The Use of Antidepressant Drugs in Patients With Heart Disease

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Both depression and cardiovascular disease are common as people age and are, therefore, likely to coexist. It has become evident recently that the rate of this comorbidity exceeds substantially what is expected by chance. A major problem arises in that there is increasing evidence that the tricyclic antidepressants (TCAs) carry more risk than originally thought in patients with ischemic heart disease. This risk increases the importance of understanding both the safety and efficacy of the serotonin selective reuptake inhibitors (SSRIs) in this population. Three recent studies on safety data in patients with overt heart disease are now available: although the total of 94 patients limits the ability to make generalizations, the data that are available give little evidence of harm and even suggest that SSRIs may have beneficial effects in ischemic heart disease. *(J Clin Psychiatry 1998;59[suppl 10]:16–21)*

My colleagues and I began treating depression in people who have both depression and heart disease more than 25 years ago. A number of times during this period it seemed that we understood everything that was to be understood about the cardiac effects of antidepressant drugs.[1] However, the field changes: new drugs become available and new issues keep arising. At the outset, we knew that this problem of co-occurring heart disease and depression would become important because depression occurred frequently in elderly populations and cardiovascular disease was even more common—50% of Americans will die of heart disease. When 2 conditions are common, they are likely to coexist in a substantial number of patients.

ASSOCIATION OF DEPRESSION WITH CARDIOVASCULAR DISEASE

Shortly after we began studying the cardiovascular effects of imipramine, an epidemiologist in Denmark reported that patients with a diagnosis of major depression or manic depressive disorder, when followed over time, were more likely to die and their death would most likely be cardiovascular in nature.[2] Over the next 15 years, 10 very similar studies appeared, and 9 of the 10 found this same increase in cardiovascular deaths among individuals with depression compared with the general population.[3] All of these studies were criticized because the effects of depressive illness were not separated from the effects of the drugs used to treat these patients.

One solution to the confound of multiple effects was to use community epidemiologic data rather than a patient sample. In community-based data, 90% of the sample have experienced no treatment whatsoever.

Two large epidemiologic studies became available in the late 1980s: 1 from Canada, the Stirling County Study,[4] and the other from the epidemiology group at Yale.[5] The Stirling County Study followed 1000 people for 16 years; the Yale study followed approximately 3500 people for almost a decade. Both used community samples; study personnel found the subjects by a door-to-door search, and follow-up interviews were conducted years later. The subjects who were assessed as depressed at baseline were more likely to die of cardiovascular disease than those who were determined to be free of depression in both samples. In these samples, treatment of depression is not a confound. Both depression and cardiovascular disease were not only common, and therefore likely to coexist, but were also associated. Patients with either cardiovascular disease or depression have an increased risk of also having the other condition. It is more common than one would expect merely from the probability of 2 common conditions coexisting in the population.

In a landmark study published in the *Journal of the American Medical Association* in 1993, Frasure-Smith

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and Lesperance[6] conducted interviews in a cardiac intensive care unit. They interviewed everybody who had a heart attack and then followed, for the next 18 months, those people who lived to leave the hospital. Of 222 consecutive postinfarction patients who were interviewed, 35 received a diagnosis of depression. The 35 depressed subjects represented about 16% of a group of a few more than 200 patients. That is an extraordinary incidence of depression, especially considering that the sample consisted entirely of patients in the intensive care unit who were interviewed during the 10-day period after a heart attack. The 16% incidence of major depression in a 10-day period is approximately the percentage expected as the lifetime incidence of major depression. We are seeing a very marked increase in depression. What is more important is that if one follows the people who are depressed and compares them with those post–myocardial infarction (post-MI) patients who do not get depressed, the former have a markedly increased mortality rate. By 6 months, their mortality rate is 3.5 times that of the people who are free of depression, which is a striking difference. The most powerful single medical predictor of mortality after a heart attack has always been heart failure, which produces a 3.5-fold increase in the mortality rate. In these data, a psychiatric condition produced the same risk of dying as the strongest single medical factor after a heart attack. This finding raises many questions. Perhaps the most important question is, "If we treated these people for depression after a heart attack, would we reduce this mortality?" It is an obvious question. The problem is, however, that it is not obvious whether it is safe to treat these people with presently available antidepressant drugs.

ADVERSE EFFECTS OF TRICYCLIC ANTIDEPRESSANTS ON PATIENTS WITH CARDIOVASCULAR PROBLEMS

It is important to discuss the safety of treating people who have overt heart disease and to review the information on tricyclic antidepressants (TCAs). The tricyclics have cardiovascular effects. It was obvious from the overdose data that were available shortly after the tricyclics were first introduced that these drugs can be lethal. In overdose, tricyclic drugs kill people, and death associated with these drugs is almost always cardiovascular in nature. At therapeutic levels in a healthy heart, there is a limited amount of cardiovascular difficulty associated with use of tricyclics, and that difficulty is essentially limited to orthostatic hypotension.[7] Probably only 2% or 3% of medically healthy people have orthostatic problems with these drugs. Although slightly more difficulty is seen in the healthy elderly, the really severe problem comes in people who have heart disease. Heart failure was originally thought to be a contraindication to tricyclic use. On the basis of animal studies, at one time it was believed that patients with heart failure might have that failure exacerbated by use of tricyclics, but in fact, it turned out that the tricyclics do not adversely affect the contractility of the heart or the heart's muscle function. Heart failure does, however, greatly increase the chance of orthostatic hypotension. One problem with the use of tricyclics is that they can become unusable in people with heart failure, because rates of orthostatic hypotension approach 50%.[8] Tricyclics also exacerbate problems associated with preexisting conduction disease. This has been recognized for 20 years. The tricyclics delay conduction in the heart, which is the major way that the drug kills people in overdose. In healthy hearts, when the plasma tricyclic levels are therapeutic, this conduction delay is not ordinarily a problem, but in people with preexisting cardiac disease, the delay can produce serious clinical problems.

Arrhythmia is a special problem. In 1977, my colleagues and I[9] published a case report in the *New England Journal of Medicine* in which we stated that imipramine was an antiarrhythmic drug. In this report, a woman had a ventricular arrhythmia of up to 800 extra beats per hour, averaging 400 beats per hour over the 24-hour period. There was a great deal of variability with quieting at night, but this was a marked degree of arrhythmia. After 4 weeks of treatment with imipramine, her arrhythmia decreased from 400 extra beats per hour to 4 extra beats per hour. At the time, we were encouraged by this result because it seemed to indicate that a single drug could be used to treat both arrhythmia and depression. The "kill two birds with one stone" adage has proved, however, to be more literally correct than we had expected.

This story took an interesting twist in the late 1980s. In the mid-1980s, a group of academic cardiologists became apprehensive about the severity of the adverse events that are seen with the usual antiarrhythmic drugs. It was very clear that arrhythmia after a heart attack is associated with a marked increase in mortality; mortality rates are 3 times as high for individuals who develop arrhythmia after a heart attack compared with the rates for those who do not. Antiarrhythmic drugs are highly effective in suppressing this post-MI arrhythmia. Quinidine was originally the drug that was used, but in the mid-1980s, 2 new antiarrhythmics, flecainide and encainide, were introduced. These academic cardiologists convinced the Heart, Lung, and Blood Institute to undertake a very large study and see exactly how much benefit accrued with use of antiarrhythmic drugs, that is, how many lives were saved, compared with how much toxicity was produced. This study was called CAST—Cardiac Arrhythmia Suppression Trial—and it was begun in 1987 and was originally planned to extend for 4 years.[10] After 2 years, the safety monitoring board stopped the study because the people who were assigned to receive placebo were living longer than the people who were taking active medication. The mortality rate was higher by nearly 3-fold for those who were on the supposedly helpful antiarrhythmic drug.

The problem for psychiatrists is that the TCAs are class I antiarrhythmic drugs just like flecainide, encainide, and quinidine. Although no one has tested the tricyclics directly, there is every reason to believe that they would carry the same risk of mortality as the antiarrhythmic drugs. Why this increased mortality occurred was not originally clear. Subsequently, evidence has accumulated that strongly suggests that in a well-oxygenated heart, these drugs are powerful antiarrhythmics, as advertised. However, when the heart becomes deprived of oxygen, as it does in a heart attack, these drugs become proarrhythmic; that is, at the very time that we would most want the agents to protect against arrhythmia, their pharmacology changes and they become proarrhythmic. After a heart attack is precisely the time that tricyclics should be avoided.[11]

USE OF SSRIs IN PATIENTS WITH CARDIOVASCULAR PROBLEMS

Because the TCAs are problematic in treating patients with cardiovascular problems, the question becomes, "What about the other antidepressants?" The largest group by far of other antidepressants is the serotonin selective reuptake inhibitors (SSRIs). We have undertaken a series of studies that looked at the safety of SSRIs in depressed patients with overt heart disease. Two of these studies have been published, and the other has been presented and should be published shortly.

Roose et al.[12] conducted the first study, in which fluoxetine was used to treat seriously depressed inpatients who also had severe but stable cardiac disease. The second study, also conducted by Roose et al.,[13] compared paroxetine with nortriptyline (N = 41 for each treatment group) in the treatment of moderately to severely depressed outpatients with moderate but stable cardiac disease. The most recent study was done with collaborators from Montreal, Duke, and Toronto and involved 26 patients treated with sertraline immediately after a myocardial infarction.[14] There were 94 patients with overt heart disease in these 3 studies.

Heart Rate

The authors had concerns about how heart rate is affected by the SSRIs. The general wisdom with these drugs has been that they slowed the heart modestly, although the exact mechanism is not understood. There is a condition in cardiology known as sinus node disease, in which the heart can become extremely slow. Occasionally, extreme slowing of the heart occurs during SSRI treatment.[15] Although such slowing is rare, it does happen. We worried that this slowing might be more frequent in people who had preexisting heart disease; however, this did not prove to be true. The data for the depressed cardiac patients treated with fluoxetine show a very modest decrease of 6 beats per minute.[12] Although this is a highly statistically significant difference, it is clinically insignificant. For the first 2 weeks, patients received 20 mg/day of fluoxetine, and if they tolerated the drug, their dosages were raised to 40 mg/day and then to 60 mg/day if possible. The average patient at 6 weeks was taking 50 mg/day of fluoxetine. Blood drug levels in patients who took fluoxetine 20 mg/day were in the range of 150 to 200 ng/mL. By 3 or 4 weeks, these patients had blood fluoxetine levels of almost 700 ng/mL, which is not an unusually high level. Strikingly, even though the blood level was triple what it was at 2 weeks, there was no increase in the slowing of the heart.

Data from the paroxetine versus nortriptyline study[13] show a similar finding with paroxetine: patients receiving paroxetine experienced a mean decrease in heart rate of 4 beats per minute after the first 2 weeks of treatment. This decrease is statistically significant, but again clinically meaningless. At 6 weeks, even though the mean dose was increased from 20 to 30 mg/day, the mean heart rate slowly returned to baseline. That seems to be a pattern with the SSRIs in general. In contrast, rates with nortriptyline tend to increase and remain elevated. There was a highly significant difference in heart rate between the 2 treatments. With sertraline, no change occurred, even though these data were obtained from patients shortly after a myocardial infarction, that is, not in the near term, at 2 weeks, or in long term, at 16 weeks.[14] There is no difference from baseline. The heart rate slowing associated with SSRI use is very modest at best. It seems to occur early on, and there seems to be a significant amount of adaptation. Small differences may exist among paroxetine, sertraline, and fluoxetine.

Blood Pressure

Blood pressure is something that psychiatrists are seldom concerned with in their patients. With the tricyclics in adults, high blood pressure is seldom a serious problem. However, one cannot always assume blood pressure will be unaffected by antidepressant drugs. With both bupropion and venlafaxine, patients can become hypertensive, especially at higher doses.[16,17] As a matter of fact, the older TCAs do cause hypertension in young people. However, changes in blood pressure are unlikely during SSRI treatment. Even with the extremely high blood level of fluoxetine, there was no change in blood pressure, and more importantly, there was no orthostatic drop.[12]

The study of patients treated with sertraline after myocardial infarction[14] extended over a much longer period of time than did the fluoxetine or paroxetine trials. We obtained data for 16 weeks of treatment in this trial. Nevertheless, there was still no change in blood pressure after sertraline treatment, even for the few individuals who were hypertensive. This is a very important issue because orthostatic hypotension is a big problem associated with

the tricyclics, and particularly so among patients with heart disease. All 3 studies comprised patients who have heart disease, and none of the studies found any evidence of cardiovascular problems associated with SSRI administration. Fluoxetine, sertraline, and paroxetine all show minimal change in resting blood pressure, no orthostatic drop, and absolutely no falls in spite of comorbid heart failure and multiple cardiac drugs.

Cardiac Conduction

Cardiac conduction intervals lengthened quite regularly with all of the TCAs. Even though the blood levels of fluoxetine were very high after 6 weeks of treatment, there was no change in the QRS or the QT interval. Similarly, there was no change in any of these conduction measures with either paroxetine or sertraline treatment. Lengthening of cardiac conduction intervals, which occurs with overdose of tricyclics, can cause death. On the other hand, deaths related to lengthening of cardiac conduction very rarely occur with SSRI use, and when they do, they usually occur at extremely high SSRI doses and most often with the coingestion of other compounds.

Ejection Fraction

A surprising finding concerning ejection fraction occurred for patients who have heart failure. Among depressed patients who had impaired ejection fraction of less than 35% after 2 weeks of fluoxetine treatment, there was a modest improvement in ejection fraction. That increase was statistically significant at both 2 weeks and at 6 weeks.[12] Even on a very high dose, there is even further improvement in their ejection fraction. We would have to replicate this finding to verify that this improvement in the pump function of the heart occurs after fluoxetine treatment. However, there is absolutely no evidence to suggest that there is an adverse effect on the contractility of the heart.

The ejection fraction data for the sertraline-treated patients[14] look much like the fluoxetine data[12]; again there was a statistically significant improvement in ejection fraction. The sertraline patients were less impaired at baseline; their average ejection fraction was between 47% and 48%, whereas the patients receiving fluoxetine were substantially impaired, having an average ejection fraction of 34%. However, the sertraline data are more complicated to interpret because measurements for this sample were made postinfarction; the baseline measurements usually were made before the patients left the hospital. Ordinarily, the impairment in ejection fraction in the immediate post-MI period is expected to improve over time if the patient survives. In this study, it is difficult to establish whether the improvement postinfarction was due to sertraline or the passage of time after a myocardial infarction. A placebo-controlled study designed to answer that question is under way.

Arrhythmia

With nortriptyline treatment, there is a substantial decrease in ventricular arrhythmias (as previously mentioned, the TCAs are known to be class I antiarrhythmics). In the paroxetine/nortriptyline study, nortriptyline decreased the amount of arrhythmia by half.[13] However, neither fluoxetine[12] nor paroxetine[13] showed any antiarrhythmic effect. The fluoxetine data seem to show an increase in ventricular premature contractions, but the variability in ventricular arrhythmias is so large that the changes were not statistically significant. Certainly, fluoxetine and paroxetine do not seem to have the potent arrhythmic activity characteristic with the TCAs.

Although there was a significant decrease in arrhythmias with sertraline treatment, the measurements were made immediately after a myocardial infarction,[14] similar to the contractility measurements. The heart can be quite irritable after a myocardial infarction, which is one of the reasons why treating persons after a myocardial infarction is different from treating patients with stable heart disease. When the heart is irritable, arrhythmias are more likely. If the person survives the myocardial infarction, those arrhythmias tend to decline naturally. In fact, ever since the CAST study, cardiologists have been reticent to treat these arrhythmias unless they happen to be particularly malignant. It is hard for us to say at present whether the reduction in ventricular premature depolarizations seen in the post-MI study with sertraline is an antiarrhythmic effect from sertraline, the recovery from the infarction, or both. In all likelihood, this effect is merely the recovery from a myocardial infarction.

OTHER FINDINGS ASSOCIATED WITH SSRI TREATMENT OF PATIENTS WITH HEART PROBLEMS

Up to now, we have absolutely no evidence of harm in these drugs. We had almost no surprises—almost nothing happened that we did not anticipate. However, life never turns out to be this simple.

When we conducted the original fluoxetine study,[12] it never occurred to us to look at the clotting issues associated with fluoxetine. The SSRIs do drastically reduce platelet serotonin, and although we could have investigated whether that decrease had any functional significance for platelets, we did not. We started the cardiac studies of fluoxetine just after the drug was released. Only gradually did it become apparent that the SSRIs all occasionally produce episodes of bleeding. Usually this bleeding is minimal, but occasionally it may be serious.[18] Also, because of the association with depression and mortality after myocardial infarction, it becomes very important to understand the effects of the SSRIs on clotting, because clotting is crucial in a myocardial infarction.[19] By the time the paroxetine study was undertaken, the importance of

any potential clotting changes that occurred with these drugs, especially in post-MI patients, was better understood. Platelet factor 4 (PF4) and β-thromboglobulin were measured by the group in Pittsburgh along with numerous other clotting factors.[19] These substances are proteins that are released into the blood when platelets are activated. They are markers of increased activation and are believed to reflect the stickiness of platelets. The normal value is 5 or 6 IU/mL. These values usually approximately double in persons with ischemic heart disease, especially after a myocardial infarction. When the Pittsburgh group measured these elements in their patients who have ischemic heart disease plus depression, they saw extremely large increases in these values.[19] People with depression and ischemic heart disease in this study had extraordinarily high values. Because this study included a relatively small number of patients, however, further research is needed to confirm the effect of SSRIs on these clotting factors.

A second group, at Emory University, that has independently studied platelets in depressed patients who were free of cardiovascular disease found similar platelet abnormalities.[20] It appears that this phenomenon does indeed occur, for when the patients were treated with SSRIs, these values returned significantly toward normal. When they were treated with nortriptyline, no change occurred, but with paroxetine, there was a significant return of PF4 toward normal.[21] This is quite an impressive finding because the patient in this study had already been treated with aspirin, and both the presence of this abnormal baseline and the response to the drug occur despite the presence of aspirin. This result suggests that these drugs not only do not harm patients with heart disease, but that there is a possibility they actually benefit these patients. Although much more information is needed to understand this phenomenon, there is already additional information available with citalopram to suggest that this SSRI also has an antiplatelet effect. It may well be that this is a general characteristic of all SSRIs that makes them useful in heart disease, independent of their effect on mood, although this remains to be seen.

SUMMARY

At this point, we see no evidence of harm with the SSRIs in depressed patients with heart disease. We have some reason to suspect that these drugs may actually be beneficial for this population. They seem safer than the TCAs in patients with ischemic heart disease. However, findings concerning 94 patients do not prove safety. It is a very limited but encouraging beginning. In addition, 2 trials are under way, both of which were begun in early 1998. One study, called ENRICH, is run by the National Heart, Lung, and Blood Institute. This study is looking at psychotherapy as a treatment for depression after myocardial infarction to see if mortality can be reduced. We believe, however, that it is unrealistic to treat the number of patients who get depressed after a myocardial infarction with psychotherapy: half a million myocardial infarctions occur in the United States every year. Close to 20% of these patients will experience major depression, and the number of therapists is inadequate to treat the approximately 100,000 people who would need some sort of intervention. We think that drug treatment is more pragmatic, and we have begun a trial comparing treatment with sertraline and placebo immediately after a myocardial infarction. We hope to examine 400 patients at 30 sites around the world to establish that sertraline works and is safe. If this hypothesis is proved true, then we will look at the question of whether it reduces mortality. It is a very exciting issue for psychiatry. If, in fact, the psychiatric treatment of a population after a myocardial infarction would decrease their risk of mortality, those findings would change the way those in the field of medicine look at depression and antidepressant drugs.

Drug names: bupropion (Wellbutrin), flecainide (Tambocor), fluoxetine (Prozac), imipramine (Tofranil and others), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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