Fluvoxamine and clomipramine in the treatment of cataplexy

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SUMMARY Fluvoxamine 25-200 mg daily and clomipramine 25-200 mg daily were given for separate three week periods to 18 subjects with narcolepsy and cataplexy. Both drugs improved cataplexy but not narcolepsy. Fluvoxamine was less active than clomipramine, but both drugs abolished cataplexy in individual subjects. Gastrointestinal side effects prevented treatment with fluvoxamine in five subjects. All patients completed the clomipramine phase of the trial, but two men complained of delayed ejaculation. Fluvoxamine is a more potent inhibitor of 5-hydroxytryptamine (5-HT) reuptake in some systems, but not in others. It is therefore uncertain whether the greater anticataplectic effect of clomipramine is due to a greater inhibition of 5-HT reuptake or to other mechanisms.

The prevalence of the narcoleptic syndrome is unknown, but it has been estimated that up to 100 000 people may be affected in the United States.¹ About 80% of narcoleptics also have cataplexy. Sympathomimetic drugs, which relieve narcolepsy, have little or no effect on cataplexy. Many patients therefore require treatment with two drugs, and occasionally more.²

Akimoto *et al*³ found that imipramine had an excellent effect selectively on cataplexy without affecting sleep attacks. Brodie *et al*⁴ later reported that desmethylinipramine had a more active and more rapid antidepressant effect than imipramine. Subsequently, Hishikawa *et al*⁵ gave desmethylinipramine to 23 patients with narcolepsy and cataplexy and found that the drug was at least as effective as imipramine in preventing cataplexy and had fewer side effects. Clomipramine, introduced by Passouant *et al*,⁶ is more active than either of these drugs and causes a 50% or greater reduction in the frequency of cataplexy in the majority of subjects; tolerance and side effects, however, can limit effective treatment.⁷⁻¹⁰

Clomipramine, and to a lesser extent the other tricyclics, have a profound effect on central 5-HT transmission resulting in an increase in post-synaptic receptor stimulation.¹¹ Other drugs with this effect, the 5-HT precursor 5-hydroxytryptophan (5-HTP) and the monoamine oxidase inhibitor phenelzine

have also been reported to improve cataplexy.¹²⁻¹³ The anticataplectic action of these agents may be due to alterations in 5-HT receptor activity in median raphe nuclei and descending serotonergic pathways that terminate in anterior horn cells.¹⁴⁻¹⁵

Fluvoxamine ((E)-5-methoxy-4'-(trifluoromethyl) valerophenone 0-2-aminomethyl) oxime maleate) is a potent inhibitor of serotonin reuptake in rat brain synaptosome preparations, and is more active than clomipramine in this system, although clomipramine has greater activity in a platelet system.¹⁶ It has little effect on other transmitter amines. Like the tricyclic drugs, which it does not resemble structurally, fluvoxamine is an effective antidepressant.¹⁷ Unlike most tricyclics including clomipramine, it has no anticholinergic effects and a very slight sedative effect even in high doses.¹⁶ In view of these properties, we studied the use of fluvoxamine in the treatment of cataplexy, and compared its action with that of clomipramine.

Patients and methods

Eighteen patients with narcolepsy and cataplexy, 11 male and 7 female, aged 31 to 68 years (mean 48.8 years) were studied. The duration of cataplexy ranged from 1-52 years (mean 19.6 years). Cataplexy, untreated, was assessed as mild in five patients, moderate in six cases and severe in seven cases. Narcolepsy was mild in two cases, moderate in eight cases and severe in the remaining eight cases. Thirteen patients suffered from sleep paralysis and the same number had hypnapompic or hypnogogic

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hallucinations. Twelve patients also had disturbed night sleep.

At the start of the trial 15 patients were taking clomipramine 25 to 100 mg daily (mean 49 mg). The remaining three patients, all with mild cataplexy, were taking maxindol 4 to 6 mg daily in two cases and on no treatment in one case. Four patients were taking clomipramine alone at a dose of 25 to 50 mg daily, five patients were taking clomipramine with mazindol 4 to 6 mg daily, five patients were taking clomipramine with dextroamphetamine 15 to 375 mg daily, and one patient was taking clomipramine with ephedrine 90 mg daily. Therapeutic response to clomipramine, as defined by a reduction of at least 50% in the number of attacks of cataplexy, was good in 12 patients.

TRIAL DESIGN

Patients were allocated at random to two groups, A and B. All patients stopped existing treatment for one week. Group A then took fluvoxamine for a three week period, and group B took clomipramine for three weeks. Both groups stopped treatment for a further week, and then took the alternative drug for three weeks.

DRUG DOSAGE

Fluvoxamine was given at an initial dosage of 50 mg twice daily. The dosage was then adjusted between 25 and 200 mg (mean 76 mg) according to clinical response. The initial dose of clomipramine was 25 mg nightly with later adjustment between 25 and 200 mg daily (mean 60 mg).

ASSESSMENT

All patients were assessed clinically by the observers on five occasions: 1 at the commencement of the trial; 2 at the end of the first week of drug withdrawal; 3 at the end of the first treatment period; 4 at the end of the second week of drug withdrawal; 5 at the end of the second treatment period.

Patient self-assessment was done at weekly intervals, using analogue scales. The following were recorded: 1 the frequency and duration of narcolepsy and cataplexy; 2 the frequency and duration of sleep paralysis and hypnagogic hallucinations; 3 the frequency of nocturnal awakenings. Patients also noted the duration of night sleep, their own assessment of mood and alertness and any apparent side effects. Scores were derived from the rating scales and comparison was made between results at the end of each week of drug withdrawal and the third week of the subsequent treatment period.

Pulse, lying and standing BP, ECG, full blood count, ESR, serum biochemistry and urinalysis were

noted at the beginning of the trial and after each treatment period.

Results

Twelve patients completed the fluvoxamine period of treatment and six did not. Five of these subjects had severe gastrointestinal side effects with belching nausea, abdominal distension and epigastric discomfort on fluvoxamine 25 to 50 mg daily. These subjects stopped taking the drug after two to 14 days. One patient experienced severe and continuous headache while on fluvoxamine 50 mg daily and stopped the drug after one week. These side effects ceased within 36 hours of fluvoxamine withdrawal. All 18 subjects completed the clomipramine phase of the trial.

THERAPEUTIC RESPONSE

The observers' impression was that fluvoxamine 25 to 200 mg daily caused a moderate reduction in the frequency of attacks of cataplexy and sleep paralysis in most subjects, and had a slight alerting effect in a minority of patients. Tolerance to the anticataplectic action of fluvoxamine did not occur during the three week period. Fluvoxamine had no effect on the frequency of hypnagogic hallucinations and did not alter mood, the duration of night sleep or the frequency of nocturnal awakenings. The therapeutic effects were apparent within 48 hours of starting treatment and persisted after fluvoxamine withdrawal for a further 48 hours.

Clomipramine 25 to 200 mg daily appeared to be more effective than fluvoxamine 25 to 200 mg daily in preventing both cataplexy and sleep paralysis. Unlike fluvoxamine, clomipramine had no apparent alerting effect in any subject. Clomipramine did not influence mood or night sleep.

Patient assessments of the effects of fluvoxamine and clomipramine are summarised in table 1. Fluvoxamine abolished cataplexy in four subjects and sleep paralysis in two subjects. The frequency of cataplexy was reduced by 50% or more. The effect of fluvoxamine was slight, but two patients reported a reduction in the frequency of day sleep attacks and an increase in alertness while on the drug.

Clomipramine abolished cataplexy in four subjects and sleep paralysis in five, and there was a 50% or greater reduction in the frequency of cataplexy in three patients. There was a similar reduction in the frequency of sleep paralysis in two subjects. Three patients reported improvement in day sleep attacks and alertness, but another three reported a deterioration in alertness.

Withdrawal of both fluvoxamine and clomipramine resulted after an interval of about 48 hours in the recurrence of frequent attacks of cataplexy, often o

Table 1 Number of patients showing percentage improvement indicated

Percentage improvement	Frequency of cataplexy		Frequency of narcolepsy		Frequency of sleep paralysis	
	F	C	F	C	F	C
100	3	4	0	1	2	5
≥50	2	3	1	2	3	2
≥25	2	3	3	2	1	1
≥0	3	1	6	4	1	0
Worse	1	0	2	3	1	0

F = Fluvoxamine

C = Clomipramine

Patients who did not complete the fluvoxamine phase of the trial are not included in Table 1.

greater severity than had occurred before pretrial clomipramine treatment was first instituted. This rebound deterioration lasted two to four days in most subjects. The order of administration of the two drugs had no detectable effect on the therapeutic response.

SIDE EFFECTS

Side effects occurred in three of the 12 patients who completed the fluvoxamine treatment period, and in five of 18 patients taking clomipramine. The side effects are listed in table 2.

BIOCHEMICAL DETERMINATIONS

Serum biochemistry remained unchanged throughout the trial as did full blood count, ESR, ECG, pulse and blood pressure. Urinalysis remained normal in all cases.

Discussion

Fluvoxamine is moderately effective in preventing cataplexy, and also partially abolishes sleep paralysis. These actions are apparent within 48 hours of starting treatment, whereas the antidepressant effects of the drug are usually not evident for one to two weeks.¹⁷ Because of this difference in timing, it seems probable that different mechanisms are involved in the antidepressant and antiepileptic actions of the

Table 2 Adverse reactions to fluvoxamine and clomipramine

	Fluvoxamine	Clomipramine
Nausea	2 (2)	0
"Indigestion"*	4 (4)	0
Weight gain	1	1
Headache	2 (1)	1
Dry mouth	0	2
Delayed ejaculation	0	2

Numbers outside brackets indicate total number of patients affected. Numbers within brackets indicate number of patients with severe reaction.

*"Indigestion" = epigastric pain, abdominal distension, belching.

drug. In addition to its definite influence on cataplexy, fluvoxamine appears to have a mild alerting action in some patients with narcolepsy. The timing of dreams, the frequency of nocturnal awakenings and the level of mood in nondepressed narcoleptics are uninfluenced by this drug. In spite of the advantages of fluvoxamine, including its apparent lack of cardiovascular toxicity, effective treatment is often limited or prevented by side effects, particularly gastrointestinal irritation.

Fluvoxamine is a slight less potent antiepileptic agent than clomipramine in equal doses, and has significantly less effect in preventing sleep paralysis. Clomipramine usually has no alerting action and, like fluvoxamine, does not cause any consistent change in mood, dreams or nocturnal sleep in narcoleptics. The side effects of clomipramine are generally different in nature from those of fluvoxamine. Previous studies of the short-term and long-term use of clomipramine in cataplexy have similarly demonstrated that the drug is very effective, although sexual side effects are common in males and tolerance develops after three to six months treatment in about a third of the patients.⁷⁻¹⁰ At doses which are effective in abolishing or reducing the frequency of cataplexy neither drug alone is an adequate treatment for daytime sleep attacks in the great majority of patients.

The mechanism of action of fluvoxamine and clomipramine remains uncertain. Narcolepsy and cataplexy occur in dogs, and canine cataplexy responds to high doses of phenytoin as well as to imipramine,¹⁸ suggesting that it may be a seizure disorder. In man there is no evidence that cataplexy is related to epilepsy. Although hydantoins have not been used in treatment, all the drugs that have proved effective including fluvoxamine and the tricyclic drugs lack significant anticonvulsant action.¹⁹ The evidence that serotonergic mechanisms are involved in the pathogenesis of cataplexy is indirect. The tryptophan hydroxylase inhibitor parachlorophenylalanine has not been given to narcoleptics, but does not cause cataplexy in patients with carcinoid or movement disorders.¹³ On the other hand, the beneficial effect on cataplexy of methysergide, a possible central 5-HT antagonist, has not been confirmed, and the antiepileptic action of 5-HTP is also doubtful.¹⁰ Wyatt *et al*¹³ gave the monoamine oxidase inhibitor phenelzine to seven patients with narcolepsy and cataplexy, and noted some improvement in both symptoms. All these drugs, in the doses used, may alter 5-HT receptor activity in the brain, but another tricyclic drug, protriptyline, is a very potent noradrenaline reuptake blocker with weak effects on the 5-HT system, also seems to be effective in cataplexy.²⁰

We conclude that, despite the somewhat contra-

dictory evidence, serotonergic mechanisms are likely to have an important role in the causation of cataplexy, although other transmitter systems are almost certainly involved. It is not possible to state unequivocally whether fluvoxamine or clomipramine is the more active 5-HT reuptake inhibitor since their potencies differ greatly in different test systems. In addition, it is possible that identical doses of fluvoxamine and clomipramine may produce very different plasma levels. Entirely comparable figures are not available, but a single dose of clomipramine 50 mg was shown to give a mean peak plasma level of about 44 ng/ml,²¹ while a single dose of fluvoxamine 100 mg gave a mean peak plasma level of about 55 ng/ml.¹⁹ It is therefore possible that the potency of a drug in the inhibition of 5-HT reuptake is the most important property determining its efficacy as an anticataplectic agent, but present evidence does not permit any definite conclusions.

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