British Heart Journal, 1978, **40**, 1005-1009

Cardiac effects of tricyclic antidepressant medication
A preliminary study of nortriptyline

D. J. E. TAYLOR AND R. A. BRAITHWAITE

From Kent and Canterbury Hospital, Canterbury; and Poisons Unit, Guy's Hospital, London

SUMMARY Systolic time intervals and drug plasma concentrations have been measured in a group of patients receiving repeated treatment with nortriptyline. Significant positive correlations between plasma nortriptyline levels and prolongation of pre-ejection phase ($P < 0.005$) and increase in the ratio pre-ejection phase, left ventricular ejection time ($P < 0.05$) were obtained. A deterioration in cardiac function, with increase in heart rate, resulting in a negative inotropic effect has been shown to occur with therapeutic doses of nortriptyline. The potential dangers of tricyclic antidepressant drugs on the heart in patients whose myocardium is already compromised or those who accumulate high plasma concentrations are emphasised.

During the past two decades the tricyclic antidepressant group of drugs has become firmly established as an effective treatment for various types of depressive illness. However, in this same period there have appeared numerous reports of cardiovascular complications following overdosage with this group of drugs (Barnes *et al.*, 1968; Sacks *et al.*, 1968; Crocker and Morton, 1969; Freeman *et al.*, 1969; Noble and Matthew, 1969; Brown *et al.*, 1971; Ruddy *et al.*, 1972; Sedal *et al.*, 1972; Brown *et al.*, 1973; Roberts *et al.*, 1973).

These complications have included sinus or supraventricular tachycardia, widening of the QRS complex, ST depression, bundle-branch block, hypotension, myocardial infarction, and heart block. Of more serious consequence, many of these changes have been observed in patients receiving only therapeutic doses of tricyclic drugs (Stoman, 1960; Kristiansen, 1961; Alexander and Niño, 1969; Williams and Sherter, 1971; Scollins *et al.*, 1972). Moreover, there have also been reports of an increased incidence of sudden death in elderly patients as a result of treatment with this group of drugs (Coull *et al.*, 1970; Moir *et al.*, 1972). In a number of these 'tricyclic deaths' necropsy has shown similar focal myocardial necrosis to that found in animals receiving prolonged noradrenaline infusions (Wexler *et al.*, 1967), or in humans with phaeochromocytoma (Northfield, 1967).

However, the majority of these early studies have concerned single case reports; very few controlled investigations have been carried out until recently.

In a study by Freyschuss *et al.* (1970), the effect of nortriptyline medication on various cardiovascular parameters was investigated in a group of 40 depressed patients. These workers reported that, apart from a general increase in heart rate, in all but one patient the electrocardiogram both at rest and during exercise showed no abnormal changes during nortriptyline medication. However, there was one patient with a very high plasma nortriptyline level who produced a right bundle-branch block during an exercise test. A similar study was later carried out by Vohra *et al.* (1975), who investigated the electrocardiograms of a group of 32 depressed patients who were being treated with various tricyclic antidepressant drugs. In these patients a moderate increase in heart rate and a small prolongation of the PR interval was demonstrated.

In contrast to these earlier findings, Burrows *et al.* (1974) reported significant effect on atrioventricular conduction during therapeutic medication with nortriptyline, though His bundle electrography was used to obtain these findings. Further, in a case reported by Kantor *et al.* (1975), a 2:1 atrioventricular block developed in an elderly patient during treatment with imipramine which was directly related to the drug-plasma concentration, the block occurring below the atrioventricular node in the His-Purkinje system.

Using a somewhat different approach, Müller and Burckhardt (1974) investigated the effect of various tri- and tetracyclic antidepressants on cardiac function using the technique of systolic time interval

Received for publication 14 October 1977

changes (STI). The results of these studies were interpreted by the authors as evidence of a reduced myocardial contractility during prolonged treatment with these drugs.

It has been shown by many workers that the measurement of systolic time intervals is a reliable, repeatable, and simple noninvasive method of assessing myocardial performance; more specifically, the technique measures the contractile state of the left ventricular myocardium (Spodick and Kumar, 1968; Weissler *et al.*, 1968; Martin *et al.*, 1971; Carliner *et al.*, 1974; Frei *et al.*, 1974). This present study is a preliminary investigation into the effects of repeated therapeutic doses of nortriptyline upon myocardial function in a small group of patients using the techniques of STI measurement, with the simultaneous determination of plasma nortriptyline concentrations.

Patients and methods

MEASUREMENT OF STI CHANGES

The STI values are obtained from a simultaneous fast speed recording of the electrocardiogram, phonocardiogram, and the carotid wave form. The total electromechanical ejection time (QS_2) is measured from the start of the QRS complex in the electrocardiogram to the first high-frequency vibrations of the second heart sound. Left ventricular ejection (LVET) is measured from the beginning upswing to the base of the incisural trough of the carotid arterial pulse tracing. Pre-ejection phase (PEP) is obtained by subtracting the left ventricular ejection time from the total electromechanical systole ($QS_2 - LVET$).

The STI values obtained vary with individual heart rates in a linear manner and previously published regression relations for the normal resting supine subject were used to calculate a further index PEPc (Weissler *et al.*, 1968). Deviation from normal (expected) values of this function were calculated as the difference between observed intervals (PEP) and those predicted from the normal regression line (PEPc). The recordings of STIs for the present studies were made using a Cambridge multichannel recorder and Statham gold cell displacement transducer. These recordings were obtained at a chart speed of 100 mm/s, at which the measurements were judged accurate to 5 ms. Recordings were taken with the subjects in a resting state, supine, with the trunk, head, and neck raised to 30°, during an arrested expiration. Measurements were made over three cycles, with the final results expressed as the mean.

Table *Age, sex, weight, diagnosis, and dose of nortriptyline for patients in study*

Case No.	*Age (y)*	*Sex*	*Weight (kg)*	*Maximum dose of nortriptyline (mg 1 day)*	*Clinical diagnosis*
1	54	M	66	150	Obstructive airways disease and mild depression
2	52	M	70	150	Mild depression
3	53	M	70	150	Mild depression
4	36	F	58	50	Mild depression
5	36	F	58	150	Mild depression
6	22	F	47	150	Anorexia nervosa and mild depression
7	71	M	64	150	Mild depression
8	44	M	89	150	Mild depression

PATIENTS

Eight patients who presented with various psychosomatic complaints were the subjects of the study. The age, sex, weight, and clinical diagnosis of these patients are shown in the Table. Before inclusion into the study patients were fully examined clinically and with chest *x*-rays and resting and exercise electrocardiograms before being judged free of cardiac disease.

After obtaining baseline (drug-free) measurements of the STIs for each subject, gradually increasing therapeutic doses of nortriptyline were prescribed over several weeks, with a period of at least 7 days on each dosage schedule; each patient acted as his or her own control. Further measurements were taken from each subject on a number of occasions during the nortriptyline treatment period, these being obtained at the same time of day on each occasion. No concomitant treatment was allowed for any patient during the study, so that the effects of barbiturates on the metabolism of nortriptyline could be avoided, and the patients were asked to abstain from alcohol during this period (Zirkle *et al.*, 1959). No patient during the trial period developed any alteration of intraventricular conduction. Finally, measurements were taken one week after the cessation of nortriptyline in order to obtain a second baseline result.

PLASMA NORTRIPTYLINE CONCENTRATIONS

Heparinised venous blood samples were obtained from each subject at the same time as the measurement of STI values. The blood was centrifuged at 3000 rpm and the plasma removed and stored in fresh plastic tubes at −20°C before analysis. The estimation of plasma nortriptyline concentration was carried out in duplicate using a modification of the gas chromatographic technique of Braithwaite and Widdop (1971). The method had a lower limit

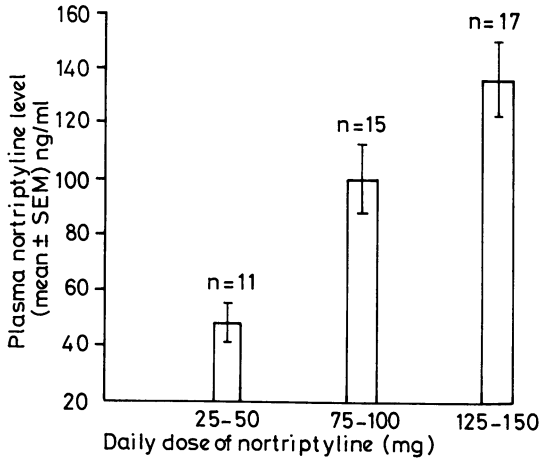

Fig. 1 *Relation between daily dose and mean plasma nortriptyline levels.*

of sensitivity of 20 ng/ml and the agreement between duplicate estimations was within 10 per cent.

Results

The relation between the daily dose of nortriptyline and mean steady-state plasma nortriptyline levels obtained in the 8 patients investigated is shown in Fig. 1, which shows that increased doses of nortriptyline produced expected rises in steady-state plasma nortriptyline levels. These results indicate that patients were obtaining therapeutic plasma nortriptyline concentrations during the trial.

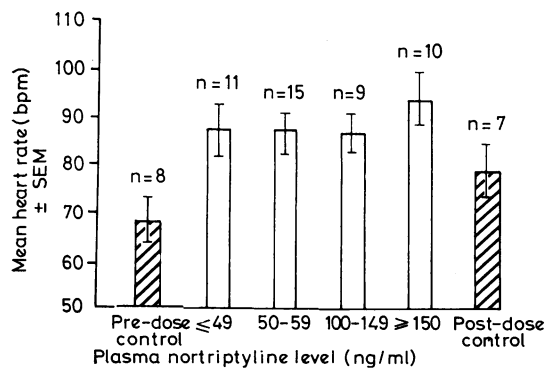

Fig. 2 *Relation between mean heart rate and plasma nortriptyline levels.*

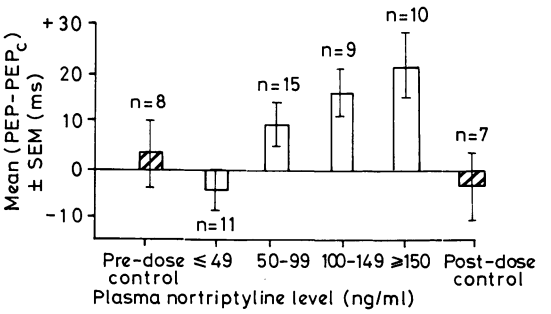

Fig. 3 *Relation between difference in observed pre-ejection phase (PEP) and normal calculated value (PEPc) and plasma nortriptyline level.*

HEART RATE (HR)

Fig. 2 shows the relation between mean heart rate and plasma nortriptyline concentrations. It can be seen that the increase in heart rate obtained during nortriptyline medication appears not to rise with increasing drug plasma concentrations. The increase in heart rate during medication was reversible upon stopping the drug and post-dosage mean heart rate was similar to that obtained before treatment.

PRE-EJECTION PHASE (PEP-PEPC)

Fig. 3 shows the relation between the difference between observed (PEP) and predicted values (PEPc) with increasing plasma nortriptyline concentration. As can be seen from this figure, there seems to be a positive relation between deviation from normal values (that is, increase in PEP disproportionate to PEPc) and increasing antidepressant concentrations. Moreover, a linear regression analysis of change in pre-ejection phase values, Δ (PEP-PEPc), against plasma nortriptyline levels for all the observations produced a statistically significant correlation ($r = +0{\cdot}42$, $n = 44$, $P < 0{\cdot}005$). Fig. 3 also shows that post-dosage PEP values returned to those obtained before dosing and the effect of nortriptyline treatment on pre-ejection phase values was reversible.

RATIO PEP/LVET

Fig. 4 shows the relation between the ratio of PEP/LVET and plasma nortriptyline concentrations. As can be seen from this figure, there appears to be a clear increase in this ratio with increasing antidepressant concentrations. A linear regression analysis of change in ratio $\left(\Delta \frac{\text{PEP}}{\text{LVET}}\right)$ against plasma nortriptyline concentrations for all observa-

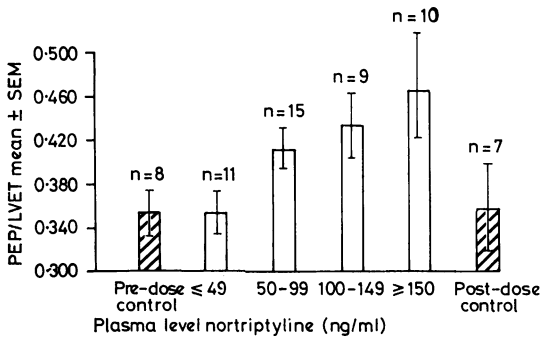

Fig. 4 *Relation between ratio of pre-ejection phase (PEP) to left ventricular ejection time (LVET) and plasma nortriptyline level.*

tions produced a statistically significant correlation ($r = +0{\cdot}32, n = 45, P < 0{\cdot}05$). Fig. 4 also shows that post-dosage values returned to those obtained before dosage.

Discussion

In the present investigation of the effect of therapeutic plasma nortriptyline concentrations on systolic time intervals, measured in a small group of patients without signs of cardiac disease, significant increases in heart rate accompanied by an elongation in PEP interval and an increase in the ratio $\frac{PEP}{LVET}$ have been found. The increases in PEP and $\frac{PEP}{LVET}$ ratio were both found to be greatest at highest plasma nortriptyline concentrations. These findings, therefore, seem to be consistent with those of Müller and Burckhardt (1974) where similar changes in STI were observed for several other tricyclic antidepressants including amitriptyline, though plasma concentrations were not measured.

The increase in heart rate produced by nortriptyline was immediate and did not appear to be influenced either by dosage or plasma nortriptyline concentration and was reversible on cessation of dosage. This chronotropic effect of nortriptyline, unrelated to drug plasma concentration, is in agreement with the findings of Freyschuss *et al.* (1970) and may be a result of the drug's anticholinergic action on the vagus.

Nortriptyline, as with other similar tricyclic antidepressants, is a potent inhibitor of the re-uptake process for noradrenaline at the presynaptic site of the adrenergic neurone, and the magnitude of this primary effect appears to be related to the plasma nortriptyline concentration (Åsberg, 1974). Thus, the relation between increase in systolic time intervals $\left(PEP \text{ and } \frac{PEP}{LVET}\right)$ and plasma nortriptyline concentration obtained in the present study is evidence that the drug has a direct effect on the myocardium, the mechanism of which may be related to the drug's interaction with adrenergic nerve function. The findings of Burrows *et al.* (1974) that atrioventricular conduction was prolonged by more than 30 ms in patients with plasma nortriptyline levels above 200 ng/ml seem to be consistent with our own findings. Further, it has been reported by Åsberg (1974) that potentially dangerous side-effects of nortriptyline medication such as electrocardiographic disturbances and 'sudden falls' have always occurred on high plasma nortriptyline concentrations.

A majority of studies have now shown that high steady-state plasma nortriptyline concentrations are associated with a poor therapeutic outcome, with optimum response being obtained within an 'intermediate' plasma level range (Åsberg *et al.*, 1971; Kragh-Sørensen *et al.*, 1973, 1976; Ziegler *et al.*, 1976; Montgomery *et al.*, 1977). A therapeutic range of 50 to 150 ng/ml is now recommended for treatment with nortriptyline (Kragh-Sørensen *et al.*, 1976). Large differences in steady-state plasma levels are routinely observed in individual patients receiving antidepressant therapy with nortriptyline, with some patients accumulating extremely high levels (Montgomery *et al.*, 1977). The occurrence of these high, and therapeutically ineffective, nortriptyline concentrations on relatively small doses is the result of a slow hepatic clearance of the drug in some patients (Braithwaite *et al.*, 1978).

The cardiac dangers associated with tricyclic antidepressant medication seem to be very real, particularly in those patients who accumulate very high plasma antidepressant concentrations, for example the elderly or those patients with impaired hepatic function. High plasma levels are also unnecessary as they now appear to produce a poorer antidepressant effect.

The present findings are of particular clinical interest. The persistent tachycardia and deterioration in inotropic state that might occur during tricyclic antidepressant treatment have a potential danger in those patients whose myocardium is already compromised. Further, the alteration in autonomic balance may be of special importance in those patients with ischaemic heart disease and may account for the episodes of sudden death reported (Coull *et al.*, 1970; Moir *et al.*, 1972).

References

Alexander, C. S., and Niño, A. (1969). Cardiovascular complications in young patients taking psychotropic drugs. *American Heart Journal*, **78**, 757-769.

Åsberg, M. (1974). Plasma nortriptyline levels—relationship to clinical effects. *Clinical Pharmacology and Therapeutics*, **16**, 215-229.

Åsberg, M., Cronholm, B., Sjöqvist, F., and Tuck, D. (1971). Relationship between plasma level and therapeutic effect of nortriptyline. *British Medical Journal*, **3**, 331-334.

Barnes, R. J., Kong, S. M., and Wu, R. W. Y. (1968). Electrocardiographic changes in amitriptyline poisoning. *British Medical Journal*, **3**, 222-223.

Braithwaite, R. A., Montgomery, S., and Dawling, S. (1978). The pharmacokinetics of nortriptyline in depressed patients with high plasma levels. *Clinical Pharmacology and Therapeutics*. In the press.

Braithwaite, R. A., and Widdop, B. (1971). A specific gas-chromatographic method for the determination of 'steady-state' plasma concentrations of amitriptyline and nortriptyline in patients. *Clinica Chimica Acta*, **35**, 461-472.

Brown, T. C. K., Barker, G. A., Dunlop, M. E., and Loughnan, P. M. (1973). The use of sodium bicarbonate in the treatment of tricyclic antidepressant-induced arrhythmias. *Anaesthesia and Intensive Care*, **1**, 203-210.

Brown, T. C. K., Dwyer, M. E., and Stocks, J. G. (1971). Antidepressant overdosage in children—a new menace. *Medical Journal of Australia*, **2**, 848-851.

Burrows, G. D., Vohra, J., Hunt, D., Sloman, G., Scogeins, B., and Davies, B. (1974). Cardiological aspects of the tricyclic antidepressants. *Journal de Pharmacologie*, **5**, 13.

Carliner, N. H., Gilbert, G. A., Pruitt, A. W., and Goldberg, L. I. (1974). Effect of maintenance digoxin therapy on systolic time intervals and serum digoxin concentrations. *Circulation*, **50**, 94-98.

Coull, D. C., Crooks, J., Dingwall-Fordyce, I., Scott, A. M., and Weir, R. D. (1970). Amitriptyline and cardiac disease—risk of sudden death identified by monitoring system. *Lancet*, **2**, 590-591.

Crocker, J., and Morton, B. (1969). Tricyclic (antidepressant) drug toxicity. *Clinical Toxicology*, **2**, 397-402.

Freeman, J. W., Mundy, E. R., Beattie, R. R., and Ryan, C. (1969). Cardiac abnormalities in poisoning with tricyclic antidepressants. *British Medical Journal*, **2**, 610-611.

Frei, F., Imhof, P., and Dubach, U. C. (1974). Effect of alpha and beta-receptor blockade on systolic time intervals. *European Journal of Clinical Pharmacology*, **7**, 1-10.

Freyschuss, U., Sjöqvist, F., Tuck, D., and Åsberg, M. (1970). Circulatory effects in man of nortriptyline, a tricyclic antidepressant drug. *Pharmacologia Clinica*, **2**, 68-71.

Kantor, S. J., Bigger, J. T., Jr., Glassman, A. H., Macken, D. L., and Perel, J. M. (1975). Imipramine induced heart block—a longitudinal case study. *Journal of the American Medical Association*, **231**, 1364-1366.

Kragh-Sørensen, P., Åsberg, M., and Eggert-Hansen, C. (1973). Plasma-nortriptyline levels in endogenous depression. *Lancet*, **1**, 113-115.

Kragh-Sørensen, P., Eggert-Hansen, C., Baastrup, P. C., and Hvidberg, E. F. (1976). Self-inhibiting action of nortriptyline's antidepressive effect at high plasma levels. *Psychopharmacologia*, **45**, 305-312.

Kristiansen, E. S. (1961). Cardiac complications during treatment with imipramine (Tofranil). *Acta Psychiatrica et Neurologica Scandinavica*, **36**, 427-442.

Martin, C. E., Shaver, J. A., Thompson, M. E., Reddy, P. S., and Leonard, J. J. (1971). Direct correlation of external systolic time intervals with internal indices of left ventricular function. *Circulation*, **44**, 419-431.

Moir, D. C., Crooks, J., Cornwell, W. B., O'Malley, K., Dingwall-Fordyce, I., Turnbull, M. J., and Weir, R. D. (1972). Cardiotoxicity of amitriptyline. *Lancet*, **2**, 561-564.

Montgomery, S., Braithwaite, R. A., and Crammer, J. L. (1977). Routine nortriptyline levels in treatment of depression. *British Medical Journal*, **3**, 166-167.

Müller, V., and Burckhardt, D. (1974). Die Wirkung tri- und tetrazyklischer Antidepressiva auf Herz und Kreisleuf. (In German.) *Schweizerische medizinische Wochenschrift*, **104**, 1911-1913.

Noble, J., and Matthew, H. (1969). Acute poisoning by tricyclic antidepressants: clinical features and management of 100 patients. *Clinical Toxicology*, **2**, 403.

Northfield, T. C. (1967). Cardiac complications of phaeochromocytoma. *British Heart Journal*, **29**, 588-593.

Roberts, R. J., Mueller, S., and Lauer, R. M. (1973). Propranolol in the treatment of cardiac arrhythmias associated with amitriptyline intoxication. *Journal of Pediatrics*, **82**, 65-67.

Ruddy, J. M., Seymour, J. L., and Anderson, N. G. (1972). Management of tricyclic antidepressant ingestion in children with special reference to use of glucagon. *Medical Journal of Australia*, **1**, 630-633.

Sacks, M. H., Bonforte, J., Lasser, R. P., and Dimich, I. (1968). Cardiovascular complications of imipramine intoxication. *Journal of the American Medical Association*, **205**, 588-590.

Scollins, M. J., Robinson, D. S., and Nies, A. (1972). Cardiotoxicity of amitriptyline. *Lancet*, **2**, 1202.

Sedal, L., Korman, M. G., Williams, P. O., and Mushin, G. (1972). Overdosage of tricyclic antidepressants: a report of two deaths and a prospective study of 24 patients. *Medical Journal of Australia*, **2**, 74-79.

Spodick, D. H., and Kumar, S. (1968). Left ventricular ejection period. *American Heart Journal*, **76**, 70-73.

Stoman, L. (1960). Myocardial infarction during imipramine treatment of depression. *Canadian Medical Association Journal*, **82**, 20-22.

Vohra, J., Burrows, G. D., and Sloman, G. (1975). Assessment of cardiovascular side-effects of therapeutic doses of tricyclic antidepressant drugs. *Australian and New Zealand Journal of Medicine*, **5**, 7-11.

Weissler, A. M., Harris, W. S., and Schoenfeld, C. D. (1968). Systolic time intervals in heart failure in man. *Circulation*, **37**, 149-159.

Wexler, B. C., Kittinger, G. W., and Judd, J. T. (1967). Response to drug induced myocardial necrosis in rats with various degrees of arteriosclerosis. *Circulation Research*, **20**, 78-87.

Williams, R. B., Jr., and Sherter, C. (1971). Cardiac complications of tricyclic antidepressant therapy. *Annals of Internal Medicine*, **74**, 395-398.

Ziegler, V. E., Clayton, P. J., Taylor, J. R., Co, B. T., and Biggs, J. T. (1976). Nortriptyline plasma levels and therapeutic response. *Clinical Pharmacology and Therapeutics*, **20**, 458-463.

Zirkle, G. A., King, P. D., and McAtee, O. B. (1959). Effect of chlorpromazine and alcohol on co-ordination and judgment. *Journal of the American Medical Association*, **171**, 1496-1499.

Requests for reprints to Dr D. J. E. Taylor, Kent and Canterbury Hospital, Canterbury CT1 3NG, Kent.