Hemodynamic Effects of Phosphodiesterase III Inhibitor in Patients With a Large Ventricular Left-to-Right Shunt

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The hemodynamic effects of olprinone, a newly synthesized phosphodiesterase (PDE) III inhibitor, were assessed in patients with a large cardiac left-to-right shunt. Ten patients with a large ventricular septal defect (VSD) were evaluated during cardiac catheterization. Olprinone was administered as a bolus, 20μg/kg body weight, and hemodynamic data were obtained before and after the administration. Heart rate and systemic flow increased significantly after administration. On the other hand, olprinone significantly reduced left and right atrial pressure, the systolic pulmonary/arterial pressure ratio, and systemic vascular resistance. However, pulmonary flow and pulmonary vascular resistance were not changed. These results suggested that olprinone had a positive inotropic effect and selective vasodilator effect on patients with a large ventricular left-to-right shunt. Thus, PDE inhibitors may be beneficial for the treatment of patients with a large VSD. *(Jpn Circ J 2000; 64: 249–253)*

**Key Words:** Olprinone; Phosphodiesterase inhibitor; Ventricular septal defect

The phosphodiesterase (PDE) III inhibitor has positive inotropic and vasodilating effects.*1–9* In patients with a large cardiac left-to-right shunt, systemic vasodilation may have the benefit of causing a reduction in left ventricular afterload resulting in the improvement of pulmonary congestion and a decrease in the pulmonary/systemic flow (Qp/Qs) ratio. However, an excessive decline in pulmonary vascular resistance may cause an increase in the Qp/Qs ratio and left-to-right shunt volume. The present study was performed to evaluate the hemodynamic effects of PDE III inhibitor in patients with a ventricular left-to-right shunt.

**Methods**

The study population consisted of 10 infants with a large cardiac left-to-right shunt (Qp/Qs>2.0) of the ventricular septal defect (VSD). The median age was 8.3 months, ranging from 4.7 to 20 months. No patient had any cardiac defect except for VSD or patent foramen ovale, and there were no chromosomal abnormalities. Six patients had been treated with a combination of digoxin and diuretics, 2 patients had received only diuretics, and no patient had received vasodilators. The study was approved by the ethics committee of the institution and informed consent was obtained from patients’ parents.

Patients received 2 mg of pentobarbital and 1 mg/kg of hydroxyzine hydrochloride as premedication. Thiopental was given intravenously during catheterization as the occasion demanded. Olprinone was given as a bolus, 20μg/kg, into the inferior vena cava over a period of 10 min after routine hemodynamic measurements. Measurements after olprinone administration were commenced 5 min after the infusion ended. Heart rate (HR) and the following types of pressure data were obtained before and after infusion: aortic (AoP), main pulmonary artery (PAP), left atrial or pulmonary capillary wedge (LAP), and right atrial (RAP). Simultaneously, we obtained pulmonary flow (Qp) and systemic flow (Qs) using the Fick method, and then the pulmonary/systemic flow ratio (Qp/Qs), systemic vascular resistance (Rs), pulmonary vascular resistance (Rp) were calculated. Oxygen consumption was estimated using body weight, height and heart rate.*10*

**Statistics**

The Students t test for paired observations was used to compare the control and postdrug mean values. A p value less than 0.05 was considered significant. All values were reported as the mean ± standard deviation (SD).

**Results**

Patients received neither respirator support nor supplemental oxygen during cardiac catheterization. Patients were stable during and after the catheterization, and urination was observed in all patients during catheterization. Plasma concentrations, measured in 2 patients during postdrug measurements, were 27.7 and 26.7μg/ml, respectively.

**Hemodynamic Parameters**

The changes in hemodynamic parameters before and after olprinone infusion are summarized in Table I.

**Heart Rate and Rhythm**

Compared with control values, the mean heart rate increased after infusion (from 123±11 to 134±13 beats/min; p<0.001). No patient had arrhythmia during and after the
infusion of intravenous olprinone.

**Right and Left Atrial Pressure**

The mean left atrial pressure, ranging from 12 to 16 mmHg (mean 13.1±1.4), decreased significantly in all patients to 9.7±2.5 mmHg (p<0.001). Similarly, the mean right atrial pressure, ranging from 2 to 7 mmHg (mean 5.3±1.7), decreased in all but 2 patients to 3.8±1.3 mmHg (p<0.01; Fig 1).

**Systemic and Pulmonary Pressure**

There were no significant changes in systolic or mean arterial pressure (from 89.1±7.1 to 90.2±7.9 mmHg for the mean, and from 69.0±5.1 to 68.1±5.1 mmHg for the systolic pressure). The maximum decrease in systolic arterial pressure was only 5 mmHg. Although systolic pulmonary pressure, ranging from 34 to 88 mmHg (mean 64.9±16.1 mmHg), decreased to 61.0±15.0 mmHg and mean pulmonary pressure, ranging from 24 to 60 (mean 44.8±12.1 mmHg), decreased to 42.1±11.4 mmHg, these were not significant changes. The systolic pulmonary/arterial pressure ratio decreased significantly from 0.74±0.20 to 0.68±0.17 (p<0.05).

**Systemic and Pulmonary Flow**

The systemic and pulmonary flow before administration...
of olprinone ranged from 2.9 to 5.1 and 6.9 to 18.1 L min⁻¹ m⁻², respectively. Although pulmonary flow was not changed significantly (from 11.2±3.8 to 11.1±3.2 L min⁻¹ m⁻²), systemic flow increased significantly from 3.7±0.7 to 4.2±0.9 L min⁻¹ m⁻² (Fig 2). Although as a group the Qp/Qs showed no significant change, in the 2 patients with Qp/Qs>4, a 25% decrease in Qp/Qs was observed following olprinone (Fig 3).

Systemic Vascular Resistance and Pulmonary Vascular Resistance

The baseline systemic vascular resistances ranged from 16.4 to 32.1 (mean 23.2±5.2 Wood U·m⁻²) and significantly decreased to 16.0±4.0 (p<0.001). Percentage changes from the baseline ranged from −15.1 to −41.7% (mean −31.0±9.0%). On the other hand, the pulmonary vascular resistances, which ranged from 0.9 to 5.7 Wood U·m⁻² before administration, did not change significantly (from 3.1±1.6 to 3.2±1.5 Wood U·m⁻²; Fig 4).

Fig 2. Systemic flow, pulmonary flow, and pulmonary/systemic flow ratio before (pre) and after (post) olprinone infusion.

Fig 3. Correlation between pulmonary/systemic flow ratio (Qp/Qs) before olprinone infusion and the percentage change in Qp/Qs.
Discussion

Phosphodiesterase inhibitors have a positive inotropic effect and a vasodilating effect by producing an increase in the cyclic adenosine monophosphate (AMP) levels of myocardial and vascular smooth muscle cells. In addition, phosphodiesterase inhibitors have been shown to cause less increase in myocardial oxygen consumption than catecholamine. Furthermore, as phosphodiesterase inhibitors act distally to the β-adrenergic receptors, they are less influenced by the adrenergic receptor downregulation phenomenon. Olprinone is a newly synthesized PDE inhibitor, whose inotropic potency was comparable with that of milrinone, and about 30 times more than that of amrinone. It is reported that the minimum effective plasma concentration of olprinone is 20 ng/ml. For patients with a large cardiac left-to-right shunt, lowering the systemic vascular resistance in addition to positive inotropic effects may have the benefit of a reduction in left ventricular afterload, resulting in a decrease of the left atrial mean pressure and improvement of pulmonary edema and respiratory disorders. On the other hand, phosphodiesterase inhibitors have been shown to reduce pulmonary vascular resistance. If the reduction is excessive, phosphodiesterase inhibitors may cause an increase in the cardiac left-and-right shunt volume, resulting in a worsening of heart failure. For this reason, it is important to confirm whether phosphodiesterase inhibitors decrease systemic or pulmonary vascular resistance selectively.

In the present study, olprinone significantly decreased the systemic vascular resistance with no significant change in pulmonary vascular resistance. In addition, olprinone caused a significant increase in systemic flow without a significant change in pulmonary flow. In 2 patients whose Qp/Qs was greater than 4.0, remarkable decreases in Qp/Qs were observed. For the vasodilating effect and positive inotropic effect, left atrial mean pressures were significantly decreased. These findings suggest that phosphodiesterase inhibitors are suitable and safe drugs to use for the management of patients with a large cardiac left-to-right shunt of VSD.

Sasaki et al. reported that amrinone significantly reduced the pulmonary vascular resistance index (PVR) in patients with a high PVRI, significantly reduced the systemic vascular resistance index (SVRI) in patients with a high SVRI, and had little effect on vascular resistance in patients with low systemic and pulmonary vascular resistance. These results may suggest that PDE inhibitors expand the most contracted vessels. Therefore, we must be aware that phosphodiesterase inhibitors may cause a decrease in pulmonary resistance and an increase in Qp/Qs in patients with highly elevated pulmonary resistance. Importantly, because the systemic vasodilator effect cannot be demonstrated, PDE inhibitors should not be used in patients with left ventricular outflow tract stenosis and/or coarctation of the aorta.

In conclusion, we have demonstrated that: (i) olprinone reduced systemic vascular resistance and increased systemic flow, resulting in a decrease in left atrial mean pressure; and (ii) olprinone did not change pulmonary vascular resistance and pulmonary flow.

References

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