Aust. N.Z. J. Med. (1974), 4, pp. 479-484

Catecholamine Levels in Tricyclic Antidepressant Self-Poisoning

R. Schwarz* and M. Esler†

From the Department of Psychiatry, Canberra Hospital, and The Department of Clinical Science, John Curtin School of Medical Research, Australian National University, Canberra.

Summary: In a consecutive series of 20 patients with tricyclic antidepressant self-poisoning, urinary catecholamine excretion was measured, and the catecholamine level compared with that in ten patients having taken an overdose of other drugs. In both patient groups the electrocardiograph was monitored continuously for a minimum of 48 hours to detect cardiac arrhythmias. Urinary noradrenaline excretion was elevated during the first 24 hours after tricyclic antidepressant self-poisoning, to a level 2-3 times that found in the other overdose group, but was normal by the third day. Cardiac tachyarrhythmias developed in four of the patients with antidepressant overdosage. The findings support the concept that sympathetic nervous system overactivity underlies the cardiac tachyarrhythmias which commonly accompany self-poisoning with this class of drugs.

There have been many reports during the last ten years of self-poisoning with tricyclic antidepressants[1, 2]. This class of drug is commonly involved in drug overdosage admissions to Australian hospitals[3, 4]. There is substantial associated mortality, averaging 10-15% in reported series. Toxic reactions noted include cardiac tachyarrhythmias and conduction disturbances, hypotension, convulsions, hyperpyrexia, and respiratory depression[2, 3, 4].

The pharmacological basis of the cardiac disturbances is not completely clear. The anticholinergic activity of tricyclic antidepressants[5] may possibly contribute to the development of tachyarrhythmias[2]. A second possibility is that the disturbances of cardiac rhythm may be catecholamine-related. The major mechanism of inactivation of noradrenaline at sympathetic nerves, and of clearance of noradrenaline from plasma, is by reuptake into the sympathetic nerve endings[6]. Tricyclic antidepressants inhibit this process of noradrenaline reuptake[7].

The concept that disturbed sympathetic nervous system function may possibly underlie the development of cardiac arrhythmias with tricyclic antidepressant self-poisoning has recently been stressed[8]. This possibility has been investigated in the present study. Urinary catecholamine excretion has been measured serially in patients with tricyclic antidepressant self-poisoning, and the catecholamine level compared with that in patients having taken an overdose of other drugs, the latter patients serving as a control population. Within the tricyclic antidepressant group, catecholamine levels in patients who did, and did not develop cardiac tachyarrhythmias have been compared.

Patients and Methods

Patients and Experimental Protocol

The patients in the tricyclic antidepressant group constituted a consecutive series of 20 patients admitted to hospital after having taken an overdose of more than 250 mg of amitryptyline, imipramine or a related tricyclic antidepressant drug. Patients in whom one or more additional drugs (including alcohol) were known to also have been taken were excluded from the study. Admission was initially to the intensive care unit, where all patients were confined for a minimum of 48 hours. A physical and neurological examination was given on admission, and a 12-lead electrocardiogram taken. Patients subsequently received regular intensive care unit nursing and medical

*Registrar in Psychiatry; Currently Resident in Psychiatry, Ypsilanti State Hospital, Ypsilanti, Michigan U.S.A.

†Research Associate; Currently Fellow in Hypertension, Department of Internal Medicine, University Hospital, Ann Arbor, Michigan U.S.A.

Correspondence: Dr. M. D. Esler
Hypertension Section
Department of Internal Medicine
University of Michigan Medical Center
Ann Arbor, Michigan 48104 U. S. A.

Accepted for publication: 29 May, 1974.

TABLE 1
Tricyclic antidepressant self-poisoning

Patient No.	Age	Sex	Drug	Estimated Dose Ingested (mg)	Dosage Prior to Self-Poisoning (mg/day)	Adjusted Noradrenaline Level First 12 Hours* ("μg/1")	Cardiac Tachyarrhythmias	Other Complications
1	19	F	Amitriptyline	600	0	0.49		
2	22	F	Amitriptyline	625	75	0.80		
3	24	M	Nortriptyline	?	50	0.99	Ventricular Fibrillation	Generalized Convulsions
4	16	M	Imipramine	800	0	0.18		
5	24	F	Amitriptyline	300	75	0.44	Multiple Ventricular Extrasystoles	
6	26	F	Trimipramine	500	0	0.52		
7	30	M	Amitriptyline	2500	200	0.74		
8	42	M	Amitriptyline	1000	50	1.01	Atrial Tachycardia	Generalized Convulsions
9	42	F	Amitriptyline	350	0	1.34		
10	18	M	Amitriptyline	625	0	0.49	Atrial Tachycardia	
11	20	M	Imipramine	2500	200	0.55		
12	23	F	Amitriptyline	500	0	0.65		
13	23	F	Nortriptyline	1000	50	0.64		Focal Convulsions
14	39	M	Amitriptyline	450	175	0.68		
15	14	F	Amitriptyline	750	0	0.53		
16	14	F	Protriptyline	700	75	0.41		
17	29	F	Imipramine	300	0	0.65		
18	27	M	Nortriptyline	750	0	0.86		
19	24	F	Amitriptyline	375	0	0.41		
20	17	M	Imipramine	275	0	0.62		

*Adjusted noradrenaline level (μg noradrenaline/litre of plasma cleared of creatinine) = urinary noradrenaline concentration (μg/l) X serum creatinine concentration (mg/l)/urinary creatinine concentration (mg/l).

care. Blood pressure, heart rate, and temperature were recorded hourly. Continuous electrocardiographic monitoring was performed for 48 hours, with surveillance of the ECG wave form on a central oscilloscope screen by trained nursing staff, and hourly sampling of the tracing. A second 12-lead electrocardiograph was taken in the convalescent period, 48 hours or more after admission to hospital. A full psychiatric history was taken from each patient as soon as was practicable. At this time, attention was given to determining which tricyclic antidepressant was taken in the overdose and in what quantity, the prescribed dose of the agent, and the circumstances under which the drug was originally prescribed. This latter information was confirmed through contact with the patient's personal physician as required.

A consecutive series of ten patients admitted to hospital with self-poisoning involving drugs other than tricyclic antidepressants served as a control group. The overdose was of a barbiturate in five patients, methaqualone (two), diazepam (one), and mixed, involving several

drugs, in two. All patients were managed identically to the tricyclic antidepressant group, with continuous monitoring of the electrocardiograph in the intensive care unit for a minimum of 48 hours.

A urine sample was collected, either as a voided specimen or by catheter drainage in unconscious patients, on three occasions in all patients; during the first 12 hours after the overdose, during the second 12 hours post-overdose, and on the third day. The urine was acidified and frozen for storage prior to the estimation of catecholamine and creatinine concentrations. Blood was drawn for assay of serum creatinine during the first 24 hours, and on the third day. Patients were maintained in bed for the three days over which urine was collected. Smoking was forbidden. In no patient included in the study was a sympathomimetic drug, which might interfere with the catecholamine assay, given to maintain blood pressure.

Laboratory Methods

Urinary free noradrenaline and adrenaline were assayed in duplicate by a modification of the trihydroxyindole method[9], with differential fluorimetry using two sets of filters[10]. Internal standards were carried through the entire procedure, and catecholamine excretion corrected for recovery. Urinary creatinine concentration was determined by a modification of the alkaline picrate method[11], and serum creatinine concentration was estimated with a Technicon AutoAnalyser. As the urine specimens were not timed samples, it was necessary to calculate catecholamine levels from the renal clearance of creatinine, as follows[12]:

Catecholamine level (μg catecholamine/litre of plasma cleared of creatinine) = urinary catecholamine concentration (μg/l) X serum creatinine concentration (mg/l)/urinary creatinine concentration (mg/l). The assumption is made that adrenaline and noradrenaline are passively filtered by the kidney, excretion being a function only of plasma concentration of catecholamine and glomerular filtration rate. This remains unproven in man, but the values for adrenaline and noradrenaline obtained by the above computation of reverse clearance closely correspond with reported plasma catecholamine concentrations as determined directly by the recently introduced double isotope derivative assay[13, 14].

Results

The particulars of age, dosage and complications in the patients with tricyclic antidepressant self-poisoning are shown in Table 1. The overdose was of amitriptyline or a related drug (nortriptyline, protriptyline) in 15 patients, and of imipramine or trimipramine in five. All 20 patients survived the self-poisoning, but short-term electrocardiographic and neurological changes were frequent.

Electrocardiographic Changes

The average heart rate for the tricyclic antidepressant group was significantly higher than

TABLE 2

Effects of self-poisoning: Comparison of Tricyclic Antidepressant and Non-Tricyclic Overdose Groups

	Age (years)	Adjusted Catecholamine Level ("μg/l")						Mean Blood Pressure First 12 Hours (mm Hg)	Mean Heart Rate First 12 Hours (per minute)	Duration of Loss of Consciousness (Hours)
		Noradrenaline			Adrenaline					
		First 12 Hours	Second 12 Hours	Third Day	First 12 Hours	Second 12 Hours	Third Day			
Tricyclic Antidepressant Self-Poisoning	25±8*	0.65±0.26†	0.77±0.39*	0.33±0.20	0.12±0.11	0.16±0.19	0.10±0.08	119/78	102±15.7†	2.7±4.4†
Self-Poisoning With Other Drugs	39±16	0.39±0.20	0.29±0.17	0.26±0.14	0.21±0.13	0.17±0.09	0.12±0.08	123/79	87±17.8	10.2±12.3

Mean values and standard deviations are shown. The symbols refer to the significance level of the differences between the two groups (*$p<0.01$, †$p<0.05$; student's t-test).

TABLE 3
Systematic electrocardiographic changes with Tricyclic Antidepressant Self-poisoning

	Heart Rate (per minute)	PR Interval (seconds)	QRS Duration (seconds)
Electrocardiograph on Admission	105 ± 11*	0.18 ± 0.02*	0.10 ± 0.01*
Electrocardiograph in Convalescence	95 ± 10	0.15 ± 0.03	0.08 ± 0.01

Mean values and standard deviations are shown. The asterisks refer to the significance level of the difference between initial and convalescence electrocardiographic findings (*$p < 0.01$, paired t-test).

for the other overdose patients (Table 2). Sinus tachycardia (heart rate greater than 100 per minute) was recorded in the admission electrocardiograph in 18 of 20 patients with antidepressant self-poisoning. Although the mean heart rate recorded in the ECG taken in the convalescent period (average 67 hours post-overdose) was significantly lower than the heart rate on admission (Table 3), there was in fact persistent sinus tachycardia in nine of 20 patients at that time, on the third day after the overdose.

A comparison of the electrocardiographs taken on admission and in convalescence disclosed a reversible and presumably drug-related disturbance in cardiac conduction in eight of 20 patients (Table 3). In three patients first degree heart block (PR interval greater than 0.2 seconds) was present in the first but not the second ECG. In six, disturbed ventricular conduction was noted in the initial tracing only: right bundle branch block in one, intraventricular conduction delay (QRS interval 0.11-0.13 seconds) in five. One of these patients had both first degree heart block and intraventricular conduction delay.

During the first 24 hours after the self-poisoning, ventricular fibrillation occurred in one patient, atrial tachycardia in two, and multiple ventricular extrasystoles in one. The patient who developed ventricular fibrillation had atrioventricular conduction delay and intraventricular conduction delay on admission. The electrical events immediately prior to the onset of the ventricular fibrillation were not documented. The patient was resuscitated and survived without adverse sequelae. Of the two patients developing atrial tachycardia, in one spontaneous reversion to sinus rhythm occurred, while in the other the disturbance of rhythm was resistant to carotid sinus pressure, but reversion occurred with intravenous practolol, 5 mg. Lignocaine adequately suppressed the multiple (frequency 1:5) unifocal ventricular extrasystoles in the fourth patient. There were no delayed tachyarrhythmias, occurring later than 24 hours after the self-poisoning, in this series.

Urinary Catecholamine Excretion

Urinary noradrenaline excretion during the first 24 hours post-overdose was significantly higher in the antidepressant group than in the other self-poisoning group (Fig. 1). The noradrenaline levels of 0.65 ± 0.26 μg/l (mean ± standard deviation) and 0.77 ± 0.39 μg/l during the first and second 12 hours post-overdose in the antidepressant group compare with the norm for this laboratory, in healthy recumbent subjects, of 0.20 ± 0.09 μg/l ($p < 0.01$) (14). Among patients with tricyclic antidepressant self-poisoning, the noradrenaline level was marginally higher in the four patients who developed cardiac tachyarrhythmias, 0.73 ± 0.27 μg/l during the first 12 hours compared with 0.63 ± 0.24 μg/l in the remainder of the group, and 0.90 ± 0.37 μg/l compared with 0.74 ± 0.40 μg/l during the second 12 hours post-overdose, but the differences were not significant. Urinary noradrenaline excretion was unrelated to the esti-

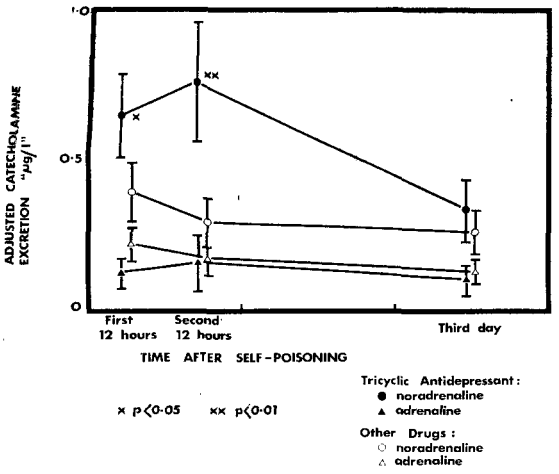

FIGURE 1. Adjusted urinary catecholamine excretion in patients with tricyclic antidepressant self-poisoning compared with catecholamine levels in patients having taken an overdose of other drugs. Mean values and standard deviations are indicated.

mated dose of antidepressant ingested.

Urinary adrenaline excretion was similar in both overdose groups, but the values throughout the three days of measurements were considerably in excess of the laboratory norm of 0.07 ± 0.06 µg/l (Table 2).

Neurological Changes

Coma was present on admission or developed soon after admission in nine patients. The loss of consciousness with tricyclic anti-depressant self-poisoning was of short duration, averaging 2.7 hours, significantly shorter than in the other overdose group (Table 2).

Generalized convulsions occurred in two patients during the first 24 hours. Paraldehyde controlled the fitting in both patients. Unilateral focal convulsions occurred once in a third patient in whom anticonvulsant medication was not required.

Psychiatric Assessment:

The tricyclic antidepressant was prescribed by a general practitioner in 16 patients, and by a psychiatrist in three. In the remaining patient, the tablets were those of another family member. Many patients were confused as to the dosage requirements, having taken the drug intermittently for symptoms only. Eleven of the 20 in fact were not taking the drug in any regular fashion at all prior to the self-poisoning. Nearly all were uninformed as to the possible dangerous toxic effects of self-poisoning.

The patients in the antidepressant group were on the average younger than the patients in the other self-poisoning group, with a mean age of 25 years (Table 2). Six of 20 were less than 20 years. A common pattern existed, to which five of the patients exactly conformed. The patient, less than 25 years of age, was prescribed the antidepressant at the time of the first visit to the doctor. The drug was initially taken intermittently, then not at all, until the time of the self-poisoning, which was precipitated by a life crisis of some sort. A formal retrospective assessment of the indications for prescribing the medication was not possible. But in many patients the drug had been prescribed for what appeared to be a situational anxiety reaction rather than depressive illness.

Discussion

In this study, urinary noradrenaline excretion was found to be elevated during the first 24 hours after self-poisoning with a tricyclic antidepressant drug. The noradrenaline level was two to three times that found in another overdose group who served as a control population. There is good reason to believe that the higher noradrenaline excretion after antidepressant self-poisoning reflected an elevated plasma concentration of noradrenaline[14] secondary to diminished reuptake of noradrenaline released at the sympathetic nerve endings[7]. Neuronal reuptake constitutes the principal method of "inactivation" of noradrenaline at sympathetic terminals, and of clearance of noradrenaline from plasma[6]. In view of the comparable effects on blood pressure and conscious state in the two overdose groups, the higher noradrenaline level with antidepressant self-poisoning clearly was not a reflection of hypotension or hypoxia. An elevated plasma noradrenaline concentration in depressive illness has been reported[15]. But as urinary noradrenaline excretion was near-normal by the third day post-overdose, the elevation during the first 24 hours was almost certainly drug-related, and not a reflection of depressive illness per se.

Disturbances of cardiac rhythm and conduction were common after tricyclic antidepressant

self-poisoning, as has been reported previously[3, 4]. Sinus tachycardia was an almost invariable accompaniment of the overdose. Some degree of disturbance of cardiac conduction was noted in somewhat less than half of all patients. Atrial or ventricular tachyarrhythmias were recorded in four. As ECG recording on electromagnetic tape was not employed, and retrieval of information was therefore not possible, it is likely that in fact these figures underestimate the true incidence of cardiac arrhythmias[16].

It has been suggested that "adrenergic dominance", from the sympathetic-potentiating and parasympathetic-blocking effects of tricyclic antidepressants, is the probable basis for tachyarrhythmias occurring with self-poisoning in man[17]. The elevated noradrenaline levels observed here are in agreement with this concept of sympathetic nervous system overactivity, and are in support of the use of β-adrenergic blocking drugs in the treatment of cardiac tachyarrhythmias occurring in this context[8]. Despite sympathetic nervous overactivity blood pressure was not elevated, but this is consistent with the direct negative inotropic and α-adrenergic blocking activities of tricyclic antidepressants[17]. Although mean urinary noradrenaline excretion was considerably elevated in the antidepressant self-poisoning group as a whole, noradrenaline level in the patients who developed atrial and ventricular tachyarrhythmias was only marginally higher than in the other patients in the group. However, since urinary noradrenaline excretion is a rather insensitive indicator of noradrenaline concentration at the adrenergic receptors, the absence of a closer relationship between noradrenaline level and the development of arrhythmias does not lessen the likelihood that the arrhythmias are catecholamine-related. The mechanism by which tricyclic antidepressants produce cardiac conduction defects is largely unexplained. Facilitation rather than impairment of conduction would be expected from enhanced sympathetic activity. A direct toxic effect associated with binding of the drug to cardiac tissue has been suspected, but with overdosage, the binding of tricyclic antidepressants to myocardium is very transient[18].

The prescribing pattern of tricyclic antidepressants seen here, in what was certainly a selected series, that of hospital admissions for self-poisoning, exhibited some unsatisfactory features. In many patients the drug was prescribed at the time of the first visit to the physician, and follow-up appointments were commonly either not made, or not kept. Patients showed a low standard of comprehension as to the aims of treatment and potential toxicity of the drug. In many patients the drug was initially prescribed for what appeared to be a situational anxiety reaction rather than depressive illness. It is emphasized that this valuable but potentially dangerous class of drugs should be prescribed only for bona fide depressive illness, and that follow-up medical supervision is essential.

Acknowledgements

We are grateful to Canberra physicians who gave us permission to study their patients. The assistance of the nursing staff of the Intensive Care Unit of Canberra Hospital, in particular Sister Pat Brown, is gratefully acknowledged.

References

1. CONNELLY, J. F. and VENABLES, A. W. (1961): A case of poisoning with "Tofranil", *Med. J. Aust.* **1**, 108.
2. STEEL, C. M., O'DUFFY, J., and BROWN, S. S. (1967): Clinical effects and treatment of imipramine and amitriptyline poisoning in children, *Brit. med. J.* **3**, 663.
3. FREEMAN, J. W., MUNDY, G. R., BEATTIE, R. R. and RYAN, C. (1969): Cardiac abnormalities in poisoning with tricyclic antidepressants, *Brit. med. J.* **2**, 610.
4. SEDAL, L., KORMAN, M. G., WILLIAMS, P. O. and MUSHIN, G. (1972): Overdosage of tricyclic antidepressants. A report of two deaths and prospective study of 24 patients, *Med. J. Aust.* **2**, 74.
5. SIGG, E. (1959): Neuropharmacologic assessment of Tofranil (imipramine), a new antidepressant agent, *Fed. Proc.* **18**, 144.
6. WURTMAN, R. J. (1965): Catecholamines, *New Engl. J. Med.* **273**, 693.
7. AXELROD, J., WHITBY, L. G. and HERTTING, G. (1961): Effect of psychotropic drugs on the uptake of H^3-norepinephrine by tissues, *Science* **133**, 383.
8. FREEMAN, J. W. and LOUGHHEAD, M. G. (1973): Beta blockade in the treatment of tricyclic antidepressant overdosage, *Med. J. Aust.* **1**, 1233.
9. CROUT, J. R. (1961): Catecholamines in urine, In *Standard Methods in Clinical Chemistry*, Vol. 3, Academic Press, London, p. 62.
10. VON EULER, U. S. and LISHAJKO, F. (1959): The estimation of catecholamines in urine, *Acta physiol. scand.* **45**, 122.
11. EDWARDS, K. D. and WHYTE, H. M. (1958): The measurement of creatinine in plasma and urine, *Aust. J. Exp. Biol.* **36**, 383.
12. ESLER, M. and GOULSTON, K. (1973): Levels of anxiety in colonic disorders, *New Engl. J. Med.* **288**, 16.
13. DEQUATTRO, V. and CHAN, S. (1972): Raised plasma catecholamines in some patients with primary hypertension, *Lancet* **1**, 806.
14. ESLER, M. and NESTEL, P. (1973): High catecholamine essential hypertension: Clinical and physiological correlates, *Aust. N.Z. J. Med.* **3**, 117.
15. PORTNOY, B., ENGELMAN, K. and WYATT, R. (1969): Plasma catecholamines in hypertensive and psychiatric disorders, *Clin. Res.* **17**, 258 (abstract).
16. ROMHILT, D. W., BLOOMFIELD, S. S., CHOU, T. and FOWLER, N. O. (1973): Unreliability of conventional electrocardiographic monitoring for arrhythmia detection in coronary care units, *Amer. J. Cardiol.* **31**, 457.
17. SIGG, E., OSBORNE, M. and KOROL, B. (1963): Cardiovascular effects of imipramine, *J. Pharmacol. exp. Ther.* **141**, 237.
18. CASSANO, G. B., SJOSTRAND, S. E. and HANSSON, E. (1965): Distribution and fate of C^{14}-amitriptyline in mice and rats, *Psychopharmacologia* **8**, 1.