Cardiovascular effects of amitriptyline, mianserin, zimelidine and nomifensine in depressed patients

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Summary

The cardiac effects of amitriptyline, mianserin, zimelidine and nomifensine on the systolic time intervals (STI) and on the high speed surface ECG have been studied in depressed patients. Amitriptyline increased pre-ejection period (PEP) index and the PEP/left ventricular ejection time (LVET) ratio of the STI ($P < 0.05$ and $P < 0.02$). It also increased heart rate significantly (< 0.02) and tended to prolong Q-T interval. Mianserin shortened QS_2I ($P < 0.05$) and LVET ($P < 0.01$) and prolonged PEP/LVET ratio ($P < 0.01$). Zimelidine did not affect the STI but tended to decrease heart rate and prolong the Q-T interval. Nomifensine decreased T wave height. These findings indicate that amitriptyline decreases cardiac contractility and confirm the quinidine-like action of the tricyclic antidepressants. The changes brought about by mianserin are probably due to effects on the peripheral circulation rather than a direct action on the heart.

Introduction

Tricyclic antidepressant drugs (TADs) have been used for approximately 20 years in clinical practice. Although they have proved efficacious, the incidence of cardiac complications, especially following overdosage, has proved distressing. Kristjansen (1961) first reported minor ST-T segment changes on the electrocardiogram (ECG) occurring in depressed patients taking imipramine following exercise. Since then, various ECG and haemodynamic changes have been described both in therapeutic dosage and after overdosage of TADs (Rasmussen and Kristjansen, 1963; Thorstrand, 1974, 1976; Jefferson, 1975; Vohra, Burrows and Sioman, 1975). Sudden death has also been reported in patients with heart disease who received amitriptyline (Coull *et al.*, 1970; Moir *et al.*, 1972). Owing to these cardiac complications,

the use of these drugs has been limited and many patients may be put at risk if given these agents. Since 1970, newer antidepressants have been marketed in an effort to overcome these and some of the other distressing side effects (notably anticholinergic effects) noted with the older TADs, amitriptyline and imipramine.

The authors investigated the cardiac effects of 4 antidepressants, namely, amitriptyline and 3 of the newer antidepressants, mianserin, nomifensine and zimelidine, in depressed patients using non-invasive techniques.

Patients and methods

The patients were participating in double-blind clinical trials to assess the clinical response to various antidepressant drugs. They were diagnosed as suffering from primary depressive illness using the criteria of Feighner *et al.* (1972). None of the patients had any history of cardiovascular disease and the cardiovascular system was normal on physical examination. Table 1 shows the sex and age distribution and dose of antidepressant taken.

The patients attended on 2 occasions, once whilst on placebo and once on the relevant antidepressant drug. All the medication and placebo, except for nomifensine, were made up in identical capsules. The study was performed under double-blind conditions. Approximately 50% of the patients attended first on their antidepressant therapy (4-6 weeks after start of therapy) and the other 50% initially on placebo and then 4-6 weeks after active treatment. If they attended initially on the active medication, they attended again at the end of a 10th-14th day wash-out period on placebo. The investigator who performed the cardiac investigations (C.D.B.) was unaware of whether the patients attended on placebo or active treatment initially. All studies were performed in the fasting state. After resting on a bed for 15 min, the following tests were performed.

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TABLE 1. Age, sex, number of patients on anti-depressant medication

Drug	Amitriptyline	Mianserin	Zimelidine	Nomifensine
Dose	150 mg at night	60 mg at night	200 mg at night	150 mg at night
No. of Patients	6	8	7	3
Male	3	2	2	1
Female	3	6	5	2
Age (mean)	41.5 years	43 years	41.8 years	34.7 years
Range	24–57 years	27–61 years	30–62 years	25–45 years

1. Systolic time intervals (STI)

The STIs were obtained using an Elema-Schonander mingograph (EMT 34) to reproduce simultaneous recordings of the ECG, phonocardiogram and carotid pulse wave at a paper speed of 100 mm/sec. From these readings the Q-S₂ 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 QS₂ and the LVET, were measured (Fig. 1). The mean values of 10 complexes were obtained for each measurement. The QS₂, LVET and PEP results were then corrected for heart rate using the regression equations of Weissler, Harris and Schoenfield (1969). The PEP/LVET ratio was calculated using the uncorrected values of PEP and LVET. Three recordings were performed over 15 min at each visit and the mean of the 3 recordings were taken as the value of the QS₂, LVET and PEP.

FIG. 1. Measurement of systolic time intervals: a, ECG; b, phonocardiogram; c, carotid pulse trace; PEP, pre-ejection period; LVET, left ventricular ejection time.

2. High speed surface ECG

This was obtained using an Elema-Schonander mingograph (EMT 34). Standard leads I, II and III and leads aVR, aVL and aVF were recorded at 100 mm/sec. From these recordings, R-R interval, P-R interval, QRS time, Q-T interval and T wave amplitude were measured. The mean values of 5 complexes were obtained and the same lead was used on each occasion. Three recordings were performed and the mean values of the 3 recordings were taken as the value of the R-R, P-R, QRS and Q-T intervals and T wave amplitude. Heart rate was calculated as follows: $HR = 60/R-R$ interval in sec. QT interval was corrected for heart rate using the Bazett formula.

3. Lying and standing blood pressure was measured

The statistics were carried out using Student's *t* test and the standard error was estimated from analysis of variance.

Results

1. (Table 2)

As can be seen from Table 2, amitriptyline prolongs both PEPI ($P < 0.05$) and the PEP : LVET ratio ($P < 0.02$). Mianserin shortened QS₂I ($P < 0.05$) and LVETI ($P < 0.01$) and prolonged the PEP : LVET ratio ($P < 0.01$). Zimelidine did not affect the STI. Nomifensine was only given to 3 patients and no trends could be discerned.

2. (Table 3)

Amitriptyline increased heart rate ($P < 0.02$), zimelidine tended to slow the heart but the result did not attain statistical significance. Both amitriptyline (5 of 6 subjects) and zimelidine (6 of 7 subjects) prolonged Q-Tc interval, but the results did not attain statistical significance. There were insufficient subjects taking nomifensine to perform statistical analysis, however in all 3 subjects T wave amplitude decreased.

3. None of the drugs affected lying or standing blood pressure

Discussion

Mianserin, nomifensine and zimelidine have been

TABLE 2. Change on STI from control: mean ($\pm$ s.e. mean)

	Amitriptyline	Mianserin	Zimelidine	Nomifensine
Δ QS ₂ I	-0.18	-10.79*	10.19	1.83
msec.	(4.26)	(4.15)	(5.12)	(7.01)
Δ LVETI	-7.8	-12.9†	5.76	0.6
msec.	(2.69)	(4.34)	(5.29)	(11.0)
Δ PEPI	9.6*	4.11	2.79	1.5
msec.	(2.50)	(4.52)	(3.05)	(4.58)
Δ PEP	0.051‡	0.035†	0.000	0.504
LVET	(0.015)	(0.018)	(0.015)	(1.34)

* $P < 0.05$, $t = 2.65$, $t = 2.93$ † $P < 0.01$, $t = 4.12$, $t = 3.58$ ‡ $P < 0.02$, $t = 3.87$ QS₂I = 2.1 hr + QS₂

PEPI = PEP + 0.04 hr

LVETI = LVET + 1.6 hr

PEPI, pre-ejection period index; LVETI, left ventricular ejection time interval;

STI, systolic time intervals

TABLE 3. Change on ECG after anti-depressant drug therapy mean ($\pm$ s.e. mean)

	Amitriptyline	Mianserin	Zimelidine	Nomifensine
Δ Heart rate	16.17*	4.13	-5.29	-1.6
b.p.m.	(5.58)	(3.16)	(3.39)	(5.55)
Δ P-R interval	-1.17	-2.13	5.71	-3.3
msec.	(6.36)	(5.68)	(4.4)	(3.67)
Δ QRS	1.0	-0.63	1.29	0.67
msec.	(2.28)	(3.1)	(2.9)	(1.76)
Δ Q-Tc	15.50	3.63	11.0	10.0
msec.	(6.00)	(3.23)	(6.87)	(7.23)
Δ T wave amplitude	-0.77	0.19	-0.33	-0.77
mm	(0.38)	(0.44)	(0.84)	(0.24)

* $P < 0.02$, $t = 3.88$

shown to be as effective as the established TADs in the treatment of depression (Coppen *et al.*, 1976; McLelland, Kerr and Little, 1977; Montgomery *et al.*, 1978). They differ from the known TADs in their chemical structure in that mianserin has a tetracyclic structure, nomifensine is a tetrahydroquinoline compound and zimelidine has a bicyclic structure. They also differ in their actions on the biogenic amines in that zimelidine is a potent inhibitor of 5-hydroxytryptamine (5-HT) re-uptake with little effect on noradrenaline (NA) re-uptake (Siwers *et al.*, 1977); nomifensine is a potent inhibitor of both NA (Schacht and Heptner, 1974) and dopamine re-uptake (Ehsannullah and Turner, 1977); mianserin does not appear to block re-uptake of NA in man (Ghose, Coppen and Turner, 1976); but in rat brain it increases turnover of NA (Leonard, 1978) and antagonizes the effect of 5-HT on blood vessels (Saxena, Houwelingen and Barta, 1971).

The changes in the STI produced by amitriptyline, i.e. increase in PEPI and the PEP : LVET ratio, indicate a negative inotropic effect of the drug (Weissler, 1977). In a previous study in normal

volunteers, Burgess, Turner and Wadsworth (1978) showed a similar effect. In other studies using the STI, Müller and Burckhardt (1974) and Burckhardt *et al.* (1978) showed a similar effect 4 weeks after treatment with a variety of antidepressants including amitriptyline. The reasons for these changes is as yet unknown, but amitriptyline like most of the TADs has a quinidine-like effect on the heart (Axelrod and Weinshilboum, 1972) and these drugs have a high affinity for myocardium (Cassano, Sjastrand and Hansson, 1965) resulting in a cardiodepressant effect.

Mianserin shortened QS₂I and LVETI, but prolonged the PEP : LVET ratio significantly. This would seem to indicate a mixed and paradoxical effect on the heart. Shortening of the QS₂I is said to be the most sensitive index in assessing the positive inotropic effect of a drug and is usually unchanged from normal unless a drug effect is present (Lewis *et al.*, 1977). However, an increase in the PEP : LVET ratio is said to indicate decreased contractility (Weissler, 1977). LVETI shortens whether there is a positive or negative inotropic

effect (Weissler, 1977). It is possible that mianserin is causing these changes by effects on the peripheral circulation. It is known to antagonize the action of NA peripherally (H. Jansen – personal communication) and in man has been shown to antagonize the venoconstrictor effect of 5-HT (Saxena *et al.*, 1971). Therefore it is possible that the drug may decrease both pre-load and after-load, both of which affect the STI in opposite directions (Lewis *et al.*, 1977).

In this study, none of the drugs affected the ECG with the exception of nomifensine which decreased T wave height in all 3 patients. In a recent study by Dumovic *et al.* (1978) nomifensine was shown to have little effect on intra-cardiac conduction in 9 patients. Amitriptyline increased heart rate significantly, a finding which was expected as it is known to have potent anticholinergic activity.

None of the other drugs affected heart rate significantly, although zimelidine tended to slow it. None of the drugs prolonged P–R interval, a finding previously described by Burrows *et al.* (1976). Both amitriptyline (5 of 6 patients) and zimelidine (6 of 7 patients) tended to increase the corrected Q–T interval, but the results did not attain statistical significance. Other investigators (Bigger *et al.*, 1977) have shown Q–Tc interval to be prolonged with the use of TADs, a finding consistent with the quinidine-like effect of these drugs.

It was not possible to demonstrate any change in blood pressure, but this was not surprising as readings were taken 4–6 weeks apart. Hayes, Born and Rosenbaum (1977) have shown that orthostatic hypotension is common in the first 2 weeks of therapy with the TADs if looked for carefully, but is rarely a problem after this period.

From this study it would seem that mianserin and zimelidine are safer antidepressants than amitriptyline and should be preferred to the latter especially in those patients with known heart disease and perhaps in the older generation who are known to develop higher plasma levels of TADs (Carr and Hobson, 1977) and thus run the risk of more complications when given these agents. Although only 3 patients were given nomifensine, this drug too seems to be safer than amitriptyline, but further studies are needed to clarify its place for the patient with cardiac disease and depression.

Acknowledgments

We thank the medical and nursing staff of Preston Hall Hospital for their help and co-operation; Drs J. Hamer and S. Warrington for advice; Organon Laboratories for supplying mianserin tablets; and Astra Chemicals Limited for supplying zimelidine and the matching placebo capsules.

References

- AXELROD, J. & WEINSHILBOUM, R. (1972) Catecholamines. *New England Journal of Medicine*, **287**, 237.
- BIGGER, J.T., GIARDINA, E.G.C., KANTOR, S.J. & GLASSMAN, A.H. (1977) Cardiac antiarrhythmic effect of imipramine hydrochloride. *New England Journal of Medicine*, **296**, 206.
- BURCKHARDT, D., RAEDER, E., MÜLLER, V., IMHOF, P. & NEUBAUER, H. (1978) Cardiovascular effects of tricyclic and tetracyclic antidepressants. *Journal of the American Medical Association*, **239**, 213.
- BURGESS, C.D., TURNER, P. & WEDSWORTH, J. (1978) Cardiovascular responses to mianserin hydrochloride – A comparison with tricyclic antidepressant drugs. *British Journal of Clinical Pharmacology*, **5** (Suppl. 1), 11.
- BURROWS, G.D., VOHIA, J., HUNT, D., STOMEN, J.G., SCOGGINS, B.A. & DAVIS, B. (1976) Cardiac effects of different tricyclic antidepressant drugs. *British Journal of Psychiatry*, **129**, 335.
- CARR, A.C. & HOBSON, R.P. (1977) High serum concentrations of antidepressants in elderly patients. *British Medical Journal*, **2**, 1151.
- CASSANO, G.B., SJAstrand, S.E. & HANSSON, E. (1965) Distribution and fate of C¹⁴ – amitriptyline in mice and rats. *Psychopharmacologia*, **8**, 1.
- COPPEN, A., GUPTA, R., MONTGOMERY, S., GHOSE, K., BAILEY, J., BURNS, B. & RIDDER, J.J. (1976) Mianserin hydrochloride: a novel antidepressant. *British Journal of Psychiatry*, **129**, 342.
- COULL, D.C., CROOKS, J., DINGWELL-FORDYCE, I., SCOTT, A. & WEIR, R.D. (1970) Amitriptyline and cardiac disease. Risk of sudden death identified by monitoring system. *Lancet*, **ii**, 590.
- DUMOVIC, P., BURROWS, G.D., VOHRA, J. & FREEMAN, S.E. (1978) Cardiological studies with nomifensine. In: *IUPHAR 7th International Congress of Pharmacology*. Abstr. p. 830.
- EHSANULLAH, R.S.B. & TURNER, P. (1977) Effects of nomifensine on *in vitro* uptake of 5-hydroxytryptamine and dopamine into human platelets. *British Journal of Clinical Pharmacology*, **4** (Suppl. 2), 159.
- FEIGNER, J.P., ROBINS, E., GUZE, S.B., WOODRUFF, R.A., WINOKUR, G. & MUNOZ, R. (1972) Diagnostic criteria for use in psychiatric research. *Archives of General Psychiatry*, **26**, 57.
- GHOSE, K., COPPEN, A. & TURNER, P. (1976) Autonomic actions and interactions of mianserin hydrochloride (Org G.B. 94) and amitriptyline in patients with depressive illness. *Psychopharmacologia*, **49**, 201.
- HAYES, J.R., BORN, G.F., ROSENBAUM, A.H. (1977) Incidence of orthostatic hypotension in patients with primary affective disorders treated with tricyclic antidepressants. *Proceedings. Mayo Clinic*, **52**, 508.
- JEFFERSON, J.W. (1975) A review of cardiovascular effects and toxicity of tricyclic antidepressants. *Psychosomatic Medicine*, **37**, 160.
- KRISTJANSEN, E.S. (1961) Cardiac complications during treatment with imipramine (Tofranil). *Acta psychiatrica neurologica*, **36**, 427.
- LEONARD, B.E. (1978) Some effects of mianserin on monoamine metabolism in the rat brain. *British Journal of Clinical Pharmacology*, **5** (Suppl. 1), 11.
- LEWIS, R.P., RITTGERS, S.E., FORESTER, W.F. & BOUDOULAS, H. (1977) A critical review of the systolic time intervals. *Circulation*, **56**, 146.
- MCLLELLAND, H.A., KERR, T.A. & LITTLE, S.C. (1977) A clinical comparison of nomifensine and amitriptyline. *British Journal of Clinical Pharmacology*, **4** (Suppl. 2), 233.
- MOIR, D.C., CROOKS, J., CORNWELL, W.B., O'MALLEY, M., DINGWELL-FORDYCE, I., TURNBULL, M.J. & WEIR, R.D. (1972) Cardiotoxicity of amitriptyline. *Lancet*, **2**, 561.

- MONTGOMERY, S.A., MCAULEY, R., RENI, G. & MONTGOMERY, D.B. (1978) A double blind comparison of antidepressant efficacy of zimeldine, a new 5HT uptake inhibitor, with amitriptyline. *IUPHAR 7th International Congress of Pharmacology*. Abstr. p. 246
- MÜLLER, V. & BURCKHARDT, D. (1974) [Effects of tri- and tetracyclic antidepressants on the cardiovascular system.] *Schweizerische medizinische Wochenschrift*, **104**, 1911.
- RASMUSSEN, E.B. & KRISTJANSEN, P. (1963) ECG changes during amitriptyline treatment. *American Journal of Psychiatry*, **119**, 78..
- SAXENA, P.R., HOUWELINGEN, P. VAN. & BARTA, I.L. (1971) The effects of mianserin hydrochloride on the vascular responses evoked by 5-hydroxytryptamine and related vasoactive substances. *European Journal of Pharmacology*, **13**, 295.
- SCHACHT, U. & HEPTNER, W. (1974) Effect of nomifensine (HOE 984), a new antidepressant. On uptake of noradrenaline and serotonin and on release of noradrenaline in rat brain synaptosomes. *Biochemistry and Pharmacology*, **Zä**, 3413.
- SIWERS, B., RINGBERGER, V., TUCK, J.R. & SJÖQUIST, F. (1977) Initial clinical trial based on biochemical methodology of zimelidine (a serotonin uptake inhibitor) in depressed patients. *Clinical Pharmacological Therapy*, **21**, 194.
- THORSTRAND, C. (1974) Cardiovascular effects of poisoning with tricyclic antidepressants. *Acta medica scandinavica*, **195**, 505.
- THORSTRAND, C. (1976) Clinical features in poisonings by tricyclic antidepressants with special reference to the E.C.G. *Acta medica scandinavica*, **199**, 337.
- VOHRA, J., BURROWS, G.D. & SIOMAN, J.G. (1975) Assessment of cardiovascular side effects of therapeutic doses of tricyclic antidepressant drugs. *Australian and New Zealand Medical Journal*, **5**, 7.
- WESSLER, A.M. (1977) Current concepts in cardiology: Systolic time intervals. *New England Journal of Medicine*, **296**, 321.
- WESSLER, A.M., HARRIS, W.S. & SCHOENFIELD, C.D. (1969) Bedside technics for the evaluation of ventricular function in man. *American Journal of Cardiology*, **23**, 577.