*Brit. J. Psychiat.* (1979), **134**, 637–39

# *Comments*

This is the second of a series of short reviews and reports on topical matters. They are intended to be useful in some aspect of clinical practice or to report an interesting new growing point in neuroscience, or to give a synopsis of the current situation in some area of psychiatry. They should reflect topical interests, what people talk about both informally and at society meetings. Some may be valuable in the training of young psychiatrists, others in the further education of consultants, and yet others will prove starting points for new investigations.

## TRICYCLICS AND THE HEART

The cardiotoxic effects of tricyclic antidepressant drugs (tricyclics) have continued to cause worldwide concern ever since Mann and his colleagues (1959) described two cases of congestive heart failure, one of them fatal, and mentioned arrhythmias. Muller and his co-workers (1961) systematically investigated the effects of imipramine on the cardiovascular system by comparing its effects on 41 patients without heart disease with 50 patients with evidence of cardiovascular disease including atherosclerosis. Whereas a few control patients showed mild postural hypotension, 4 of the cardiovascular disease group developed congestive heart failure, 2 myocardial infarction and 10 severe and 7 moderate postural hypotension. Subsequently the cardiovascular toxicity of tricyclics has been frequently reviewed (Jefferson, 1975; Hollister, 1975; Blackwell, 1977, 1978).

Readily absorbed from the gut, tricyclics are concentrated selectively in certain tissues, notably the kidneys, lungs, liver and heart so that plasma and tissue levels are poorly correlated. In the liver they are demethylated to potentially more toxic forms before being converted to inactive glucuronides and excreted in the urine. Unlike antipsychotic drugs, they exert no appreciable effect on dopamine receptors but their reactions on noradrenaline and 5-hydroxytryptamine have contributed to the development of the biogenic amine theory of depression. All tricyclics block the re-uptake of noradrenaline by adrenergic nerve terminals, the demethylated analogues being particularly potent in this regard while the methylated forms are more active in the blockade of 5-hydroxytryptamine re-uptake. Toxic effects are inconstantly related to plasma levels (Glassman *et al*, 1974) and seem to be more dependent on tissue concentrations. The wide variations in plasma values between individuals may be genetically determined (Alexanderson and Sjoquist, 1971). The mechanisms by which tricyclics act on the heart (Rose, 1977; Wood *et al*, 1976; Jeong *et al*, 1976) are thought to include atrophine-like anticholinergic effects, quinidine-like conduction changes, blockade of noradrenaline receptors with increase of catecholamine concentrations and sympathomimetic effects on rhythm, rate and the myocardium and impaired contractility of cardiac muscle with reduced output.

In *therapeutic* doses, tricyclics can cause postural hypotension, tachycardia, cardiac arrhythmias and conduction defects, and in patients with cardiac disease congestive heart failure (Rose, 1977). There is evidence that they may provoke heart failure in patients without myocardial disease (Hollister, 1975) but the suspicion that they precipitate myocardial infarction is unproven. Reports of sudden unexpected death (Coull *et al*, 1970; Williams and Sherter, 1971) were not confirmed by the findings of the Boston Collaborative Drugs Surveillance Committee (1972) who found no increase in sudden death in patients with myocardial disease receiving tricyclics. Conversely, Moir *et al* (1972) found a significant excess of sudden unexpected deaths in tricyclic-treated in-patients with myocardial disease compared with a control group carefully matched for diagnosis, age, sex and duration of hospital stay. However, Avery and Winokur (1976), comparing mortality in 519 patients adequately and inadequately treated with ECT and antidepressants, failed to confirm increased mortality in the adequately treated group, nearly all of whom received imipramine or amitriptyline. They commented that it is insufficiently appreciated that depression itself carries an enhanced risk of cardiovascular death.

Tricyclics provoke similar ECG changes in animals and man. In experimental cats amitriptyline induced significant S–T segment and T wave changes and conduction effects (Glisson *et al*, 1978). Dumovic and his colleagues (1976) studied the *in vivo* effects until death of amitryptiline, imipramine, nortriptyline and doxepin on the heart rate and ECG of anaesthetized guinea pigs; and *in vitro* on guinea pig atria. Though there were no significant differences with respect to the onset of widening of QRS or prolongation of

Q-R and Q-T intervals, the animals perfused with doxepin survived longer than the rest. Burrows *et al* (1976), investigating the effects of the same drugs on heart rate and atrioventricular conduction in 32 depressed patients, found significant increases. They also studied conduction defects in patients who had taken overdoses of several tricyclic drugs, by bundle of His electrocardiography, and found distal conduction defects in all but the doxepin overdose subjects.

ECG changes are dose-related, may occur with therapeutic quantities (Robinson and Barker, 1976) and are frequently symptomless. ECG abnormalities observed in tricyclic-treated patients are sinus and ventricular tachycardia, arrhythmias, falling of premature ventricular contractions in a prolonged period of repolarization, lengthened P-R and Q-T intervals, mild S-T segment and T wave changes, prominent U waves and various conduction defects and degrees of heart block (Hollister, 1975; Rose, 1977). In 17 depressives treated with amitriptyline comparison of pre-treatment ECGs with readings taken three weeks later showed significant increases in rate, S-T abnormalities and T wave changes, and there was a weak positive correlation between change in rate and plasma nortriptyline concentrations (Ziegler *et al*, 1977). The quinidine-like properties of tricyclics on rhythm and conduction have been used to treat arrhythmias (Bigger *et al*, 1977), However, amitriptyline increased the incidence of ECG changes during the induction of anaesthesia (Glisson *et al*, 1978) and ECG changes are especially likely in the elderly and in the presence of myocardial disease (Moir *et al*, 1972).

Children tolerate tricyclics much less well because they have smaller lipid compartments, less plasma-binding capacity and proportionately larger livers with potentially greater production of the more toxic demethylated derivatives (Robinson and Barker, 1976). Rose (1977) advises that they should not be given to children under 6 years of age or in doses exceeding 2.5 mg per Kg daily.

*Overdoses* of tricyclics cause seizures, respiratory depression, blood pressure changes and cardiopulmonary arrest: cardiovascular changes are magnified and there are conduction defects and arrhythmias of every kind, ventricular tachycardia and fibrillation and asystole (Jeong *et al*, 1976; Wood *et al*, 1976). Non-bacterial endocarditis, multiple emboli in heart, spleen and kidneys and invasion of pulmonary alveoli by connective tissue leading to progressive respiratory insufficiency have also been reported (Lindstrom *et al*, 1977). The overdose triad of coma, seizures and arrhythmias is frequently fatal; indeed the prescription of a hundred 25 mg tablets to a suicidal depressive may well be presenting him with a lethal weapon (Hollister, 1975).

In view of the risks of cardiovascular side effects and of sudden death alternatives may be considered for patients with cardiovascular disease. Other drugs such as doxepin, the tetracyclics or the bicyclic compound viloxazine may have less action on the heart, but we have a much shorter experience of these than of imipramine or amitriptyline. Alternatively the use of monoamine oxidase inhibitors involves risks which may have been overemphasized: thus 1 death was reported per 100,000 patients treated (British Medical Journal, 1964). ECT is a relatively safe treatment (Kendell, 1978) with one death in 22,210 treatments given in the course of a year (Heshe and Roeder, 1976), is effective in depression resistant to tricyclics, for example where there is marked psychomotor change or delusional formation, and may be preferred to tricyclics in milder depressives who are physically vulnerable or who are on drugs reported to give adverse effects when combined with tricyclics. These include antihypertensives, sympathomimetic amines (Jefferson, 1975), thioridazine (which may accentuate quinidine-like effects), and monoamine oxidase inhibitors. Drugs which induce enzymes capable of retarding the metabolism of tricyclics, for example methyl phenidate and antipsychotic agents, may increase body concentrations and tendencies to toxicity (Gram and Overo, 1972).

Though there are doubts about the therapeutic efficacy of tricyclics (in 30 per cent of the controlled studies of these drugs reviewed by Morris and Beck (1974) drug-placebo differences were not found), they are widely employed in the treatment of depression, and, when used in healthy adults, their advantages outweigh possible risks. Moreover, Avery and Winokur (1976) showed that deaths from suicide, non-suicidal causes and myocardial infarction were significantly more in untreated patients or those given inadequate courses of antidepressants than in treated patients.

A personal view is that one should be cautious about prescribing tricyclics in the presence of evidence of myocardial disease, cardiac arrhythmias or conduction defects, an abnormal ECG, marked atherosclerosis, cardiovascular disease or a history of severe drug reactions, particularly when these involved the cardiovascular system. Proposed combinations of tricyclics with other drugs require careful consideration. The elderly are more at risk than younger people because they tend to be more sensitive to adult doses and show more unwanted effects of all kinds, especially confusion. Particular caution should also be exercised when prescribing tricyclics to children.

In cases of doubt, particularly when it is proposed to use very large doses, i.e. in excess of 300 mg daily, it is prudent to do an ECG, seek cardiological advice or consider an alternative like doxepin, an antidepressant of another series, or ECT. In any case tricyclics should normally be commenced in small doses and built up by stages to the appropriate therapeutic amount. In view of the high mortality of overdoses of tricyclics it is folly to give large quantities at any one time to a potentially suicidal patient. Equally it should be remembered that suicide is the most frequent cause of death in depression and effective treatment should not be withheld.

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