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CARDIOVASCULAR RESPONSES TO MIANSERIN HYDROCHLORIDE: A COMPARISON WITH TRICYCLIC ANTIDEPRESSANT DRUGS

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1 The cardiovascular responses of mianserin hydrochloride and tricyclic antidepressant drugs were investigated using non-invasive methods of cardiac investigation. A study of the interaction of mianserin and antihypertensive drug therapy is reported.

2 In six normal volunteers, mianserin hydrochloride 20 mg was shown to prolong the corrected Q–T interval at 150 min ($P<0.001$). It did not affect heart rate, systolic time intervals or the peak normalized derivative of the apexcardiogram. Amitriptyline 50 mg increased the corrected pre-ejection period interval (PEPI) and the PEP/left ventricular ejection time (LVET) ratio of the systolic time intervals at 150 min ($P<0.001$). Q–T interval was shortened at 90 minutes.

3 In a double-blind patient study, clomipramine increased heart rate, P–R interval, QRS and corrected Q–T interval in one patient at 2 weeks. Mianserin prolonged corrected Q–T interval at 1 week but this returned to the pretreatment time by 2 weeks in two patients.

4 In an open study, mianserin 20 mg three times daily did not antagonize the hypotensive action of propranolol or propranolol and hydrallazine in three patients.

5 In a double-blind study in three patients with desmethylimipramine 25 mg three times daily, mianserin 20 mg three times daily did not antagonize the hypotensive action of either guanethidine or bethanidine.

Introduction

TRICYCLIC antidepressant drugs (TADs) have been used in psychiatric practice for the past 20 years and are now the first choice in pharmacological therapy for most depressed patients. Initially, no cardiovascular complications were found and it was thought that they could be used even if patients had cardiovascular abnormalities. In 1961, Kristjansen reported minor ST–T segment changes on the electrocardiogram (ECG) and hypotension occurring in depressed patients while on imipramine following exercise. He concluded that stress or cardiovascular disease may predispose patients to imipramine-induced ECG changes. Since then, various ECG abnormalities, including sinus tachycardia, conduction defects, supraventricular arrhythmias, ventricular arrhythmias, bradycardia and asystole, have been described both in therapeutic dosage and after overdosage (Rasmussen & Kristjansen, 1963; Vohra & Sloman, 1975; Jefferson, 1975; Thorstrand, 1974, 1976). In 1970, Coull *et al.* reported sudden death occurring in 6 out of 53 patients with cardiac disease after taking amitriptyline, compared with none out of 53 in a matched control group. Moir *et al.* (1972) reported 13 sudden deaths in 119 patients with heart disease being treated with amitriptyline compared with three in a matched control group. It is since these latter two reports that more stress has been placed on the cardiovascular abnormalities and especially the conduction disturbances caused by these agents. The reasons for these abnormalities are not clear since TADs have a complex system of actions, including anticholinergic activity and prevention of re-uptake of noradrenaline (NA) and 5-hydroxytryptamine (5-HT); and, as all these systems exert potent effects on the cardiovascular system (CVS), it is not surprising that interference with the metabolism of biogenic amines may cause serious effects on the CVS (James *et al.*, 1975; Dauchot & Gravenstein, 1971; Innes & Nickerson, 1975). In addition to these effects, TADs also demonstrate a quinidine-like activity on the heart, which is seen as a prolongation of the QRS and the Q–T interval on the ECG (Bigger *et al.*, 1977); it is thought that this may account for their myocardial depressant activity.

TADs have also been found to block the antihypertensive action of the adrenergic neurone blocking

agents, guanethidine, bethanidine and debrisoquine (Skinner *et al.*, 1969; Meyer *et al.*, 1970); and also to interfere with the antihypertensive action of clonidine (Briant *et al.*, 1973). It is thought by some that they are also contraindicated when patients are receiving methyldopa (White, 1965).

Mianserin hydrochloride is a new tetracyclic antidepressant drug with similar therapeutic efficacy to amitriptyline (Coppen *et al.*, 1976). At therapeutic dosage, it does not have anticholingergic activity nor does it effect the tyramine pressor response (Ghose *et al.*, 1976). Crome & Newman (1977) discuss their findings following 20 cases of overdosage with mianserin. There were no arrhythmias but in two cases sinus tachycardia occurred, three patients developed hypertension and one hypotension.

With these things in mind, we decided to investigate the effect of mianserin on the CVS using non-invasive techniques.

Methods

Three studies were carried out.

Study 1

Six normal male volunteers aged 21–23 yr were studied. They had no symptoms or signs of cardiovascular or respiratory abnormality. Standard ECGs were normal. The volunteers attended on two occasions, 2 weeks apart, in the fasting state. They received either mianserin 20 mg or amitriptyline 50 mg using a randomized, double-blind cross-over technique. The following parameters were measured before drug administration and at 30-min intervals for 3 hours.

Systolic time intervals (STIs) The STIs were obtained using a mingograph four-channel recorder (Elema-Schonander) to reproduce simultaneous recordings of the ECG, phonocardiogram and carotid pulse wave at a paper speed of 100 mm/second. From these tracings the Q–S_2 interval (the interval from the onset of the Q wave on the ECG to the start of the aortic second sound), the left ventricular ejection time (LVET) (from the start of the upstroke of the carotid pulse to the incisura), and the pre-ejection period (PEP), which is the difference between the Q–S_2 and the LVET, were measured. The mean values of ten complexes were obtained for each measurement. The LVET and PEP results were then corrected for heart rate using the regression equations of Weissler *et al.* (1969). The PEP/LVET ratio was calculated using the uncorrected values of PEP and LVET.

High speed surface ECG This was carried out using a four-channel mingograph (Elema-Schonander EMT34). Standard leads I, II and III and leads aVR, aVL and aVF were recorded at 100 mm/second. From these recordings, R–R interval, P–R interval, QRS time and Q–T interval were measured. The mean values of five complexes were obtained and the same leads were used for each value over the 3-h period. The Q–T interval was corrected for heart rate using the Bazett formula

$$\frac{\text{Q–T}}{\text{R–R}} = \text{Q–Tc}$$

Heart rate was calculated from the formula

$$\frac{60}{\text{R–R interval in seconds.}}$$

Apexcardiogram The volunteers were then placed in the left lateral position and a left apexcardiogram was

Table 1 Change in STIs after mianserin 20 mg and amitriptyline 50 mg (±s.e.m.)

Time (min)	*Amitriptyline*			*Mianserin*		
	ΔPEPI (ms)	*ΔLVETI (ms)*	*ΔPEP/LVET*	*ΔPEPI (ms)*	*ΔLVETI (ms)*	*ΔPEP/LVET*
30	0.233 ±1.92	4.7 ±3.38	−0.002 ±0.009	1.95 ±1.58	6.1 ±2.07	−0.002 ±0.006
60	3.1 ±2.83	2.23 ±3.93	0.010 ±0.014	1.42 ±3.27	2.07 ±3.69	0.003 ±0.012
90	0.73 ±2.24	2.02 ±5.03	0.001 ±0.012	−0.3 ±3.63	3.02 ±2.94	−0.004 ±0.013
120	1.97 ±1.25	−1.5 ±4.23	0.008 ±0.005	−2.15 ±2.36	0.93 ±2.67	0.004 ±0.008
150	4.27* ±1.51	−3.13 ±2.52	0.017† ±0.005	−1.23 ±2.03	3.48 ±1.54	−0.008 ±0.008
180	−1.2 ±1.18	−0.65 ±3.55	−0.003 ±0.005	3.35 ±2.69	2.53 ±1.97	0.005 ±0.010

*$P<0.01$, t 3.752; †$P<0.01$, t 4.537.

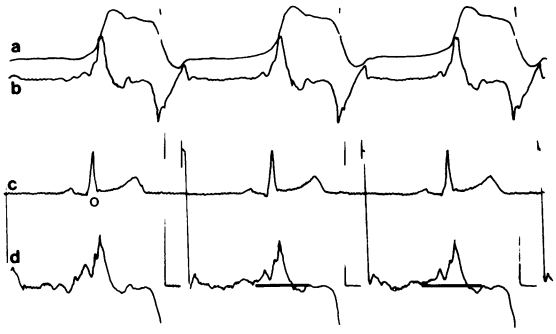

Figure 1 a, Filtered signal of apexcardiogram; b, dA/dt (first derivative); c, ECG; d, $dA/dt/Dt$ (normalized first derivative). Peak value of $dA/dt/Dt$ was called $(dA/dt/Dt)_{max}$.

recorded in full expiration. The recording device is a pulse-phono microphone (Siemens-Elema E117E), and a simultaneous ECG was recorded. The signal is passed through a Siemens-Elema Normaliser 869, which enables the calibrated apexcardiogram A to be differentiated (dA/dT), and by means of automatic zero clamping the zero point of the apexcardiogram is held at a constant level. This enables the peak normalized first derivative ($dA/dt/Dt_{max}$) to be measured (Figure 1). This latter measurement correlates with left ventricular end diastolic pressure (LVEDP) and ejection fraction, and thus provides useful information on left ventricular function (Denef *et al.*, 1975).

Lying blood pressure This was measured and blood samples were taken at hourly intervals for the relevant drug. Amitriptyline was measured by Miss A. Jeffrey of St Bartholomew's Hospital (Department of Clinical Pharmacology). Mianserin was measured by Dr J. de Ridder of Organon International, Holland. The statistics were carried out using Students t test and the standard error was estimated from analysis of variance.

Study 2

Three depressed patients (two male, one female) were sent from the Department of Psychiatry for assessment, and were studied in the fasting state before receiving any medication and 2 weeks after starting antidepressant therapy. The investigator did not know what medication was prescribed.

Two of the patients (one male, one female) took mianserin and the other took clomipramine. In two patients (one on mianserin, one on clomipramine), both the STI and high speed surface ECG were carried out; on the third patient, only the high speed surface ECG was measured. Both STIs and ECGs were measured on three occasions over a 30-min period and after the patient had rested for 15 minutes. The mean value was obtained from the results of the three readings.

Study 3

Interaction with different antihypertensives

Open study Three patients were admitted to the ward and maintained on their normal antihypertensive therapy. After 3 d they were challenged with mianserin 20 mg three times daily. Blood pressure (BP) was measured at 4 h intervals in the lying and standing position (after standing for 2 min) using a London School of Hygiene sphygomomanometer. The mean of three recordings was taken. They received mianserin for 3 or 4 days. Mean BP was calculated from the formula: mean BP = diastolic pressure + (systolic

Table 2 Change in ECG following mianserin 2 Omg and amitriptyline 50 mg (±s.e.m.)

Time (min)	*Amitriptyline*				*Mianserin*			
	ΔR–R (ms)	*ΔP–R (ms)*	*ΔQRS (ms)*	*ΔQ–Tc (ms)*	*ΔR–R (ms)*	*ΔP–R (ms)*	*ΔQRS (ms)*	*ΔQ–Tc (ms)*
30	33.2 ±27.5	3.07 ±1.11	−0.27 ±0.86	−1.38 ±3.68	67.5 ±18.9	2.13 ±2.79	0.05 ±1.73	−6.77 ±1.96
60	87.5 ±21.1	2.90 ±4.81	0.07 ±0.79	5.38 ±3.26	43.3 ±20.9	3.97 ±3.76	0.05 ±0.85	1.90 ±2.82
90	129.5* ±32.1	5.4 ±3.60	1.57 ±1.12	−6.22† ±3.29	80.1 ±49.3	5.97 ±2.14	1.28 ±0.92	2.73 ±5.08
120	92.0 ±27.5	9.23 ±2.95	1.07 ±0.76	4.45 ±3.47	51.8 ±18.2	4.8 ±3.62	1.45 ±0.98	9.57 ±2.12
150	126.8† ±20.4	1.07 4.12	1.07 ±0.84	−2.38 ±2.58	−19.0 ±58.2	2.8 ±5.33	2.72 ±0.29	26.1§ ±8.9
180	99.3 ±20.5	5.4 ±5.32	1.23 ±1.81	−2.38 ±5.14	105.0 ±75.6	3.97 ±3.27	0.77 ±1.49	11.57 ±9.78

*$P<0.001$, t 6.462; †$P<0.001$, t 5.365; ‡$P<0.01$, t 3.697; §$P<0.001$, t 5.640.

pressure − diastolic pressure/3), over the 3- or 4-d period.

Double-blind study This study was carried out on three patients taking adrenergic neurone blocking drugs (two on guanethidine, one on bethanidine). After allowing time for BP to settle in the ward, the patients were given either desmthylimipramine (DMI) 25 mg three times daily or mianserin 20 mg three times daily in a randomized fashion. They received each drug for 2 d and there was a 3-d washout between treatments. The results for each patient are given in Table 6.

Results

Volunteer study

There was no change in either the peak normalized derivative of the apexcardiogram or the BP at any time during this study. Amitriptyline increased the PEPI and the PEP/LVET ratio significantly at 150 min ($P < 0.01$), compared with the control value (Table 1). LVETI was not affected. Mianserin did not affect the systolic time intervals. In the ECG study (see Table 2), mianserin prolonged the Q–Tc interval at 150 min ($P < 0.001$), whereas amitriptyline shortened the Q–Tc at 90 min ($P < 0.01$). Amitriptyline also decreased heart rate at 90 and 150 min ($P < 0.001$), that is, the R–R interval was prolonged. Mianserin did not affect heart rate. The P–R interval was prolonged by amitriptyline but the results did not achieve statistical significance. Neither drug prolonged QRS duration. Plasma levels of amitriptyline were below the therapeutic range, ranging from trace values to 54 ng/ml. Peak levels occurred between 120 and 180 min except in subject two and in subject three, in whom only trace levels could be measured. Plasma levels of mianserin varied from 0–41.8 ng/ml and peak levels occurred at either 120 or 180 minutes.

Depressed patient study

ECG analysis (Table 3) Mianserin prolonged the Q–Tc interval at 1 week in both subjects; however, by week 2 of therapy this value had returned to pretreatment levels. It had no other effect on the ECG. Clomipramine increased heart rate from 69 to 100 beats/minute. The P–R interval was prolonged, as was QRS duration and the Q–Tc interval.

STI analysis (Table 4) Neither drug affected STIs sufficiently for any comment to be made.

Effect in hypertensive patients

In the open study (Table 5), mianserin did not affect lying or standing BP, in combination with either propranolol or propranolol and hydrallazine.

Table 3 ECG study, comparing mianserin with clomipramine

Patient (and day)	*Heart rate*	*P–R*	*QRS*	*Q–Tc*	*Drug*	*Dose*
1 (1)	62	155	71	399	—	—
1 (7)	75	155	72	409	Mianserin*	30 mg
1 (14)	66	152	62	382	Mianserin*	40 mg
2 (1)	83	174	88	426	—	—
2 (7)	85	171	91	449	Mianserin†	10 mg
2 (14)	91	172	85	424	Mianserin†	10 mg
3 (1)	69	152	71	368	—	—
3 (14)	100	170	77	392	Clomipramine†	20 mg

P–R, QRS and Q–Tc are in ms.
Doses: *at night-time; †three times daily.

Table 4 STIs for mianserin and clomipramine

Patient and day	*Drug*	*Dose**	*Heart rate*	*PEPI (ms)*	*LVETI (ms)*	*PEP/LVET*
1 (0)	—	—	81	117.4	413.4	0.300
1 (7)	Mianserin	10 mg	83	114.2	422.8	0.279
1 (14)	Mianserin	10 mg	91	112.9	411.6	0.288
2 (0)	—	—	66	144.6	400.6	0.400
2 (14)	Clomipramine	20 mg	97	140.7	400.2	0.416

PEPI = PEP + 0.4 × heart rate; LVETI = LVET + 1.6 × heart rate.
*Dose three times daily.

In the double-blind study with adrenergic neurone blocking agents (Table 6, 7 and 8) DMI only elevated BP in patient one (Table 7) and in this patient mianserin lowered the BP to less than the pretreatment level (that is, while on the regular antihypertensive agents). In the other two patients, mianserin did not elevate the BP above control levels. DMI, on the other hand, decreased BP below control levels in patients two and three (see Tables 7 and 8).

Discussion

The results of these studies indicate that mianserin hydrochloride seems to have little effect on the CVS compared with known TADs. In the volunteer study the only consistent change shown by mianserin was prolongation of the Q–Tc interval at 150 min after taking the drug. The significance of this change is difficult to assess, since in the depressed patient study, although mianserin prolonged the Q–Tc interval at 1 week, by the second week of therapy it had returned to normal. Prolongation of the Q–T interval has many causes and has been reported in overdosage with TADs (Thorstrand, 1976). It is thought to be due to a quinidine-like action on the heart and has also been shown to occur at therapeutic doses of imipramine (Bigger *et al.*, 1977). Besides drugs with class I antiarrhythmic activity (for example, lignocaine, procaineamide, and so on), other drugs are known to prolong the Q–Tc interval: for example, prenylamine (Bens, 1973) and also drugs that prolong repolarization (for example, amiodarone; Morgan & Mathison, 1976). In most drug-induced Q–T prolongation, the

Table 5 Mianserin interaction with antihypertensives

Subject	Mean Pretreatment BP Lying	Mean Pretreatment BP Standing	Antihypertensive	Duration and dose of mianserin†	Mean Post-treatment BP Lying	Mean Post-treatment BP Standing
1	114	110	Propranolol (Navidrexk)	20 mg 4 d	113	109
2	132	115	Propranolol (Moduretic)	20 mg 3 d	122	99
3	147	139	Propranolol (Hydrallazine)	20 mg 4 d	144	145

*Mean BP = diastolic pressure + ((systolic pressure − diastolic pressure)/3).
†Dose three times daily.
Pretreatment BP (antihypertensive agent alone).

Table 6 Interaction with guanethidine 20 mg daily (patient 1)

	Control (guandethidine) Lying SP	Control (guandethidine) Lying DP	Control (guandethidine) Standing SP	Control (guandethidine) Standing DP	DMI + guanethidine Lying SP	DMI + guanethidine Lying DP	DMI + guanethidine Standing SP	DMI + guanethidine Standing DP	Mianserin + guanethidine Lying SP	Mianserin + guanethidine Lying DP	Mianserin + guanethidine Standing SP	Mianserin + guanethidine Standing DP
	185	120	—	—	190	110	170	110	140	80	120	80
	170	100	—	—	230	140	200	140	190	100	160	100
	170	100	170	110	210	120	200	135	170	100	90	90
	150	95	165	110	180	110	170	115	150	90	130	90
	150	90	170	115	160	120	205	140	160	95	130	90
	140	90	135	80	190	130	150	120	160	90	120	85
	140	90	140	100	150	100	170	120	140	80	120	80
	185	100	160	90	140	90	110	80	160	90	160	90
	200	100	170	100	150	100	160	110	150	90	140	90
	190	100	—	—	180	110	140	80	180	120	130	90
	190	100	—	—	190	130	160	120	170	120	120	90
	215	115	205	120	230	160	180	130	170	90	170	90
	205	120	210	130	180	140	—	—	140	90	140	90
	210	110	—	—	170	110	150	110	130	90	120	85
	—	—	—	—	170	120	150	120	140	100	130	90
Mean	178.6	102.1	169.4	106.1	181.3	119.3	165.4	116.4	156.7	95	135.3	88.7

SP, Systolic pressure; DP, diastolic pressure (mm Hg).

QRS interval is also prolonged, a finding absent in this study. Hypocalcaemia can also prolong the Q–Tc interval (Schamroth, 1973). Whether mianserin has a temporary effect on myocardial calcium metabolism is unknown.

The changes produced by the TADs, amitriptyline and clomipramine, in this study merit comment. In the volunteer study, amitriptyline slowed the heart rate at 90 and 150 min, and shortened the Q–T interval at 90 minutes. The P–R interval was prolonged at 120 min but the result just escaped significance. Prolongation of the P–R interval by TADs is a well-known feature and has been demonstrated previously by Burrows *et al.* (1976) and by Ziegler *et al.* (1977). The reason for the P–R interval prolongation is not known, but both NA and 5-HT may cause P–R prolongation (Innes *et al.*, 1975; James *et al.*, 1975). Although quinidine can prolong the P–R interval, it is unlikely to be the cause after a single dose of a TAD, because one would expect the QRS and the Q–Tc intervals to be prolonged, which did not occur in the volunteer study.

All previous studies with TADs in therapeutic dosage have noted a consistent tachycardia, confirmed here in the one patient taking clomipramine. In the volunteer study, however, heart rate slowed. We suggest that the reason for this finding is as follows. The tachycardia produced by TADs is thought to be due to their anticholinergic or atropine-like action; however, in this study the plasma levels of amitriptyline were subtherapeutic (highest level 54 ng/ml). Thus, one would expect the anticholinergic response to be lessened. It has been shown by Gravenstein *et al.* (1969) and Dauchot & Gravenstein (1971) that atropine at low doses causes slowing of the heart;

Table 7 Interaction with guanethidine 25 mg daily (patient 2)

	Control (guanethidine)				*DMI + guanethidine*				*Mianserin + guanethidine*			
	Lying		*Standing*		*Lying*		*Standing*		*Lying*		*Standing*	
	SP	*DP*	*SP*	*DP*	*SP*	*DP*	*SP*	*DP*	*SP*	*DP*	*SP*	*DP*
	190	105	190	105	230	120	130	100	190	115	140	100
	190	105	190	105	185	80	125	70	175	110	120	85
	170	110	150	100	200	100	170	90	260	130	130	90
	200	100	175	85	200	100	120	80	150	90	135	85
	180	100	140	80	200	130	140	80	190	120	160	110
	230	110	190	120	165	95	115	70	210	120	170	120
	230	110	190	110	170	90	130	85	200	110	180	100
	230	130	190	130	185	95	140	80	210	130	180	100
	235	140	165	110	220	110	130	80	180	120	140	90
	230	110	180	110	200	120	160	100	—	—	—	—
	190	110	140	100	—	—	—	—	—	—	—	—
	175	85	—	—	—	—	—	—	—	—	—	—
	210	100	160	90	—	—	—	—	—	—	—	—
Mean	204.6	108.8	171.7	103.8	195.5	104.0	136.0	84.5	196.1	116.1	150.6	97.8

SP, Systolic pressure; DP, diastolic pressure (mm Hg).

Table 8 Interaction with bethanidine 10 mg three times daily (patient 3)

	Control				*DMI*				*Mianserin*			
	Lying		*Standing*		*Lying*		*Standing*		*ying*		*Standing*	
	SP	*DP*	*SP*	*DP*	*SP*	*DP*	*SP*	*DP*	*SP*	*DP*	*SP*	*DP*
	170	100	150	90	180	110	130	90	160	100	150	95
	165	100	155	100	160	100	160	110	150	100	150	100
	170	100	155	100	170	115	140	100	150	90	150	90
	160	100	155	110	170	100	150	105	140	90	140	90
	175	110	130	90	150	110	170	110	160	100	150	100
	150	100	150	95	135	100	115	100	160	110	155	110
	150	90	150	100	150	110	140	100	160	110	155	120
	150	100	150	100	140	90	120	90	180	140	180	120
	—	—	—	—	140	90	125	90	200	110	180	110
	—	—	—	—	130	70	130	70	170	110	160	110
Mean	161.3	100	149.4	98.1	152.5	99.5	138.0	965	163.0	106.0	157.0	104.5

SP, Systolic pressure; DP, diastolic pressure (mm Hg).

thus, it is not surprising that in this case heart rate slowed. Confirmation of the low anticholinergic effect was shown by the fact that none of the volunteers complained of dry mouth.

The other changes on the ECG (namely, QRS prolongation and Q–T prolongation) which occurred with clomipramine have been described previously for other TADs (Bigger *et al.*, 1977; Thorstrand, 1976). The shortening of the Q–T interval with amitriptyline was unexpected and difficult to explain; it has not been described previously. The Q–T shortening is a relatively uncommon drug effect, but has been described with digoxin, hypocalcaemia (Schamroth, 1973), and also with carbamazepine (Singh & Hauswirth, 1974). We do not know the reason for this change and feel that it requires further study.

Neither drug effected the peak normalised derivative of the left apexcardiogram; however, we have not found this method as sensitive as the STI in assessing cardiac function non-invasively.

The changes in the STI produced by amitriptyline, that is, increase in PEP and PEP/LVET ratio, were not unexpected. Müller & Burckhardt (1974) showed similar findings following 4 weeks of therapy with antidepressant drugs, but we could not produce the same findings with mianserin which in our studies did not effect the STI. Müller *et al.* (1974) grouped all their results together, however, so we do not know how their three patients with mianserin fared on an individual or collective basis, compared with the other 27 patients on TADs. The finding of an increased PEP and PEP/LVET ratio can be interpreted as demonstrating a decrease in myocardial contractility, provided the patient is not on other cardioactive drugs or has valvular heart disease (Weissler, 1977).

In the depressed patient study, neither mianserin nor clomipramine affected the STI enough to comment on; however, the latter drug did increase the PEP/LVET ratio.

Mianserin did not affect heart rate in either of the studies; this is not surprising, as it does not possess anticholinergic activity (Ghose *et al.*, 1976).

Peak plasma levels, which occurred at either 120 or 180 min after single dosage, seem to correlate with the changes associated with both drugs (all significant changes occurred at 150 min, besides Q–T shortening with amitriptyline). Unfortunately we did not take samples at 150 min, but perhaps further studies will take this into account. The fact that the ECG changes occur at a similar time as the peak levels of mianserin in plasma is interesting because its antidepressant activity is not related to its plasma level (Coppen *et al.*, 1976).

BP was not affected by either drug in the volunteer study. This is not surprising, as all readings were taken in the supine position. This is important, as in a recent study, Hayes *et al.* (1977) showed that in 20 patients receiving TADs all suffered orthostatic hypotension during the first 14 d of therapy.

In the open antihypertensive study, mianserin did not antagonize nor potentiate the hypotensive effect of propranolol or propranolol and hydrallazine in either the supine or standing position. One of the patients had ventricular bigeminy before mianserin was started and the drug did not effect the arrhythmia adversely.

Mianserin did not antagonize the antihypertensive effect of the adrenergic neurone blocking agents, guanethidine or bethanidine. This was not surprising, as mianserin, unlike TADs, does not influence the tyramine pressor response and thus does not prevent uptake of the antihypertensive agent used. Adrenergic neurone blocking agents are taken up in a similar manner to NA; thus, TADs which interfere with this mechanism would interfere with the antihypertensive activity of adrenergic neurone blocking agents (Mitchell *et al.*, 1970). Further, DMI decreased BP in patients two and three. TADs are known to have an hypotensive action (Hayes *et al.*, 1977); in addition, the onset of reversal of adrenergic neurone blocking agents effects may be delayed (Jefferson, 1975). The guanethidine or bethanidine already at its site of action would continue to have its effect and this could be another reason for delayed action. Interestingly, all three of these patients showed wide variability in their BP readings, showing that mean BP calculations are no substitute for the actual readings. It also emphasizes the importance of including a reference drug, such as DMI, in controlled studies of this kind.

From these studies it would seem that mianserin is a safer antidepressant agent than the TADs. Further study in depressed patients with cardiac disease is indicated, as it is in such patients that TADs may be contra-indicated.

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