

THERAPEUTIC EFFICACY OF DOXEPIN IN DIVIDED AND SINGLE DOSE REGIME

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Doxepin Hydrochloride is an anti-depressant which though widely used abroad, is relatively new on the Indian scene. Chemically, Doxepin, is N, N-Dimethyl-dibenz (b, e) oxepin- ii(6H) propylamine hydrochloride (Krakowski, 1968). Doxepin, being a tricyclic compound, has its basic action similar to other compounds of the group (Groton, 1967). It is tertiary amine like Amitriptyline and Imipramine which confers mood improving properties on the compound (Arieti, 1975). Some workers have rated it as good or slightly superior to Imipramine and Amitriptyline whereas Swiss Psychiatrists have not found it so. (Frank, 1969).

In India few research workers have used Doxepin to compare its effect in Anxiety neurosis with Trifluoperazine (Kishore *et al.*, 1973), or to determine an optimum dose of the drug in patients suffering from anxiety state associated with depression (D'Souza, 1978) or to compare its effectiveness with Placebo (Vahia *et al.*, 1974).

Recently, it has been reported by some workers that steady-state levels of a tricyclic antidepressant can be maintained by administering the drug as a single dose at night (Kramer, 1962, Dimascio *et al.*, 1969, Marshall, 1971) and clinical experience suggests that this method of administration is effective in relieving symptoms of depression.

MATERIAL AND METHOD

The study was conducted at the Department of Psychiatry and Human Be-

haviour, Goa Medical College, Panaji-Goa. In this double-blind trial, 43 patients suffering from depression as a primary illness, and in whom treatment with anti-depressants was thought suitable, were selected. Diagnosis of depression was made by two qualified psychiatrists independent of each other. The duration of depression varied from 15 days to 36 months with a mean of 5.7 months. Patients receiving previous therapy were given a drug-free wash out period of minimum 10 days.

The minimum score (on Hamilton Depressive Rating Scale) for inclusion into the trial was 30. The duration of the trial was four weeks. Routine haematological studies, liver function tests and fasting blood sugar determinations were done in all patients.

The patients admitted into the trial were randomly allocated to either group D (three times daily dose) or Group N, (single nocturnal dose) and there was no attempt to make the two sexes equal in the sampling. The group receiving three times daily dose of doxepin (25 mg) was given equal, total number of placebo capsules as a single dose (75 mg) at night and the group receiving single dose of doxepin at night received identical placebo capsules 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 capsule of doxepin three times daily and patients in Group N were given single nocturnal dose of three doxepin capsules. Thereafter,

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depending on the patient's response, dose was increased every week, the maximum number of doxepin capsules being six (150 mg) daily. To every change in the daytime dose there was a corresponding change in the number of capsules given as a single dose at night and vice versa. Doxepin and placebos were supplied in identical looking capsules containing 25 mg. of the active or the inert agent. Capsules for daytime use were dispensed in white bottles and for use at night in amber coloured bottles so as to avoid confusion in dispensing.

Assessment was done on Hamilton Rating Scale before treatment and at the end of 1st, 2nd, 3rd and 4th week of treatment. At each interview, physiological concomitants like bodyweight, pulse rate and blood pressure in supine and standing positions were measured and side effects noted. Out of 43 patients 11 patients occasionally needed supportive treatment with diazepam to control insomnia. The patients were considered to have their symptoms cleared when the final score on Hamilton rating scale dropped to the range of 0 to 5, marked improvement 6 to 15, moderate improvement 16 to 25, slight improvement 26 to 29, no change when range remained between 30 and above and worse when it exceeded the pretreatment score.

RESULTS

Of the 43 patients enrolled in the study, 5 were dropped from the study in the first week due to their non-co-operation. Otherwise there was not a single case of drop out due to side-effects of the drug itself. Out of the remaining 38 patients 21 belonged to group D (Day) and 17 to group N (Night).

Table I shows profile of the two groups. No significant difference between groups N and D was found in terms of age, sex, pretreatment mean Hamilton score, number of attacks of depression and the numbers

TABLE I—Profile of patients

	Group D (drug during day)	Group N (during ni- ght)
No. of Patients	21	17
Sex— Male	7	7
Female	14	10
Age— Range	28-66 years	35-56 years
Mean	39.43 years	39.18 years
No. of attacks of depression		
Range	1—8	1—15
Mean	2.3	2.5
*Mean Pre-treatment Hamilton score.	35.33	32.76
No. of patients who received previous therapy	12	12

$t=0.72$, $d.f.=36$, N.S.

that received previous treatment. Both the regimens were effective in reducing Hamilton score.

Table II shows degree of response to the individual symptoms in both the groups of drug therapy. The effect of nocturnal dose (Group N series) on the target symptoms of depression, anxiety and insomnia was quite impressive. Nevertheless, the difference in the amelioration of symptoms between group N and D series did not reach statistical significance.

Table III shows results of the Clinician's overall assessment. In Group D, 5 showed symptoms cleared, 12 showed marked improvement, 3 showed moderate improvement and one no change.

In group N, 6 were cleared of their symptoms, marked improvement was seen in 10, moderate in 1. No patient from

TABLE II—Degree of response to the individual symptoms in both the groups of drug therapy

Symptoms	Thrice daily dose		Single Nocturnal dose	
	Total	Responded	Total	Responded
Depression	21	18 (85.7%)	16	1 (94.1%)
Anxiety	20	17 (85%)	17	15 (88.2%)
Insomnia	21	13 (61.9%)	17	14 (82.4%)
Agitation	7	7 (100%)	8	8 (100%)
Retardation	16	14 (87.5%)	12	12 (100%)
Hypochondriasis	14	5 (35.7%)	10	4 (40%)
Somatic symptoms	19	6 (31.6%)	16	6 (37.5%)
Obsessional symptoms	9	4 (44.4%)	2	2 (100%)

TABLE III—Global clinical improvement based on reduction in M. H. R. scale

Total Hamilton score at the end of 4th week	Group D (N=21)	Group N (N=17)
0—5 (symptoms cleared)	5	6
6—15 (marked improvement)	12	10
16—25 (Moderate improvement)	3	1
26—29 (slight improvement)	—	—
30—Original score (no change)	1	—
More than original score (work).	—	—

either group became worse with treatment.

Table IV shows incidence of side-effects. Side-effects reported were mild and did not require discontinuation of medication.

It was noteworthy that in group N, there was no incidence of side-effects like palpitation, nausea, vomiting or blurred vision.

Table V shows the increase in body weight in both groups. In group D, the gain in weight was between 0.5 to 3.5 kg.

TABLE IV—Side effects

	Number of patients	
	Group D (drug during day) (N=21)	Group N (drug at night) (N=17)
Dryness of mouth	17 (81.0)	14 (82.4)
Palpitations	6 (28.6)	
Dizziness	6 (28.6)	5 (29.4)
Constipation	5 (23.8)	5 (29.4)
Fatigue	3 (14.3)	2 (11.8)
Tachycardia	2 (9.5)	3 (17.6)
Sweating	3 (14.3)	4 (23.5)
Drowsiness	1 (4.8)	3 (17.6)
Vomiting	2 (9.5)	
Nausea	1 (4.8)	
Mild excitement	2 (9.5)	1 (5.9)
Blurred vision	2 (9.5)	
*Mild urinary retention	1 (4.8)	
Tremor	1 (4.8)	4 ((23.5)
Orthostatic hypotension		
Total number of side-effects.	52	41

Figures in parenthesis indicate percentage.

*This refers to a patient who developed mild urinary retention, after the second week of therapy. With additional symptomatic treatment the condition was relieved and the specific therapy could continue.

TABLE V—Gain in body weight

	Increase in weight in Kgs. in 4 weeks	
	Range (Kgs)	Mean (Kgs)
Group D (N=21 pts.)	1.43	0.5 to 3.5
Group N (N=17 pts.)	1.75	0.5 to 3.0

in 4 weeks, with a mean of 1.43 kg. In group N, weight gain was in the range of 0.5 to 3.0 kg. with a mean of 1.75 kg.

DISCUSSION

On analysis of data, it was observed that of 38 patients who completed the trial, in 11 the symptoms were cleared, 22 showed marked improvement, 4 moderate improvement, 1 slight improvement and in 1 there was no improvement. These findings show that the response to Doxepin was satisfactory taking into consideration that all the patients had moderate to severe depression, with a mean score of 35.33 in group D and 32.76 in group N.

There was no attempt to make the two sexes equal in the sampling. However, the higher number of females in the total sample could be explained due to a high mental illness morbidity among females in our centre, which also holds true for depressive illness.

The second aim of the study was to compare the efficacy and tolerability of the drug when given in divided doses during the day and as a single nocturnal dose. 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 favour-

able results were achieved with patients taking the single nocturnal dose of Dothiepin 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 the symptoms of depression and the side-effects were mild in both the groups but incidence of side effects like palpitation, nausea, vomiting and blurred vision were not observed in group N. This finding is not surprising in view of the half lives of tricyclic compounds in general and the fact that attainment of a steady concentration is reached when the patient is sleeping, thus avoiding the mild subjective distress.

Body weight

A moderate increase in body weight with Doxepin was similar to weight-gain seen with other antidepressants. This weight gain was usually small but in some cases it was quite large (above 3 kg. in 4 patients). Various reasons have been ascribed in the literature for this gain in weight.

Target symptoms

Clinically the target symptoms which responded best to Doxepin were agitation, depression and anxiety.

It was observed that the divided and single dosage regimens did not cause any differences in therapeutic effectiveness. Similarly there was no significant difference in the incidence of side-effects. The present study suggests that the single nocturnal dosage of doxepin is well tolerated and is as effective as the thrice daily dosage schedule.

Haematological and biochemical studies did not reveal any significant changes in both the groups.

CONCLUSION

Doxepin, the new tricyclic antidepressant, produced good results in patients

with moderately severe depression. It was observed that the divided and single dosage regimens did not cause any difference in therapeutic effectiveness. Similarly there was no significant difference in the incidence of side-effects ($P > .05$).

Since the introduction of the drug in the management of depression, thrice daily dose is so far generally recommended but the present study indicates that the therapeutic effects are as satisfactory with single nocturnal doses with the added advantage of better tolerance. It thus offers the choice of flexibility in the management of depression with the nocturnal therapy offering an additional advantage of patient's compliance and convenience. Though we do not have enough data to offer a firm conclusion, it is suggested that single dose therapy may be avoided in the geriatric population, till more data are available.

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