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MIANSERIN, MAPROTILINE AND INTRACARDIAC CONDUCTION

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1 High speed surface electrocardiograms were recorded in 35 patients during the baseline and after four weeks' treatment in a placebo-controlled trial of mianserin and maprotiline in primary depressive illness.

2 Measurements of the RR, PR and QT intervals, QRS width and T wave height were made blind to patient, drug and treatment interval and compared with plasma drug concentrations. The presence or absence of cardiac arrhythmias was recorded.

3 The only significant findings were an increased heart rate and PR interval and decreased QTc interval in the maprotiline group. Only one patient receiving maprotiline had a cardiac arrhythmia. There was no significant correlation between measurements of ECG parameters and plasma drug levels.

4 The results confirm the lack of cardiac effects of mianserin and show both anticholinergic activity and effects of an intracardiac conduction in the case of maprotiline. The mechanisms of these effects are discussed.

Introduction

The effects of antidepressant drugs taken in therapeutic doses and overdoses on cardiac conduction, haemodynamics and blood pressure have been reviewed by Burgess & Turner (1981) while the experimental background to these effects has been described by Burrows *et al.* (1981). Our paper concerns only the effects of mianserin and maprotiline on intracardiac conduction.

There have been a number of previous studies of electrocardiographic changes following the administration of both mianserin (Peet *et al.*, 1977; Burgess *et al.*, 1978; Burckhardt *et al.*, 1978; Burrows *et al.*, 1979; Burgess *et al.*, 1979, 1980; Khan, 1980; Kopera, 1980; Wester & Siegers, 1980) and maprotiline (Briant & George, 1974; Khan, 1980; Ghose, 1981). The subjects in some of these studies have been healthy volunteers, in other patients with depression and/or cardiac disease. Different doses were used in different studies, ranging in the case of mianserin, for example, from 30 to 120 mg a day. Electrocardiograms (ECGs) were carried out at times following the administration of drugs ranging from 30 min to 13 months. Few studies have attempted to correlate ECG changes with plasma drug levels. Some studies have demonstrated effects of mianserin and maprotiline on the ECG while others have found no change.

There is clearly need for more research into the effects of these drugs on intracardiac conduction so we carried out electrocardiographic assessments during the course of a placebo controlled comparative trial of mianserin and maprotiline in primary depressive illness, the results of which are reported elsewhere in this workshop (Edwards & Goldie, 1983, this issue).

Method

In this study ECGs were recorded during the baseline and after four weeks' treatment in 35 patients given either mianserin, maprotiline or placebo under double-blind conditions. Patients gave their informed consent to participate in the study which had been approved by our local Ethical Committee. No patient in the trial had a serious physical illness (although it was later discovered that one patient had a history of ischaemic heart disease), organic brain syndrome, epilepsy or history of alcohol or illegal drug abuse. No patients were taking cardioactive drugs. A battery of haematological and biochemical investigations revealed no clinically relevant abnormalities.

Prior to inclusion in the study an attempt was made to withdraw previous medication for six to eight days wherever possible. Only three patients on maprotiline (who were off drugs for three, three and five days) and one on placebo (who was off drugs for four days) failed to complete the washout period.

Patients were then randomly allocated to treatment with either 30 mg mianserin, 75 mg maprotiline or placebo taken at night. The only other medication allowed was 5 mg of nitrazepam also taken at night if absolutely necessary. This was given to three patients in the mianserin and maprotiline groups and five in the placebo group at

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one stage or other during the course of the study. Only one patient in each of the two active treatment groups and two patients on placebo received nitrazepam during the 10 day period prior to the 28 day ECG.

After four weeks' treatment blood samples were taken within an hour of the ECG being recorded and the plasma was separated and stored at −20°C until drug levels were assessed, in the case of mianserin by gas-liquid chromatography and maprotiline by a double radio-isotope derivative technique (Riess, 1974).

High-speed surface ECGs were recorded at a paper speed of 50 mm/s. Standard limb leads were used and recordings were made at rest 12 to 18 h after administration of the previous night's antidepressant. The recordings were coded and the following were measured blind to patient and drug and whether the recordings were made before or after treatment in five consecutive waves: RR, PR(PQ) and QT intervals, QRS width and T wave height. The heart rate was derived from the RR interval and the corrected QT interval calculated using Bazett's hyperbolic correction factor, QT corrected = QT observed/$\sqrt{RR}$ interval, which corrects to a heart rate of 60 beats/min (Bazett, 1920). The presence or absence of arrhythmias in each tracing was recorded.

Means were calculated from each of the five consecutive readings and comparisons between groups were made for each parameter using non-parametric statistical methods. The Kruskal–Wallis one-way analysis of variance was used to test for overall differences between groups and the Mann–Whitney *U*-test for individual between-group comparisons. Correlations between variables were calculated using Kendall's rank correlation coefficient (Canover, 1971).

Results

When the code was broken at the end of the study it was found that 12 patients had received mianserin, 10 maprotiline and 13 placebo. The imbalance was due to some patients being dropped from the study or being unable to attend for one or other of the ECG recordings. The sexes and ages of the patients and plasma drug levels are shown in Table 1.

The mean age of the patients in the mianserin group was 43 years with a standard deviation of 13.0, while the means of the maprotiline and placebo groups were 35 (standard deviation 12.7) and 42 (standard deviation 13.1), respectively. Although the age range of patients in the maprotiline groups was lower than that of the other groups, the differences were not statistically significant. By the fourth week of treatment, each patient had required the maximum dose of mianserin, namely 90 mg, and all but one patient (who required 150 mg) received the maximum dose of maprotiline, 225 mg. The means and standard errors of the ECG measurements, together with the changes that occurred during treatment are shown in Table 2.

Table 1 Sex, age and plasma drug levels

Mianserin			*Maprotiline*			*Placebo*	
Sex	*Age*	*Plasma level (ng/ml)*	*Sex*	*Age*	*Plasma level (ng/ml)*	*Sex*	*Age*
M	55	103	M	44	236	F	24
F	34	31	F	18	205	M	50
M	63	80	F	38	99	F	52
M	25	30	M	37	230	F	38
F	36	60	F	35	237	F	50
F	45	25	F	55	305	F	22
F	56	60	M	29	112	M	36
F	33	31	F	26	294	M	34
M	31	—	F	19	294	M	25
M	52	121	M	52	158	M	54
M	56	99				F	46
F	24	27				F	64
						F	49

There were no statistically significant differences in any of the parameters during the baseline and no significant difference between mianserin and placebo at four weeks. There were, however, significant differences between maprotiline and placebo at four weeks. There were increases in heart rate and PR interval and a decrease in the corrected QT interval in the maprotiline group, and these were significant compared with the placebo group at the 5% level. In fact, every patient on maprotiline had an increase in heart rate and all but one, in whom there was no change, had an increase in PR interval. All but one (who had an increase) also had a decrease in the observed QT interval.

There were no significant correlations between changes in the ECG parameters and plasma drug levels. All patients were in sinus rhythm during the baseline. Only one patient developed a cardiac arrhythmia; she was a 38-year-old woman who had ventricular ectopic beats during treatment with maprotiline.

Discussion

Heart rate

There were no significant changes in the RR

Table 2

	Mianserin (n=11)		*Maprotiline (n=10)*		*Placebo (n=13)*	
Parameter	*Baseline*	*Change at 4 weeks*	*Baseline*	*Change at 4 weeks*	*Baseline*	*Change at 4 weeks*
Heart rate (beats/min)	72.5	6.5	72.5	22.6[a]	74.8	−8.3
SE	4.2	4.5	4.3	4.6	4.4	5.6
PR interval (s)	0.145	−0.001	0.154	0.022[a]	0.149	0.004
SE	0.006	0.006	0.008	0.004	0.007	0.004
QRS width (s)	0.095	0.004	0.097	−0.005	0.088	0.002
SE	0.007	0.006	0.013	0.010	0.005	0.003
QTc interval (s)	0.045	0.003	0.046	−0.009[a]	0.044	−0.002
SE	0.003	0.003	0.003	0.002	0.002	0.003
T wave height (mm)	2.51	0.03	2.36	0.25	1.93	0.14
SE	0.24	0.12	0.37	0.20	0.30	0.25

[a]Significant differences from placebo ($P<0.05$) using Mann–Whitney U-test

Table 3 Heart rate

Investigators	*Subjects*	*Dose (mg/day)*	*Duration*	*Change*
Mianserin				
Peet *et al.* (1977)	13 depressed patients	80–120	3 weeks	—
Burgess *et al.* (1978)	6 healthy volunteers	20	3 h	—
	2 depressed patients	Not specified	2 weeks	—
Burckhardt *et al.* (1978)	4 depressed patients	40	13 months	Significant increase (see discussion)
Burgess *et al.* (1979, 1980)	8 depressed patients	60	2–4 weeks	—
Burrows *et al.* (1979) (using His bundle electrodes)	10 depressed patients	60	3 weeks	Non-significant increase
Khan (1980)	12 depressed patients	30–60	5 weeks	Increase within normal limits
Kopera (1980)	6 healthy volunteers	20–60	8 days	—
	50 patients with heart disease	30–60	3 weeks	—
Wester & Siegers (1980)	10 healthy volunteers	30–60	6 days	—
Maprotiline				
Imhof (1972)	7	35–65		Slight decrease
Reale & Motolese (1972)	10 patients undergoing diagnostic cardiac catheterization	25–50 intravenous	10–20 min	—
Briant & George (1974)	5 healthy volunteers	75	10–14 days	—
Burckhardt *et al.* (1978)	7 depressed patients	100–150	13 months	Significant increase (see discussion)
Khan (1980)	11 depressed patients	75–150	5 weeks	Increase within normal range
Bethge *et al.* (1982)	20 depressed patients	75	3 weeks	Average increase of 5 beats/min in 70% of patients

interval and therefore in the heart rate in the mianserin and placebo groups. Reference to previous work is made in Table 3. The only study that suggested a significant increase in heart rate during treatment with mianserin was that of Burckhardt *et al.* (1978) but patients in their study received tricyclic and tetracyclic antidepressants. No significant differences were noted between drugs so heart rates and other ECG parameters were not analysed in relation to

individual drugs. The conclusion of the authors that the patients treated with mianserin had an increased heart rate is not justified, as only four of the total population studied were on mianserin and their contribution to the group as a whole is unclear. The results of all other previous work and our own shows that mianserin does not cause a significant change in heart rate which is in keeping with its relative lack of anticholinergic activity (Ghose *et al.*, 1976).

In contrast we found that patients on maprotiline had a significant increase in heart rate. This is to be compared with the results of previous work listed in Table 3 and a survey of data from 3459 patients that showed an incidence of sinus tachycardia of only 4.2% (Hattab, 1977). Our above comments on the work of Burckhardt *et al.* (1978) apply also to maprotiline as only seven of the total group were on this drug. Overall the balance of evidence from previous work and our own suggests that maprotiline produces an increase in heart rate due to its anticholinergic properties.

PR interval

We found no significant change in the PR interval in patients receiving mianserin, which is in keeping with the results of previous work (Peet *et al.*, 1977; Burgess *et al.*, 1978, 1979, 1980; Kopera, 1980; Wester & Siegers, 1980). Khan (1980) showed a decrease in PR interval within normal limits while Burckhardt *et al.* (1978) showed a significant increase which reverted to normal after 13 months but, as already discussed, this could have been due to the tricyclic antidepressants that were prescribed for most patients in the group. Discounting these findings, it appears that mianserin has no significant effect on the PR interval, thereby indicating that, in therapeutic doses, it causes no delay in conduction through the atrium.

In contrast our patients in the maprotiline group had a significant increase in PR interval. Previous work has shown different results. Briant & George (1974) noted no effect, Khan (1980) an increase within the normal range and Ghose (1981) a significant increase. Burckhardt *et al.* (1978) also reported an increase (again reverting to normal by 13 months). The balance of evidence suggests that maprotiline increases the PR interval, thereby showing a delay in conduction through the atrium. The mechanism of this delay is not fully understood. In the case of conventional tricyclic antidepressants, it is thought to be due to the inhibition of the re-uptake of noradrenaline and 5-hydroxytryptamine (5HT). Maprotiline has only a very weak action on the re-uptake of 5HT so one must presume that any effect due to re-uptake inhibition involves noradrenaline. An alternative possibility is that the PR interval prolongation is due to a quinidine-like effect, although it is difficult to incriminate this in the present study as there was no increase in QRS width and QT interval.

QRS width

We showed that neither mianserin nor maprotiline produced any change in the QRS width which is in keeping with the results of other investigators of mianserin (Peet *et al.*, 1977; Burgess *et al.*, 1978, 1979, 1980; Khan, 1980; Kopera, 1980; Wester & Siegers, 1980) and of maprotiline (Khan, 1980; Ghose, 1981). There appears therefore to be unanimous agreement that neither drug has a quinidine-like effect on depolarization in the ventricles when taken in therapeutic doses. If this is true the findings are inconsistent with the alleged quinidine-like and antiarrhythmic properties of maprotiline as a result of which one would expect an increased QRS width (Raeder *et al.*, 1979).

QT intervals

We were unable to show any significant effect on the corrected QT interval in patients receiving mianserin. Burgess *et al.* (1978) had previously shown increases occurring shortly after the administration of mianserin but reverting to normal after two weeks, while Khan (1980) observed an increase in the second and third week of treatment which also reverted to normal. Subsequent work involving different doses and durations of treatment showed no change (Burgess *et al.*, 1978, 1979, 1980; Kopera, 1980; Wester & Siegers, 1980). Overall the changes reported are slight and occur early in treatment; they are not sustained. The QT interval is a measure of the time taken for both depolarisation and repolarisation in the ventricles and can be increased by drugs that have a direct quinidine-like or cocaine-like local anaesthetic effect on the myocardium. It is apparent that mianserin has little or no such effect.

We found a significant decrease in the corrected QT interval during treatment with maprotiline. The QTc was, however, correlated with heart rate in each of the three treatment groups (Kendall's rank correlation coefficient -0.769, -0.614, -0.821 for mianserin, maprotiline, placebo, respectively; $P<0.05$ in each case) implying that the correction factor had not removed its dependence on heart rate. Similar findings were obtained when another (unpublished) correction factor used by C.D.

Burgess and F.A. Warrington, namely corrected QT = measured QT + 1.7 × heart rate, was applied.

A decreased QT interval is an uncommon effect, although it has been observed in patients receiving digoxin, propranolol (Stern & Eisenberg, 1969; Seides *et al.*, 1974), carbamazepine (Singh & Hauswirth, 1974) and amitriptyline (Burgess *et al.*, 1978) and in patients with hypocalcaemia (Schamroth, 1973).

Recent work has also shown that atropine shortens the QT interval during atrial pacing (Ahnve & Vallin, 1982). The authors of this work conclude that alterations of heart rate and inhibition of cholinergic tone independently affect the duration of the QT interval. This suggests that our findings could be due either to the increase in heart rate caused by maprotiline or due to an anticholinergic effect independent of heart rate. The results clearly call for further investigations, and the best method of doing this would probably be to carry out assessments of QT changes at identical atrial paced rates (Milne *et al.*, 1980). This, however, necessitates an invasive procedure and may therefore be unethical, despite the importance of investigating further a drug that alters both the heart rate and electrophysiological properties of the ventricle.

The length of the QT interval may increase the period of vulnerability of the ventricular myocardium during which ventricular arrhythmias may be precipitated by ventricular premature beats (Han & Goel, 1972). Drugs which shorten the QT interval may therefore have therapeutic advantages. If our findings are not due to the correlation with heart rate, the shortened QT interval could possibly explain maprotiline's alleged antiarrhythmic effect (Raeder *et al.*, 1979).

T wave height

We noted no significant changes in the height of the T waves in any of the treatment groups, suggesting that the antidepressants had no effect on depolarization or repolarization. As far as mianserin is concerned this is in keeping with the findings of Peet *et al.* (1977), Burgess *et al.* (1980) and Kopera (1980) while Ghose (1981) found only a non-significant decrease in T wave height in patients receiving maprotiline.

Arrhythmias

We identified only one patient with an arrhythmia other than sinus arrhythmia, namely the woman who had ventricular ectopic beats following treatment with maprotiline. In general, short electrocardiographic recordings allow for the recognition of frequently occurring arrhythmias but not occasional abnormalities. Prolonged monitoring is required to identify the latter. Using Holter monitoring, Raeder *et al.* (1979) found a decreased incidence of ventricular premature beats and a significant decrease in the severity of ventricular arrhythmias in 10 patients treated with 75 mg of maprotiline a day showing that this drug has an antiarrhythmic effect which they suggest is related to its quinidine-like properties. Bethge *et al.* (1982) were also unable to show an increase in ventricular ectopic beats or supraventricular extrasystoles.

Correlation with plasma drug level

We found no significant correlation between the ECG parameters and plasma drug concentrations. Previous investigators reported differing results with tricyclic antidepressants. Veith *et al.* (1980) found no correlation between plasma desmethylimipramine (desipramine) levels and PR interval prolongation, but a significant though relatively weak correlation with heart rate, QRS width, QTc interval and T wave amplitude, while Giardina *et al.* (1979) showed a significant relationship between plasma imipramine and desipramine levels and heart rate, PR interval and QRS width, though not QTc interval and T wave height. Burgess, Harries and George have shown similar weak correlations between imipramine and desipramine levels and QTc intervals and T wave amplitudes (personal communication).

There are a number of possible explanations for the results of previous work and our own; they include the time of sampling and the possibility that not all cardioactive metabolites are being measured.

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