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CARDIAC EFFECTS OF ANTIDEPRESSANT DRUGS. A COMPARISON OF THE TRICYCLIC ANTIDEPRESSANTS AND FLUVOXAMINE

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1 The cardiovascular effects of the tricyclic antidepressants (TCAs) are reviewed and compared with those of fluvoxamine, a new 5-hydroxytryptamine (5-HT) re-uptake inhibitor.

2 The TCAs have important effects on the heart, related to their anticholinergic and quinidine-like properties. The major side effects in therapeutic dosage include heart rate increase, postural hypotension and slight prolongation of the intraventricular conduction time and QT interval. In toxic dosage (or normal dosage in patients with severe heart disease) both advanced heart block and ventricular arrhythmias can occur, together with clinically important loss of myocardial contractile force.

3 Fluvoxamine has no effects on the heart except for a statistically (but not clinically) significant slowing of the heart rate.

Introduction

Tricyclic antidepressant drugs (TCAs) have very complex pharmacological effects, including anticholinergic activity, a blocking effect on noradrenaline re-uptake in adrenergic nerve terminals and myocardial depression. Because of these complex activities, cardiovascular effects are to be expected and, indeed, soon after its introduction Kristjansen (1961) reported hypotension and ST-segment changes as side-effects of imipramine. Since then almost all thinkable cardiac impulse-formation and conduction disturbances have been described both in patients treated with normal doses and in patients having taken an overdose of a TCA, including supraventricular and ventricular arrhythmias, sinus tachycardia, bradycardia, conduction defects, asystole and sudden death. Although normal doses are generally well tolerated, discrete effects on the ECG may be found in cardiologically healthy subjects, and serious problems may occur in patients with heart disease treated with a TCA. Thus, Coull *et al.* (1970) and Moir *et al.* (1972) reported an increase in sudden death in patients with heart disease treated with amitriptyline.

The ideal drug treatment of the depressed patient would consist of administration of a drug which would specifically and exclusively influence brain metabolism. Since ideal drugs do not exist, understanding of the mechanism of the side-effects is essential in the choice of a particular drug for a particular patient. It is the purpose of this article to review the cardiac effects of the TCAs and to compare these with those of fluvoxamine, a new drug which was specifically developed as a non-cardiotoxic antidepressant.

Tricyclic antidepressant drugs

The cardiovascular effects of TCAs can be subdivided as follows:

1. effects on blood pressure.
2. effects on myocardial contractility.
3. effects on the electrophysiological properties of the heart.

Effects on blood pressure

Theoretically, TCAs can raise blood pressure by potentiating the pressor effects of catecholamines due to their blocking effect on noradrenaline uptake in adrenergic neurones. Although low doses of imipramine have been shown to raise blood pressure in animals, reports in man on this subject are few and mostly deal with the interaction between the TCAs and the adrenergic-neurone-blocking antihypertensive drugs such as guanethidine and clonidine (Meyer *et al.*, 1970; Briant *et al.*, 1973).

TCAs potentiate the effects of sympathomimetic drugs, widely used in the treatment of upper and

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lower airways disease (Boakes *et al.*, 1973). This drug interaction is of clinical importance and should be kept in mind when prescribing TCAs to patients using these drugs.

TCAs may have clinically important effects on the blood pressure in the upright position, and this side effect has to be considered as the most common and potentially serious in clinical practice. Muller *et al.* (1961) found postural hypotension in 24% of their patients. In elderly patients, it occurred three times more often than in younger patients. Likewise, Hayes *et al.* (1977) found significant postural hypotension in the first 2 weeks of treatment of 20 patients with depressive illness. Glassman *et al.* (1979) studied prospectively 44 depressed patients treated with imipramine in doses achieving therapeutic plasma levels. They found no effect on recumbent blood pressure, but, on standing up, systolic blood pressure decreased by an average of 20 mm Hg ($P < 0.001$). This fall in blood pressure was independent of age, pre-existent cardiac status or plasma drug level. In a retrospective study of 148 patients, these authors found symptoms of postural hypotension in 20%, which were severe enough to cause physical injury in 4%. The best predictor of postural hypotension due to imipramine was the pretreatment postural fall in blood pressure and this finding may be helpful in selecting patient and drug.

The mechanism of postural hypotension caused by the TCAs is not fully understood. The most probable mechanism is the blocking of noradrenaline reuptake in central adrenergic neurones, resulting in increased receptor stimulation, which causes in turn inhibition of peripheral sympathetic activity and a drop in blood pressure. There are differences in the hypotensive effects between the various TCAs. Thus, nortriptyline and chlorimipramine have less postural effects than imipramine.

In clinical practice it is probably justified to state that postural hypotension is the major side-effect of the TCAs and that the drugs may have to be withdrawn in one out of every five patients because of this side-effect. In elderly patients, especially those with heart disease, postural hypotension or autonomic neuropathy, extra caution is necessary.

Effects on myocardial contractility

Several animal studies suggest that the TCAs depress the force of myocardial contraction. Laddu & Somani (1969) found, in open-chested dogs infused with desipramine, a marked decrease of myocardial contractile force and blood pressure. Perel *et al.* (1977) showed that several metabolites of TCAs share these effects. Human studies on the subject are scarce and have approached the problem necessarily in an indirect, non-invasive way.

Müller & Burckhardt (1974) who studied 30 patients by means of systolic time interval measurement, found that therapeutic doses of TCAs increased the pre-ejection period and its ratio to the left ventricular ejection time, findings which are considered to be indicative of loss of myocardial contractility. Burgess *et al.* (1979) and Guerrera & Melina (1980) equally found depressant effects on myocardial contractility in patients. Congestive heart failure has been described in patients with heart disease taking TCAs (Williams & Sherter, 1971).

From the clinical point of view, this effect will seldom pose a problem unless severe heart disease is already present. It should be kept in mind that this is only true in patients taking normal doses of TCAs. In massive overdose, even in healthy subjects, heart failure can occur (Mann *et al.*, 1959).

Effects on the electrophysiological properties of the heart

Heart rate Because of their anticholinergic effects, the heart rate can be expected to increase with administration of TCAs. Vohra *et al.* (1975b) in a study of 32 patients treated mostly with nortriptyline, found a mean increase in the sinus rate of 9 beats/min ($P < 0.005$). Bigger *et al.* (1978) similarly found a statistically significant increase in heart rate in seven patients treated with imipramine. These patients were studied by means of 24 h ambulatory ECG recording and the results were related to the plasma levels of imipramine and desipramine. The most striking increase of heart rate occurred in the early morning, and the lower the pretreatment rate, the greater the heart rate increase.

Atrioventricular conduction Contrary to expectations on the basis of their anticholinergic properties, TCAs have been shown to prolong the PR interval, (Vohra *et al.*, 1975b; Bigger *et al.*, 1978). Since the PR interval represents the total time necessary for the sinus impulse to travel through the atria, the AV-node, His bundle and bundle branches before it reaches the ventricular muscle, such an increase could be caused by a delay in any of these parts. The introduction in 1969 by Scherlag *et al.* of a catheter technique by means of which it is possible to make an intracardiac recording of His bundle activation, enabled a more exact localization of the site of the delay. Vohra *et al.* (1975a) studied 12 patients with this technique before and while taking nortriptyline and found that the increase of the PR time was due to a prolongation of the HV-time, i.e. a delay in conduction time in the His bundle and bundle branches. This delay correlated with the plasma level. They

found no change of the AH-interval, which represents mostly the AV-nodal conduction time.

The TCAs share this effect on distal conduction with the Class I anti-arrhythmic drugs (e.g., lignocaine and quinidine), which explains the conduction defects (right and left bundle branch block) observed in intoxication.

QRS-duration As demonstrated by Giardina *et al.* (1979) in their study of seven patients with imipramine, a slight but consistent increase of QRS duration occurs, indicating a slowing of the process of electrical activation of ventricular muscle. Intoxication with TCAs usually produces extreme broadening of the QRS complex (Thorstrand, 1974).

QT interval and ST interval The QT interval measures the total duration of depolarization and repolarization of ventricular muscle. This interval is related to the heart rate and becomes shorter with increasing heart rate. To interpret changes of the QT interval, the heart rate should be taken into account which is usually done by calculating the quotient of the QT interval and the square root of the R-R-interval. Bigger *et al.* (1978) (seven patients) and Giardina *et al.* (1979) (44 patients) demonstrated that imipramine caused a consistent prolongation of this corrected QT interval. Likewise, Veith *et al.* (1980) found a significant increase in this interval in a study of 26 patients treated with desipramine.

The ST segment may show non-specific changes during treatment with TCAs, with flattening of T-waves, occasional T-wave inversion and ST segment depression. Guerrera & Melina (1980) found these effects more frequently in patients with pre-existent heart disease.

TCAs: arrhythmogenic or anti-arrhythmic (or both)?

As mentioned above, the TCAs share some important electrophysiological effects on the heart with the Class I anti-arrhythmic drugs (e.g., quinidine, procainamide, disopyramide, mexiletine and lignocaine).

In animal experiments, these drugs uniformly depress the rate of rise of the action potential (caused by the rapid inward current of sodium into the cell), influence the duration of the action potential and depress the slow diastolic depolarization. Since the velocity of the upstroke of the action potential is the main determinant of the conduction velocity, the common effect of these drugs is that they slow conduction in certain areas and this property is held responsible for their anti-arrhythmic effect. Both in animals (Weld & Bigger, 1980) and in man (Bigger *et al.*, 1978; Giardina *et al.*, 1979) the TCAs have been shown to share these effects with the Class I anti-arrhythmic drugs.

It is beyond the scope of this article to go into the details of the mechanism of re-entry tachycardia. Generally, these can occur when non-homogeneous conduction exists in two pathways (as, for instance, in two branching Purkinje fibers). An antegrade impulse, blocked in the first, could travel via the other pathway and retrogradely invade the first, giving rise to a circus movement. By further depression of conduction in the first pathway, anti-arrhythmic drugs prevent retrograde invasion, thereby blocking re-entry. Since the TCAs share so many of the electrophysiological effects of the Class I anti-arrhythmic drugs, it might be expected that they could be used as such. Indeed, there are strong indications that patients with ventricular arrhythmias and depression can be successfully treated for both with a TCA. Chojnacki *et al.* (1981) studied the effects of imipramine, amitriptyline and nortriptyline in one patient with ectopic beats, by means of 24 h Holter recordings and found that all three drugs had quinidine-like effects on the number of premature beats. Giardina *et al.* (1979) studied 44 depressed patients, 11 of whom had more than 10 premature beats/h. In 10 of these 11 patients imipramine reduced the number of premature contractions by 50% or more.

At the present time, there is still little clinical experience with the anti-arrhythmic properties of the TCAs. The evidence, however, is convincing and this offers interesting possibilities for this category of drugs. Despite these facts, TCAs are generally considered to be contra-indicated, and even feared, in patients with arrhythmias. There appear to be several reasons for this:

1. An epidemiological study by the Aberdeen General Hospital group (Moir *et al.*, 1972) in 864 patients (119 of whom had cardiovascular disease) treated with a TCA demonstrated a statistically significant difference in sudden death rates in comparison with a matched control group (13/23 sudden deaths in the study group *vs* 3/15 in the control group, $P < 0.05$). Although it is by no means certain that arrhythmias were the cause of sudden death, it is at least likely that a number of patients died from ventricular arrhythmias. In contrast, the Boston Collaborative Drug Surveillance Program (1972), studying 80 patients with cardiovascular disease treated with a TCA, found no difference in the occurrence of arrhythmias, heart block, shock, syncope, hypotension, heart failure or mortality compared with a matched control group.

2. Like Class I anti-arrhythmic drugs, *toxic* doses of TCAs can cause arrhythmias. Marked prolongation of the action potential duration may cause prolongation of the vulnerable period in which premature beats could easily provoke ventricular tachycardia and even ventricular fibrillation. A

special type of ventricular tachycardia, 'torsade de pointes,' which occurs in patients with prolonged QT intervals, can be caused by anti-arrhythmic drugs. It is conceivable that overdosage of a TCA may produce the same type of tachycardia, although no literature reports are available. Vohra *et al.* (1974) have pointed out that many patients with TCA intoxication are wrongly diagnosed as having ventricular tachycardia, while in fact they have supraventricular tachycardia (or even sinus tachycardia) with extreme intraventricular conduction delay and broad QRS complexes simulating ventricular tachycardia.

3. Pre-existing conduction disturbances in the His bundle or bundle branches can be aggravated by even normal doses of TCA (and Class I anti-arrhythmic drugs). Kantor *et al.* (1975) described a patient with right bundle branch block and block in one of the divisions of the left bundle branch who reproducibly progressed to 2:1 AV block when treated with low doses of imipramine. Vohra *et al.* (1975b) described in their study of 32 patients, three patients who developed broad QRS complexes while on nortriptyline.

Some practical conclusions can be drawn from the foregoing:

normal doses of TCAs are not associated with increased risk of conduction disturbances or arrhythmias in patients without cardiovascular disease.

normal doses of TCAs can aggravate conduction disturbances in patients with severe intraventricular conduction disease, and the drugs should therefore not be given to patients with bilateral bundle branch block, bundle branch block with prolonged PR interval or patients with alternating bundle branch block and certainly not to patients with second or third degree AV-block.

in *toxic* doses, TCAs can provoke both conduction disturbances and ventricular arrhythmias. Since these effects are due to Class I effects, treatment of arrhythmias due to overdosage of a TCA with Class I anti-arrhythmic drugs is contraindicated.

TCAs can be beneficial in depressed patients with ventricular arrhythmias due to their Class I anti-arrhythmic effect.

Fluvoxamine

The search for an antidepressant drug with more specific influence on brain 5-hydroxytryptamine (5-HT) metabolism and fewer side-effects has led to the development of fluvoxamine. The pharmacological properties of the drug have been reported by Claassen *et al.* (1977), who found that fluvoxamine is an almost exclusively 5-HT re-uptake inhibiting drug. It appeared to decrease 5-HT turnover in rat brain, as a result of the interference with neuronal 5-HT re-uptake. Fluvoxamine does not inhibit noradrenaline re-uptake, and has no anticholinergic activity, both of which are properties of the TCAs.

Cardiovascular effects in animals

In dogs and cats no effect on blood pressure was found and in rats with renal hypertension, the drug had no hypotensive activity. In dogs, intravenous injection of 10 mg/kg fluvoxamine produced a decrease in heart rate and a related prolongation of the QT-interval. In guinea pig atria *in vitro*, fluvoxamine had less depressant effect on contractility than the TCAs.

An animal study, specially designed to study the cardiac effects of fluvoxamine, was carried out by Wouters & Deiman (1983) in rabbits. Fluvoxamine was compared with amitriptyline and mianserin. The drugs were infused intravenously in increasing doses until death of the animal. Fluvoxamine induced arrhythmias sporadically and only at nearly lethal doses whereas amitriptyline provoked serious arrhythmias at relatively low doses. The myocardial contractile force (as measured by left ventricular dp/dt) was depressed markedly by amitriptyline and only slightly decreased with fluvoxamine in moderate to nearly lethal doses. Mianserin had an effect somewhere between that of amitriptyline and fluvoxamine.

Cardiovascular effects in man

Saletu *et al.* (1977) studied 17 patients and found a statistically significant mean decrease of heart rate (mean 14 beats/min) in the fifth week of treatment. Blood pressure in the upright position did not change, while recumbent systolic blood pressure decreased from a mean of 122 to 109 mm Hg, which was statistically significant. The diastolic blood pressure remained unchanged. In four of the 12 patients non-specific ST segment changes were seen.

Klok *et al.* (1981) studied 36 female patients in a double-blind study of fluvoxamine *vs* chlorimipramine. Non-specific ST segment changes were found in six patients on fluvoxamine and seven patients on chlorimipramine. They found no consistent effect on blood pressure and heart rate.

One special study has been performed, dealing exclusively with the cardiac effects of fluvoxamine in man. Robinson & Doogan (1982) studied 26 healthy male volunteers between 40 and 60 years of age. The study was double-blind and randomized in a three way-cross-over fashion and compared the effects of placebo, fluvoxamine and clovoxamine (a drug of the same chemical series). A pretreatment period was

followed by three treatment periods of 9 days in which the patients took 50 mg of drug three times daily on the first and last two days, and 100 mg three times daily in between. The treatment periods were separated by a 5-day wash-out period.

Twenty-four hour ambulatory ECG recordings were made in the pretreatment period, during each treatment period and after the last treatment period. Representative 15 s strips were printed every hour and analysed. Blood pressure was measured both recumbent and in the upright position.

Fluvoxamine produced a statistically significant slowing of the sinus rate during the day and night (6.5 and 6.2 beats/min, respectively). The PR interval and the QRS duration were not affected. The QT interval was prolonged in relation to the slowing of the heart rate (0.013 s during the day and 0.011 s during the night). When corrected for the heart rate, there was a slight and statistically insignificant shortening of the QTc. The mean blood pressure (recumbent) was 119/76 mm Hg, both during placebo and during fluvoxamine treatment. Upright blood pressures were, respectively, 118/77 and 116/76 mm Hg. From these findings it appears that fluvoxamine has no effect on blood pressure.

ST segment changes were more frequently observed during treatment with fluvoxamine than placebo but only in the day-time. Thus, during fluvoxamine treatment there were 33 episodes of ST segment depression of 1 mm or less against 20 during placebo treatment and this was statistically significant ($P = 0.015$).

This finding could easily lead to the erroneous conclusion that fluvoxamine causes ST-segment changes but this is not felt to be the case for two reasons: (i) 24 h ambulatory ECG recordings are not suited for analysis and comparison of ST segments because electrode placement cannot be standardized. ST segment variations occur normally in 24 h recordings in normal subjects and are dependent on electrode placement, body position of the subject, state of physical exercise and technical factors. Different placement of electrodes during subsequent 24 h ECG analyses makes comparison of ST segment changes illusory. (ii) For statistical purposes, only printouts during placebo and during fluvoxamine treatment were compared and the printouts were then only compared when no hourly recordings were missing due to technical failure. This has led to the discarding of a considerable number of ST depression episodes, which happened to occur mostly in the placebo group.

When, however, all episodes (both in the pretreatment period and in the placebo period) are compared with the episodes of ST-segment depression during fluvoxamine, a different calculation can be made. Thus, there were 101 episodes of ST depression out of 616 recordings during pretreatment and placebo treatment (16.3%) and 55 out of 334 in the fluvoxamine period (16.4%), indicating that fluvoxamine probably does not have any influence on the ST segment.

Analysis of ECGs from double-blind studies — fluvoxamine vs *TCAs*

To increase the knowledge of the effects of fluvoxamine on the cardiovascular system, the ECGs from four double-blind studies were subjected to a standardized analysis (Klok *et al.*, 1981; De Wilde & Doogan, 1982; De Wilde *et al.*, 1983; Guelfi *et al.*, 1983). Inclusion criteria for the analysis were (i) a pretreatment ECG to be made before or on the first day of study drug intake; (ii) the patient to have had at least 14 days study drug intake; (iii) the treatment ECG to have been made no more than 48 h after stopping drug intake. The data from patients treated with the TCA reference agents, chlorimipramine and imipramine, have been combined to facilitate analysis.

The following variables were examined without knowledge of drug allocation:

1. quantitative: R-R, P-R, QRS and QTc intervals
2. qualitative: ST segments and T-wave configuration, drug effect (quinidine or digoxin-like effects), comparison of pretreatment and treatment ECGs and diagnosis (normal/abnormal). The qualitative analysis was partly derived from an ECG coding system, based on the system of Robles de Medina (1972).

One hundred and thirty-nine patients had two or more ECGs available for comparative analysis; 64 patients on fluvoxamine and 75 on the TCAs.

Quantitative results

R-R interval The effect of fluvoxamine on the R-R interval (i.e., heart rate) has previously been described. The data from this ECG analysis confirmed the finding of a small, and clinically unimportant, decrease in heart rate, i.e., an increase in the R-R interval was seen. For the TCAs, a decrease in R-R interval was seen, corresponding with an increase in heart rate, known to occur with this group of drugs. The treatment difference between the two groups was statistically significant ($P = 0.024$).

P-R interval Neither fluvoxamine nor the TCAs exerted any important influence on the P-R interval.

QRS interval Fluvoxamine had no effect on the QRS interval and was not statistically or clinically different from the TCAs in this respect.

QT interval In the fluvoxamine group, there was a small mean increase in QT interval. In the TCA group

there was a small decrease in QT interval. This latter result is consistent with the finding of a decrease in QT interval as the heart rate increases and was most pronounced in the largest study analysed. Comparison of the differences between the two treatments was statistically significant (P = 0.024).

QTc interval The rate-corrected QT interval (QTc) was analysed using the formula:

$$QTc = \frac{QT}{\sqrt{R\text{-}R}}$$

In both study groups there was a tendency for a very small increase in QTc (0.001 s with fluvoxamine and 0.005 s with TCAs). The treatment difference between fluvoxamine and the TCAs was just short of statistical significance.

Qualitative results

S-T segments The ECGs analysed from all four studies showed that neither fluvoxamine nor the TCAs exerted any systematic effect on the character of the ST segment.

T-waves Fluvoxamine had no important clinical effect on T-wave configuration. The TCAs on the other hand showed a tendency to change T-wave configuration. This was expressed mainly as a flattening or slight inversion of the T-wave.

Drug effects (digoxin-quinidine-like effects). Quinidine-like effects were reported for three patients in the fluvoxamine group and one patient in the TCA group.

Comparison of ECGs (baseline *vs* on treatment) There were 28 patients, nine on fluvoxamine and 19 on a TCA, who had ECGs on treatment which were abnormal when compared with their baseline recordings. The ECG changes which gave rise to those comments were mainly confined to T-wave configuration (repolarisation disturbances, i.e. flattening or inversion of the T-wave). It is difficult to attribute any of these changes directly and definitely to drug intake. However, in view of the known properties of the TCAs, it is likely that these effects on the T-wave are drug-induced rather than coincidental, at least in the TCA group.

From this analysis it appears that fluvoxamine has no effect on electrocardiographic intervals, with the exception of a slight reduction in the heart rate. A small number of patients (nine out of 64) showed minor T-wave changes. Although it is difficult to decide whether this is a direct drug effect, the possibility cannot be excluded. The clinical importance is certainly small and in comparison to the TCAs (19 out of 75 patients with T-wave abnormalities) quantitatively negligible.

Conclusions

In conclusion, it can be stated that the cardiac effects of both fluvoxamine and the TCAs are those that might be expected from their pharmacological profiles (Table 1).

Table 1 Pharmacological profiles of fluvoxamine (FLU) and tricyclic antidepressant drugs (TCA)

Property	*TCA*	*FLU*
Anticholinergic activity	+	0
Noradrenaline re-uptake inhibition	+	0
5-HT re-uptake inhibition	+/−	+
α-adrenoceptor blocking activity	+	0
Class I anti-arrhythmic effects	+	0

Fluvoxamine seems to have no cardiac effects apart from a slight and clinically unimportant reduction of the heart rate. In contrast with the TCAs, fluvoxamine exclusively influences brain 5-HT metabolism and therefore lacks their characteristic (and sometimes useful) side-effects on the heart. Although much more clinical experience will be needed, it might be speculated that even overdoses of fluvoxamine will not give rise to the serious cardiac problems for which the TCAs are feared.

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