Cardiovascular Effects of the Standard Tricyclic Antidepressants

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Cardiovascular effects of tricyclic antidepressants are reviewed.

In the early 1970s, as methods gradually developed for measuring tricyclic antidepressants (TCAs), it became clear that there were large interindividual differences in metabolism, and that these resulted in large differences in plasma steady-state concentrations of various TCAs from one patient to another. Initially, the interest in this metabolic variability was focused around the question of whether rapid metabolism resulted in patients with low concentrations in plasma and poor response to these drugs. Only gradually did interest shift to include patients who were slow metabolizers and had high concentrations in plasma, and to the question of these high concentrations producing toxicity.

Since the TCAs were first discovered in the 1950s, it has been apparent that overdoses of these drugs can result in death, most frequently cardiac in origin (1). As the interest in metabolic variability began to include slow metabolizers with high concentrations of the drug in plasma, the most important question seemed to be whether these serious cardiac consequences could follow from this metabolic variability. However, the issues are more complex than were really appreciated, and the cardiac pharmacology of these drugs, as we understood them in the mid-1970s, has changed enormously over the last decade. In many ways, the ability to measure plasma concentrations of these drugs has contributed heavily to our changing understanding of the cardiovascular toxicity of the TCAs.

Early reports on imipramine and other tricyclic drugs indicated that otherwise-normal patients occasionally developed an abnormal electrocardiogram (EKG) when they took these medications. Only gradually has it become clear that all of the standard tricyclic drugs will delay cardiac conduction. The degree of this delay depends both on the concentration of the drug and the pre-existing cardiac disease of the patient. In a depressed but otherwise healthy patient, therapeutic doses of the various antidepressant drugs may or may not influence conduction times. These times are characteristically measured by the PR, QRS, or QT intervals in the standard EKG. Thus patients on normal doses of antidepressant drugs may show no change or only minor prolongations of these conduction measures, or occasionally they even develop what would appear to be EKG abnormalities such as first-degree heart block (slowed atrial to ventricular conduction) or bundle-branch (intra-ventricular conduction) patterns. In general, these tricyclic-induced conduction delays are of no clinical significance. Although they may or may not be present in patients who are receiving the usual therapeutic oral dosages, as the concentration of the drug increases in the plasma these conduction changes become consistent phenomena, and in overdose it is the prolonged conduction delays that are characteristic of the syndrome and likely to produce serious sequelae.

Vohra et al. (2) were among the first to identify precisely where TCAs exert their influence on conduction. They measured cardiac conduction using intracardiac His bundle electrocardiography, and they showed that the AH interval (atrial or nodal conduction) was little affected by these drugs. They found that the major effect was on HV (intra-ventricular) conduction, and this has subsequently been supported by electrophysiological studies of others (3, 4).

Although the prolongation of conduction induced by TCAs is seldom significant in people who are free of heart disease, in those patients with pre-existing intraventricular conduction disease a significant risk develops with these drugs. We have recently completed a prospective study of 41 depressed patients with first degree AV block and (or) bundle-branch block compared with 151 patients with normal pretreatment EKGs (5). Both groups were treated with therapeutic dosages of imipramine or nortriptyline. The rate of 2:1 atrioventricular block was significantly (P <0.05) higher (9%) in patients with pre-existing bundle-branch block as compared with the rate (0.7%) in patients with normal pretreatment EKGs. In fact, the one patient with a normal pretreatment EKG who developed 2:1 block on tricyclics had an abnormal His Purkinje conduction that was apparent only on catheterization. This type of block is a symptomatic extension of the conduction delays seen on the EKG. In this condition some of the impulses beginning in the atrium fail to reach the ventricles and actual ventricular beats are skipped. This can progress to complete heart block, cardiac standstill, and death.

Because the TCAs can cause severe arrhythmia in overdose, it has been widely assumed that their use would be contra-indicated in patients with pre-existing arrhythmias. Although this logic is attractive, it has not proved to be the case. During the past 10 years it has been established that at antidepressant concentrations in plasma approximating therapeutic levels, these drugs have powerful anti-arrhythmic activity. The anti-arrhythmic effect of imipramine was first reported in 1977 (6). Subsequent studies have shown that imipramine is similar to quinidine in its anti-arrhythmic activity. The available data indicate that nortriptyline is similar to imipramine with respect to its anti-arrhythmic activity, and that other TCAs also show similar anti-arrhythmic activity (7). These drugs share electrophysiological properties characteristic of Type 1 anti-arrhythmic compounds and currently are being used in cardiac-disease patients for the purpose of controlling ventricular arrhythmias.

The confusion in the literature has arisen primarily because, in very severe overdoses, patients can develop—and can die of—ventricular arrhythmias. However, this is not a primary arrhythmogenic activity of these drugs, but is due to the previously described extensive conduction delays that develop in these patients. As the QRS interval begins to exceed 160 ms these patients become particularly vulnerable to re-entry arrhythmias and "circus" rhythms (8). To treat these arrhythmias with standard anti-arrhythmic drugs would only make the condition worse. Arrhythmias in the presence of tricyclic overdose represent a very serious sign, and they are not seen in mild overdoses. An overdose of
tricyclics manifesting ventricular arrhythmias should be considered critical.

Until the early 1980s it had been widely assumed that the tricyclic antidepressants adversely affect left ventricular function (LVF). A number of earlier studies on nortriptyline, amitriptyline, and imipramine produced evidence of TCA-induced impairment of LVF (9, 10). However, the criterion used to assess LVF was usually the systolic time interval, a measurement that depends in part on the duration of the QRS interval. Because QRS prolongation is characteristic of the effects of TCAs, it is possible that the effect of TCAs on the systolic time interval in these early studies was due to their effect on conduction rather than on left ventricular function. The introduction of radionuclide angiography provided a more reliable means of assessing TCA effect on left ventricular function. Using this angiography technique, Veith et al. (11) showed that both imipramine and doxepin had no effect on LVF, either in the resting state or after exercise. However, they used only relatively low doses of the drug, and they included few patients with seriously impaired ejection fractions. Subsequently, our group reported radionuclide data on a series of 15 depressed patients with moderate to severe impairment of their ejection fraction (12). These patients were all treated to produce therapeutic concentrations of imipramine in their plasma, and, as Veith et al. had observed, the drug had no measurable effect on left ventricular function. However, it did produce intolerable orthostatic hypotension in about half of the patients (imipramine is measured as the parent compound, and its desmethyl metabolite). Subsequently, we replicated this finding in a second series of 10 patients with heart failure, where again there was no further impairment in LVF, but half of the 10 patients developed orthostatic hypotension so severe that they were unable to stand. Thus, in examining the direct effects on the heart of standard tricyclic antidepressants, the only serious adverse sequelae are conduction delays. These effects occur irregularly at the usual therapeutic doses, but their occurrence increases predictably with increasing doses and is characteristic of overdose. No adverse effect on the pump function of the heart is seen in TCA-treated patients even with seriously impaired ventricular function. And, finally, in patients with arrhythmias, the TCAs will usually prove beneficial. The most frequent serious cardiovascular side effect of the tricyclic antidepressants is not cardiac at all, but vascular. This is orthostatic hypotension, which can result in fractures, lacerations, and sudden death (13). By far the most frequently studied drug in this context is imipramine. The data available on the orthostatic effects of the other tricyclic drugs are not as complete, but work by Nelson et al. (14), Hayes et al. (15), Kopera (16), and our own group, strongly implies that there is an orthostatic effect for amitriptyline, desipramine, and doxepin as well.

Nortriptyline is the only TCA currently marketed for which a decreased risk of orthostatic hypotension has been clearly documented. Freyschuss et al. (17) reported that the orthostatic effect of nortriptyline in 40 healthy and relatively middle-aged depressed patients was negligible. Thayse et al. (18) also reported that there were no posture-related systolic pressure drops with nortriptyline. In the United States, our group has also clearly documented this lesser risk of orthostatic hypotension with nortriptyline (19).

A recent study of over 100,000 elderly subjects in the state of Michigan (20) showed that during a three-year period this population suffered more than 1000 hip fractures. There was a strong association between the use of psychotropic medication and the risk of occurrence of these fractures. The odds that a patient taking a tricyclic antidepressant would suffer a hip fracture were three times greater with even modest doses of these drugs than for comparably aged patients who were free of such medication. Given the morbidity and mortality, not to mention the costs involved in these fractures, this is not a trivial issue.

The mechanisms by which tricyclics induce orthostatic hypotension are not entirely clear. Interestingly, a significant risk factor for the development of orthostatic hypotension with imipramine may be the diagnosis of depression itself. Giardina et al. (21) reported that, of 22 non-depressed cardiac patients with some degree of congestive failure (mean ejection fraction of 33%) who were being treated with imipramine for arrhythmia, only one discontinued medication because of orthostatic hypotension. This compares with a rate of approximately 50% of the patients developing intolerable orthostatic hypotension in our depressed patients with a similar degree of left ventricular impairment who were treated to produce comparable concentrations of imipramine in plasma. Thus it would seem that, when treated with imipramine, patients with heart disease and melancholia are at significantly greater risk of developing orthostatic hypotension than are patients with heart disease alone.

What is the incidence of orthostatic hypotension in patients who are being treated with imipramine? It can vary from 1% for cardiovascular patients free of depression to 5% or 6% for melancholic patients free of heart disease, to 25% for cardiac patients with hypertension but who are free of cardiac failure, to almost 50% for patients with both melancholia and heart failure. Thus, the incidence of orthostatic hypotension is not simply related to the antidepressant drug; it involves both the illness of the patient and other drugs that the patient may be ingesting. Although nortriptyline is not free of orthostatic hypotension, it does have a well-documented clinical advantage over the other standard tricyclic antidepressants in those patients at particular risk for this adverse event. Many of the newer antidepressants would appear to be free of cardiac effects in depressed patients without heart disease. However, none of these compounds has been carefully tested in patients with both depression and cardiovascular difficulties. Thus, comparison with standard antidepressant drugs remains difficult.

References