Severe pulmonary hypertension (PH) is a frequent postoperative condition in congenital heart disease (CHD) patients with left to right shunt. Unless timely surgical repair is achieved, this group of patients may develop persistent PH, which could increase the risk of mortality in patients who undergo surgery. Previous study in Japan showed a decrease in the mortality rate of patients who died after CHD surgery, however, in Thailand and in other countries this mortality rate is still high. Elevated pulmonary arteriolar resistance (Rpa) is a risk factor for acute deterioration, known as a pulmonary hypertensive crisis, during surgical repair for CHD.

Acute pulmonary vasodilating testing has become part of the routine clinical work-up for pulmonary arterial hypertension because it determines the patients in whom surgical repair can still be safely performed. Several pulmonary vasodilating agents, including calcium channel blockers, nitric oxide (NO) and more recently, prostacyclin, have been used and a favorable response to these vasodilating agents in PH correlates with an improved clinical outcome.

Inhaled NO (iNO) has been the preferred agent because of its trivial effect on cardiac output and lack of effect on the systemic circulation. Although it is increasingly used for PH in congenital heart defects, one of the main complications is deterioration of oxygenation following the withdrawal of iNO (rebound effect). Pulmonary vasodilatation in response to iNO is observed in some but not all patients, particularly those in the late stage of the disease. Responsiveness to other pulmonary vasodilating therapies may identify patients with advanced obstructive PH who could benefit from surgical repair of the CHD.

The newly developed oral analog of prostacyclin, beraprost sodium (BPS: Toray Industries, Inc, Tokyo, Japan), is a stable agent with a structure similar to prostaglandin I2 and has vasodilatory, antiplatelet and cytoprotective effects. Its tmax (time to reach maximal concentration) is as early as 36 min, which enables it use as an acute vasodilating agent. Treatment of patients with PH over a period of time with BPS significantly decreased pulmonary vascular resistance by 17%. The aim of our study was to compare the central hemodynamic effects of orally administrated BPS with those of iNO and 100% oxygen in PH patients with CHD.
Methods

There were 90 patients who underwent cardiac catheterization during January to December 2003. The CHD cases were 22 atrial septal defect (ASD), 50 ventricular septal defect (VSD), 10 patent ductus arteriosus (PDA), 5 atrioventricular septal defect and 3 others complex lesions. Six patients had Down syndrome. PH was defined as a mean pulmonary artery (mPA) pressure greater than 75% of systemic arterial pressure or Rpa >4 Wood unit m² at the time of cardiac catheterization. Written, informed consent was obtained using a protocol approved by the ethics committees of the participating hospitals. The study was performed as a multicenter trial among large centers for congenital cardiac disease in Thailand.

Hemodynamic Assessment

All investigations were performed in the fasting state with minimal sedation and all oral vasodilating drugs were withheld 24 h prior to the cardiac catheterization. Standard right heart catheterization including hemodynamic measurements and oximetry was performed. Oxygen consumption was obtained from the data of LaFrage and Miettinen.18

Results

Patient Characteristics

The patients’ ages ranged from 9 months to 56 years with an average of 16.5±16. Their weights were from 5 to 69 kg with an average of 26.4±17.8. The baseline mPA pressure was 69.6±14.8 mmHg and the Qp:Qs was 1.7±1.0. The Rpa was 13.8±8.3 Wood unit m². Table 1 shows the baseline hemodynamic data during room air, 100% oxygen via face mask, 40 ppm iNO and BPS. Inhaled NO and oral BPS were well tolerated, and no complications such as bradycardia, chest pain or altered mental state were apparent in any patients. Three patients developed hypotension, bradycardia, chest pain or altered mental state were apparent.

Table 1 Baseline Hemodynamic Data

<table>
<thead>
<tr>
<th>Room air</th>
<th>100% O₂</th>
<th>40 ppm iNO</th>
<th>BPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ao saturation (%) (min – max: median)</td>
<td>88.4±7.5 (62–99): 91</td>
<td>97.6±3.1 (85–100): 99</td>
<td>92.6±5.7 (73–99): 94</td>
</tr>
<tr>
<td>Mean Ao pressure (mmHg)</td>
<td>81.4±16.7 (49–130): 78</td>
<td>79.4±14.9 (44–120): 77</td>
<td>78.4±14.9 (41–120): 78</td>
</tr>
<tr>
<td>Mean PA pressure (mmHg)</td>
<td>69.±14.8 (45–120): 65</td>
<td>64.±16.1 (42–118): 60</td>
<td>61.8±14.3 (43–122): 60</td>
</tr>
<tr>
<td>Qp:Qs</td>
<td>1.7±1.0 (0.4–2.8): 1.6</td>
<td>4.7±7.5 (0.3–20): 2.7</td>
<td>3.2±3.4 (0.4–26): 2.6</td>
</tr>
<tr>
<td>Rpa (Wood unit m²)</td>
<td>13.8±8.3 (1.1–55): 9</td>
<td>8.1±7.5 (0.3–54.6): 4.3</td>
<td>9.2±8.1 (0.5–45): 5.8</td>
</tr>
<tr>
<td>Rpa:Rs</td>
<td>0.78±0.6 (0.1–3): 0.46</td>
<td>0.4±0.4 (0.1–0.9): 0.2</td>
<td>0.4±0.3 (0.1–1.3): 0.3</td>
</tr>
</tbody>
</table>

Inhaled nitric oxide; BPS, beraprost sodium; Ao, aortic oxygen saturation; PA, pulmonary arterial pressure; Qp:Qs, degree of left to right shunt; Rpa, pulmonary arteriolar resistance; Rpa:Rs, ratio of Rpa to systemic vascular resistance.

Each data set consists of mean ± standard deviation (above), and range: median in parenthesis (below).

Table 2 Pair-Wise Comparison of the Hemodynamic Data for Each of the Pulmonary Vasodilating Agents

<table>
<thead>
<tr>
<th>Room air vs 100% O₂</th>
<th>iNO vs BPS</th>
<th>iNO vs 100% O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ao saturation (%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Ao pressure (mmHg)</td>
<td>0.834</td>
<td>0.014</td>
</tr>
<tr>
<td>Mean PA pressure (mmHg)</td>
<td>0.151</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Qp:Qs</td>
<td>0.354</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rpa (Wood unit m²)</td>
<td>0.973</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rpa:Rs</td>
<td>0.606</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Adjusted p-value <0.009 considered to be significant.

See Table 1 for abbreviations.
which required an intravenous fluid bolus to maintain systolic blood pressure.

Response to Acute Vasodilating Agents

Using the criterion for change in pulmonary vascular reactivity as a drop in Rpa ≥20% from the baseline data, we found that the response to 100% O₂, iNO and BPS was 84%, 72.7% and 64%, respectively. However, the Kolmogorov–Smirnov test showed a non-normal distributed data set and the ratio of pulmonary to systemic vascular resistance (Rpa:Rs) ≤0.001. In order to compare the results for each pulmonary vasodilating agent, pair-wise comparisons of the data were also performed. The Bonferroni method was used to adjust for p-value, which revealed p<0.009 to be significant (Table 2). In general, except for AoSat, which was higher in the 100% O₂ and iNO groups, there were no significant differences in the effect of iNO or BPS on each hemodynamic parameter. The main finding was that BPS had the same pulmonary vasodilating effect as iNO. iNO and BPS has a similar acute effect on lowering Rpa (p=0.973), but there were 38 patients (42%) who had a lower Rpa after BPS than after iNO. We found an average difference in Rpa of 2.5 Wood unit m² using BPS compared with iNO. Although inhalation of 100% oxygen appeared to have the greatest effect on lowering Rpa from baseline, it showed no significant effect when compared with iNO (p=0.268).

Follow-up Results of Surgery

All of the patients’ data were presented to the weekly cardiac catheterization conference. There were 17 patients who were not suitable for surgery and another 18 patients were either denied surgery on the basis of the high risk involved or were still on the waiting list, leaving 55 patients who underwent surgery, 2 of whom died from a pulmonary hypertensive crisis. The patients who had shown a lowering of Rpa ≥20% from baseline during acute pulmonary vasodilating testing had a shorter ICU time (1.2±1.0 days) when compared with those who had no response (3.46±4.2 days for those who did not show any response p=0.017). We speculate that the shorter ICU time in those patients indicates less advanced PH (thus lower risk) and it is this group of patients who potentially may also benefit from using BPS as the vasodilator testing agent during the postoperative period.

Evidence that oral BPS may induce a selective pulmonary vasodilatation in both primary and secondary PH was first provided by Saji et al in 1996 and recently, iNO was shown to have an effect on pulmonary vascular resistance that is the equivalent of 100% oxygen during acute pulmonary vasodilator testing in a cardiac catheterization laboratory. However, the problem with 100% oxygen is that the Qp:Qs can be overestimated, which could result in underestimating Rpa.

It has demonstrated that short-term aerosol therapy with prostacyclin iloprost in adult patients with PPH had a favorable effect on pulmonary hemodynamics without a significant decrease in systemic blood pressure. However, there are few published reports of the acute hemodynamic effects of BPS in children and adults with PH secondary to CHD. Uncontrolled studies in patients with PH have reported improved exercise capacity, hemodynamic, and survival with chronic BPS administration. In the present investigation, iNO and oral BPS were both effective in lowering Rpa in patients with severe PA hypertension with the mean Rpa being almost 14 Wood unit m². An acute pulmonary vasodilating effect after oral BPS administration was achieved, as indicated by the decrease in Rpa and a small effect on systemic arterial pressure. In one-third of the present patients, BPS had a better effect than iNO in lowering Rpa and the advantage of oral BPS over iNO is its nontoxicity and simple administration.

Conclusions

Although there was no statistical significant difference in the effect of BPS and iNO regarding the change in Rpa, some patients demonstrated a stronger pulmonary vasodilating effect after oral BPS than after iNO. Patients who showed a decrease in Rpa by more than 20% had a shorter ICU time after surgical repair of the CHD.

Acknowledgment

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References


