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CLINICAL TRIALS OF FLUVOXAMINE *VS* CHLORIMIPRAMINE WITH SINGLE AND THREE TIMES DAILY DOSING

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1 Two double-blind, randomised studies were performed to compare the efficacy of fluvoxamine and chlorimipramine in depressed patients. In the first study the effects of a single daily dosage of between 100 and 300 mg of fluvoxamine were compared with those of chlorimipramine at a dosage of 50–150 mg daily in 43 out-patients with endogenous depression.

2 In a second study using three times daily dosing with a daily dosage of 150–300 mg for both fluvoxamine and chlorimipramine, 30 in-patients with unipolar or bipolar depression were assessed.

3 Four weeks of treatment with single daily dosing resulted in a mean improvement of 61.4% (± s.d. 31.7) on the Hamilton Rating Scale for Depression (HAMD) for fluvoxamine and of 65.3% (± s.d. 25.8) for chlorimipramine. In the study with three times daily dosing the mean results were 72.9% (± s.d. 22.3) improvement for fluvoxamine and 62.1% (± s.d. 28.5) for chlorimipramine.

4 At similar dosages, fluvoxamine had significantly less untoward effects on blood pressure than chlorimipramine. Anticholinergic effects were also fewer in the fluvoxamine group, as were nervous system symptoms, with the latter difference reaching statistical significance ($P = 0.02$).

5 We conclude that fluvoxamine, given in a single daily dose of 150–250 mg, provides antidepressant efficacy similar to chlorimipramine. At this dosage it may be expected to produce less anticholinergic effects and have less influence on blood pressure than chlorimipramine.

Introduction

Fluvoxamine maleate, a specific neuronal 5-hydroxytryptamine (5-HT) re-uptake inhibitor, has been shown to be safe and efficacious in depression, when given at up to 300 mg/daily in three divided doses (Claassen *et al.*, 1977; Klok *et al.*, 1981; De Wilde *et al.*, 1982).

Once daily dosing of antidepressants is believed to have advantages over three times daily dosing with respect to patient compliance (Braithwaite *et al.*, 1974; Montgomery *et al.*, 1978). The plasma half-life of fluvoxamine is approximately 15 h, which, theoretically, should allow the drug to be given in a once daily dosing regimen (Claassen *et al.*, 1977).

Presented here are data of two double-blind studies conducted in Belgium. The safety, tolerance and efficacy of fluvoxamine was compared with that of chlorimipramine. The protocols of both studies were similar with the exception of the dosage scheme. In one study a three times daily regimen was employed while in the other study drug was given once daily, in the evening.

Chlorimipramine (Anafranil®, Ciba-Geigy) was chosen as the comparative drug since it is widely accepted as an antidepressant and it is the most potent 5-HT re-uptake inhibitor among available antidepressants (Waldemeier *et al.*, 1976).

Methods

Subjects

Thirty in-patients were studied in the three times daily dosing regimen, while 43 out-patients were included in the once daily study. Patients were endogenously depressed males and females between the ages of 18 and 70 years. The patients were required to meet a minimum of four of the Feighner Criteria for depression (Feighner *et al.*, 1972) and have a score of 16 or more on the first 17 items of the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1967). Excluded were patients with a significant concurrent organic disease and patients whose depression was a secondary manifestation of other psychiatric

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illnesses. Also excluded were pregnant or lactating women, patients who had received ECT or lithium within the last 4 weeks, patients with a high suicide risk and those with a history of drug allergy.

Study design

These were prospectively randomized, double-blind comparative clinical studies. The study employing three times daily dosing lasted 4 weeks, while the study using a single-dose (in the evening) regimen lasted 6 weeks. The treatment-free period for both these studies was at least 4 days. Patients previously on monoamine oxidase inhibitor therapy remained treatment-free for 14 days.

In the three times daily study, identical capsules containing 25 mg of fluvoxamine or chlorimipramine were provided. In the once daily study, medication was contained in identical capsules of 50 mg fluvoxamine or 25 mg chlorimipramine.

During the treatment-free period and the study period the following concurrent medication was allowed: benzodiazepines as hypnotics, sedatives or tranquillizers, chloral hydrate as a hypnotic, antibiotics, non-narcotic analgesics, antacids and laxatives.

Antihypertensive agents, anticoagulants and alcohol were not allowed. Psychotropic medication other than the benzodiazepines or chloral hydrate were forbidden.

As far as possible, concurrent medication once given, was to be kept at the same dosage throughout the study.

Study drug dosage

Table 1 shows the mean daily doses of the two drugs in both studies.

Table 1 Mean daily dosing (mg) in three times daily and once daily studies

Study/drug	n	*Week 1*	*Week 2*	*Week 3*	*Week 4*
Once daily					
Fluvoxamine	21	223	300	300	300
Chlorimipramine	23	109	150	147	144
Three times daily					
Fluvoxamine	15	151	210	236	259
Chlorimipramine	15	125	191	218	231

Assessments

Efficacy was measured by means of the 17-item HAMD (Hamilton, 1967). In addition, the Clinical Global Impression Scale (CGI) was used (Guy, 1976). Safety and tolerance were measured by means of blood pressure and heart rate recordings, ECG, and laboratory tests. Unwanted signs and symptoms were volunteered by the patient and recorded on a check list. In the three times daily study, all assessments except ECG were done at pretreatment and weekly thereafter; ECGs were done at pretreatment and at the final assessment on day 28. Patients who were on the once daily dose regimen were assessed at pretreatment and in weeks 2, 4 and 6; ECGs were done at pretreatment and at the end of week 4 and 6. Thus, results of the two studies were compared at pretreatment, weeks 2 and 4.

Data were compared statistically by means of the two-sided Wilcoxon test. The level of significance was $P < 0.05$.

Results

Pretreatment comparison of the patient populations was similar with regard to diagnosis and previous history of depression. The within-study comparison of the drug groups indicated that in both studies the severity of illness was similar. Between-study comparison indicated that in the three times daily study patients were slightly more ill than those in the single dose study (see Table 2). There were no drop-outs in either study.

Efficacy

The total HAMD score indicates a clinically significant improvement in the depressive symptomatology for both drugs in both studies (see Table 3). There was, however, a slight tendency for fluvoxamine to perform better than chlorimipramine in the three times daily study. The reverse was true for the single-dose study. The differences in efficacy between the two drugs were not statistically significant.

Analysis of the Hamilton Factors 1 (anxiety/somatisation), 3 (cognitive disturbance), 5 (retardation) and 6 (sleep disturbance) revealed no significant difference in improvement between the two drug groups in either study.

Bipolar patients

In the three times daily study, three of the four bipolar patients in the fluvoxamine group responded well (i.e., very much or much improved on CGI Global Change Scale). The one bipolar patient on fluvoxamine in the once daily study showed only minimal improvement.

Of the six bipolar patients on chlorimipramine (five in three times daily and one in once daily) only one patient (three times daily) showed a good response to therapy.

Table 2 Pretreatment comparability of the severity of depression in the two treatment groups in each study.

Study/drug	*CGI severity-of-illness score**				*HAMD*	
	n	*4*	*5*	*6*	*7*	*median score*	*range*
Once daily							
Fluvoxamine	22	1	3	15	3	23.0	16–30
Chlorimipramine	21	0	5	15	1	24.0	18–29
Three times daily							
Fluvoxamine	15	0	1	8	6	29.0	24–39
Chlorimipramine	15	0	2	11	2	29.0	21–33

* CGI severity scores: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = extremely ill.

Concurrent signs and symptoms

There were no unwanted effects which necessitated suspension of drug therapy in either study. In the three times daily study, four fluvoxamine patients (n = 15) and 13 chlorimipramine patients (n = 15) reported unwanted effects at some time during treatment. In the once daily study, 13 fluvoxamine patients (n = 22) and 17 chlorimipramine patients (n = 21) reported unwanted effects during the first 4 weeks of the study (see Table 4).

In both studies, the incidence of anticholinergic symptoms was greater in the chlorimipramine group (Table 5). The difference between the drug groups almost reached statistical significance (P = 0.08) in favour of fluvoxamine in the once daily study.

In the two studies, fine tremor was seen as a treatment emergent effect in both drug groups. The incidence, however, was low. The frequency of reporting for both groups was higher in the once daily study.

There was one report of vertigo and another of rigidity in the chlorimipramine group in the three times daily study; these symptoms were not reported in the fluvoxamine group in either study.

Symptoms of hypotension were reported by one patient in the fluvoxamine group and by six patients in the chlorimipramine group of the three times daily study. In the once daily study, symptoms of hypotension were reported by two patients in each drug group. All these patients received counteractive medication.

Cardiovascular variables

Table 6 shows the effect of both drugs on the cardiovascular variables in the two studies. The mean changes in these variables upon changing posture were minimal and are therefore not included in the table. In the three times daily study, blood pressure changes were unremarkable in the fluvoxamine group, while there was a small but statistically significant (P < 0.01) mean fall in heart rate over time; heart rate increased slightly in the chlorimipramine group. In the chlorimipramine group there were clinically noteworthy falls in blood pressure, resulting in statistically significant treatment differences in favour of fluvoxamine. In the once daily study, fluvoxamine and chlorimipramine were both associated with marked falls in blood pressure. Thus, no statistically significant treatment differences occurred.

There were no clinically noteworthy changes seen in the ECG which could be attributed to fluvoxamine or chlorimipramine administration.

Laboratory tests

Routine haematology and biochemistry tests were

Table 3 Course of improvement of the total study population (mean scores) as evaluated by the HAMD and CGI

Study/drug	*Pretreatment*		*Week 2*		*Week 4*		*Week 6*		*HAMD % improvement*	
	HAMD	*CGI*	*HAMD*	*CGI*	*HAMD*	*CGI*	*HAMD*	*CGI*	*Week 4*	*Week 6*
Once daily										
Fluvoxamine	23.4	5.9	16.5	4.7	8.9	3.2	6.4	2.5	61.4	72.3
Chlorimipramine	24.2	5.8	17.7	4.8	8.1	3.0	5.1	2.2	65.3	78.0
Three times daily										
Fluvoxamine	29.2	6.3	19.8	4.8	7.9	2.4	—	—	72.9	—
Chlorimipramine	28.9	6.0	20.7	4.8	11.1	2.8	—	—	62.1	—

CGI severity scores: see footnote to Table 2.

Table 4 Number of patients reporting unwanted effects

Study/drug	n	*Pretreatment*	*Week 2*	*Week 4*
Once daily				
Fluvoxamine	22	10	13	10
Chlorimipramine	21	14	17	15
Three times daily				
Fluvoxamine	15	2	3	4
Chlorimipramine	15	2	12	9

done. There were no overall changes in either study which could be regarded as clinically relevant.

Drug plasma levels

Plasma levels of 11 fluvoxamine patients and of 14 chlorimipramine patients were measured at week 2 and at the end of treatment (week 4) in the three times daily study. Both chlorimipramine and its metabolite, desmethylchlorimipramine were measured. Fluvoxamine has no known pharmacologically active metabolite(s) (Wakelin, 1982). In the once daily study, plasma levels of 20 fluvoxamine and of 20 chlorimipramine patients were measured at week 2 and at the end of treatment (week 6). There was no relationship between drug plasma level and response in either study; neither was there a direct relationship between drug dosage and plasma level.

Discussion

Comparison of once daily and three times daily dosing regimens of fluvoxamine showed a slightly better clinical response when fluvoxamine was administered in three divided doses. After 4 weeks of treatment, however, there was no statistically significant difference in efficacy ($P = 0.34$) between the two dosage regimens. In both studies, the efficacy of fluvoxamine was comparable to that of chlorimipramine. Both drugs were associated with an amelioration of depression in approximately 70% of the patients studied.

Chlorimipramine was associated with a clinically noteworthy lowering of blood pressure in the three times daily study, whilst in the fluvoxamine group the blood pressure remained stable. In the once daily study, both chlorimipramine and fluvoxamine were associated with a clinically noteworthy lowering of blood pressure over the treatment period.

It was noteworthy that, in the three times daily study, the mean daily dosing of fluvoxamine was similar to that of chlorimipramine while in the once daily dosing study, fluvoxamine was administered at a mean dosage double that of chlorimipramine. This may explain the effect of fluvoxamine on the blood pressure in the once daily study. However, in another study (Guelfi *et al.*, 1983), where 26 out of 70 patients on fluvoxamine received 300 mg daily in two divided doses from week 2 onwards, no such effect was observed.

In general, fewer patients reported unwanted effects in the fluvoxamine groups. The incidence of anticholinergic effects was lower with fluvoxamine, with an almost statistically significant ($P = 0.08$) treatment difference in favour of fluvoxamine in the once daily study. It has been suggested by others (Montgomery *et al.*, 1978) that the incidence of unwanted effects relate more closely to depressive symptomatology than to drug-effects. There was an indication in the

Table 5 Number of patients reporting anticholinergic symptoms

Study/drug	n	*Pretreatment*	*Week 2*	*Week 4*
Once daily				
Fluvoxamine	22	3	3	3
Chlorimipramine	21	6	8	7
Three times daily				
Fluvoxamine	15	1	2	3
Chlorimipramine	15	1	5	5

Table 6 Mean changes in cardiovascular responses after 4 weeks treatment (adjusted for pretreatment values).

Variable	*Drug/study*	*Week 4*	P *value**
Heart rate supine (beats/min)	Flu (3)	− 7.7	0.052
	Chl (3)	+ 0.8	
	Flu (1)	+ 0.4	0.76
	Chl (1)	+ 1.0	
Heart rate standing (beats/min)	Flu (3)	− 8.4	0.09
	Chl (3)	+ 1.2	
	Flu (1)	+ 1.3	0.70
	Chl (1)	0.0	
Systolic BP supine (mm Hg)	Flu (3)	− 1.7	0.02
	Chl (3)	−13.3	
	Flu (1)	− 7.0	0.90
	Chl (1)	− 5.5	
Diastolic BP supine (mm Hg)	Flu (3)	− 1.7	0.02
	Chl (3)	− 7.7	
	Flu (1)	− 6.4	0.45
	Chl (1)	− 4.3	
Systolic BP standing (mm Hg)	Flu (3)	− 2.0	0.06
	Chl (3)	−11.7	
	Flu (1)	− 8.9	0.34
	Chl (1)	−10.5	
Diastolic BP standing (mm Hg)	Flu (3)	− 1.7	0.02
	Chl (3)	− 7.7	
	Flu (1)	− 7.0	0.49
	Chl (1)	− 5.0	

Flu = fluvoxamine; Chl = chlorimipramine; BP = blood pressure.
(1) once daily, (3) three times daily.
*Difference between drugs at week 4.

chlorimipramine-treated patients, that more unwanted effects were reported by the patients who did not respond (response defined as 'much improved' or 'very much improved' on the CGI). The same indication was found in patients on fluvoxamine once daily. In the three times daily study there were too few unwanted effects reported by patients on fluvoxamine to find a relationship.

No relationship was seen between plasma levels and unwanted effects or plasma levels and response for either drug.

On the basis of these two studies, we conclude that fluvoxamine is an antidepressant whose efficacy is equal to that of chlorimipramine but with fewer side-effects. Fluvoxamine can be successfully given once daily in the evenings. We recommend that it be dosed between 150 and 250 mg daily, to obtain sufficient efficacy with a minimum of unwanted effects.

Fluvoxamine maleate was supplied by and plasma levels were measured by Duphar B.V., Weesp, The Netherlands. A.E.P. de Jong and P.J.M. Guelen from Applied Bioresearch Laboratories B.V., Assen, The Netherlands, determined the plasma levels of chlorimipramine and *N*-desmethylchlorimipramine.

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