Cardiovascular Effects of Bupropion in Depressed Patients With Heart Disease

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Objective: The cardiovascular effects of therapeutic plasma levels of tricyclic antidepressants in depressed patients with and without preexisting cardiac disease have been well characterized and include orthostatic hypotension and conduction delay. Bupropion, structurally unrelated to tricyclic antidepressants, is relatively free of cardiac side effects in depressed patients without cardiac disease. However, it is unknown whether bupropion is safe for depressed patients with preexisting heart disease, so the authors studied the cardiovascular effects of bupropion in such patients. Method: The subjects were 36 inpatients with DSM-III major depression and preexisting left ventricular impairment (N=15), ventricular arrhythmias (N=15), and/or conduction disease (N=21). The patients continued their cardiac drug regimens and received bupropion for 3 weeks (mean±SD dose=442±47 mg/day). Cardiovascular functioning was measured by pulse, blood pressure, high-speed ECG, 24-hour portable ECG, and radionuclide angiography. Results: Although bupropion caused a rise in supine blood pressure, it did not cause significant conduction complications, did not exacerbate ventricular arrhythmias, had a low rate of orthostatic hypotension, and had no effect on pulse rate. However, bupropion treatment was discontinued for 14% of the patients because of adverse effects, including exacerbation of baseline hypertension in two patients. Conclusions: The cardiovascular profile of bupropion may make this drug a useful agent in the treatment of the depressed patient with preexisting cardiovascular disease. Further studies, with longer durations of bupropion treatment and more subjects, are needed to confirm these findings.


There has been longstanding concern over the cardiovascular effects of tricyclic antidepressants, originally prompted by the observation that patients who took overdoses of tricyclic antidepressants died from heart block and/or arrhythmias (1). Over the past 15 years, a number of careful studies have established the characteristic effects and cardiovascular complications of tricyclic treatment in depressed patients with and without heart disease (2–4).

Bupropion is a new antidepressant of the aminoketone class that is structurally unrelated to the tricyclic antidepressants, and it is relatively free of cardiac side effects in healthy depressed patients (5, 6). However, it was unknown whether bupropion is safe for depressed patients with preexisting heart disease. Therefore, the goal of this study was to evaluate the cardiovascular effects of bupropion in depressed patients with pre-existing congestive heart failure, conduction disease, and/or ventricular arrhythmias. Some of these data have been previously reported (7).

METHOD

Subjects

This paper contains the findings of a 3-year study of bupropion in depressed patients with cardiovascular disease. All of the data reported in this study were obtained from inpatients admitted to the Affective Disorders Research Unit of the New York State Psychiatric Institute who had both cardiac disease and DSM-III major depression severe enough to warrant
treatment with an antidepressant medication. On admission, each patient was examined by a psychiatrist and a cardiologist. To be included in this study, a patient had to have 1) a history of congestive heart failure and/or an enlarged heart according to chest roentgenogram (cardiac thoracic ratio greater than 0.5 in the frontal view), 2) evidence of bundle branch block, defined as a QRS interval greater than 0.10 seconds, or 3) more than 10 ventricular premature depolarizations per hour, as determined by two separate, continuous 24-hour ECG recordings. All patients gave informed consent, and the study was approved by the Institutional Review Board of the New York State Psychiatric Institute/Columbia University Department of Psychiatry.

Thirty-six patients met the protocol criteria: 15 with congestive heart failure, 21 with conduction disease, and 15 with ventricular arrhythmias; some patients had more than one cardiac problem concurrently. There were 14 men and 22 women, and their mean ± SD age was 69 ± 9 years (range, 49–86 years).

Procedure

Treatment with all psychotropic drugs except benzodiazeepines was discontinued; stable doses of digoxin, diuretics, and antihypertensives were maintained. Each patient's cardiac drug regimen was maintained for 7 to 10 days, and then baseline cardiovascular measurements were obtained. Left ventricular ejection fraction was derived from first pass radionuclide angiography, as previously described by Goldman et al. (8). High-speed ECG (2) was used to measure duration of PR and QRS intervals (in milliseconds), and 24-hour ECG recordings with a movable monitor were used to determine 1) intermittent periods of higher-degree AV block in patients with bundle branch block that were not evident on the ECG, 2) ventricular arrhythmias, and 3) mean 24-hour pulse rate.

Blood pressure was measured three times daily. Supine blood pressure was measured after at least 5 minutes of quiet rest. After the patient stood for 1 minute, the blood pressure measurement was repeated. To obtain mean supine and standing blood pressure measurements for the predrug and drug periods, the daily blood pressure readings were pooled and averaged for the drug-free week and for the third week of drug treatment. Orthostatic drop is defined as the supine systolic blood pressure minus the standing systolic blood pressure. For the purposes of this study, a patient was considered to have orthostatic hypotension that required discontinuation of drug treatment if 1) an orthostatic drop of 50 mm Hg or more was recorded on 3 separate days and/or 2) the patient was unable to maintain a standing position because of symptoms associated with an orthostatic drop of 30 mm Hg or more.

After baseline cardiovascular measurements were obtained, bupropion treatment was started. The initial dose was 150 mg/day, given by mouth, which was increased to 450 mg/day by day 7. Drug was administered in three equal doses during the day. In two cases the dose was raised above 450 mg/day (550 mg for one patient, 600 for the other) because only partial response was noted (these doses are higher than currently recommended). The mean ± SD daily dose of bupropion was 442 ± 47 mg (range, 350–600 mg). The plasma level of drug, based on a sample obtained 12 hours after the last dose, was measured 2 weeks after the patient reached the full dose. This produced an average concentration of bupropion and its major metabolites of 3719 ± 1530 ng/ml at steady state, as determined with the method of Cooper et al. (9). After 3 weeks of drug treatment, the cardiovascular measures were repeated.

The results are expressed as mean ± SD. For statistical analysis, we calculated mean change (±SD) and used paired t tests to compare baseline measurements with those during bupropion treatment. Statistical significance was defined as p < 0.05.

RESULTS

Pulse rate measurements were available at baseline and during bupropion treatment for 34 of the 36 patients in the study. The mean 24-hour pulse rate at baseline was 74.8 ± 11.9 bpm, compared with 76.6 ± 10.4 bpm with bupropion (mean change, 1.8 ± 10.2 bpm; t = −1.03, df = 33, n.s.).

As shown in table 1, bupropion induced a statistically significant increase in lying systolic and diastolic blood pressures. The mean standing systolic and diastolic blood pressures were not significantly different during bupropion treatment. Bupropion induced a statistically significant, but clinically insignificant, increase in orthostatic drop (table 1). However, one patient developed dizziness and fell in conjunction with an orthostatic drop of 40 mm Hg, and bupropion was discontinued.

Effects on Cardiac Functioning

In the 15 patients with impaired left ventricular function, the mean ejection fraction during the baseline period was 34% ± 13% (range, 11%–54%). At maximum dose of bupropion the mean ejection fraction was 32% ± 14% (range, 16%–64%), and the mean change between the baseline and bupropion periods was 2% ± 6% (t = 1.18, df = 14, n.s.). Thus, bupropion had no significant effect on ejection fraction.

We analyzed separately the data on orthostatic drop in the 15 patients with impaired left ventricular function. Their orthostatic drop was 3 ± 7 mm Hg before treatment and 3 ± 10 mm Hg with bupropion (t = 0.16, df = 14, n.s.). No patient in this group stopped taking bupropion because of orthostatic hypotension.

For the 21 patients who had preexisting conduction disease, the mean PR interval was 0.162 ± 0.02 second
at baseline and 0.167±0.03 during drug treatment (mean change, 0.005±0.01 second; t=−2.02, df=20, p=0.06). The mean QRS interval was 0.126±0.01 second before treatment and 0.128±0.02 with drug (mean change, 0.002±0.01; t=−0.94, df=20, n.s.). There were no significant conduction complications and no evidence of a higher degree of AV block during drug treatment than at baseline.

Fifteen patients had 10 or more ventricular premature depolarizations per hour during two continuous 24-hour ECG recordings: 164±133 per hour at baseline and 69±149 at the maximum dose of bupropion (mean change, −95±222; t=1.66, df=14, p=0.12). One patient had a mean of 56 ventricular premature depolarizations per hour at baseline, which increased to 588 per hour with bupropion and subsequently to 1439 per hour after drug treatment. This fluctuation probably represents day-to-day variability in the frequency of ventricular premature depolarizations. When this patient was excluded from the data set, the remaining 14 patients had 172±134 ventricular premature depolarizations per hour at baseline and 32±40 with drug, i.e., 82% suppression (mean change, −140±144; t=3.64, df=13, p<0.005) (see figure 1).

Complications

Five patients could not complete treatment because of adverse effects. One patient had psoriasis and developed a skin rash after 10 days at a dose of 450 mg/day of bupropion. The rash resolved after cessation of bupropion treatment. The results of a skin biopsy were consistent with a drug eruption. For two other patients, both of whom had mild hypertension at baseline, bupropion treatment was discontinued because of further elevation of systolic and diastolic blood pressures. One had a mean baseline standing blood pressure of 165/92±12/12 mm Hg and a highest single recording at baseline of 188/108 mm Hg. During bupropion treatment the systolic blood pressure increased to 180–200 mm Hg frequently and reached a maximum of 214/120 mm Hg. Bupropion treatment was discontinued, and the average blood pressure returned to the baseline range (170/86±14/10 mm Hg), and the maximum was 178/90 mm Hg. Another patient’s mean baseline standing blood pressure was 163/89±18/9 mm Hg, and the highest single baseline recording was 204/96 mm Hg. After 2 weeks of taking bupropion, the patient’s systolic blood pressure was frequently in the 190–210 mm Hg range, and the maximum was 210/110 mm Hg. Again, bupropion treatment was discontinued, and after 3 days the average standing blood pressure was 151/88±8/6 mm Hg, and the maximum was 160/98 mm Hg. A fourth patient, who had a history of hypertension but did not have impaired left ventricular function, became dizzy and fell in association with a 40 mm Hg orthostatic drop after 8 days of treatment. Major orthostatic drops ceased within a day after discontinuation of bupropion treatment. The fifth patient, who had a history of myocardial infarction, syncope, lightheadedness, and New York Heart Association class III stable angina, developed a changing anginal pattern after 19 days of taking bupropion.

While cause-and-effect relationships are difficult to establish, in four of the five cases the adverse conditions resolved after discontinuation of bupropion administration.

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**TABLE 1. Blood Pressure Before and During Bupropion Treatment in 36 Patients With Major Depression and Cardiac Disease**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline Mean (SD)</th>
<th>Bupropion Mean (SD)</th>
<th>Change Mean (SD)</th>
<th>Paired t Test</th>
<th>t (df=35)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supine blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>140 (16)</td>
<td>145 (20)</td>
<td>5 (10)</td>
<td>−2.79</td>
<td>&lt;0.01*</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>76 (7)</td>
<td>79 (9)</td>
<td>3 (5)</td>
<td>−3.00</td>
<td>&lt;0.005*</td>
<td></td>
</tr>
<tr>
<td><strong>Standing blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(after 1 minute)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>136 (18)</td>
<td>137 (19)</td>
<td>1 (10)</td>
<td>0.70</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>80 (8)</td>
<td>82 (9)</td>
<td>2 (6)</td>
<td>1.93</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Orthostatic drop</td>
<td>4 (9)</td>
<td>7 (12)</td>
<td>4 (9)</td>
<td>2.57</td>
<td>&lt;0.02*</td>
<td></td>
</tr>
</tbody>
</table>

*The magnitude of drug effect, although statistically significant, was not clinically significant. However, the relatively small changes in the group means did not imply safety for all patients. One patient developed symptomatic orthostatic hypotension, and two patients developed significant systolic hypertension (see text).
DISCUSSION

Previous studies have focused on whether tricyclics are safe for depressed patients with preexisting heart disease, specifically congestive heart failure, conduction delay, or ventricular arrhythmias (10, 11).

A number of investigators have concluded that imipramine, nortriptyline, and doxepin do not have a deleterious effect on left ventricular function (12–14), even in patients with severe preexisting left ventricular impairment. However, the rate of orthostatic hypotension induced by imipramine in the patients studied approached 50% (14), making its use problematic. In contrast, the rate of orthostatic hypotension associated with nortriptyline is much lower (12). Thus, in depressed patients with left ventricular impairment, nortriptyline can usually be used safely even when imipramine treatment has been discontinued because of orthostatic hypotension (12).

With respect to the effect on cardiac conduction, early studies (2) demonstrated that in patients without heart disease, tricyclics, at plasma concentrations effective for treatment of depression, frequently prolong the PR, QRS, and QTc intervals but rarely, if ever, cause symptomatic conduction disturbance. Subsequently, Roose et al. (15) compared the risks of cardiovascular complication at therapeutic plasma tricyclic concentrations in 155 patients with normal ECGs and 41 patients with prolonged PR interval and/or bundle branch block. The prevalence of 2:1 AV block was significantly greater in the patients with preexisting bundle branch block (9%) than in the patients with normal ECGs (0.7%). In an additional 10% of the patients with preexisting bundle branch block, treatment with tricyclics was discontinued because of prolongation of the QRS interval by more than 25%. Thus, although nortriptyline can be relatively safely used to treat depressed patients with left ventricular impairment, all of the tricyclics, including nortriptyline, should be used with caution with patients who have bundle branch disease.

The data reported herein allow comparison of the cardiovascular effects of bupropion in a comparable group of patients. This study had six major findings: 1) bupropion did not affect pulse rate, 2) bupropion caused an elevation in supine blood pressure, 3) bupropion did not affect left ventricular function, even in patients with severe preexisting left ventricular impairment, 4) bupropion induced orthostatic hypotension in only one of 36 patients with cardiovascular disease, but in none of the patients with impaired left ventricular function, 5) bupropion did not significantly prolong cardiac conduction or induce higher degrees of AV block in patients with preexisting bundle branch block, and 6) bupropion did not exacerbate preexisting ventricular arrhythmias and, indeed, may have had some antiarrhythmic effect.

Thus, when treating a depressed patient with severe heart disease, bupropion may have some advantages over tricyclic antidepressants. These are, most notably, minimal orthostatic hypotension and lack of prolongation of intraventricular conduction. In addition, in the limited number of bupropion overdose cases to date, there have been no major cardiovascular complications (data on file at Burroughs Wellcome).

However, conclusions regarding the relative safety of bupropion treatment for patients with preexisting cardiovascular disease must be tempered by recognition of the limitations of our study. We have reported the cardiovascular effects of bupropion over a 3-week treatment period. It is possible that over a longer period of treatment for depression other effects might emerge. In addition, bupropion may have uncommon but important cardiovascular effects that we did not detect in our small study group. Lastly, 14% of our patients, who had both severe depression and significant cardiac disease, were unable to tolerate the medication. Of particular concern were two patients with preexisting hypertension who had significant increases in blood pressure that resolved after bupropion treatment was discontinued. Overall, we found a modest but statistically significant rise in blood pressure with bupropion. The question remains whether there is a subpopulation who are particularly sensitive to the hypertensive effect of the drug.

The cardiovascular advantages of bupropion must be weighed against other clinical considerations. Specifically, because of the well-established relationship between plasma concentration and clinical outcome for a number of the standard tricyclic antidepressants (16), tricyclics can be used with greater effectiveness than can newer compounds for which such a relationship has not been established. Furthermore, while we have considered bupropion from a cardiovascular point of view, bupropion has its own profile of adverse effects; of these, seizures have been a particular concern (17).

In the 3 years of this study, five patients who could not tolerate tricyclics because of cardiovascular side effects were treated and maintained with bupropion. Because of such patients, bupropion may be a clinically important addition to the antidepressant armamentarium.

REFERENCES

7. Roose SP, Glassman AH, Giardina EGV, et al: Cardiovascular effects of imipramine and bupropion in depressed patients with