Fatal tricyclic antidepressant poisoning[1]

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Introduction

In 1975 there were 234 deaths in the United Kingdom attributed to tricyclic antidepressants and a further 111 cases where these drugs had been taken along with others. Thus, these drugs were involved in 11.6% of the total 2984 deaths from solid and liquid poisons (OPCS 1977). There have been numerous case reports describing the clinical features of poisoning but only a few of these have included large numbers of fatal cases (Frejaville *et al.* 1965, 1966). Because fatal poisoning appears to be a growing problem, we decided to conduct a survey of all deaths from these drugs, in a single year, to ascertain the epidemiological and clinical features and to see in which particular areas management proved most difficult.

Methods

The Office of Population Censuses and Surveys (OPCS) kindly supplied us with photocopies of all death certificates issued in 1976 where antidepressants were mentioned as the sole or as a contributory factor in the patient's death[2]. Where death was reported to have occurred in hospital we then wrote to the physician in charge of the patient, explaining the purpose of the study and requesting the loan of the case notes. Wherever possible, the following information was collected: age and sex of the patient, verdict, whether death was ascribed to the drug alone or to some other pathological process, which antidepressants were involved, whether other drugs were also taken, the clinical features on arrival in hospital, the clinical course, the treatment, and the times taken between ingestion and arrival in hospital and between admission and death. The results were then coded to facilitate computer analysis, but data which might have identified the patient were excluded.

Results

In all, 345 death certificates were provided by the OPCS[2]; 135 deaths (39.1%) occurred in hospital and 210 (60.9%) outside hospital. The age and sex distribution of these patients is shown in Figure 1. One hundred and forty-seven deaths (42.6%) occurred in the 40–59-year age group, there were only four deaths in children, and women outnumbered men in the ratio of 1.6:1. In 217 (62.9%) a verdict of suicide was returned, in 89 (25.8%) the verdict was open and in 39 (11.3%) death was said to be accidental. In 282 cases (81.7%) death was reported to be due to the drug alone, in 54 (15.7%) to some related physical cause such as pneumonia, and in 9 (2.6%) to some unrelated physical cause such as cancer.

Amitriptyline was the commonest drug accounting for 193 deaths (55.9%). The others, in order of frequency, were: imipramine, 40 patients (11.6%); dothiepin, 35 patients (10.1%); trimipramine, 34 patients (9.9%); nortriptyline, 20 patients (5.8%); maprotiline, 15 patients (4.3%); doxepin, 13 patients (3.6%); clomipramine, 9 patients (2.6%); desipramine, 2 patients (0.6%); and iprindole, one patient (0.3%). Twenty-two patients (6.4%) took more than one antidepressant and 2 took three different antidepressants. In 156 cases (45.8%) other drugs were implicated. These included: benzodiazepines, 64 cases; alcohol, 34 cases; barbiturates, 19 cases; salicylates, 18 cases; major tranquillizers, 17 cases; paracetamol, 14 cases; and minor narcotics (dextropropoxyphene, dihydrocodeine, codeine), 10 cases.

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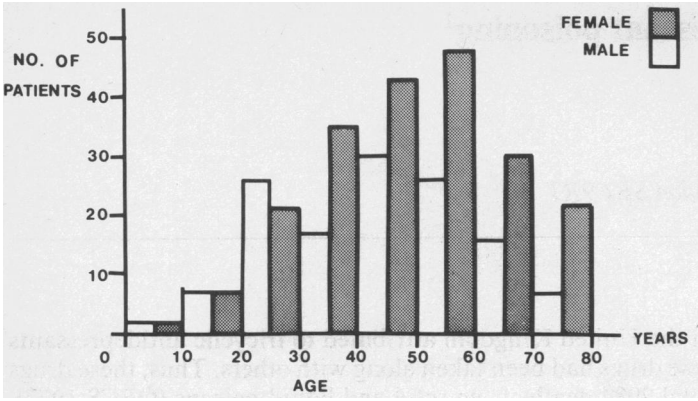

Figure 1. Age and sex distribution of 345 patients with tricyclic antidepressant poisoning

Case notes were obtained in 113 (83.7%) of the 135 patients who died in hospital and the remainder of this report deals with these patients. Patients with suicide, accident and open verdicts have been included together because there is strong evidence to suggest that they form part of the same population (Barraclough 1974, *British Medical Journal* 1977).

The patients' notes revealed a past history of depression in 48 (42.5%), of overdose in 36 (32.1%), of serious physical disease in 10 (8.9%) and of some other psychiatric disorder such as schizophrenia or alcoholism in 7 (6.3%).

The clinical symptoms recorded on arrival in hospital are shown in Table 1. Nineteen (17.0%) of these patients were already dead and a further 12 (10.7%) died following a cardiac arrest shortly afterwards. The commonest cardiac complications were hypotension and sinus tachycardia, but tachydysrhythmia was reported in only 2 patients. Twenty-six patients were reported to have both a normal heart rate and a normal blood pressure and their clinical course is shown in Table 2. Depressed respiration was noted in 32 patients.

The subsequent clinical course in the 81 patients who were neither brought in dead nor who died in casualty is shown in Table 3. Sudden cardiac arrest occurred in 16 patients and sudden respiratory arrest in a further 11. Tachydysrhythmia was again uncommon, occurring in only 9 patients. Of the 17 patients who developed convulsions, cardiac arrest was precipitated in 6. Only 4 patients regained consciousness and only one of these patients then died suddenly.

The treatment regimes used were very diverse. These included diazepam (18 patients), phenytoin (2), chlormethiazole (2), phenobarbitone (1), practolol (6), lignocaine (4), cholinesterase inhibitors (2), corticosteroids (7), isoprenaline (5), metaraminol (4), adrenaline (2) and dopamine (1). In addition, cardiac arrest procedures were carried out in 40 patients. Twenty-seven patients were artificially ventilated. Seven patients had a transvenous pacemaker inserted but this was only successful in 2 patients. Elective cardioversion proved successful in 2 patients and unsuccessful in another one. Four patients (who had all also taken salicylates) were treated with forced alkaline diuresis. One patient, who had not taken any other drugs, was treated with resin haemoperfusion.

The mean time between ingestion and admission to hospital was 3.2 hours, but this information was only available in 19 cases. Eighty of the patients died within twenty-four hours of admission and only 8 lived for more than one week.

Discussion

Since the majority of deaths occurred outside hospital, any major reduction in mortality must depend on prevention rather than on any improvements in management. Nevertheless, the study did reveal that some of the commonly-held assumptions about serious tricyclic antidepressant poisoning are not true and that the management of some of the common complications could, in some cases, be improved.

Table 1. Fatal tricyclic antidepressant poisoning. Clinical features on admission to hospital in 113 patients

Symptoms	No. of patients
Brought in dead	19
Drowsiness	12
Coma	70
Normal heart rate●	45
Normal blood pressure●	43
Sinus tachycardia	20
Tachydysrhythmia	2
Bradycardia	8
Hypotension	26
Cardiac arrest in casualty	14
Normal respiration●	42
Depressed respiration, not ventilated	19
Depressed respiration, ventilated	13
Convulsions	15
Hypothermia	4
Hyperthermia	3

●Patients were included in these categories only if this was expressly stated in the notes. Patients in whom this information was not recorded were not assumed to have normal heart rates, blood pressures or respiration

Table 2. Clinical course in 26 patients who arrived in hospital with both normal heart rates and normal blood pressure

	No. of patients	No. dying suddenly
Drowsy, normal respiration	7	4
Drowsy, depressed respiration	12	5
Coma, normal respiration	1	1
Coma, depressed respiration	6	0

We found that the commonest cardiac complications were hypotension and sinus tachycardia. Tachydysrhythmias were uncommon, being seen altogether in only 11 patients. This contrasts with the high proportion of patients reported in other series to be suffering from arrhythmias. The explanation may be due to differences in definition. For our part, we have included patients reported to have tachycardia of atrial, nodal or ventricular origin, atrial fibrillation or flutter and sinus tachycardia with ectopics. Others have included patients with additional arrhythmias (Biggs *et al.* 1977, Serafimovski *et al.* 1975).

Dumovic *et al.* (1976) found in animal experiments that in moderate doses amitriptyline produced tachydysrhythmias, but when the infusion was continued the animals developed bradycardia and atrioventricular block. It is possible that a similar situation exists in massive tricyclic poisoning in man. In animal experiments performed with His-Bundle electrocardiography, true tachydysrhythmias were not demonstrated, although the surface electrocardiograph could have been interpreted as such (O'Keefe *et al.* 1979).

The pharmacological actions of tricyclic antidepressants on the heart are complex. In addition to the anticholinergic effect, and the potentiation of noradrenaline (Sigg 1959), there is also a quinidine-like action which can be demonstrated at therapeutic doses in man (Burrows *et al.* 1976). The combination of a fast heart rate with a wide QRS complex, which is seen frequently in non-fatal poisoning, may cause diagnostic confusion as to the origin of the tachycardia. Tricyclic antidepressants have negative inotropic effects which with large doses lead to decrease in cardiac output and arterial blood pressure. In the present study it appears that drug treatment for cardiotoxicity was directed mainly at reversing the electrocardiographic changes and the drugs used, lignocaine and the beta-adrenergic receptor blockers, also have negative inotropic actions and may therefore aggravate rather than improve myocardial function, as has been shown in animal experiments (Elonen 1975). A more logical approach would be to use drugs such as isoprenaline or dopamine which have positive inotropic actions. Cholinesterase inhibitors were used only twice. Physostigmine salicylate appears to have

Table 3. Fatal tricyclic antidepressant poisoning. Subsequent clinical course in 81 patients

Symptoms	No. of patients
Sudden cardiac arrest	16
Hypotension	13
Tachydysrhythmia	9
Bradycardia	8
Sinus tachycardia	1
Cardiac arrest after developing another cardiac symptom	18
Sudden respiratory arrest	11
Respiratory depression	9
Respiratory arrest following respiratory depression	2
Pneumonia	11
Pulmonary oedema	2
Convulsions	11
Convulsions leading to cardiac arrest	6
Recovered consciousness	4
Cardiac arrest after regaining consciousness	1
Coma	6
'General decline'	30

some effect in reversing severe amitriptyline cardiotoxicity although its effect is short-lived and not very large (O'Keefe *et al.* 1979).

The question arises as to exactly when antiarrhythmic agents should be used. Correction of hypovolaemia and acidosis may in themselves improve cardiotoxicity. If there is still hypotension then drugs such as isoprenaline should be tried in slowly increasing doses. Only if this too does not result in an improvement should antiarrhythmic drugs be tried. For the patient *in extremis*, however, DC shock should be attempted first. If a patient is admitted to a hospital where there are facilities for intracardiac electrocardiography it would seem sensible to use these when treating such patients, both to aid diagnosis and to monitor therapy.

Although respiratory depression was not recorded at all in one large series of non-fatal poisoning (Noble & Matthew 1969), it was a common feature in our study. Yet artificial ventilation was instituted in only half of these patients, sometimes even when arterial blood gases revealed hypoxia. Patients with hypnotic drug poisoning may be able to tolerate a degree of hypoxia, but in patients with severe tricyclic poisoning the hypoxia may aggravate the cardiotoxicity to such an extent that recovery proves impossible. Sutherland *et al.* (1977), who found that barbiturate and tricyclic antidepressants affected blood gases similarly, have drawn attention to the unreliability of measuring tidal volume as an indicator of hypoxia. We agree with them that it is prudent to measure arterial blood gases in all patients with coma, respiratory depression, convulsions or serious cardiotoxicity. We feel strongly that, with antidepressant overdose, artificial ventilation should not be regarded as a last resource.

A number of patients suffered a series of convulsions before they were brought under control and this precipitated cardiac arrest in six. Some patients proved resistant to several anticonvulsant drugs, but the alternative method of treatment, by paralysis and artificial ventilation, was not instituted.

It must be emphasized that in this study we were not responsible for the management of these patients. Our conclusions have been drawn from the case records of physicians who might want to interpret the findings differently from ourselves. Nevertheless, by this survey technique we have been able to concentrate on the serious, indeed the fatal cases, whereas other series have often included a large proportion of mildly-poisoned patients. It is our opinion that by using this method certain conclusions about severely intoxicated patients can be drawn – namely that the incidence of tachydysrhythmias has been overrated and that of

respiratory depression underrated. Although most deaths occur outside hospital, management could be improved by the better application of the principles of intensive supportive care. In particular, the assessment of respiratory function is often ignored, respiratory depression and convulsions could be more aggressively treated and the use of antiarrhythmic drugs restricted.

Summary

In 1976, 345 deaths were reported in which tricyclic antidepressants were cited as the sole or contributory cause of death: 42.6% of the patients were aged between 40 and 59 and women outnumbered men in the ratio 1.6:1. Amitriptyline accounted for over half the deaths. Examination of the case notes of 113 (83.7%) of the 135 patients dying in hospital revealed that coma (70 patients), hypotension (26 patients) and sinus tachycardia (20 patients) were the commonest presenting symptoms. Tachydysrhythmias, in contrast, were uncommon occurring in only 2 patients on first presentation, and 9 thereafter. Sudden cardiac or respiratory arrest occurred in 27 of the 81 patients who were neither brought in dead nor who died in the accident department. This survey indicates that the importance of cardiac arrhythmias has been overestimated and the importance of respiratory depression underestimated in the management of severe tricyclic poisoning. Although most deaths occur outside hospital, better application of the principles of intensive supportive care could reduce the hospital mortality.

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Addendum

Since this study was carried out, the 1976 mortality statistics have been published (OPCS 1978); tricyclic antidepressants were cited as the sole or contributory cause of death in 370 cases.

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