Acute Effects of Toborinone on Vascular Capacitance and Conductance in Experimental Heart Failure

Lisa M. Semeniuk, MSc; Israel Belenkie, MD; John V. Tyberg, MD, PhD

Background—Toborinone (OPC-18790), a phosphodiesterase III inhibitor, enhances cardiac contractility and is an arterial dilator. However, its effects on the venous system have not yet been clearly defined. Because toborinone administration reduces left ventricular (LV) end-diastolic pressure, it is probably also a venodilator. Because of the known arterial effects and the hypothesized venous effects, we compared changes in systemic vascular conductance (the inverse of resistance) with changes in venous capacitance.

Methods and Results—In 15 anesthetized, splenectomized dogs (10 treatment, 5 control), pressures were measured in the right atrium, aorta, portal vein, and LV. A cuff constrictor was placed around the portal vein. Cardiac output was measured by thermodilution, and splanchnic vascular capacitance was measured by blood-pool scintigraphic methods. Data were collected at baseline, after induction of heart failure (microsphere embolization into the left coronary artery), and then after toborinone boluses of 0.1, 0.2, 0.4, and 0.8 mg/kg. Heart failure was associated with decreased capacitance and conductance (to 87±3% and 64±4% of baseline values, respectively, \(P<0.05\)). After administration of the lower doses of toborinone, capacitance increased more than conductance; however, the effects were more balanced at the higher doses. Compared with nitroglycerin, hydralazine, and enalaprilat (results of an earlier study) in the same model, toborinone increased capacitance to a degree similar to that with nitroglycerin, at higher doses increased conductance similarly to hydralazine, and increased both capacitance and conductance considerably more than did enalaprilat.

Conclusions—Toborinone is a potent balanced venous and arterial dilator in experimental acute heart failure. These marked effects suggest that it may prove to be a clinically important alternative to other vasodilators. (Circulation. 1998;98:58-63.)

Key Words: circulation • vasodilation • heart failure • veins • hemodynamics

Toborinone \([\pm]-6-\text{[3-(3,4-dimethoxy)benzylamino-2-hydroxy]-propyl-2(1H)-quinolinone}] (OPC-18790, Otsuka Pharmaceuticals Co Ltd), a phosphodiesterase III inhibitor, has coronary vasodilator activity and has been shown in both experimental and clinical studies to increase contractility and cardiac output, with only slight changes in heart rate and mean blood pressure. In addition, it has no significant effect on myocardial oxygen consumption and improves cardiac energetics in ischemic hearts. Although toborinone is known to be a vasodilator, previous studies have focused on arterial dilatation, with little being known about its venous effects. Our current understanding of its effects on veins is based on indirect hemodynamic measurements. LV end-diastolic volume decreased substantially when a low dose \((5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})\) of toborinone was administered to patients with dilated cardiomyopathy; a higher dose \((10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})\) also reduced systemic vascular resistance and arterial pressure. To the best of our knowledge, no direct assessment of the effects of toborinone on vascular capacitance has been reported, although Fujiki et al found a decrease in mean circulatory filling pressure that was not statistically significant. Because toborinone decreases LV end-diastolic pressure at lower doses and also decreases arterial pressure at higher doses in patients with heart failure, we hypothesized that it would increase vascular capacitance at lower doses, in addition to increasing systemic conductance at higher doses.

We used a previously described experimental model to study the effects of toborinone on splanchnic vascular capacitance and systemic vascular conductance (the inverse of systemic vascular resistance) in acute heart failure. Splanchnic vascular capacitance was measured by a blood-pool scintigraphic technique. These results were compared with those in our previous report of the vascular effects of other vasodilators in the same model. Our data indicate that toborinone has substantial venodilator effects that may have important clinical implications.

Methods

Animal Preparation

Adult mongrel dogs (10 experimental [3 males, 7 females], 5 control [3 males, 2 females]; weight, 13 to 21 kg) were initially anesthetized with sodium thiopental (25 mg/kg IV) (Abbott Laboratories) and...
intubated. Anesthesia was maintained by ventilation with a mixture of oxygen and nitrous oxide (30:70) and isoflurane (Anaquest) with a constant-volume respirator (model 607, Harvard Apparatus). Blood gases and body temperature were maintained at physiological levels throughout the experiment. To ensure adequate hydration, a 15-mL/kg infusion of 3.3% dextrose in 0.3% NaCl was given 2 hours before the experimental protocol was begun. A splenectomy was performed through a midline abdominal incision to minimize changes in hematocrit. A pneumatic cuff was placed around the portal vein. To measure portal venous pressure, a fluid-filled catheter (OD 1.5 mm, ID 1.00 mm; Dural Plastics Engineering) was introduced into an arcade branch of the portal vein and positioned so that the tip lay just upstream from the pneumatic cuff. To correct for radioactivity from the ventral abdominal wall, a 4 × 4-cm sheet of radiographic apron material was fixed to the ventral surface of the liver (Velbond, 3M Animal Care Products) just under the ventral abdominal wall.12 The abdominal wall was reapproximated with towel clips. Fluid-filled catheters (7F, Abbott) were inserted into the proximal aorta through the right femoral artery and right atrium through the jugular vein to measure aortic and right atrial pressures, respectively. LV pressure was measured with an 8F micromanometer-tipped catheter (model SPC-485A, Millar Instruments) introduced through the left carotid artery. Cardiac output was measured by thermodilution with a triple-lumen balloon thermistor catheter (7F, Abbott) placed in the pulmonary artery via the right internal jugular vein. A catheter for removing reference blood samples for radioactivity analysis was inserted into the right femoral vein. The fluid-filled catheters were connected to pressure transducers (model P233b, Statham-Gould). The ECG and pressures were recorded with a multichannel recorder (model VR-16, Electronics for Medicine–Honeywell). Hemodynamic data were acquired and analyzed with a custom-designed program (CVSOFIT, Odessa Computer Systems Ltd).

Toborinone was dissolved by use of sonication in a 1.5 × 10⁻² mol/L solution of D,L-lactate (Sigma Chemical Co) in distilled water to yield a final concentration of 10⁻² mol/L.

Induction of Heart Failure
Heart failure was induced by repeated microsphere (DuPont; 50-μm diameter, 4 mg/mL) embolizations into the left coronary artery as previously described11 until LV end-diastolic pressure was ≥20 mm Hg or cardiac output was decreased by ≥50% of the baseline value. Induction of failure took 100 ± 23 (SD) minutes.

Measurement of SBV
In vivo, red blood cells were labeled by injection of stannous pyrophosphate 7 mg IV followed by 20 mCi of [⁹⁹ᵐTc]pertechnetate. This was performed at least 30 minutes before data collection was begun to minimize the amount of unbound radionuclide. Scintigrams were recorded from 5 cm above the abdomen for 45 seconds with a gamma camera (model DYNAMO 4, Picker) interfaced to a nuclear medicine computer system (model DPS-3300, ADAC Laboratories). The numbers of counts per pixel were obtained from manually defined mesenteric regions of interest (excluding the liver, kidneys, bladder, and large blood vessels). The regions of interest were computer-duplicated and redefined only if the camera or the dog was moved. We made corrections for physical decay (⁹⁹ᵐTc half-life, 6.02 hours), “biological decay” (using the count rates of 100 μL reference blood samples taken every 3 to 5 minutes throughout the experiment), and the contribution of the ventral abdominal wall.12

Abdominal scintigrams were obtained at three different portal pressures, including baseline (7 ± 2 mm Hg), 13 ± 2 mm Hg, and 18 ± 2 mm Hg, the latter two by inflating the cuff around the portal vein to raise the pressure to the desired level.

Experimental Protocol
In the toborinone-treatment group, hemodynamic (heart rate, cardiac output, and aortic, right atrial, LV, and portal venous pressures) and radionuclide data were obtained in duplicate at baseline, after the induction of heart failure, and at 15 and 30 minutes after each IV bolus (administered over 1 minute) of toborinone (0.1, 0.2, 0.4, and 0.8 mg/kg). The same protocol was followed in the control dogs, except that only the toborinone vehicle (D,L-lactate) was administered, in the same volume as had been used to dissolve toborinone.

Analysis of Toborinone Plasma Concentrations
Three dogs in the experimental group were used for the determination of toborinone plasma levels. In these 3 dogs, additional blood samples (8 mL) were obtained at baseline, after induction of heart failure, and 1, 15, and 30 minutes after administration of each dose of toborinone. Samples were collected in heparinized vacuum containers (sodium heparin glass beads, Becton Dickson Vacutainer Systems) and centrifuged (HN-II centrifuge, International Equipment Co) at 3000 rpm for 10 minutes. The plasma was transferred into cryogenic vials (Nalge Co) and frozen at −70°C. The samples were packaged on dry ice and sent by overnight courier for analysis. Analyses were performed by Kansas City Analytical Services, Inc. Their reference numbers for the high-performance liquid chromatography analysis of toborinone are V0483P1 and B1294P1/B1294P2.

Analysis of Data
Systemic Conductance
Systemic conductance was calculated as the inverse of systemic vascular resistance (ie, conductance = cardiac output/[mean aortic pressure–mean right atrial pressure]).

Vascular Capacitance
PP-SBV relations (linear fits of the PP-SBV data points measured at the 3 portal pressures) were defined for each set of data (duplicate measurements were taken at baseline and after the induction of heart failure, and single measurements were taken after the administration of each dose of toborinone). By interpolation, vascular capacitance was defined as the SBV at PP = 7.5 mm Hg. One hundred percent capacitance was defined as the mean of the 2 baseline SBVs, and subsequent values were expressed as percentages of that value. Rightward or leftward shifts of the PP-SBV relations reflect increased or decreased capacitance, respectively, compared with the baseline value. Thus, we measured relative rather than absolute changes in capacitance. The reported values were recorded 15 minutes after the administration of the drug.

Statistical Analysis
Mean baseline values were compared with the values obtained after induction of heart failure by Student’s paired t test. Toborinone values were compared with the control values by repeated-measures, two-way ANOVA and the Student-Neuman-Keuls test. Because of a slight difference in baseline values of cardiac output between the treatment and control groups, analysis was performed using percentage changes from the means of the two baseline values. Absolute values were used for all other data except for venous capacitance, which is always expressed relative to the baseline value. To assess hemodynamic stability after induction of heart failure in the control group, toborinone-vehicle data were compared with their heart failure, and single measurements were taken after the administration of each dose of toborinone.

These analyses were performed by Kansas City Analytical Services, Inc. Their reference numbers for the high-performance liquid chromatography analysis of toborinone are V0483P1 and B1294P1/B1294P2.
Vascular Effects of Toborinone

TABLE 1. Hemodynamic Data

<table>
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<th></th>
<th>Baseline</th>
<th>HF</th>
<th>0.1 mg/kg</th>
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<tr>
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<td>85±3</td>
<td>80±3</td>
<td>68±5†</td>
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<td>106±5</td>
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<tr>
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<td>153±5</td>
<td>152±5</td>
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<tr>
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<td>5.0±0.5‡</td>
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<td>94±8</td>
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<td>66±6</td>
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<td>68±7</td>
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<tr>
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<td></td>
<td></td>
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<td>111±5†</td>
<td>123±6†</td>
<td>118±5‡</td>
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<tr>
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<td>84±3</td>
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</tbody>
</table>

HF indicates heart failure; AoP, mean aortic pressure; HR, heart rate; RAP, mean right atrial pressure; LVEDP, LV end-diastolic pressure; CO, cardiac output; Cond, conductance; and Cap, capacitance. Values are mean±SEM; n = 10 for toborinone 0.1, 0.2, and 0.4 and n = 8 for toborinone 0.8 mg/kg; n = 5 for control.

*P < 0.05 (baseline vs HF values); † P < 0.05 (toborinone vs toborinone-vehicle values); and ‡ P < 0.05 (HF vs toborinone-vehicle values). Toborinone and control values shown were measured 15 minutes after administration.

regression model. Data are expressed as mean±SEM with statistical significance accepted at the 95% confidence level (P < 0.05).

Results

Of 11 dogs originally in the toborinone-treatment group, data from 1 were excluded because they differed from the means by more than 4 SD. Of the 10 remaining animals, 2 received only 3 of the 4 doses of toborinone (0.1, 0.2, and 0.4 mg/kg). Of the 5 control dogs, 1 was given a lidocaine bolus (1 mg/kg IV) during heart-failure induction to suppress an idioventricular rhythm. The hemodynamic measurements were not different between this and the other 4 control dogs.

Hemodynamic Changes Due to Heart Failure

As seen in Table 1, heart failure was associated with significant increases in heart rate and right atrial and LV end-diastolic pressures and significant decreases in cardiac output, conductance, and capacitance in both the control and treatment groups. The only difference between the two groups was that the decrease in aortic pressure from 112±2 to 106±5 mm Hg was not statistically significant in the control group (P = 0.42) and that the decrease from 106±5 to 83±5 mm Hg in the treatment group was significant (P = 0.03).

Hemodynamic Effects of Toborinone

As seen in Table 1, toborinone increased cardiac output from 2.0±0.2 to 3.3±0.3 L/min and decreased mean aortic pressure from 83±5 to 68±5 mm Hg and LV end-diastolic pressure from 22.6±1.0 to 18.3±2.1 mm Hg (all P < 0.05). The decreases in right atrial pressure and heart rate were not statistically significant. In the control group, the only further statistically significant hemodynamic change after the induction of heart failure was in right atrial pressure, which increased from 3.7±0.7 to 5.2±0.7 mm Hg (P < 0.05). Toborinone increased LV maximum dP/dt from 1160±90 mm Hg/s to 1370±80, 1570±110, 1750±150, and 1930±280 mm Hg/s for the 0.1-, 0.2-, 0.4-, and 0.8-mg/kg doses, respectively (all P < 0.05, one-way ANOVA).

There were no significant differences in any of the hemodynamic parameters between the subgroup used for the toborinone plasma level determination and the remainder of the toborinone-treatment group.

Vascular Capacitance

As illustrated in the top panel of Figure 1, heart failure was associated with a parallel leftward shift in the PP-SBV relation, reflecting vasoconstriction. Subsequent administration of toborinone was associated with parallel rightward shifts in the relation (venodilatation) beyond baseline values.
In the control group (bottom panel of Figure 1), there was a similar leftward shift of the curves after the induction of heart failure, but the toborinone vehicle had no significant effects on these relations. There were no significant slope changes in either the toborinone-treatment ($P=0.34$) or control ($P=0.99$) groups. These data are summarized in Figure 2: after induction of heart failure, there was a significant decrease in capacitance to $87\pm 3\%$ compared with baseline ($P<0.002$). Subsequent administration of toborinone caused significant increases in capacitance to $105\pm 4\%$, $111\pm 5\%$, $123\pm 6\%$, and $118\pm 5\%$ for the 0.1-, 0.2-, 0.4-, and 0.8-mg/kg doses, respectively ($P<0.05$ for the 0.8 mg/kg dose). In the control group, heart failure was associated with a similar decrease in capacitance ($65\pm 5\%$ versus baseline, $P=0.018$), but there were no further significant changes during the remainder of the experiment.

Comparative Capacitance-Conductance Effects

In Figure 4, the effects of toborinone on capacitance and conductance from the present study are compared with the data obtained in our previous study of the effects of hydralazine, enalaprilat, and nitroglycerin in the same model. In all groups of animals, heart failure was associated with a significant decrease in capacitance ($78\pm 8\%$, $94\pm 8\%$, $109\pm 14\%$, and $128\pm 18\%$ for the 0.1-, 0.2-, 0.4-, and 0.8-mg/kg doses, respectively ($P<0.05$ for the 0.8 mg/kg dose). In the control group, heart failure was associated with a similar decrease in capacitance ($65\pm 5\%$ versus baseline, $P=0.018$), but there were no further significant changes during the remainder of the experiment.

Systemic Conductance

As illustrated in Figure 3, heart failure was associated with a significant decrease in conductance to $64\pm 4\%$ compared with baseline ($P<0.001$). After administration of toborinone, conductance increased to $78\pm 8\%$, $94\pm 8\%$, $109\pm 14\%$, and $128\pm 18\%$ for the 0.1-, 0.2-, 0.4-, and 0.8-mg/kg doses, respectively ($P<0.05$ for the 0.8 mg/kg dose). In the control group, heart failure was associated with a similar decrease in conductance ($65\pm 5\%$ versus baseline, $P=0.018$), but there were no further significant changes during the remainder of the experiment.
heart failure capacitance and conductance effects are expressed in relation to the heart failure data (ie, decrease in both capacitance and conductance, and the drug effects are expressed in relation to the heart failure data (ie, heart failure capacitance and conductance = 100%). Lower doses of toborinone (0.1 and 0.2 mg/kg) caused a greater increase in capacitance than conductance. This effect was similar to that obtained with nitroglycerin. At higher doses (0.4 and 0.8 mg/kg), there was a pronounced and more balanced effect that was similar to but considerably greater than that obtained with enalaprilat. At higher doses, toborinone increased conductance similarly to hydralazine, which, in contrast to toborinone, had no effect on capacitance.

**Toborinone Plasma Concentrations**

Table 2 lists plasma concentrations of toborinone. Plasma concentrations doubled with each doubling of the dose, thus indicating that there was no measurable accumulation of drug.

**Discussion**

In this study of anesthetized dogs in which acute heart failure had been induced by coronary artery embolization, toborinone decreased LV end-diastolic pressure and increased systemic vascular conductance as expected. However, there was also substantial venodilatation that was at least as great as that observed with nitroglycerin and much greater than that observed with enalaprilat in our previous study in the same model. Thus, our data clearly demonstrate that the arterial dilator effects of toborinone are associated with substantial venodilatation. The parallel rightward displacements of the pressure-volume curves (top panel, Figure 1) suggest that toborinone increased splanchnic venous volume by increasing venous unstressed volume, which implies an active reduction in smooth muscle tone. The increased conductance that resulted from toborinone administration clearly reflects reduced arteriolar tone.

The effects of toborinone on capacitance and conductance are in keeping with previously reported findings. Thus, the decrease in LV filling pressure after toborinone administration both in patients with heart failure and in this study is consistent with venodilatation. Increased capacitance tends to decrease LV end-diastolic pressure, whereas decreased systemic vascular resistance tends to increase central venous pressure (ie, raise it toward mean circulatory pressure) and therefore LV end-diastolic pressure. Thus, the venodilatation was more than sufficient to negate the tendency of arteriolar dilation to raise filling pressure.

Although toborinone dilates both veins and arterioles after the development of heart failure, the relative effects appeared to be dose dependent (see Figure 4). Thus, at lower doses, capacitance increased more than conductance, whereas at the higher doses, both effects were prominent. These data are consistent with observations in patients with heart failure. Although capacitance was not measured directly, decreases in right atrial pressure, peak pulmonary artery pressure, and LV end-diastolic volume were also more prominent at a lower dose, whereas decreased systemic vascular resistance was most evident with a higher dose. It is possible that the lack of a further increase in capacitance at higher doses may have been due to maximum or near-maximum venodilatation at the lower dose. Another possible explanation is that baroreceptor activity was decreased by the fall in aortic blood pressure and caused reflex venoconstriction. This mechanism appears unlikely, however, because heart rate did not increase, nor did conductance decrease.

The precise mechanism of action of toborinone has not yet been fully elucidated, but the increase in capacitance and conductance may be partially explained by its PDE inhibition, it being somewhat selective toward the PDE III isoenzyme (cGI-PDE). The accumulation of cAMP that results from PDE III inhibition enhances calcium extrusion across the sarcolemma by two possible mechanisms: (1) cAMP-dependent protein kinase present in vascular smooth muscle is known to stimulate the sarcolemmal calcium pump, and (2) cAMP stimulation of sarcolemmal Na\(^+\)/K\(^+\)-ATPase causes hyperpolarization and removal of intracellular sodium. Extracellular sodium then exchanges with intracellular calcium (Na\(^+\)/Ca\(^2+\) exchanger), resulting in relaxation of both arterial and venous smooth muscle.

Although PDE III inhibition can explain many of the hemodynamic effects of toborinone, the absence of the expected reflex-mediated increase in heart rate discriminates toborinone from other PDE III inhibitors and conventional \(\beta\)-agonists.
Comparison of Toborinone With Other Vasodilators

In this same experimental model of acute heart failure, we recently described the different effects of 3 vasodilators (nitroglycerin, enalaprilat, and hydralazine, each given in a dose that produced approximately the same degree of hypotension). With all toborinone doses, the degree of venuodilation obtained was at least comparable to that caused by nitroglycerin. At higher toborinone doses, venous and arterial dilatation were approximately balanced, but both were greater with toborinone than with enalaprilat. At the highest toborinone doses, arterial dilatation was comparable to that of hydralazine. Thus, the substantial venuodilating effects of toborinone suggest that it might be effective in treating patients with heart failure, and the dose-dependence of the conductance effect might prove useful in titrating the proportion of venous versus arterial effects.

Consideration of the Model

The model used in the present study has important limitations that need to be considered. Clearly, the anesthetic itself has the potential of substantially altering the vasculature. Because of the vasodilator effect of the anesthetic, the potential vasoactive effects of toborinone may be even greater when used in conscious subjects with heart failure, given that vasoconstriction may be prominent in heart failure. Brief inflation of the splanchic constrictor tended to reduce aortic blood pressure, but as demonstrated previously, the effect at portal pressures <20 mm Hg is minimal. In addition, acute heart failure induced by microsphere embolization may be quite different in some respects from either acute or chronic congestive failure in patients. Despite these considerations, the vasculature responded to induction of failure in the expected fashion, and toborinone proved to be a potent arterial and venous dilator. Thus, although our findings cannot be assumed to apply to conscious patients with all forms of heart failure, there are clear and prominent effects in our model, and some clinical reports suggest that similar effects will be observed in patients. It therefore appears reasonable to do similar studies of toborinone in patients with congestive heart failure.

Conclusions

The hemodynamic effects of toborinone were substantial in our model of acute heart failure and included a large increase in capacitance (in addition to the expected increase in conductance) that was considerably greater than that previously observed with enalaprilat, another balanced vasodilator. These marked and balanced effects suggest that toborinone has the potential to be clinically important.

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References

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