Comparative Hemodynamic Effects of Procainamide, Tocainide, and Encainide in Severe Chronic Heart Failure

Stephen S. Gottlieb, MD, Marrick L. Kukin, MD, Norma Medina, RN, Madeline Yushak, RN, and Milton Packer, MD

Many of the newer antiarrhythmic agents are said to cause minimal myocardial depression, but their hemodynamic effects have not been invasively evaluated and compared in patients with severe chronic heart failure. In a randomized, crossover study, the hemodynamic responses to single oral doses of procainamide (750 mg), tocainide (600 mg), and encainide (50 mg) given to 21 patients with severe chronic heart failure were compared. Cardiac performance decreased with all three drugs, but the magnitude of deterioration differed among the three agents. Stroke volume index decreased with procainamide (−5±1 ml/m², p<0.001), tocainide (−7±1 ml/m², p<0.001), and encainide (−8±1 ml/m², p<0.001), but the decline was significantly greater with encainide than with procainamide (p<0.05). Similarly, left ventricular filling pressure increased with tocainide and encainide (+4±1 and +5±2 mm Hg, respectively; both p<0.05), but not with procainamide; the increase was significantly greater with tocainide and encainide than with procainamide (p<0.001). These deleterious hemodynamic effects were accompanied by worsening symptoms of heart failure in six patients with encainide and seven patients with tocainide but in only two patients with procainamide. Serum levels for all drugs were in the therapeutic range. In conclusion, although the three type I antiarrhythmic agents tested may all adversely affect left ventricular function in patients with heart failure, encainide and tocainide are more likely than procainamide to cause hemodynamic and clinical deterioration. (Circulation 1990;81:860–864)

Recent attention has focused on the potential negative inotropic effects of antiarrhythmic drugs because most patients who have serious ventricular arrhythmias have impaired ventricular function. Attempts to assess the cardiodepressant risks of antiarrhythmic therapy, however, have been accompanied by several methodologic difficulties. Previous reports have largely used noninvasive techniques (e.g., radionuclide ventriculography) to measure the hemodynamic response to pharmacologic interventions, but noninvasive tests often fail to detect clinically significant changes in cardiac performance. Previous hemodynamic studies have generally included only patients with normal left ventricular function, but such individuals are unlikely to show cardiodepressant effects even with potent negative inotropic agents. Finally, few previous studies have been able to evaluate the relative risk of various antiarrhythmic agents because the hemodynamic effects of specific drugs were not compared in the same patients. These limitations have made it difficult to interpret the available data concerning the hemodynamic safety of antiarrhythmic therapy.

The only means of addressing the limitations of previous reports is to conduct a direct comparative study of the hemodynamic effects of antiarrhythmic drugs in patients with chronic heart failure. Such patients are ideal candidates for such trials because they are particularly susceptible to the depressant effects of cardiovascular drugs and commonly undergo invasive testing for clinical purposes. Moreover, given the high prevalence of complex atrial and ventricular arrhythmias, these individuals are likely to receive antiarrhythmic drugs in the clinical setting. The present study is the first study designed to compare the
hemodynamic effects of oral antiarrhythmic drugs in patients with impaired ventricular function.

Methods

Patient Population

We studied 21 patients with severe left ventricular dysfunction who were referred for the treatment of refractory heart failure. There were eight men and 13 women (age, 28–87 years; mean, 68 years). All patients had a left ventricular ejection fraction less than 40% by radionuclide angiography (range, 9–39%; mean, 21±2%). The cause of heart failure was ischemic heart disease in 15 patients and dilated cardiomyopathy in six patients. Thirteen patients were in New York Heart Association functional class III, and eight were in class IV. All patients were receiving constant doses of digitalis and diuretics; previous therapy with vasodilator drugs was withdrawn for at least 24 hours before entry into the study.

Hemodynamic Measurements

After written, informed consent was obtained, right heart catheterization and arterial cannulation were performed for the measurement of intracardiac and systemic pressures, using procedures that have been described previously. All hemodynamic determinations were carried out at least 12 hours after the catheterization to allow for the dissipation of hemodynamic changes related to intravascular instrumentation. Patients were then assigned to one of six treatment sequences in which they received either procainamide (750 mg), encainide (50 mg), or tocainide (600 mg), in random order, on the morning of each of the next 3 days. These doses were selected to achieve therapeutic blood levels within hours of treatment with each drug. Before the administration of the antiarrhythmic agent, mean arterial pressure, heart rate, left ventricular filling pressure, mean right atrial pressure, and cardiac output were measured repeatedly in the fasting state until stability was achieved. After administration of the drug, all hemodynamic variables were reassessed every 30 minutes for 3 hours.

Blood was collected for the measurement of serum levels of the parent compound and its active metabolites at the expected peak effect of each antiarrhythmic agent. Samples were obtained 2 hours after the administration of encainide (for the determination of serum encainide, O-desmethylenencainide [ODE], and 3-methoxy-O-desmethylenencainide [MODE]), 2 hours after tocainide (for the determination of serum tocainide), and 75 minutes after procainamide (for the determination of serum procainamide and N-acetyl procainamide).

Throughout the 3-day study period, doses of digitals and diuretics remained constant, but these drugs were administered in the evening so that their acute effects would not complicate interpretation of the hemodynamic response to the antiarrhythmic drugs.

Data Analysis

Mean systemic pressures were determined by electronic filtration. Derived hemodynamic variables were calculated as follows: cardiac index is cardiac output/body surface area (l/min/m²), stroke volume index is cardiac index/heart rate (ml/m²), and systemic vascular resistance is 80×(mean arterial pressure–mean right atrial pressure)/cardiac output (dynes·sec/cm²).

The hemodynamic response to each drug was assessed at its peak effect (60–90 minutes after procainamide, 1.5–2.5 hours after tocainide, and 90–120 minutes after encainide) using the t test for paired data. The hemodynamic effects of the three drugs were compared with each other by repeated-measures analysis of variance using the Fisher’s PLSD test. Group data are expressed as mean±SEM.

Results

Cardiac performance deteriorated with each of the three antiarrhythmic drugs tested in this study, but the magnitude of deterioration differed among the three agents (Table 1, Figures 1 and 2). Cardiac and stroke volume indexes decreased significantly with procainamide, tocainide, and encainide, but the decline in stroke volume index was greater with

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**TABLE 1. Hemodynamic Effects of Procainamide, Encainide, and Tocainide in Patients With Chronic Heart Failure**

<table>
<thead>
<tr>
<th></th>
<th>CI (l/min/m²)</th>
<th>SVI (ml/m²)</th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>LVFP (mm Hg)</th>
<th>RAP (mm Hg)</th>
<th>SVR (dynes · sec/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procainamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>2.3±0.1</td>
<td>29±1</td>
<td>80±3</td>
<td>82±2</td>
<td>19±2</td>
<td>8±1</td>
<td>1,677±78</td>
</tr>
<tr>
<td>Post</td>
<td>1.9±0.1*</td>
<td>24±1*</td>
<td>82±4</td>
<td>77±3†</td>
<td>17±2</td>
<td>7±1</td>
<td>1,863±90†</td>
</tr>
<tr>
<td>Tocainide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.2±0.2</td>
<td>29±2</td>
<td>78±3</td>
<td>84±3</td>
<td>19±2</td>
<td>8±1</td>
<td>1,795±128</td>
</tr>
<tr>
<td>Post</td>
<td>1.8±0.1*</td>
<td>22±2*</td>
<td>81±3</td>
<td>83±4</td>
<td>24±2†</td>
<td>10±1‡</td>
<td>2,077±143†</td>
</tr>
<tr>
<td>Encainide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
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<td>29±1</td>
<td>78±3</td>
<td>83±3</td>
<td>19±2</td>
<td>8±1</td>
<td>1,697±130</td>
</tr>
<tr>
<td>Post</td>
<td>1.8±0.1*</td>
<td>21±1*</td>
<td>87±4*</td>
<td>81±4</td>
<td>24±2‡</td>
<td>9±1</td>
<td>1,990±124†</td>
</tr>
</tbody>
</table>

*tp<0.001, †p<0.01, ‡p<0.05, as compared with baseline.

CI, cardiac index; SVI, stroke volume index; HR, heart rate; MAP, mean arterial pressure; LVFP, left ventricular filling pressure; RAP, mean right atrial pressure; SVR, systemic vascular resistance.
Shown failure.

indicates shown each group. p
significance (p<0.05) indicates
and encainide was significantly greater than
with procainamide only with respect to left ventricu-
lar filling pressure (p<0.001). All three antiarrhyth-
mic drugs produced a significant increase in systemic
vascular resistance (all p<0.01). Only encainide pro-
duced a significant increase in heart rate (p<0.001).

Clinically, new onset of dyspnea at rest was noted
after procainamide in two patients, after tocainide in
seven patients, and after encainide in six patients.
This increased dyspnea coincided with the peak
hemodynamic effects of the drugs.

The following serum levels were measured at
peak drug effect: procainamide 0.5–11.2 µg/ml
(mean, 6.2±0.5 µg/ml), N-acetyl procainamide 0–
7.6 µg/ml (mean, 2.2±0.4 µg/ml), tocainide 2.2–9.2
µg/ml (mean, 5.3±0.5 µg/ml), encainide 20–610
ng/ml (mean, 181±33 ng/ml), and ODE 10–570 ng/ml
(mean, 239±31 ng/ml). Serum levels of MODE were
undetectable in 15 patients and ranged from 80 to
290 ng/ml in the remaining six patients. The mea-
sured serum concentrations were within the therape-
utic range for nearly all patients. However, three
patients had levels of procainamide less than 4
µg/ml, and one had a level of more than 10 µg/ml;
eight patients had levels of tocainide less than 4
µg/ml (therapeutic range, 4–10 µg/ml). Therapeutic
levels of encainide and its metabolites are not well
defined, but the levels that we measured were similar
to those of reports that demonstrated the antiar-
rhythmic activity of the drug.6 Changes in stroke work
index were not related to levels of procainamide
(r=0.32), N-acetyl procainamide (r=0.31), tocainide
(r=0.04), encainide (r=0.24), or ODE (r=0.19).

**Discussion**

The present study is the first to compare the
hemodynamic effects of class IA, IB, and IC anti-
arhythmic agents in patients with chronic heart
failure. All three drugs produced important cardio-
depressant actions in our patients with severe left
ventricular dysfunction. Yet, despite the generally
held perception that encainide and tocainide exert
minimal negative hemodynamic effects, procaina-
mide caused the least hemodynamic and clinical
deterioration of the three agents tested.

**Hemodynamic Effects of Procainamide**

Our results are consistent with previous studies that
have demonstrated that procainamide can produce
negative inotropic effects.7–11 Procainamide has been
shown to decrease cardiac performance in dogs (as
assessed by changes in left ventricular dP/dt)8 and in
man (as assessed by changes in systolic time intervals,9
invasively measured hemodynamic variables,10 and
intraoperative strain gauge analysis11). In subjects with
normal ventricular function, the cardio depressant
effect of the drug is partially offset by its direct
vasodilator effects12; despite this action, procainamide
may depress cardiac performance when ventricular
function is impaired.
Interestingly, in the few comparative studies that have been carried out, procainamide has produced fewer adverse hemodynamic effects than many other antiarrhythmic agents. In a study of isometrically contracting papillary muscle in the cat, procainamide caused less cardiodepression than quinidine, phenytoin, or lidocaine.13 Similarly, in an invasive hemodynamic study in patients recovering from an acute myocardial infarction, lidocaine produced significant decreases in cardiac index and increases in left ventricular filling pressure that were not seen with procainamide.14 The findings of the present study are consistent with these earlier reports; procainamide produced less cardiodepression than either encainide or tocainide (a lidocaine analogue).

**Hemodynamic Effects of Encainide and Tocainide**

Many previous investigations have shown that both encainide and tocainide can produce a negative inotropic effect in vitro,15 in experimental animals,16,17 and in man,18–22 but the investigators considered the magnitude of this effect to be small. Yet, the perception that these agents cause less cardiodepression than the older drugs is derived principally from noncomparative studies that enrolled patients at low risk of hemodynamic deterioration and used techniques that were too insensitive to detect a negative inotropic effect. For example, the Cardiac Arrhythmia Pilot Study (CAPS) concluded that encainide did not increase the risk of congestive heart failure in patients after an acute myocardial infarction,23 but this trial excluded patients with an ejection fraction less than 20% and with New York Heart Association functional class IV symptoms. This bias is not uncommon; nearly all reports that have demonstrated the hemodynamic safety of encainide20,24,25 and tocainide19,26–28 have excluded patients with severe heart failure. Moreover, studies that have concluded that tocainide and encainide are free of negative inotropic effects have relied on the measurement of left ventricular ejection fraction or other noninvasive determinations of systolic performance.28–31 Such measurements, however, often do not detect clinically significant changes in left ventricular function; the ejection fraction may fail to increase in patients who improve clinically,2 and it may remain unaltered in patients who deteriorate symptomatically.32

**Limitations of the Study**

In contrast to the adverse clinical reactions observed with loading doses, it is possible that an antiarrhythmic agent may be better tolerated when it is initiated in low doses that are gradually increased over time. If this proves to be the case, such a finding would suggest that the rate of change of the blood level of a drug may be as important as the absolute steady-state concentration in determining the drug’s hemodynamic effects. Therefore, the cardiodepressant risk of various antiarrhythmic drugs ideally should be assessed by comparing their hemodynamic effects after long-term therapy. This approach necessitates the performance of multiple right heart catheterizations in a large number of patients who are intentionally exposed to each drug (in random fashion) for prolonged periods. Unfortunately, many patients with chronic heart failure tolerate antiarrhythmic therapy poorly (because of either hemodynamic deterioration, proarrhythmia, or noncardiac side effects) and may fail to undergo repeat invasive testing. Furthermore, the potential life-threatening side-effects of antiarrhythmic agents prohibit their long-term administration to patients without demonstration of efficacy. For these reasons, a long-term study conducted for the purpose of comparing the hemodynamic effects of antiarrhythmic agents is not feasible.

We attempted to approximate the hemodynamic effects seen during long-term therapy by assessing the responses to a single loading dose of each antiarrhythmic drug. The loading doses we selected for each agent achieved plasma levels of the parent drug similar to those associated with an antiarrhythmic effect during long-term therapy.6,26,33 Such loading doses, however, do not necessarily produce the same circulating levels of metabolites, which, if active, may alter the drug’s hemodynamic profile. The metabolites of both procainamide and encainide (but not tocainide) are known to have important cardiovascular actions. Indeed, the derivatives of encainide—ODE and MODE—appear to exert a more potent negative inotropic effect than encainide itself.17 In contrast, the active metabolite of procainamide, N-acetyl procainamide, has been reported to have no negative hemodynamic effects in patients with and without congestive heart failure,34 and the metabolite may possess vasodilator activity that may act to counterbalance any negative inotropic effect of the parent compound.35 In addition, eight patients had levels of tocainide less than the commonly accepted therapeutic range (4–10 µg/ml), but this was true for only three patients after dosing with procainamide. These observations suggest that the results of our short-term study may have underestimated the magnitude of the difference between the hemodynamic effects of procainamide and the newer antiarrhythmic agents, encainide and tocainide.

**Conclusions**

The recently published Cardiac Arrhythmia Suppression Trial (CAST) concluded that the use of encainide and flecainide increased mortality in patients with asymptomatic arrhythmias after an acute myocardial infarction.36 In the aftermath of this trial, physicians have sought alternative antiarrhythmic agents (primarily those in class IA and IB) in an effort to suppress atrial and ventricular arrhythmias, based on the concept that these agents are less proarrhythmic and cardiodepressant than the class IC drugs. Our findings, however, indicate that alternative agents may also be associated with significant cardiovascular risks. Although procainamide produced less cardiodepression than both encainide and
tocainide, all three antiarrhythmic drugs produced important negative inotropic effects in patients with severe left ventricular dysfunction. Hence, all antiarrhythmic agents must be used cautiously in patients with heart failure, particularly as there is no evidence that the treatment of asymptomatic ventricular arrhythmias is beneficial in this population.

References


KEY WORDS • antiarrhythmic agents • procainamide • tocainide • encainide • heart failure
Comparative hemodynamic effects of procainamide, tocainide, and encainide in severe chronic heart failure.
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Circulation. 1990;81:860-864
doi: 10.1161/01.CIR.81.3.860
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/81/3/860

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