The Hemodynamic Effects of Intravenous Tocainide in Patients with Heart Disease

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SUMMARY In order to evaluate its hemodynamic actions, tocainide, a new orally effective antiarrhythmic drug, was given intravenously over a 15 minute period to 12 patients with compensated left ventricular dysfunction. Doses were 0.5 (4 patients) or 0.75 (8 patients) mg/kg/min. Hemodynamics and drug plasma concentrations were measured at the end and 15 minutes after the end of the infusion. Tocainide infusion produced small but statistically significant increases in the pulmonary and systemic vascular resistance, aortic and pulmonary arterial pressure, and left and right ventricular end-diastolic pressure. There was no significant change in left ventricular dp/dt, heart rate, or cardiac index. In patients with compensated left ventricular dysfunction, tocainide produces a small rise in vascular resistance and arterial pressure. Overall cardiac function is maintained with a small increase in left ventricular end-diastolic pressure.

Tocainide is a new antiarrhythmic drug which is effective for treating ventricular arrhythmias.1, 2 Clinically it is well tolerated at effective doses and it has several desirable pharmacokinetic properties. These include a high oral bioavailability, a low clearance, and a long plasma half-life.3 There is a wide range of intersubject variability in the relationship between antiarrhythmic effect and plasma concentration. For most patients the antiarrhythmic effects are observed at a plasma concentration above 6 μg/ml.1, 4 In our clinical experience, tocainide has been well tolerated hemodynamically, including patients with compensated left ventricular dysfunction. Since there has been no formal evaluation of tocainide’s hemodynamic effects in man, the present study was performed to evaluate the hemodynamic effects of acute administration of intravenous tocainide in patients.

Methods

Twelve male patients with suspected or known coronary artery disease were studied at the time of diagnostic cardiac catheterization. The nature of the study and all risks were explained to the patients, and written informed consent was obtained. The protocol was approved by the Stanford Medical Committee on the Use of Human Subjects in Research. The age of the patients ranged from 40 to 67 years. Four patients were on chronic digitalis therapy at the time of this study. Six patients were taking propranolol; this medication was withheld before cardiac catheterization in three of the six patients. At the time of diagnostic cardiac catheterization, right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge phasic and electronically measured pressures were recorded with a 7 or 8F end-hole catheter connected to a Statham P23Db pressure transducer. Systemic arterial and left ventricular pressure tracings were recorded by percutaneous catheterization of the femoral artery with a 6.7F end-hole or multiple side-hole catheter connected to a Micron MP-15 transducer. The first derivative of the left ventricular pressure tracing (dp/dt) was obtained by electronic differentiation. The zero pressure reference level was taken at mid-chest. Cardiac output was determined by the Fick technique, using the arteriovenous O2 difference and a 5-minute collection of expired air. After routine cardiac catheterization, each patient performed exercise using a bicycle ergometer, and underwent left ventriculography using a 50 cc bolus of meglumine diatrizoate and sodium diatrizoate administered over three or four cardiac cycles. Approximately 30 minutes after the ventriculography and after the left ventricular end-diastolic pressure measurement, aortic pressure and pulmonary artery pressure had returned to control values, tocainide was administered, using a Harvard infusion pump via a 19-gauge scalp vein needle inserted into an antecubital vein. The dose of tocainide administered to four patients was 0.50 mg/kg/min and 0.75 mg/kg/min to eight patients. Tocainide was provided as a 50 mg/ml solution and was diluted to a total volume of approximately 50 ml for each patient. Tocainide was infused into an intravenous solution of 5% dextrose in water running at a rate of 200 cc per hour for the 15-minute period of the infusion and for five minutes following the infusion. Blood samples for tocainide analysis were collected from the antecubital vein of the arm not used for drug infusion. A 30 cc blank was obtained prior to drug infusion and 10 cc samples were obtained at 1, 3, 5, 7, 9, 11, 13, 15, 17, 20, 25, 30, 40, and 60 minutes after initiation of the infusion. Samples were immediately placed in heparinized vacutainer tubes. Samples were spun at the end of the study, and the plasma frozen until subsequent analysis. The timing of the entire study was carried out using a precision timer. Tocainide plasma concentrations were analyzed using previously described high pressure liquid chromatographic assay.5

During the tocainide infusion, systemic arterial pressure and heart rate were monitored continuously and recordings were made at 5 and 10 minutes after the onset of the infusion. At 15 minutes (immediately after the infusion was terminated) and 30 minutes (15 minutes after the end of the infusion) right atrial, right ventricular, pulmonary artery, pulmonary capillary wedge, aortic, and left ventricular phasic and electronically measured pressures were repeated. Left ventricular dp/dt was also repeated at these times. Fick cardiac outputs were measured at 20 minutes (5 minutes after the end of the infusion) and 35 minutes (20 minutes after the end of the infusion). For all data, pulmonary vascular resistance (PVR) was obtained by the following formula:

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Received August 8, 1977; revision accepted November 14, 1977.
Patients were frequently questioned for subjective sensations and were observed carefully for objective signs of side effects. Coronary arteriography, using the Judkins technique, was performed on the subsequent day.

All hemodynamic measurements were compared with control values, using the two-tailed t-test for matched pairs. The changes for the patients receiving 0.50 mg/kg/min and 0.75 mg/kg/min were compared, using the two-tailed t-test for unpaired data.

**Results**

**Patient Population**

Ten of the twelve patients were found to have coronary artery disease at the time of coronary arteriography. One of the remaining two patients had documented coronary artery spasm and the other had normal coronary arteries with mild diffuse left ventricular hypokinesis and an ejection fraction of 0.48. Seven of the ten patients with coronary artery disease had three-vessel disease, including critical left main coronary occlusions in two. The remaining three patients had two-vessel coronary artery disease. Eight patients showed contraction abnormalities on left ventricular angiograms, including aneurysms with dyskinesia in four patients. Eleven patients were exercised before tocainide administration and all demonstrated serious left ventricular dysfunction during exercise, with the mean left ventricular end-diastolic pressure increasing from 10.3 ± 5.1 mm Hg to 25.2 ± 5.9 mm Hg (P < 0.001). The patients' diagnoses, as well as the drug plasma concentrations and hemodynamic effects, are summarized in table 1.

**Tocainide Plasma Concentration**

Tocainide concentrations for the two infusion rates are shown in figure 1. At 15 minutes the mean plasma concentration for the four patients receiving the 0.5 mg/kg/min dose was 6.78 ± 1.88 μg/ml. For the eight patients receiving 0.75 mg/kg/min, the 15-minute value was 11.22 ± 4.55 μg/ml. Corresponding values at 30 minutes for the two groups were 4.64 ± 0.37 and 7.15 ± 1.92 μg/ml.

\[
PVR = \frac{PA \text{ mean} - PCW \text{ mean}}{CO}
\]

where \( PA \) = pulmonary artery pressure, \( PCW \) = pulmonary capillary wedge pressure, and \( CO \) = cardiac output. Systemic vascular resistance (SVR) was obtained by the formula:

\[
SVR = \frac{AO \text{ mean} - RA \text{ mean}}{CO}
\]

where \( AO \) = aortic pressure, \( RA \) = right atrial pressure, and \( CO \) = cardiac output. The left ventricular stroke work index (SWI) was derived from the formula:

\[
SWI = (LV \text{ stroke index}) \times (\text{mean LV systolic pressure during ejection}) \times (0.0136).
\]
### TABLE 1. Plasma Concentrations and Hemodynamic Effects of Tocainide

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<tr>
<th>Pt.</th>
<th>Dx.</th>
<th>Dose</th>
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<th>RA</th>
<th>Ao</th>
<th>LVEDP</th>
<th>LV dp/dt</th>
<th>HR</th>
<th>LV SWI</th>
<th>PVR</th>
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<td>±16.0</td>
<td>±14.9</td>
<td>±322</td>
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</table>

### Peripheral Effects

Tocainide caused a small but statistically significant rise in the systemic vascular resistance and aortic pressure. The mean systemic arterial pressure increased from 89.6 ± 8.7 mm Hg to 96.1 ± 11.3 (P < 0.05) at 15 minutes. By 30 minutes (15 minutes post-infusion) the pressure had fallen to 95.6 ± 12.1 which was not statistically significantly different from control (fig. 2a). The rise in systemic arterial pressure appeared to be due to an increase in systemic vascular resistance from 15.9 ± 3.6 resistance units (RU) to 17.8 ± 5.1 RU at 15 minutes (P < 0.025) and to 17.6 ± 4.7 RU at 30 minutes (P < 0.02) (fig. 2b). Although these measurements tended to rise during infusion and fall minimally by 15 minutes post-infusion, no strong correlation could be made between the percent change in mean arterial pressure and plasma tocainide concentration. The pulmonary circulation showed similar rises in pulmonary arterial pressure (fig. 3a) and the pulmonary vascular resistance (fig. 3b) during tocainide infusion.

### Cardiac Effects

Tocainide caused no change in heart rate. There was a statistically significant rise in left ventricular end-diastolic pressure (fig. 4a), from 10.3 ± 5.1 to 13.2 ± 6.2 (P < 0.05) at 15 minutes. By 30 minutes the left ventricular end-diastolic pressure was 11.0 ± 3.9, not statistically
significantly different from control values. The right ventricular end-diastolic pressure also increased at 15 minutes from a control of 3.4 ± 1.8 to 5.6 ± 1.8 (P < 0.005) but was not significantly different from control by 30 minutes. Left ventricular dp/dt was reduced slightly from 1343 ± 322 to 1225 ± 308 at 15 minutes, and 1259 ± 313 at 30 minutes (fig. 4b). Neither of these values were statistically significantly different from control. The control left ventricular stroke work index was 43.5 ± 10.0 gm-m/m² and the 15- and 30-minute values were unchanged (42.9 ± 8.4 and 43.6 ± 10.3, respectively). Cardiac output, cardiac index and right atrial pressure were not significantly changed by tocainide.

Side Effects

Six patients experienced subjective symptoms during the study. One patient experienced angina pectoris shortly after the infusion was terminated, at a time when plasma concentration was 4.7 µg/ml. He had had several other spontaneous episodes prior to tocainide and had a long history of stable severe rest angina. It was not possible to state for certain whether his angina was precipitated by tocainide. Five patients had symptoms definitely related to tocainide infusion. One patient expressed a sensation of facial coldness and cold breath at 10 min, at a time when plasma concentration (CP) was 15 µg/ml. Another experienced warm lips at 11 min of infusion (CP = 9.34 µg/ml) and cold lips at 12 min (CP = 10.0 µg/ml). The third patient experienced slight confusion at 7 min (CP = 9.3 µg/ml), difficulty in focusing at 8 min (CP = 10.0 µg/ml), warmth of chest and arms at 9 min (CP = 11.9 µg/ml), nausea at 15 min (CP = 17.5 µg/ml), generalized warmth at 16 min (CP = 17 µg/ml) and one single episode of vomiting at one hour (CP = 6.8 µg/ml). A fourth patient noted a cold throat at 3 min (CP =

**Figure 3.** a) The pulmonary artery pressure increased during tocainide infusion. b) Tocainide caused an increase in the pulmonary vascular resistance.

**Figure 4.** a) Left ventricular end-diastolic pressure (LVEDP) showed a small but statistically significant increase at the end of the infusion (15 minutes) but had returned to control values by 15 minutes after the infusion (30 minutes). b) Tocainide's effect on left ventricular dp/dt. Although left ventricular dp/dt fell slightly during the drug infusion, this change was not statistically significant.
2.7 μg/ml). A fifth patient noted a cold throat at 7 min (CP = 2.59 μg/ml), cold hands and feet at 11 min 30 sec (CP = 4.5 μg/ml) and chest tightness at 14 min (CP = 5.0 μg/ml). This latter patient had a slight tremor of his right hand at 14 min and the infusion was terminated at that time. This was the only patient in whom the infusion was terminated before 15 min. One additional patient, not included in this study, experienced catheter-induced venospasm during the 15 min hemodynamic measurements. Shortly thereafter, at a time when the tocainide concentration was 9.3 μg/ml, he experienced a vasovagal reaction and the protocol was terminated. Although the vagal episode seemed related to the painful venospasm, we cannot entirely exclude tocainide as a contributory cause.

Discussion

The patients participating in this hemodynamic study had considerable left ventricular dysfunction. Ten of the patients had coronary artery disease, including left main coronary arterial lesions in two patients. Eight patients demonstrated contraction abnormalities including dyskinetic left ventricular aneurysms in four patients. Although all patients were compensated at rest, the patients as a group demonstrated severe left ventricular dysfunction during exercise. None of these patients had experienced cardiac arrest or major ventricular arrhythmias. However, they are hemodynamically similar to many of the patients who have had, or are at high risk of developing, serious ventricular arrhythmias. These types of patients may in the future be candidates for chronic antiarrhythmic therapy, with a goal of preventing sudden cardiac death.

Tocainide was well-tolerated hemodynamically by these patients. The primary effect was a small rise in vascular resistance, resulting in small increases in aortic and pulmonary arterial pressures. There was a small rise in left ventricular end-diastolic pressure observed immediately at the end of the tocainide infusion in these patients, which had returned to control by 15 minutes post-infusion. This rise may have resulted from a direct myocardial depressant effect or from the small increase in peripheral vascular resistance. Although there was a slight reduction in left ventricular dp/dt at the end of the infusion, this change was not statistically significant. The failure of the left ventricular stroke work index to rise, and the fall or absence of rise in left ventricular dp/dt, despite the increases in left ventricular end-diastolic pressure and aortic pressure, may represent a minor depressant effect of tocainide. However these changes may represent the common response of a compromised left ventricle to increased afterload and may or may not represent added depressant effect of tocainide on the myocardium. At rest, any adverse effects on left ventricular function appear to be small and may be clinically unimportant, since all patients were able to maintain cardiac output throughout the period of tocainide infusion. However, it must be emphasized that in some individual patients marked rises in left ventricular end-diastolic pressure may occur. Additionally, although the increases were well tolerated at rest, it is possible that for some patients left ventricular end-diastolic pressure may rise to intolerable levels with exercise.

Tocainide structurally resembles the de-ethylated metabolites of lidocaine; it is therefore of interest to examine the hemodynamic effects reported for lidocaine. Harrison et al. noted a slight rise in systemic arterial pressure following a 1 mg/kg lidocaine bolus; this rise was not statistically significant. Schumacher et al. noted that four of five patients with previously elevated left ventricular end-diastolic pressures had further rises after administration of 100 mg of lidocaine. In addition, six of eight patients showed a small fall in the left ventricular stroke work index. Grossman et al. also noted a slight rise in mean arterial pressure; however, again this was not statistically significant. Recently, Boudoulas et al., using systolic time intervals, demonstrated a negative inotropic effect after administration of lidocaine. Other studies have demonstrated no effect on arterial pressure or cardiovascular function after lidocaine administration. Unfortunately, most reported studies either measured hemodynamic effects after administering a bolus of lidocaine, at which time there are rapidly fluctuating plasma concentrations, or failed to obtain lidocaine plasma concentrations at the time the hemodynamic parameters were measured. This makes direct comparison with this study difficult.

We have shown previously that tocainide is effective for suppressing premature ventricular contractions in patients at plasma concentrations ranging between 6 and 10 μg/ml. Careful analysis of concentration response data for individual patients suggests a wide range of intersubject variability in the plasma concentration necessary for reducing premature ventricular contractions. Both individual patients and the group as a whole showed a relationship between antiarrhythmic effect and tocainide plasma concentration. The infusion rates used in the present study were chosen to provide tocainide concentrations in the range that was clinically tolerated and proved effective during our studies of oral tocainide administration.

The importance of studying antiarrhythmic drugs at plasma concentrations similar to those required for antiarrhythmic activity, and drug administration at rates that are not excessive, is apparent from recent experiences with propranolol and quinidine. The hemodynamic effects of both these antiarrhythmic agents were initially evaluated after very rapid administration of the drugs. This frequently resulted in severe hypotension and profound myocardial depression. Although plasma concentrations were rarely described, it is quite likely that very high plasma concentrations were transiently achieved during the administration of these drugs. More recent studies using slower infusion rates to achieve plasma concentrations in the clinically effective range suggest that although both drugs are associated with a potentially clinically important fall in blood pressure, the drugs do not exert severe direct myocardial depressant effects at clinically effective plasma concentrations.

Although in our study we attempted to correlate any observed hemodynamic responses to plasma concentrations of tocainide, we were unable to do so. For many patients, parameters which changed significantly tended to demonstrate their maximum effect immediately at the end of the infusion, with some return toward baseline by 15 minutes post-infusion. However there was substantial individual patient variation and we were unable to confirm a definite relationship between these changes and plasma concentration for the group as a whole. Due to the small number of
observations for each patient, it was difficult to evaluate concentration response curves for individual patients. Even for mean arterial pressure where there were four measurements and a control for each patient, only a small number of patients demonstrated a relationship between plasma concentration and change in mean arterial pressure. The inability to consistently correlate response with plasma concentration may be due to several factors, including the small number of patients in the study, the small number of observations made in each patient, the small size of hemodynamic changes observed, spontaneous variability in the parameters being studied, and/or individual variations in response to tocainide. Comparison of the hemodynamic changes for the 0.5 and 0.75 mg/kg/min infusion groups suggested no significant difference between the two groups.

There were a large number of subjective responses to tocainide infusion. These occurred over a wide range of plasma concentrations. In many patients, these occurred early or midway through the infusion and did not worsen as more drug was infused. The side effects were transient in all instances. The most frequent complaints were related to hot and cold sensations. For the most part, these side effects were very mild and would not have limited the clinical usefulness of the drug during intravenous administration. The occurrence of a wide range of subjective complaints over a relatively wide range of plasma concentrations is similar to our experiences during oral therapy with tocainide.

In summary, tocainide, when given as an intravenous infusion achieving plasma concentrations in the range required for premature ventricular contraction suppression during oral therapy, caused small elevations in pulmonary and systemic vascular resistances and in mean systemic and pulmonary arterial pressures. There was a small rise in left and right ventricular end-diastolic pressures, but overall cardiac function was not significantly depressed. The observed changes were small and may have little clinical significance for most patients, including those with compensated ventricular dysfunction. The data suggest, however, that the drug should be used with caution in patients with pulmonary or systemic hypertension or uncompensated left or right ventricular failure. Further studies will be required in these patient populations to determine the safety of intravenous tocainide. Finally, it must be recognized that the present study was an acute intravenous intervention study and its relationship to hemodynamic effects seen during chronic oral therapy is unknown.

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The hemodynamic effects of intravenous tocainide in patients with heart disease.
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Circulation. 1978;57:787-792
doi: 10.1161/01.CIR.57.4.787

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

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http://circ.ahajournals.org/content/57/4/787