

A COMPARATIVE STUDY OF DOTHIEPIN (PROTHIADEN) AND IMIPRAMINE IN DEPRESSION

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SUMMARY

In a single-blind, randomised, parallel-group study comparing the efficacy and tolerability of dothiepin (50-150 mg per day) and imipramine (50-150 mg per day) for 6 weeks, involving 60 adult patients with depression, it was observed that dothiepin was comparable to imipramine in terms of efficacy as assessed by Hamilton Rating Scale for depression, global scale for severity of illness and clinician's overall assessment of efficacy. Dothiepin was found to have a significantly earlier onset of anxiolytic action compared to imipramine. Dothiepin was well tolerated.

Dothiepin (Prothiaden) is a tricyclic antidepressant which was first synthesized by Rajsner and protiva in 1962. It is a thio analogue of amitriptyline. Early clinical work on dothiepin suggested that the drug has both antidepressant and anxiolytic properties (Rydzynski, 1966). In subsequent clinical studies, the drug has been shown to be an effective antidepressant with associated anxiolytic action in depression (Lipsedge et al., 1971; Johnson et al., 1973 and Sharma, 1981). Dothiepin has been shown to be well tolerated in clinical studies (Goldstein and Claghorn, 1980). The present study was planned to evaluate the efficacy and safety of dothiepin in comparison to imipramine, a commonly used tricyclic antidepressant, in patients suffering from depression.

Material and Methods

The study was conducted at the Department of Psychiatry, S.M.S. Medical College, Jaipur. In this single-blind parallel group study, 60 patients suffering from depression as a primary illness and not as a secondary manifestation of any other psychiatric illness, and in whom treatment with antidepressants was deemed necessary, were included, after obtaining their informed consent. The duration of the trial was six weeks.

Selection of the patients in the study was as per the criteria of Feighner et al. (1972). The exclusion criteria were pregnancy, lactation, prostatic hypertrophy, glaucoma, renal, hepatic or cardiovascular disorders, history of epilepsy, history of allergy to trial drugs, receipt of antidepressant medication during the preceding 14 days of commencing the

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trial, an immediate danger of suicide and need for electroconvulsive therapy for the present episode.

The patients admitted into the trial were randomly allocated to receive either imipramine or dothiepin. The following was the dosage administration of trial therapy : Day 1 to Day 3 : 50 mg as a single dose at night; Day 4 to Day 14 : 75 mg as a single dose at night; Day 15 (week 3) to Day 42 (week 6) : If response was considered inadequate to single dose of 75 mg daily, the dose of the drug was increased gradually, as per the clinician's judgement, upto 150 mg per day. The dose in excess of 75 mg was given in divided doses.

Clinical assessment of drug efficacy was based on the following parameters; these being carried out by an independent psychiatrist who was not aware of the drug received by the patient :

- (1) Severity of depressive illness using Hamilton Rating Scale for depression (Hamilton, 1960) prior to and at weekly intervals after commencing drug therapy.
- (2) Global scale for severity of illness—using the subjective judgement of the clinician as 0—not ill, 1—mild, 2—moderate, 3—severe and 4—very severe. This was recorded prior to initiation of drug therapy and thereafter at weekly intervals.
- (3) Clinician's overall assessment of efficacy—recorded at the end of 6 weeks of drug therapy on a 0-6 scale as 0—symptoms cleared, 1—marked improvement, 2—moderate improvement, 3—slight improvement, 4—no change, 5—worse and 6—withdrawn.

Assessment of tolerability and safety was carried out using the following parameters :

- (1) Side-effects—those observed by the physician or volunteered by the pa-

tient were recorded and the severity graded as 1—mild, 2—moderate, or 3—severe. A checklist of symptoms was completed prior to initiation of drug therapy so as to rule out disease-related symptoms being reported as 'drug' side-effects.

- (2) Cardiovascular examination—this included recording the supine and erect blood pressure and pulse rate prior to and at weekly intervals during therapy. A 12-lead electrocardiogram was recorded before commencing drug therapy and after 3 and 6 weeks of therapy.
- (3) Laboratory investigations—routine haematological and biochemical investigations and urinalysis were carried out before and after drug therapy.

Results

Sixty patients were enrolled in the study of whom 32 patients were randomised to receive dothiepin and 28 to receive imipramine. Five patients in each group did not fulfill the protocol requirements and were excluded from the analysis. Five patients receiving dothiepin and 4 receiving imipramine failed to attend the clinic regularly and therefore, their data were excluded for analysis of efficacy. Three patients receiving dothiepin and one receiving imipramine developed hypomanic/manic features such as elated mood, increased psychomotor activity, grandiose delusions, distractibility and flight of ideas and hence could not continue their medication. It is known that tricyclic antidepressants may unmask mania in bipolar disorder (American Medical Association, 1986). The data of these patients have not been included for efficacy assessments but have been included in safety evaluation. Thus the data for 19 patients in the dothiepin group and 18 in the imipramine group were analy-

Table 1. Demographic details of patients receiving dothiepin and imipramine

Parameter	Dothiepin (n=19)	Imipramine (n=18)
Age (years) Mean±S.E.M.	37.0*±2.40	45.8*±2.56
Sex (Male : Female)	10:9	10:8
Body weight (kg) Mean±S.E.M.	55.2±2.24	49.5±2.03
Duration of disease (months) Mean±S.E.M.	7.4±2.61	4.1±1.34
No. of previous episodes Mean±S.E.M.	1.2±0.38	1.0±0.32
No. of patients with suicidal attempts	3	2
Employment status-No. of patients working: those not working	6:13	4:14

*p<0.05 (t test)

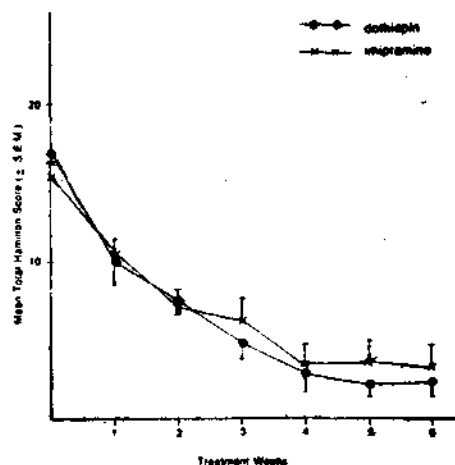
sed for efficacy and 27 in the dothiepin and 23 in the imipramine groups for tolerability.

The demographic details of the two treatment groups are presented in Table 1. The groups were comparable except that patients in the imipramine group (mean age 45.8 years) were older compared to those in the dothiepin group (mean age 37.0 years). The dosage of the two drugs used in the study ranged from 50-150mg per day.

CLINICAL EFFICACY

Hamilton Rating Scale : The mean total Hamilton scores for dothiepin and imipramine treated groups of patients before and during 6 weeks of drug therapy are depicted in Figure 1. Both the drugs produced significant reduction in the mean total Hamilton scores at each assessment period during therapy (weeks 1-6) compared to the baseline scores (p<0.01, Wilcoxon matched-pairs, signed-ranks test). There was no significant difference between the two groups in terms of reduction in total Hamilton scores (p>0.05, Mann-Whitney test).

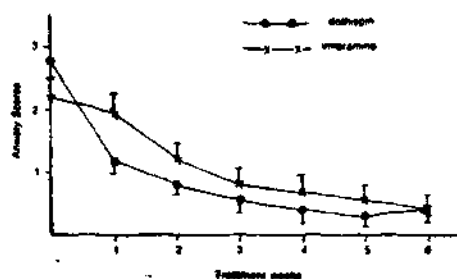
Figure 1 Mean Total Hamilton Score (± S.E.M.)



The anxiety scores were analysed separately and are graphically presented in Figure 2. It was observed that dothiepin resulted in significant reduction in anxiety scores from week 1 to week 6 of therapy; with imipramine, a significant reduction was observed only from week 3 of therapy (p<0.05, Wilcoxon matched-pairs, signed-rank test). The difference between the two drugs was significant in favour of dothiepin at week

1 of therapy suggesting an earlier onset of anxiolytic effect ($p < 0.05$, Mann-Whitney test).

Figure 2 Anxity Score (Mean \pm S.E.M.)



Global Scale for Severity of Illness: Both dothiepin and imipramine produced significant reduction in severity of illness from week 1 of therapy (Table 2). The patients in the dothiepin group had a significantly greater severity score prior to commencing drug therapy than those in the imipramine group ($p < 0.05$, Mann-Whitney test). Therefore, the percentage from pre-therapy was calculated and used for comparison between the two groups. The difference between the two drugs did not reach a level of statistical significance in this regard ($p > 0.05$, Mann-Whitney test).

Clinician's Overall Assessment of Efficacy: All 19 patients (100%) in the dothiepin group and 16 patients (88.9%) in the imipramine group had improved at the sixth week of assessment, as rated by the clinician (Table 3). The difference between the two groups was not statistically significant ($p > 0.05$, Mann-Whitney test).

TOLERABILITY

Side-effects: Out of 27 evalua-

ble patients receiving dothiepin, 14 reported side-effects, while 12 of the 23 evaluable patients receiving imipramine reported side-effects ($p > 0.05$, X^2 test). With dothiepin, 14 patients complained of a total of 21 side-effects and with imipramine, 12 patients complained of a total of 25 side-effects. The side-effects reported were typical of those reported with tricyclic antidepressants (Table 4). The mean composite severity score (\pm S.E.M.) was 0.93 ± 0.2 for dothiepin and 1.34 ± 0.39 for imipramine. Total number of side-effects and severity of side-effects was higher with imipramine than with dothiepin; however, the difference between the two drugs did not reach a level of statistical significance ($p < 0.05$, Mann-Whitney test).

Cardiovascular Examination: The drugs under study did not affect the pulse rate, supine and erect blood pressure to a clinically significant level, except for one patient receiving imipramine who experienced postural hypotension and sudden fall during end of week 1 of therapy. Imipramine therapy was continued in this patient for six weeks. No ECG changes were observed in either the dothiepin or imipramine groups.

Laboratory Investigations: Haematological and biochemical investigations and urinalysis showed no clinically significant changes.

Discussion

The results of the study corroborated the findings of Sim *et al.* (1975) and Eilenberg (1980) who have also observed that dothiepin is comparable in efficacy to imipramine. In this study, dothiepin was found to have an earlier onset of anxiolytic action compared to imipramine. The earlier onset of anxiolytic action of dothiepin has also been reported by Sharma (1981) and Vencovsky *et al.* (1964). This feature of dothiepin will be of benefi-

Table 2. *Global scale for severity of illness*

Drug	Severity score Mean \pm S.E.M.						
	Pre-therapy	Treatment week					
		1	2	3	4	5	6
Dothiepin (n=19)	2.1 $\pm 0.05^*$	1.40 $\pm 0.14^{**}$	0.9 $\pm 0.13^{**}$	0.5 $\pm 0.12^{**}$	0.4 $\pm 0.14^{**}$	0.5 $\pm 0.14^{**}$	0.3 $\pm 0.13^{**}$
Imipramine (n=18)	1.7 $\pm 0.16^*$	1.1 $\pm 0.14^{**}$	0.9 $\pm 0.14^{**}$	0.8 $\pm 0.20^{**}$	0.4 $\pm 0.14^{**}$	0.4 $\pm 0.17^{**}$	0.5 $\pm 0.17^{**}$

*p<0.05, (Mann-Whitney test)

**p<0.05 (Wilcoxon matched-pairs, signed-rank test).

Table 3. *Clinicians overall assessment of efficacy*

Clinician's Assessment	No. (%) of patients	
	Dothiepin (n=19)	Imipramine (n=18)
Symptoms cleared	12(63.2)	10(55.6)
Marked improvement	7(36.8)	6(33.3)
No change	—	2(11.1)

p<0.05, (Mann-Whitney test)

al value since anxiety is frequently associated with depression and early relief of anxiety is likely to aid patient compliance.

Dothiepin has been reported to have lower incidence of side-effects (Sim et al., 1975 and Eilenberg, 1980) and lesser severity of side-effects compared to imipramine (Sim et al., 1975). In this study the frequency and severity of side-effects were less with dothiepin compared to imipramine but this difference did not reach a level of statistical significance.

In conclusion, dothiepin was comparable to imipramine in terms of efficacy with an earlier onset of anxiolytic action and it was well tolerated.

Table 4. *Nature of side-effects with dothiepin and imipramine*

Nature of side effect	Dothiepin (n=27)	Imipramine (n=23)
Dryness of mouth	8	6
Constipation	3	3
Urinary difficulty	—	1
Nausea	—	1
Vomiting	—	1
Anorexia	—	1
Indigestion	2	1
Drowsiness	2	1
Restlessness	1	1
Tremors	1	3
Mania	3	1
Giddiness	1	3
Sweating	—	1
Sudden fall	—	1

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