A CONTROLLED DOUBLE BLIND COMPARATIVE STUDY OF SINGLE DOSE ADMINISTRATION OF IMIPRAMINE PAMOATE AND DIVIDED DOSE OF IMIPRAMINE HYDROCHLORIDE IN DEPRESSIVE ILLNESS*

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Summary : A double blind therapeutic comparison of single dose administration of imipramine pamoate and divided dose of imipramine hydrochloride was made in 40 indoor patients suffering from depressive illness. A fixed dose of 150 *mg* was used for both drugs for four weeks, employing randomized methodology with placebo capsules and teblets to balance dosage schedules. Four patients two from each group were dropped, leaving 36 patients for final analysis. The criteria of assessment were Hamilton Rating Scale and global evaluation by both the psychiatrist and the patients. Both the dosage forms were found to be highly effective as anti-depressants. Imipramine pamoate seemed to provide more consistent impovement but statistically the differences were not significant at the end of four weeks treatment. The major conclusion drawn from the study was the confirmation of therapeutic equivalence between a single daily dose of 150 *mg* of imipramine pamoate and divided dose of 150 *mg* of imipramine hydrochoride. Generally mild side-effects occured with equal frequency in both the groups and no adverse effects on haemopoietic, renal or hepatic function were seen with either dosage form.

Key words: depression, anti-depressant, imipramine pamoate, comparative study, imipramine hydrochloride

INTRODUCTION

Many investigators have reported poor patient compliance to drug therapy on multiple and repeated drug dosage and have expressed the importance of a single dosage therapy as an important aspect in the management of depression (5,6).

The total daily dosage of most medications is commonly divided into several doses in order to maintain a steady state of drug concentration in the plasma and to reduce the intensity of dose-dependent side-effects. This multi-dose schedule is questionable for

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psychotropic drugs. Since they are characterised by a long half-life, (8,13) slow metabolism, (14,22) slow excretion, (10) slow onset of action (1,7) and an extensive accumulation in the body tissues (9,20). The unidose scheduling of neuroleptics (3,15,18) and tricyclic anti-depressants (2,4,12,23) has been reported to be equivalent to or better than the divided dosage for reasons of tolerance, effectiveness, compliance and convenience.

In an editorial (21), it was emphasised that there is a need to have a tricyclic anti-depressant which can be prescribed as a single dosage at bed time as it will preclude the need for a hypnotic; the patient will be unaware of pharmacological effects that may be annoying during the waking hours, it will be more economical and convenient and as a result the patient compliance will increase.

The recent introduction of imipramine pamoate has created renewed interest in single daily dose anti-depressant therepy. This dosage form can be used to deliver the total daily dose required for depressed patients in a single capsule, preferably administered at bed time. When imipramine pamoate 150 *mg* given once daily was compared with 50 *mg* imipramine hydrochloride given three times daily, 24 hr plasma curves were almost indentical (23) which suggested that both forms of imipramine are absorbed to a similar extent.

Because earlier studies of imipramine pamoate suggested a definite place for this drug in the treatment of depression (11,17) the present study was designed to compare the efficacy and safety of imipramine pamoate and imipramine hydrochloride in a double blind study of patients with various forms of depression.

MATERIALS AND METHODS

Patients :

Forty patients who fulfilled the criteria of selection were included in this study. The criteria of selection were a definite diagnosis of depression, minimum score of 15 of the Hamilton Depression Rating Scale, willingness for admission and to participate in the trial. The patients with schizophrenia, organicity, alcoholism or drug dependence were excluded.

Assessment of depression :

The symptoms of depression were scored on Hamilton Depression Rating Scale before commencing treatment and then once a week for 4 weeks. The mean scores so obtained at the end of second and fourth weeks were compared with the corresponding initial scores.

Drugs and dosage schedule :

The investigation was conducted as a double blind controlled clinical trial. The control drug was imipramine hydrochloride. Forty consecutive patients who fulfilled the

above criteria of selection were studied. They were assigned according to random number table to one of the two groups of treatment. Randomization was done by the statistician and each patient was alloted a code number. The same number was given on the case record and as well as the bottles from which the drugs were dispensed. All patients received identical two tablets three times a day and two capsules at bed time. For the group receiving imipramine hydrochloride each tablet contained 25 *mg* of the drug and the capsule served is the placebo. For the group receiving imipramine pamoate, each capsule contained 75 *mg* of the drug whereas the tablet served as the placebo. Thus, neither the patients nor the psychiatrist knew which dosage form was being administered to any patient. However, sealed key to the code was given to the treating psychiatrist who could decode in the case of emergency. The treatment was administered for four weeks and printed proforma was employed for recording.

Therefore, each patient received either 150 *mg* imipramine hydrochloride in three divided doses or 150 *mg* imipramine pamoate as a single dose.

Parameters of evaluations :

At each weekly follow-up, the overall condition of the patient was assessed by (a) computing the percentage reduction in total score; (b) making a global evaluation, i.e. (i) asking the patients to make their own assessment and (ii) taking into account the improvement in social and occupational handicaps besides the fall in score, employing four arbitrary categories, viz. excellent, good, fair and no change/worse, (c) recording side-effects if voluntarily complained by the patients and action taken therefore, if any. Laboratory tests were done before and after four weeks of treatment included haemogram, urinanalysis, blood urea, serum bilirubin, alkaline phosphatase, SGOT and SGPT.

RESULTS

On decoding the treatments it was found that 20 patients had received imipramine hydrochloride in divided doses and 20 had received imipramine pamoate as a single dose.

Drop-outs :

Two patients on imipramine pamoate group and two on imipraime hydrochloride who deviated from the protocol were dropped and were not included for final analysis. The reason for drop out in all the four cases was failure to continue the therapy and leaving the hospital against medical advice. None of the above patients had significant adverse effects which warranted stoppage of therapy. Thus 18 patients in each group completed the study .

Comparability of the groups :

The details regarding sex, age, duration of illness and diagnosis of patients are given in Table I. It can be seen that there was no significant difference between the two groups. Most of the patients had either endogenous or involutional depression.

Therapeutic response :

Global assessment : Though the observations were recorded every week, the analysis was done at the end of second and fourth weeks' treatment. At the end of second week, global improvement by the psychiatrist indicated that excellent recovery was seen in 22.2% with imipramine pamoate while only 5.6% showed improvement with imipramine hydrochloride implying perhaps early onset of action of the former. Again, according to the assessment both by the psychiatrist and patients, there was higher incidence of failure with imipramine hydrochloride (38.9%) compared to imipramine pamoate (16.7%) (Table II).

TABLE I : Characteristics of patients treated with imipramine pamoate/imipramine hydrochloride.

Characteristics	*Single dose imipramine pamoate (No. of patients = 18)*	*Divided dose imipramine hydrochloride (No. of patients = 18)*
1. *SEX*		
Male	8	12
Female	10	6
2. *AGE* (years)		
18 – 25	2	1
26 – 35	4	5
36 – 45	4	5
46 – 55	6	3
56 – onwards	2	4
Range (years)	(18 – 75)	(21 – 62)
Mean age (years)	(44.44)	(44.00)
3. *Duration of illness* (months)		
1	2	—
1 – 6	9	12
7 – 14	3	5
14 and above	4	1
4. *Diagnosis*		
Involutional depression	6	4
Endogenous depression	6	11
Unspecified depression	3	2
Reactive psychotic depression	2	1
Neurotic depression	1	—

At the end of four weeks' treatment, the assessment both by the psychiatrist and the patients indicated excellent recovery (88.9%) with imipramine pamoate as well as with imipramine hydrochloride (77.8%). None of the patients failed to respond to both the treatments. However, there was apparently better improvement with imipramine pamoate (Table III).

TABLE II : Global improvement at the end of second week's treatments with imipraimine pamoate/imipramine hydrochloride.

(Number of patients showing improvement)

	Imipramine pamoate (n = 18)		*Imipramine hydrochloride* (n = 18)	
Rating	*Psychiatrist's assessment*	*Patient's own assessment*	*Psychiatrist's assessment*	*Patient's own assessment*
Excellent	4 (22.2%)	4 (22.2%)	1 (5.6%)	1 (5.6%)
Good	6 (33.3%)	4 (22.2%)	7 (38.9%)	7 (38.9%)
Fair	5 (27.8%)	7 (38.9%)	3 (16.7%)	3 (16.7%)
Failure	3 (16.7%)	3 (16.7%)	7 (38.9%)	7 (38 9%)

TABLE III : Global improvement at the end of fourth week's treatment with imipramine pamoate/imipramine hydrochloride.

(Number of patients showing improvement)

	Imipramine pamoate (n = 18)		*Imipramine hydrochloride* (n = 18)	
Rating	*Psychatrist's assessment*	*Patient's own assessment*	*Psychatrist's assessment*	*Patient's own assessment*
Excellent	16 (88.9%)	16 (88 9%)	14 (77.8%)	14 (77.8%)
Good	2 (11.1%)	2 (11.1%)	3 (16.7%)	2 (11.1%)
Fair	—	—	1 (5.6%)	2 (11.1%)
Failure	—	—	—	—

Hamilton Rating Scale : Statistical test of significance (analysis of variance) was carried out to find out the difference within the treatment and between the two treatments. The mean initial score in the imipramine pamoate group was 31.1 $\pm$ 1.2 and with imipramine hydrochloride it was 31.8 $\pm$ 1.2. At the end of second week's treatment the mean scores dropped to 17.4 $\pm$ 2.2 and 19.9 $\pm$ 2.2 with imipramine pamoate and imipramine hydrochloride respectively. The test of significance indicated that both the drugs were highly potent (Table IV).

At the end of fourth week's treatment the mean scores came down to 2.3 $\pm$ 0.7 and 3.6 $\pm$ 1.7 with imipramine pamoate and imipramine hydrochloride respectively. However, the statistical test of significance between the two treatments failed to show any difference between the two drugs either at two or four weeks' treatment (Table IV).

TABLE IV : Hamilton Rating Scale at the end of (A) – second week's treatment and (B) – fourth week's treatment with imipramine pamoate/imipramine hydrochoride.

	Treatment	*Mean initial score*	*Mean score at the end of second week's treatment*	*Statistical significance within treatment*	*Statistical significance between two treatments*
(A)	Imipramine pamoate	31.1±1.2	17.3±2.3	t=5.5 P<0.001 highly significant	t=0.8 P<0.1 *statistically highly insignificant*
	Imipramine hydrochloride	31.8±1.2	19.9±2.2	t=4.9 P<0.001 highly significant	
(B)	Imipramine pamoate	31.1±1.2	2.3±0.7	t=18.1 P<0.001 highly significant	t=0.7 P>0.1 *Statistically highly insignificant*
	Imipramine hydrochloride	31.4±1.2	3.2±1.7	t=14.0 P<0.001 highly significant	

Side-effects :

The incidence and severity of anti-cholinergic effects were not prominent. One of the eighteen patients in the imipramine pamoate group had symptoms of constipation and dryness of mouth as compared to two of the eighteen with the other group. The side-effects responded to symptomatic treatment and did not warrant discontinuation of the therapy. In addition, 2 patients receiving imipramine pamoate reported uneasiness while one developed nausea and one giddiness. One patient receiving imipramime hydrochloride complained of blurred vision. All the above symptoms responded to assurance and did not require discontinuation of the therapy.

Laboratory tests :

All the pre-treatment and post-treatment results were within normal limits which indicated that neither dosage form had haematologic, hepatic or renal toxicity (Table V).

TABLE V : Side effects of the two modalities of treatment in paients of depression.

Side-effects	*Imipramine pamoate* (n = 18)			*Imipramine hydrochloride* (n = 18)		
	No. of patients	*% of patients*	*Severity*	*No. of patients*	*% of patients*	*Severity*
Constipation	1	5.56	mild	2	11.11	moderate
Blurred vision	1	5.56	mild	—	—	—
Dryness of mouth	1	5.56	mild	—	—	—
Change in B.P.	none	—	—	—	—	—
Tachycardia	none	—	—	none	—	—
Change in other lab. parameters	none	—	—	none	—	—

DISCUSSION

The results of this study confirm the findings of other investigators (16,19) regarding the therapeutic equivalence of imipramine pamoate and imipramine hydrochloride in the treatment of patients with various forms of depression. Every patient who completed the study showed excellent improvement.

Global assessment at the end of second and fourth week's treatment indicated that imipramine pamoate had marginal superiority over imipramine hydrochloride. However, it was not substantiated when the results of Hamilton Rating Scale were statistically evaluated Thus, it was possible to compare the results even at the end of second week's treatment with both the dosage forms . Also at the end of the fourth week's treatment, the results were comparable with both the dosage forms for all parameters. Adverse reactions were limited to dry mouth and constipation, while blood pressure and laboratory values remained clinically stable throughout the study.

The problem of dosage compliance appears to be a major advantage with the use of imipramine pamoate in depressed patients. Ayd (3,4) reported that 60% of the chronic medical and psychiatric out-patients when instructed to take a single drug three times daily omitted between 25 and 50% of the prescribed dosage. He concluded that the problem of patient compliance can be minimised by once a day therapy.

The results of the present study confirm that a single dose of imipramine pamoate is therapeutically equivalent to three divided doses of imipramine hydrochloride in the treatment of depression. Further, it is pertinent to note from the study that with imipramine pamoate there were overall better results than with imipramine hydrochloride at the end of four weeks' treatment, although the results are statistically insignificant between the two groups. Patient tolerance of moderately high doses of imipramine pamoate was excellent, incidence of side-effects low and its acceptance quite favourable.

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