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Cardiovascular effects of fluvoxamine and maprotiline in depressed patients

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Abstract In the choice of an antidepressant drug the clinician must often consider the presence of a cardiovascular comorbidity in depressed patients. In the present study the cardiovascular effects of fluvoxamine and maprotiline were compared in a double-blind trial in which the quantitative changes in ECGs were assessed before and during a 3-week treatment. A total of 33 patients (mean age 44 years; range 20–65 years) with major depressive disorder (RDC) who were free from clinically relevant organic diseases were investigated. After a 7-day wash-out period, a 3 week treatment phase was started with 200 mg daily of either fluvoxamine (n = 18) or maprotiline (n = 15). On days 0, 7, 14 and 21 a 12-lead standard ECG was performed and the drug plasma levels were determined. All ECGs were analysed in a blind fashion by an internist. Maprotiline caused a significant prolongation of the PR interval ($P < 0.001$) and of the QRS interval ($P < 0.01$) was well as an increase in heart rate ($P < 0.001$). The QT_c interval was only tendentially prolonged ($P < 0.10$) and the P-wave duration and T-wave amplitude were not affected by maprotiline. No significant changes in ECG parameters were observed during treatment with fluvoxamine; and there was a nonsignificant trend ($P < 0.10$) for a lower heart rate during treatment. Blood pressure was not affected by treatment with either antidepressant. In both groups no significant correlations were found between ECG findings and the plasma levels of the drugs. Our results confirm that fluvoxamine in therapeutic dose causes no alteration in surface ECG regarding cardiac conduction and repolarization. Conversely, maprotiline caused a significant prolongation of atrioventricular and intraventricular conduction and a rise in heart rate. Although these effects were not clinically relevant in our sample of patients without overt heart disease, they should be taken into account when treating depressed patients with concomitant cardiac disease.

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Introduction

It is commonly known that patients with depressive disorder very often have some medical comorbidity. This applies especially to cardiovascular disease, which must be given particular attention to when antidepressant medication is considered. It has long been known that the use of tricyclic antidepressants can be associated with potent cardiovascular effects, e.g. by their quinidine-like action on cardiac electrophysiology or in the form of a sinus tachycardia due to anticholinergic effects as well as altered noradrenergic activity (Glassman and Preud'homme 1993; Marshall and Forker 1982; Veith et al. 1994).

In the past 10 years several studies reported that despite these side effects tricyclic antidepressants can be administered to the majority of cardiac patients (Roose et al. 1991). The clinical practice, however, shows that in many cases these drugs are contraindicated because of cardiovascular disorder, e.g. in patients with severe conduction problems. An additional difficulty are the multiple drug interactions e.g. with antiarrhythmics, antihypertensives or anticoagulants. This explains why, in view of the increasing mean age of depressed patients, antidepressants without cardiovascular side effects are of the utmost importance to the clinical psychiatrist. In this context it should be mentioned above all the specific serotonin reuptake inhibitors (SSRI). A drug of this group that is already commercially used is fluvoxamine, which seems to be free from cardiotoxic effects as the data from animal experiments suggest (Wouters and Deimann 1983). Recent investigations provide evidence that this statement can be maintained also for the application of fluvoxamine to humans (for review see Benfield and Ward 1986). Apart from a minor, mostly not clinically relevant, reduction in the heart rate, no cardiovascular effects could be found. This assessment is based essentially on the studies

of Prager et al. (1986), Robinson and Doogan (1982) and of Roos (1983, 1984). Nevertheless, their findings cannot be used without reservation as a guideline for psychiatric pharmacotherapy for the following reasons:

1. In two of these studies fluvoxamine was administered to nondrepressive individuals either in a single dose (Prager et al. 1986) or over a comparatively short period of nine days (Robinson and Doogan 1982).

2. The findings reported by Roos are based on the pooled data from a total of 15 clinical studies on depressed patients examining response and tolerance of fluvoxamine compared with tricyclic antidepressants or placebo (Roos 1983, 1984). The ECG findings during these three methods of treatment were compared and assessed by cardiologists who were blind as to the applied treatment regimes. However, the publications by Roos state neither dosages nor duration of treatment. Moreover, there are no details about inclusion or exclusion criteria nor about the exact drug plasma levels found.

In light of this data situation, the statement that fluvoxamine is free from clinically relevant cardiovascular side effects cannot yet be made with certainty (Benfield and Ward 1986; Jefferson 1989). Therefore, it was the objective of the present study to compare ECG findings under fluvoxamine treatment with the course of ECG parameters under the regimen of a conventional antidepressant. This investigation was made within the framework of a more comprehensive research project studying efficacy, tolerance and latency of action of fluvoxamine and maprotiline. The reference substance maprotiline is known to be a tetracyclic antidepressant with marked noradrenaline reuptake inhibition, but mainly without impact on serotonin reuptake (Pinder et al. 1977). Whereas it was first assumed that maprotiline produced less cardiovascular effects than tricyclic antidepressants (Pinder et al. 1977), it was subsequently shown that the cardiac effects of maprotiline do not differ either in quality or quantity from those of the tricyclic substances (Blackwell 1986; Burckhardt 1983; Glassman and Preud'homme 1993).

In the present study the ECG findings under a fixed dosage of 200 mg daily of either fluvoxamine or maprotiline are compared with the initial findings before treatment and with each other. In contrast to other studies, where usually one ECG was performed before and during treatment, we conducted a total of four ECGs, three of them in weekly intervals during the treatment period. Various ECG parameters were assessed quantitatively, and in addition the results of the clinical ECG general assessment are reported.

Patients and methods

A total of 38 patients were included in the trial. Five patients discontinued the study, but in no case due to cardiovascular side effects. Thus, 33 inpatients completed the trial: They were aged 20 to 65 years with RDC diagnosis "major depressive disorder", who had been informed about objective and course of the study and had declared their consent to participate. The number of patients examined in the fluvoxamine group was 18 and in the maprotiline group 15. Both groups were comparable as to gender and age distribution, the mean age of the fluvoxamine group being 42.1 ± 11.5 years, and of the maprotiline group, 46.2 ± 9.4 years. Before the beginning of the study, all patients were submitted to a comprehensive medical check-up including laboratory tests, ECG and chest X-ray. Exclusion criteria were severe organic diseases present or past as known from entries in the medical record. They comprise especially cardiac, renal disorders or insulin-dependent diabetes mellitus. Further exclusion criteria were drug or alcohol abuse and simultaneous treatment with other psychoactive drugs (other antidepressants, neuroleptics, antiparkinsonian etc.) except a benzodiazepine (diazepam 10 mg), which was allowed in case of persisting insomnia. In no case were drugs with cardiovascular effect administered as comedication.

A 7-day wash-out period was followed by a treatment period of 3 weeks under double-blind conditions when the patients were given 200 mg daily of fluvoxamine or maprotiline. Pulse rate and blood pressure (Riva-Rocci) were measured three times daily. On days 0, 7, 14 and 21 a 12-lead standard ECG was performed. The plasma levels of fluvoxamine (gaschromatography) and maprotiline (HPLC) were determined on days 7, 14 and 21 with the blood samples taken 10–12 h after the last drug intake.

The ECG recordings were all performed by the same equipment (Hellige-Multiscriptor EK 33) with a paper speed of 50 mm/s. All ECGs were analysed by an internist according to identical criteria and blind as to the medication given. The quantitative ECG parameters were assessed from lead II by forming mean values based on three measurements. The frequency correction of the QT interval was conducted in the usual way according to the Bazett formula (Bazett 1920), which allows to determine the frequency-independent corrected QT_c interval. The amplitude of the T-wave was determined relative to the amplitude of the QRS complex and calculated in percent. In the qualitative ECG evaluation possible deviations from normal values were described. Finally, each ECG was submitted to a semiquantitative general assessment with a clinically oriented 5-grade scale (grade 1: normal findings; grade 2: dubious deviations from normal values, e.g. reduced T-amplitude or discrete ST segment depression; grade 3: slight pathological change, e.g. monomorphic ventricular premature complexes [VPCs] or more marked ST segment depression; grade 4: medium-grade pathological changes, e.g. signs of left ventricular hypertrophy or polimorphic and/or bigeminiform VPCs; grade 5: severe pathological changes, e.g. marked ischaemia-type repolarization disorder or complex ventricular dysrhythmia).

For the statistical analysis the initial values of day 0 were compared using student's *t*-test for independent samples. Changes in the course of the treatment period were, for both groups separately, examined for significance by analysis of variance with repeated measures. Concerning the relationship between drug plasma levels and ECG parameters, Spearman rank correlations were calculated.

Results

On day 0 both groups showed no difference concerning heart rate and blood pressure. Whereas in the course of the 3-week treatment period no significant changes in the blood pressure profiles were observed, neither within groups nor between groups, the pulse rate showed converse deviations from the initial values (Table 1). In the fluvoxamine group a slight reduction in the pulse rate was found (approximately 4–6 beats/min; $P < 0.10$). In the maprotiline group, however, a highly significant increase by approximately 10 beats/min was recorded ($P < 0.001$). For the quantitative ECG parameters no changes occurred in the fluvoxamine treated group of patients during the

Table 1 Heart rate and blood pressure profiles in fluvoxamine and maprotiline groups (means ± SD). SBP systolic blood pressure; DBP diastolic blood pressure

		Day 0	Day 7	Day 14	Day 21	*P*
Fluvoxamine:	Heart rate	81.5 ± 13.3	74.9 ± 13.1	75.0 ± 12.0	77.3 ± 10.0	< 0.10
	SBP	117.7 ± 14.7	121.3 ± 18.7	120.3 ± 18.2	118.5 ± 8.9	n.s.
	DBP	77.7 ± 10.6	78.5 ± 14.3	77.0 ± 13.7	73.5 ± 10.0	n.s.
Maprotiline:	Heart rate	79.8 ± 14.6	87.3 ± 12.9	89.8 ± 10.9	89.1 ± 12.4	< 0.001
	SBP	119.5 ± 18.4	123.3 ± 16.4	120.6 ± 17.4	121.8 ± 22.2	n.s.
	DBP	76.7 ± 12.7	80.9 ± 10.6	77.5 ± 11.9	79.4 ± 13.6	n.s.

Table 2 Quantitative ECG parameters and drug plasma levels in fluvoxamine group (means ± SD)

Parameter	Day 0	Day 7	Day 14	Day 21	*P*
P (s)	0.084 ± 0.010	0.086 ± 0.009	0.090 ± 0.011	0.086 ± 0.009	n.s.
PR (s)	0.141 ± 0.019	0.131 ± 0.015	0.132 ± 0.024	0.135 ± 0.015	n.s.
QRS (s)	0.076 ± 0.009	0.076 ± 0.009	0.074 ± 0.008	0.074 ± 0.010	n.s.
QT_c (s)	0.378 ± 0.020	0.373 ± 0.018	0.376 ± 0.024	0.380 ± 0.017	n.s.
T (%)	25.0 ± 10.9	25.9 ± 10.9	22.3 ± 8.2	24.7 ± 12.2	n.s.
Plasma levels (ng/ml)		130.7 ± 69.6	173.5 ± 110.5	188.5 ± 117.5	

Table 3 Quantitative ECG parameters and drug plasma levels in maprotiline group (means ± SD)

Parameter	Day 0	Day 7	Day 14	Day 21	*P*
P (s)	0.086 ± 0.013	0.097 ± 0.010	0.092 ± 0.010	0.087 ± 0.026	n.s.
PR (s)	0.138 ± 0.021	0.153 ± 0.019	0.155 ± 0.019	0.152 ± 0.020	< 0.001
QRS (s)	0.071 ± 0.007	0.075 ± 0.008	0.075 ± 0.010	0.077 ± 0.009	< 0.01
QT_c (s)	0.379 ± 0.020	0.383 ± 0.018	0.383 ± 0.021	0.389 ± 0.018	< 0.10
T (%)	23.4 ± 16.2	19.8 ± 7.1	21.1 ± 8.5	18.1 ± 6.4	n.s.
Plasma levels (ng/ml)		139.2 ± 46.9	200.5 ± 81.3	209.2 ± 93.1	

treatment period (Table 2). Under maprotiline treatment (Table 3), however, the PR interval was prolonged by approximately 0.015 s ($P < 0.001$) and the QRS interval by approximately 0.006 s ($P < 0.01$). The QT_c interval showed a trend for a prolongation by 0.01 s ($P < 0.10$). Whereas the changes in heart rate and PR interval under the influence of maprotiline could be clearly identified already after 1 week, QRS and QT*c* intervals revealed a tendency to increase and reached their maximum values by day 21. On the other hand, the slightly lowered heart rate in the fluvoxamine-treated patients became most obvious after 1 week. No significant correlations were established between the quantitative parameters and the plasma levels of both test substances.

The semiquantitative ECG assessment revealed no differences between the two groups nor any significant changes in the treatment course. For both groups the mean scores in the 5-grade assessment at baseline and during therapy varied slightly between 1.5 and 2.0. A marked pathological ECG finding of severity grade 5 was found in none of the patients. Medium-severity ECG changes (grade 4) were observed in one case. This was a female patient who under the effect of fluvoxamine for the first time developed ventricular extrasystoles to the point of an intermittent bigeminal pulse. After the end of the study period the medication was changed to maprotiline and the patient was subsequently free from cardiac dysrhythmia. Another female patient who had shown ventricular extrasystoles of low frequency before the beginning of the treatment period initially responded to fluvoxamine by increased dysrhythmia, but in the later course no arrhythmia became manifest. All 33 patients completed the 3-week study protocol without intolerable cardiovascular side effects either from a subjective or from an objective aspect.

Discussion

In the present study the two substances tested had no specific impact on the blood pressure. Concerning the heart rate a tendency to decrease by approximately 4–6 beats/min was observed under fluvoxamine, which has been described by other authors as well (Prager et al. 1986; Robinson and Doogan 1982). Thus far no conclusive explanation has been given for this finding. However, one may speculate that the decrease in heart rate under fluvoxamine could be caused by central serotonergic effects on cardiovascular function (Gradin and Persson 1993) as well as by vagal mechanisms triggered in the context of the comparatively frequent sickness under this

drug. In any event, the lack of an increase in the heart rate can be considered as evidence that this substance has no anticholinergic side effects (Benfield and Ward 1986). Among the patients treated with maprotiline an increase in the heart rate was observed – in accordance with the literature (Ahles et al. 1984; Bethge et al. 1982; Rudorfer and Young 1980) – of high statistical significance, namely by approximately 10 beats per min, which is essentially explained by the anticholinergic and noradrenaline reuptake blocking properties of the substance (Edwards and Goldie 1983).

As in the aforementioned studies, it was impossible to find evidence for fluvoxamine affecting the quantitative ECG parameters in our patients. Therefore, it can be concluded that fluvoxamine causes no alteration in the conduction and repolarization as assessed by the surface ECG. This is in accordance with the fact that in postmarketing surveys an increased rate of cardiovascular events in patients treated with fluvoxamine could not be found (Wagner et al. 1993). Also, no cardiac complications in connection with fluvoxamine intoxications have been observed thus far (Benfield and Ward 1986; Warrington et al. 1989).

In patients treated with maprotiline clear alterations of the quantitative ECG parameters were found. They consisted mainly of the prolongation of atrioventricular conduction, measured by the PR interval, and in a prolonged QRS interval, which is determined by intraventricular conduction velocity. The corrected QT_c interval, in which both intraventricular conduction and repolarization interval are involved, showed a tendency to being prolonged. The length of the P wave, which corresponds to the intraatrial conduction time, was not increased, nor did a significant alteration in T-wave amplitude appear. A review of the literature shows that Ahles et al. (1984), who treated depressive elderly patients with maprotiline at a daily dose of 75–225 mg, described a significant prolongation of PR and QRS intervals, manifested at 0.012 and 0.010 s, which is similar to the dimension found in our patients. Edwards and Goldie (1983) report that a mean maprotiline dose of 218 mg/die corresponded to an increase in PR duration of 0.022 s, but found no significant alteration in QRS interval. Kalelioglu et al. (1992) reported a prolongation of PR duration under medium doses of maprotiline (75–150 mg daily), whereas QRS- and QT_c-intervals were shortened. Finally, the data of Mielke et al. (1979), who found a significant rise in QT_c among medium-aged patients treated with 150–300 mg daily of maprotiline, should be mentioned, but reported no details of other ECG parameters. Concerning the two latter publications one reservation muste be made, namely that it contains no detailed information on the methodology of ECG analysis.

In summary, our findings are essentially in accordance with the data reported in the literature. The electrocardiographic alterations under treatment with maprotiline can be accounted for by a quinidine-like effect inherent in the substance, which could be validated in animal experiments (Zbinden et al. 1980) as well as under therapeutic intervention with maprotiline in humans (Burckhardt 1983; Raeder et al. 1979). This property may be responsible for the fact that, as with tricyclics, with maprotiline lethal intoxication may occur due to cardiac arrhythmia (Glassman and Preud'homme 1993).

Although the mentioned statistically significant changes in heart rate and ECG parameters were observed during maprotiline treatment, it must be emphasized that these effects are of only limited importance from a clinical point of view, because they remained within the normal range of the respective variables. This statement is supported by the clinician's general assessment of the ECG during maprotiline treatment, which revealed no significant diminution in the mean score, as likewise there was no specific change found during fluvoxamine treatment. In none of the patients of the maprotiline group were clinically relevant ECG changes observed during the treatment phase, especially no disturbed conduction; nor could any other cardiovascular side effects be observed.

In one female patient ventricular extrasystoles occurred for the first time with fluvoxamine, which abated upon subsequent change to maprotiline. A similar individual case is reported in the literature (Wright and Denber 1978). However, the great spontaneous variability of ventricular arrhythmia must be taken into account to the effect that single observations of this type must certainly be registered, but cannot be taken as sufficient evidence for an arrhythmogenic activity of fluvoxamine.

The lacking relationship between plasma levels and the intervals measured in the ECG of the fluvoxamine-treated patients requires no additional explanation, because no alteration of the latter had occurred during treatment. Even with maprotiline no such correlation could be established. This is in accordance with the findings of Edwards and Goldie (1983), the only publication thus far presenting respective data on maprotiline. With regard to tricyclic antidepressants, a review of the literature does not permit a concrete statement. Whereas some authors found no consistent correlation between plasma levels and ECG parameters (McCue et al. 1989; Smith et al. 1980), others reported significant correlations. In this context atrioventricular conduction time (PR interval) showed the most marked correlation with the plasma levels of the available antidepressants (Giardina et al. 1987; Rudorfer and Young 1980; Schneider et al. 1988; Stern et al. 1991). Significant correlations, particularly for QRS and QTc intervals, can possibly be expected for the OH metabolites of tricyclic antidepressants, rather than for the nonmetabolized initial substances. Respective data are available at least for desipramine and nortriptyline (Kutcher et al. 1986; Schneider et al. 1988). The lacking correlation between maprotiline and ECG parameters in our own data may best be accounted for by the fact that with therapeutic dosage the quantitatively measurable ECG changes are statistically significant, but clinically discrete, showing no correlation with plasma levels. To the extent, however, that the plasma levels approach the toxic range it seems likely that also with maprotiline – similarly to tricyclic antidepressants (Smith et al. 1980) – marked correlations be-

tween ECG and drug concentrations will become evident.

With regard to the clinical use of fluvoxamine, the findings reported in the literature and our own data suggest that this substance – similar to other SSRI, e.g. fluoxetine and paroxetine (Fisch 1985; Kuhs and Rudolf 1990) – usually does not cause relevant cardiovascular side effects. The described slightly lowered heart rate has no relevance for patients without heart disease. On the other hand, in cardiac patients especially disposition to bradycardia in connection with sick sinus syndrome, a decrease in the heart rate of potential clinical concern, may occur. Thus, syncopes due to bradycardia have been reported in patients treated with fluoxetine (Ellison 1990). Because fluvoxamine has not yet been sufficiently evaluated in the treatment of depressed patients with cardiovascular comorbidity (Jefferson 1989; Roose 1992), it seems strictly indicated in such cases to check pulse, blood pressure and ECG parameters at regular intervals. In this context the findings of Prager et al (1991) should be mentioned. They report on 48 patients with mild or moderately severe cardiovascular disease treated with a daily dosage of 100 mg fluvoxamine. They conducted comprehensive research including, for example, ECG under resting and stress conditions, Holter monitoring and echocardiography, and found no adverse cardiac effects. This result suggests that therapeutic use of fluvoxamine can be initiated even in cardiac patients at least at the mentioned rather low dosage without increased risk of side effects.

Concerning our ECG findings during maprotiline treatment, it must be considered that a comparatively high daily dose of 200 mg was administered. The identified ECG changes cause no adverse effects in patients without cardiac condition. Nevertheless, ECG controls are strictly recommended, at least with higher maprotiline doses (if plasma levels are not determined), because in the so-called slow metabolizers even therapeutic application may reach toxic concentrations, which are associated with the risk of cardiac complications (Preskorn et al. 1989). For patients with cardiovascular disease the same restrictions apply for maprotiline as for the traditional tricyclic antidepressants, i.e. there is an increased risk of side effects particularly with severely disturbed conduction. If such cases are treated with maprotiline at all, they must be submitted to a closely meshed system of clinical examinations and ECG controls. The antiarrhythmic activity of maprotiline (Ahles et al. 1984; Raeder et al. 1979; Warrington et al. 1989) can be a desired therapeutic effect in individual cases. It should be pointed out, however, that all substances with antiarrhythmic activity may have a paradoxical arrhythmogenic effect in 5–10% of patients treated (Burckhardt 1983). In addition, sinus tachycardia is a possible side effect of maprotiline treatment, as we were able to observe in a few patients of our study. This must be taken into account especially in patients with coronary artery disease, because it can lead to a critical deterioration of the myocardial oxygen balance. Finally, when maprotiline as well as tricyclic antidepressants are applied, potential drug interactions must be taken into consideration that may lead to enhanced effects on conduction if cardiac glycosides, antiarrhythmics or beta blockers are administered at the same time.

In conclusion, it should be stated that fluvoxamine has apparently only marginal effects on the cardiovascular system that are generally of no clinical relevance. Nevertheless, it seems prudent to keep cardiac patients treated with fluvoxamine under close observation especially with regard to heart rate and rhythm. Conversely, clear cardiovascular effects were established for maprotiline. Provided these are known to the medical practitioner in charge and the specific contraindications are observed, there are no fundamental objections against therapeutic use of maprotiline even in the presence of cardiovascular disease. The investigation of the cardiovascular activity profile of antidepressants by means of experimental and clinical studies therefore helps to provide effective and safe pharmacotherapy even to medically ill depressive patients. This aspect deserves attention particularly because the outcome of antidepressant use in depressive patients with somatic comorbidity has not been satisfactory to date.

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