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Comparative effects of fluoxetine and amitriptyline on cardiac function

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1 The effects of fluoxetine and amitriptyline on the electrocardiogram (ECG) and systolic time intervals (STIs) were measured during a double-blind parallel-group study in depressed patients.
2 ECGs and STIs were measured after a 1 week placebo run-in, following 1 week's treatment with fluoxetine 40 mg daily or amitriptyline 100 mg daily, and then after 3 weeks' treatment with fluoxetine 60–80 mg daily or amitriptyline 150–200 mg daily.
3 Fluoxetine had no effect on the ECG or STIs at any dose. Amitriptyline 150–200 mg daily shortened the sinus cycle length by a mean of 12%, prolonged the PR interval by 8% and the QRS duration by 10%. Amitriptyline did not significantly alter the STIs.

Keywords antidepressants electrocardiogram systolic time intervals

Introduction

Unwanted cardiovascular effects of tricyclic antidepressant agents are well recognised, not only in overdose (Sacks *et al.*, 1968; Cassidy & Henry 1987) but also in therapeutic doses (Blackwell, 1981; Cassem, 1982; Risch *et al.*, 1982; Veith *et al.*, 1982). These include conduction disturbances, tachyarrhythmias, myocardial depression and postural hypotension. Although concern over these effects of conventional antidepressants may have been exaggerated (Orme, 1984), the more serious effects have stimulated the search for safer alternative drugs.

Fluoxetine is a straight chain phenylpropylamide which is structurally unrelated to the tricyclic antidepressants. In common with several tricyclics, fluoxetine inhibits serotonin reuptake by nerve endings, but it has no effect on noradrenaline reuptake and little anticholinergic activity (Wong *et al.*, 1975, 1983). Comparative studies suggest that the clinical efficacy of fluoxetine in depressed patients is similar to that of imipramine (Cohn & Wilcox, 1985; Levine *et al.*, 1987) and amitriptyline (Chouinard, 1985).

The detailed effects of fluoxetine on the heart and circulation during a prospective study in depressed patients have not previously been reported. The present study evaluates the effects of fluoxetine and amitriptyline on the electrocardiogram and systolic time intervals during a parallel-group study of patients treated for depressive illness.

Methods

Twenty-seven out-patients entered in the study after giving their informed written consent. The protocol was approved by the local ethics committee. No patient had a history of serious physical illness or illegal drug abuse and physical examination was normal. In particular there was no clinical or electrocardiographic evidence of heart disease nor biochemical evidence of renal or hepatic dysfunction. The characteristics of the patients are summarised in Table 1.

After 1 week on placebo, patients were randomly allocated in a double-blind design to treatment either with fluoxetine or amitriptyline.

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Table 1 Patient details

	Fluoxetine				*Amitriptyline*		
Number	*Age (years)*	*Sex*	*Weight (kg)*	*Number*	*Age (years)*	*Sex*	*Weight (kg)*
1	54	M	77.5	12	39	F	71.0
2	41	M	90.7	13	61	F	78.0
3	46	F	66.8	14	29	F	69.0
4	57	F	64.0	15	50	M	102.5
5	42	M	72.0	16	57	F	62.3
6	27	M	99.5	17	36	M	80.0
7	30	F	66.8	18	57	M	64.8
8	38	F	67.5	19	24	F	52.3
9	48	F	54.2	20	53	F	50.5
10	30	F	56.5	21	35	M	85.0
11	24	M	61.0	22	63	F	70.5
				23	36	M	83.0
Mean (± s.e. mean)	40(±3.2)		70.6(±4.2)		45(±3.8)		72.4(±4.2)

The initial dosage of fluoxetine was 40 mg daily increasing after 1 week to 60 mg, with a further increase to 80 mg after another week if the therapeutic response was inadequate (eight patients). The starting dose of amitriptyline was 100 mg daily, increasing after 1 week to 150 mg and to 200 mg after a further week if clinically indicated (eight patients). The only other medication allowed was 10–20 mg of temazepam given as an hypnotic at night which was administered to four patients in the fluoxetine group and to six patients in the amitriptyline group.

At the end of the placebo run-in and after 1 and 4 weeks' active treatment, the following procedures were carried out: 1) High speed electrocardiograms were recorded at 100 mm s^{-1}, and measurements taken from five complexes. The QT interval was corrected for heart rate (QT_c) (Bazett, 1920), 2) Simultaneous high speed (100 mm s^{-1}) recordings of the electrocardiogram, carotid pulse wave and phonocardiogram (S.E. oscillograph 3006/DL, U.V. recorder) were used to measure the systolic time intervals corrected for heart rate, from 10 consecutive beats (Lewis *et al.*, 1977) and 3) Supine and standing blood pressures were recorded with an automatic recording sphygmomanometer.

Psychiatric assessments were also performed and electroencephalograms recorded, the results of which will be reported elsewhere.

Blood samples were taken immediately after the cardiac investigations. Plasma was separated and stored at −20° C until assay for both parent drug and the major active metabolite based on the methods described by Nash *et al.* (1982) and Abernethy *et al.* (1984).

Statistical methods

Electrocardiographic and systolic time interval measurements during placebo therapy were compared with those at the two dosage levels of active drug using two-way analysis of variance. When a significant variance was found, Student's *t*-test for paired data was used to locate differences from the control value. The control data for the two treatment groups were compared using the unpaired Student's *t*-test. Data are expressed as mean ± s.e. mean.

Results

Full data were obtained from 23 patients, 11 of whom received fluoxetine and 12 amitriptyline. Ten were male and 13 female with a mean age of 43 years (range 24–63 years). Four additional patients (two taking fluoxetine and two amitriptyline) were withdrawn from the study during the active treatment phase; two were receiving fluoxetine and one stopped treatment because of symptomatic deterioration of his depression, the other was withdrawn following an overdose of temazepam. One patient receiving amitryptyline refused to continue treatment without giving reasons, the other took an overdose of amitriptyline. One patient taking fluoxetine also received treatment with chlorpromazine at an average dose of 100 mg daily for 10 days prior to the final study because of the emergence of depressive psychotic phenomena.

Electrocardiogram (Table 2)

There were no significant differences between the two groups in baseline measurements. Fluoxetine produced no significant changes in the ECG measurements.

With amitriptyline 150–200 mg daily, there was a significant shortening of the sinus cycle length ($P < 0.006$), while the PR-interval was increased ($P < 0.02$) and the QRS duration pro-

Table 2 Effects of fluoxetine and amitriptyline on the electrocardiogram and systolic time intervals.

	Fluoxetine			*Amitriptyline*		
	Baseline	*40 mg daily (Week 1)*	*60–80 mg daily (Week 4)*	*Baseline*	*100 mg daily (Week 1)*	*150–200 mg daily (Week 4)*
QS_2I	518(±7)	519(±8)	521(±7)	518(±5)	525(±5)	530(±6)
LVETI	409(±5)	414(±7)	421(±6)	405(±4)	406(±3)	410(±3)
PEPI	109(±4)	105(±5)	108(±5)	113(±3)	120(±5)	119(±5)
PEP/LVET ratio	0.28(±0.02)	0.26(±0.02)	0.27(±0.02)	0.29(±0.01)	0.31(±0.01)	0.32(±0.02)
SCL (ms)	826(±46)	870(±35)	879(±44)	739(±44)	695(±28)	651(±28)ø
PR-interval (ms)	149(±6)	148(±6)	150(±5)	160(±7)	165(±7)	172(±7)*
QRS-duration (ms)	75(±3)	74(±2)	74(±2)	73(±3)	73(±2)	80(±3)øø
QT_c	401(±5)	407(±4)	411(±4)	418(±9)	411(±6)	424(±8)

QS_2I, LVETI and PEPI are respectively the duration of electromechanical systole, the left ventricular ejection time and the pre-ejection period, each corrected for changes in heart rate.
SCL = sinus cycle length.
QT_c = QT interval corrected for changes in heart rate.
* $P < 0.02$)
ø $P < 0.006$) Compared with baseline.
øø $P < 0.003$)

longed ($P < 0.003$). The QT_c was not significantly altered.

Systolic time intervals (Table 2)

There were no significant differences between the two groups in baseline measurements. No significant changes were produced by either fluoxetine or amitriptyline.

Systolic blood pressure

With fluoxetine 60–80 mg daily, the mean supine systolic blood pressure (123(±6) mmHg) was not significantly different from the pre-treatment value (124(±6) mmHg) and the average systolic pressure did not change on standing. In one patient there was a postural fall in blood pressure of 14 mmHg and in another 21 mmHg. The latter had taken chlorpromazine before the postural drop was recorded.

While receiving amitriptyline 150–200 mg daily, the mean supine blood pressure (133(±5) mmHg) was also not significantly different from the pre-treatment value (134(±7) mmHg). Nor was there any fall in the mean systolic blood pressure (131(±6) mmHg) on standing. However, in three patients there was an asymptomatic postural fall in systolic blood pressure of 10–14 mmHg.

Plasma fluoxetine and amitriptyline concentration

Mean plasma concentrations of amitriptyline were 28.3(±3.9) and 87.2(±14.9) $\mu g\ ml^{-1}$ and of nortriptyline 29.2(±3.6) and 89.7(±14.1) $\mu g\ ml^{-1}$ after 7 and 28 days treatment respectively. Those of fluoxetine were 87.8(±14.8) and 440.6(±62.8) $ng\ ml^{-1}$ and of norfluoxetine 95.5(±19.7) and 380.0(±54.1) $ng\ ml^{-1}$ at the same time. Plasma drug concentrations suggested that compliance was suspect in one subject receiving fluoxetine. Both log amitriptyline and nortriptyline concentrations respectively were independently, if weakly correlated with prolongation of PR interval ($r = 0.495$ $P < 0.05$, $r = 0.506$ $P < 0.05$) and QRS duration ($r = 0.551$ $P < 0.01$, $r = 0.598$ $P < 0.01$), but not to the change in sinus cycle length.

Discussion

In the current study, amitriptyline caused an increase in heart rate and a significant lengthening of the PR-interval and QRS-duration. These effects have been reported in previous experimental and clinical studies at therapeutic doses (Nemec, 1973; Fisch, 1985), although they are more pronounced in overdose (Thorstrand, 1976).

In contrast, fluoxetine produced no significant changes in cardiac conduction intervals or in the QT_c. Neither did it produce the increase in heart rate seen with agents which have significant anticholinergic activity (Burgess & Turner, 1981), in fact, there was a trend towards a slowing of the heart rate. Thus the present study is consistent with the findings of a previous retrospective study in which ECGs were recorded at conventional speeds (Fisch, 1985). The patient receiving chlorpromazine was included since similar doses of chlorpromazine have not been found to have effects on the ECG (Moyer *et al.*, 1954). At higher doses (150 mg day^{-1} and above) effects which might alter the PR interval, and prolong the QRS duration have been reported (Backman & Eluoso, 1964) but none was detected in this patient. Such an effect would increase the

chances of detecting an adverse change during treatment with fluoxetine.

It has been reported previously in single and multiple dose studies that amitriptyline reduces myocardial contractility (Burgess *et al.*, 1978, 1979). Although a trend to a prolongation in PEPI and PEP/LVET ratio were seen after amitriptyline but not fluoxetine in the current study, the changes were not significant. The only patient who experienced a fall in systolic blood pressure of greater than 20 mmHg was receiving chlorpromazine in addition to his fluoxetine therapy.

Our overall findings suggest that fluoxetine administered in therapeutic doses could be a safer antidepressant than amitriptyline in the treatment of patients with heart disease. Future research should include trials of this drug in elderly subjects and patients with cardiac disease and cardiovascular studies of patients who have taken overdoses.

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