets. Tablets for daytime use were dispensed in white bottles and for use at night in amber coloured bottles.
bottles, so as to avoid confusion.

Response to treatment was evaluated using the Hamilton rating scale before treatment, daily in the first week and thereafter at the end of the second, third and fourth weeks of treatment. The patients were considered to have marked improvement when the final score was between 1 and 10, moderate improvement when it was between 11 and 20, slight improvement when it was between 21 and 30, no change when between 31 and pretreatment score, and worse when it exceeded the pretreatment score. Side-effects observed were recorded at each interview.

RESULT

Of the 30 patients who were enrolled in the study, two discontinued treatment. In the remaining 28 patients, there were no significant differences in age, sex, number of attacks of depression, pretreatment Hamilton scores and the number of patients who received previous treatment, with respect to their assigned treatment group (Table 1).

**Table 1—Profile of Patients**

| Group | No. of patients | Sex—Male | Sex—Female | Age—Range | No. of attacks of depression | Mean pretreatment | No. of patients who received previous therapy |
|-------|----------------|----------|------------|-----------|-----------------------------|------------------|-----------------------------------------------|
| D     | 14             | 6        | 8          | 22-62 yrs. | 1-5                         | 35.6 ± 3.86      | 8                                             |
| N     | 14             | 4        | 10         | 36-59 yrs. | 1-10                        | 37.1 ± 5.34      | 8                                             |

Efficacy of both the dosage regimens: A significant reduction in mean Hamilton rating scores was seen in the first week of treatment in both the groups compared to their mean pretreatment scores indicating quick onset of action of dothiepin hydrochloride (p<.01). Further gradual reduction in mean Hamilton rating scores was seen up to the fourth week in both the groups. However, maximum reduction was seen in the first week of treatment which is significantly more than the reduction in scores during subsequent weeks of treatment.

Comparison of efficacy of both the dosage regimens: An analysis of variance for Hamilton rating score was carried out to compare the efficacy of both the dosage regimens (Table 2). No significant difference was observed between the groups in terms of reduction in mean Hamilton scores, indicating that the single nocturnal treatment schedule is as effective as the thrice daily dosage regimen. No significant interaction between weeks and groups was seen, indicating that the pattern of reduction in the mean Hamilton scores is similar to both the groups. The efficacy and pattern

**Table 2—Analysis of Variance (variate—weekly reduction in score)**

| Source          | d.f. | Sum of squares | Mean square | F     |
|-----------------|------|----------------|-------------|-------|
| Weeks           | 3    | 870.5          | 290.2       | 5.384 *|
| Groups (within groups) | 26   | 1233.6         | 47.4        | 0.88  NS |
| Weeks × Groups  | 3    | 89.2           | 29.7        | 0.552 NS |
| Error           | 78   | 4203.8         | 53.9        |       |
| Total           | 111  | 6400.7         |             |       |

NS=Not significant (p>0.05); *Significant (p<0.01)
of reduction in the mean Hamilton scores was similar with the single nocturnal dosage schedule and thrice daily dosage schedule.

**Sex difference in response to the two dosage regimens**: Further analysis was carried out to find out sex differences in response to both the dosage regimens.

The average reduction in scores by the first week was $-12.9$ with the day time dosage schedule compared to $-6.3$ with the single nocturnal dosage schedule in the female group. The male group showed an average reduction of $-6.7$ with the day time dosage schedule compared to $-14.0$ with the single nocturnal dosage schedule (Table 3). It was seen that in the first week of treatment, the female group responded better with the day time dosage schedule while the male group responded better with the single nocturnal dosage schedule. This difference, however, did not reach a level of statistical significance (Table 4). The male and female groups also did not differ in the final responses to both the dosage regimens (Table 5).

**Comparison between responses of individual symptoms to both dosage regimens**: Favourable response (more than 50% reduction in pretreatment scores) of individual symptoms was analysed to see the differences between both the dosage regimens (Table 6). It is seen that both the dosage schedules on the whole were equally effective.

**Clinician’s overall assessment**: Table 7 presents the results of the clinician’s overall assessment which indicates that although both the dosage schedules were effective in improving the majority of patients, no significant difference was observed when both the dosage regimens were compared.

### Table 3—Sex differences in response to the two dosage regimens

| Average change in score | Female | Male |
|-------------------------|--------|------|
| N                      | D      | N    | D    |
| No. of patients         | 10     | 8    | 4    | 6    |
| Week                    |        |      |      |      |
| First week              | $-6.3$ | $-12.9$ | $-14.0$ | $-6.7$ |
| Fourth week             | $-16.4$ | $-20.0$ | $-21.0$ | $-18.0$ |

$N=$Single nocturnal dose $D=$Thrice daily dose.

### Table 4—Analysis of variance (variate—1st week score—pretreatment score)

| Source    | DF | Sum of squares | Mean square | F   |
|-----------|----|---------------|-------------|-----|
| Group     | 1  | 19.7          | 19.7        | 0.25 NS |
| Sex       | 1  | 0.9           | 0.9         | 0.01 NS |
| Sex $\times$ Group | 1 | 301.5 | 301.5 | 3.77 NS |
| Error     | 24 | 1920.3        | 80.0        |     |
| Total     | 27 | 2242.4        |             |     |

NS=Not significant ($p>0.05$).

### Table 5—Analysis of variance (variate—4th week score—pretreatment score)

| Source    | DF | Sum of squares | Mean square | F  |
|-----------|----|---------------|-------------|----|
| Group     | 1  | 11.3          | 11.3        | 0.06 NS |
| Sex       | 1  | 9.3           | 9.3         | 0.05 NS |
| Sex $\times$ Group | 1 | 67.9        | 67.9        | 0.33 NS |
| Error     | 24 | 4860.4        | 202.5       |    |
| Total     | 27 | 4948.9        |             |    |

NS=Not significant ($p>0.05$).

### Table 6—Response (50% reduction in pretreatment score) of various symptoms

| Symptoms | Total Responded | Thrice daily dose | Single nocturnal dose |
|----------|-----------------|-------------------|-----------------------|
| Depression | 14 10 (71.4%) | 14 10 (71.4%) |
| Anxiety | 14 9 (64.3%) | 14 6 (42.9%) |
| Insomnia | 14 9 (64.3%) | 14 7 (50%) |
TABLE 7—Clinician's overall assessment

|                | Moderate Marked Improvement | Slight Improvement | No Improvement | Marked Improvement | Worse |
|----------------|-----------------------------|-------------------|---------------|-------------------|-------|
| Group D (Day treatment) | 5 4 4 1 0                  |                   |               |                   |       |
| Group N (Night treatment) | 5 3 2 1 3                  |                   |               |                   |       |

Side-effects: The nature of side-effects observed is summarised in Table 8. Side-effects reported were mild and did not necessitate discontinuation of treatment.

TABLE 8—Side-effects

|                | Group D (Day treatment) | Group N (Night treatment) |
|----------------|-------------------------|---------------------------|
| A No. of patients, who had side effects | 6 | 6 |
| B. Symptoms: | | |
| Dryness of mouth | 3 | 2 |
| Constipation | 2 | 3 |
| Lack of appetite | 1 | 2 |
| Giddiness on standing | 2 | 4 |
| Drowsiness and sleep | 0 | 2 |
| Burning sensation | 1 | 0 |
| Vomiting | 0 | 1 |

DISCUSSION

Onset of action of antidepressants is of great importance, particularly in severe cases where risk of suicide is high. With dothiepin hydrochloride, maximum reduction in mean pretreatment scores was seen in the first week of treatment in both the groups compared to reduction seen in subsequent three weeks. Overall response to dothiepin hydrochloride in both the groups was good, taking into consideration that all the patients had severe depression.

The once-a-day dosage schedule has the advantage that it is more likely to be taken than divided doses (General Practitioner Research Group, 1970; Porter, 1969), particularly since depressed patients seldom keep to prescribed drug schedules (Wilcox et al., 1965). A similar study carried out by Pearce and Rees (1974) showed that more favourable results were achieved with patients taking the single nocturnal dose which was well tolerated in addition to being effective in relieving the symptoms of depression. However, we have observed that both the dosage regimens are equally effective in relieving symptoms in patients with depression. In the first week of treatment, female patients responded better (i.e. more reduction in mean Hamilton score) to thrice daily dosage regimen and male patients responded better to single nocturnal dosage regimen compared to thrice daily dosage regimen. By the fourth week of treatment, this sex difference in response to both the dosage regimens disappeared. Side-effects were mild with both the dosage regimens and the incidence was the same.

Since the clinical response was similar in both dosage regimens, we feel that patient compliance would be better with single nocturnal administration of the total daily dose of dothiepin.

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