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Acute Effect of Oral Prostacyclin and Inhaled Nitric Oxide on Pulmonary Hypertension in Children

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Abstract

The hemodynamic effects of acute oral administration of a newly-developed prostacyclin analogue (beraprost sodium; 1–2 μg/kg), inhaled nitric oxide (NO; 20 ppm) and tolazoline hydrochloride (1 mg/kg) were measured in 17 children (mean age 1 year and 9 months) with pulmonary hypertension complicating congenital heart disease or primary pulmonary hypertension. Beraprost, NO and tolazoline achieved approximately equivalent reductions in pulmonary vascular resistance (20%, 26% and 18%, $p<0.05$), but the greatest percentage decrease of pulmonary to systemic resistance ratio was obtained after administration of NO (33%, $p<0.05$). Furthermore, combined administration of beraprost and NO produced the maximum effect of pulmonary vasodilation without adverse effects (49%). Beraprost appears to be an effective and available substitute for NO and tolazoline in screening for pulmonary vasodilator responsiveness. The combined use of beraprost and NO may provide an alternative treatment for pulmonary hypertension in children without serious complications.

Key Words

Hypertension, pulmonary, Congenital heart disease, Prostacyclin (analogue, oral)

INTRODUCTION

Nitric oxide (NO) and prostacyclin (PGI_2) are known endothelial products that are released from the endothelium in sufficient quantities to achieve relaxation and hyperpolarization in blood vessels[1]. Intravenous PGI_2[2–7] and inhaled NO[8–11] have been successfully used for the treatment of pulmonary hypertension. However, intravenous PGI_2 has major drawbacks because of systemic hypotension, and is limited in use especially in children[11]. We report the hemodynamic effects of acute oral administration of a newly-developed prostacyclin analogue (beraprost sodium : Procylin®) and inhaled NO in children with pulmonary hypertension complicating congenital heart disease or primary pulmonary hypertension in comparison with the conventional vasodilator tolazoline.

METHODS

Patient population

Seventeen patients (mean age 1 year and 9 months, range 4 months–6 years) suffering from pulmonary hypertension were evaluated. Eight patients had preoperative congenital heart disease and eight had postoperative disease. The diagnoses were

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Selected abbreviations and acronyms

mPAP=mean pulmonary artery pressure
mSAP=mean systemic arterial pressure
NO=nitric oxide
Pp/Ps=pulmonary to systemic pressure ratio
PGI_2=prostacyclin
PVR=pulmonary vascular resistance
Qp/Qs=pulmonary to systemic blood flow ratio
Rp/Rs=pulmonary to systemic resistance ratio
TSR=total systemic resistance

ventricular septal defect in 12 patients, atrial septal defect in 3, and patent ductus arteriosus in 1. Four patients were also diagnosed as having 21 trisomy. One patient with primary pulmonary hypertension was also included. The diagnosis of pulmonary hypertension was established by the presence of a mean pulmonary artery pressure of higher than 20 mmHg. Patients with Eisenmenger's syndrome were excluded in this study.

Drug testing protocol

All evaluations were performed in the catheterization laboratory of Toyama Medical and Pharmaceutical University. Informed consent was obtained from the parents of the patients before enrollment in this study. Any drug suspected of having the potential to vasodilate the pulmonary vascular bed was discontinued at least 2 days before the study; all medications were withheld on the morning of the catheterization. Right and left heart catheterization was performed on all patients using standard techniques. Baseline hemodynamics were obtained using the Fick principle prior to drug administration. Vascular resistance and central shunt were determined with standard formulae, and resistance was indexed to body surface area[12].

The vasodilator protocols were as follows. Tolazoline hydrochloride (Imidarin®) was infused continuously into the pulmonary artery at a total dose of 1 mg/kg for 4 min, and the hemodynamic measurements were repeated immediately after the infusion. NO was inhaled at 20 ppm with FIo_2 0.3, and the hemodynamic variables were obtained after 10 min inhalation. Beraprost was administered at a dosage of 1–2 μg/kg, and the hemodynamic measurements were repeated 30 min after administration. Furthermore, four of the patients received combined administration of beraprost and inhaled NO (20 ppm). After each agent was administered, sufficient time was allowed for the hemodynamic values to return to the baseline before the next agent was administered.

Nitric oxide delivery system

Nitric oxide gas was mixed with oxygen shortly before introduction into the reservoir of a nonrebreathing mask worn by the patients. This system allowed separate regulation of the inspired concentrations of NO as quantified by chemiluminescence (CLD 700 AL med ECO PHYSICS, Durnten) and oxygen. Exhaled gases, as well as those discharged from the chemiluminescence instrument, were scavenged.

Comparison of vasodilator responses

Data are presented as mean ± standard deviations (SD). The hemodynamic responses to each vasodilator were evaluated by calculating the percentage change in pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (mPAP). Patients who exhibited a decrease of at least 15% in calculated PVR to a test agent were classified as "responders"; all other patients were classified as "nonresponders". Statistical analysis was performed using the ANOVA test, and a p value of less than 0.05 was taken as significant.

RESULTS

Baseline hemodynamic profile

In all patients, resting mPAP was abnormally high (40.9±14.4 mmHg, range 25–68 mmHg), and PVR was also high (6.8±5.4 Um^2, range 3.1–19.9 Um^2). Pulmonary to systemic pressure ratio (Pp/Ps), resistance ratio (Rp/Rs) and blood flow ratio (Qp/Qs) were 0.41–1.03 (0.62±0.24), 0.18–0.78 (0.41±0.23) and 0.97–3.49 (2.25±1.15), respectively.

Vascular responses

Comparison of responses to tolazoline, beraprost and nitric oxide

Tolazoline, beraprost and NO elicited a vasodilator response in 14, 14 and 16 of the patients, respectively. Although three patients responded to neither tolazoline nor beraprost, two also had 21 trisomy (**Table 1**), only one of whom did respond to NO. Two of the three nonresponders also had 21 tri-

Table 1 Nonresponders to administration of tolazoline, beraprost and NO

Case	Age	Diagnosis	PVR (Um^2)			
			Baseline	Tolazoline	Beraprost	NO
1	5 m	VSD, 21 trisomy	6.3	NR	NR	−23%
2	1 y 6 m	VSD	9.4	NR	NR	NR
3	5 y	p/oVSD, 21 trisomy	4.8	NR	NR	NR

y=year(s); m=months; VSD=ventricular septal defect; NR=no response.

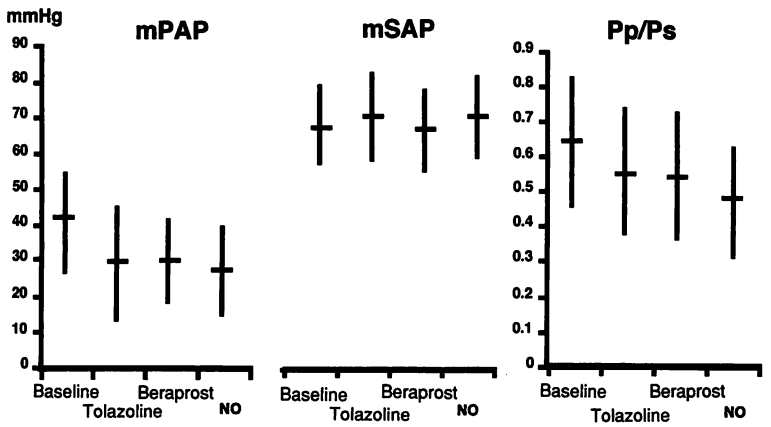

Fig. 1 Mean values ± standard deviation (SD) of mPAP, mSAP and Pp/Ps recorded at baseline after administration of tolazoline, beraprost and NO

There were no significant decreases in mPAP, mSAP and Pp/Ps after each drug administration compared to the baseline.

somy. Tolazoline, beraprost and NO elicited a decrease only in PVR without decrease in mPAP, in four, three and two patients, respectively. Conversely, none of the responders showed a decrease only in mPAP without decrease in PVR.

Effects of vasodilators on mean pulmonary arterial pressure and mean systemic arterial pressure

After administration of tolazoline, beraprost and NO, a slight but insignificant decrease was observed in mPAP and Pp/Ps (**Fig. 1**). No significant differences were observed in the percentage change of mPAP and Pp/Ps between the vasodilators (**Fig. 2**). In addition, tolazoline, beraprost and NO did not produce systemic vasodilation and did not change the mean systemic arterial pressure (mSAP; **Figs. 1, 2**).

Effects of vasodilators on pulmonary vascular resistance and total systemic resistance

Tolazoline, beraprost and NO achieved approximately equivalent reductions in PVR, from 6.8±5.4 to 4.9±3.2, to 4.8±3.1 and to 4.9±3.0 Um^2, respectively (20%, 26% and 18%, $p<0.05$). Rp/Rs also decreased from 0.41±0.23 to 0.26±0.72, to 0.27±0.65 and to 0.26±0.60, respectively ($p<0.05$; **Fig. 3**). Although no significant differences were observed in the percentage decrease of PVR between the vasodilators, the greatest percentage decrease of Rp/Rs was obtained after administration of NO ($p<0.05$; **Fig. 4**). In addition, NO did not cause reduction of total systemic resistance (TSR), whereas a modest reduction of TSR was recognized after administration of beraprost. NO is a more selective pulmonary vasodilator than beraprost.

Effect of drugs on Qp/Qs

After administration of each vasodilator, Qp/Qs increased modestly, and the percentage change of Qp/Qs was the greatest with NO. In patients with intracardiac shunts, NO increased left-to-right shunt and pulmonary blood flow with reduction of pulmonary vascular resistance, without decrease of pulmonary arterial pressure (**Fig. 5**).

Effects of combined administration of beraprost and nitric oxide

In addition to beraprost, inhalation of 20 ppm NO was administered in four patients. The greatest decrease of PVR (49%) was observed with combined administration of NO and beraprost in all four patients. Although 100% oxygen inhalation did not elicit reduction of pulmonary artery pressure (PAP)

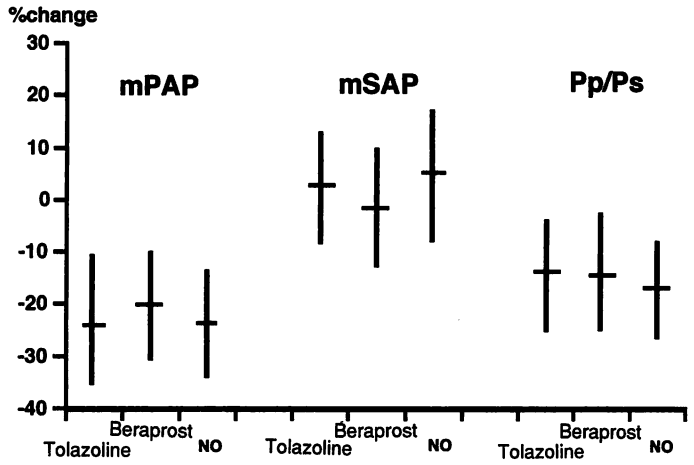

Fig. 2 Mean values ± SD of percentage change of mPAP, mSAP and Pp/Ps after administration of tolazoline, beraprost and NO

There were no significant differences in percentage change of mPAP, mSAP and Pp/Ps between each vasodilator.
Abbreviation as in Fig. 1.

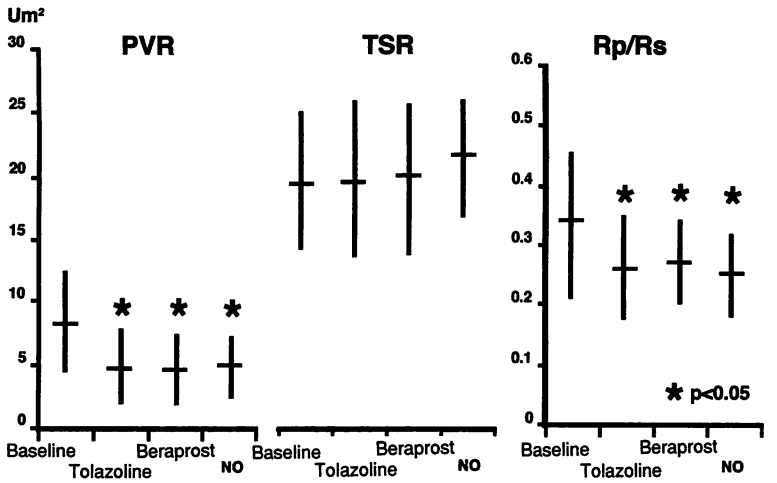

Fig. 3 Mean values ± SD of PVR, TSR and Rp/Rs recorded at baseline after administration of tolazoline, beraprost and NO

PVR and Rp/Rs were significantly different ($p < 0.05$) after administration of tolazoline, beraprost and NO compared to the baseline.
Abbreviation as in Fig. 1.

or PVR in the patient with primary pulmonary hypertension, NO and beraprost reduced PAP and PVR to the same extent and similarly increased cardiac index from 2.8 to 3.2 *l*/min/m² (**Fig. 6**). Furthermore, the maximum reductions of PAP and PVR were achieved by combined administration of NO and beraprost, and the cardiac index increased dramatically to 4.1 *l*/min/m².

The vasodilating effect of NO developed rapidly after the administration, and returned to the baseline within minutes of cessation. In contrast to NO inhalation, beraprost acted gradually on pulmonary vascular bed, and the maximum effects of vasodilation were observed from 15 to 30 min after administration. No adverse effects such as systemic hypotension were observed during the administration of each vasodilator.

DISCUSSION

The continuous intravenous infusion of PGI_2 has been used successfully for the treatment of primary pulmonary hypertension and pulmonary hypertensive crisis after operation[2–7]. Unfortunately, intravenous PGI_2 lacks specificity for the pulmonary circulation and its use is frequently limited by the systemic hypotensive effect, especially in children[11]. Furthermore, since intravenous PGI_2 is unstable at pH values below 10.5, it cannot be given orally, and continuous intravenous infusion is necessary because of its short half-life in the blood[13]. Long-term use is limited by the complex delivery system of continuous infusion and potential complication of sepsis caused by central venous catheters, especially in children[14].

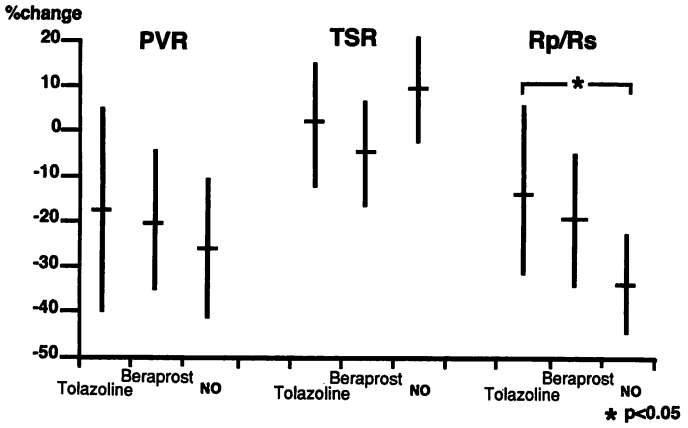

Fig. 4 Mean values ± SD of percentage change of PVR, TSR and Rp/Rs after administration of tolazoline, beraprost and NO

Percentage change of Rp/Rs with tolazoline was significantly different ($p<0.05$) compared to that with NO. Abbreviation as in Fig. 1.

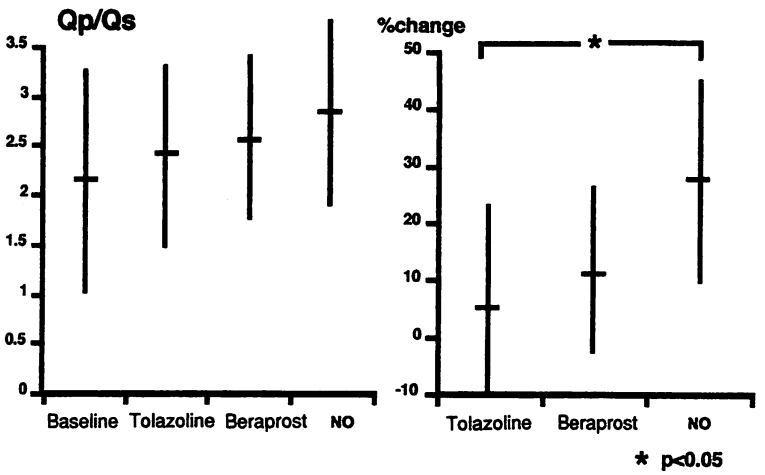

Fig. 5 Mean values ± SD of Qp/Qs recorded at baseline after administration of tolazoline, beraprost and NO

Percentage change of Qp/Qs with tolazoline was significantly different ($p<0.05$) compared to that with NO.
Abbreviation as in Fig. 1.

Recently, aerosolized PGI_2 has been shown to cause selective pulmonary vasodilation in patients with adult respiratory distress syndrome[15] and in an infant with primary pulmonary hypertension[16]. However, long-term treatment with aerosolized PGI_2 has not been performed because no nebulizer is available which allows reliable control of the amount of drug to avoid the potential hazards of an accidental PGI_2 overdose, *i.e.*, systemic hypotension due to spillover of PGI_2 into the systemic circulation.

The newly-developed oral prostacyclin analogue, beraprost, is a stable agent with a PGI_2-like structure, causes strong vasodilation, and inhibits platelet aggregation and adhesion in humans and experimental animals[17]. Clinical studies indicate the usefulness of beraprost in patients with peripheral vascular diseases[18], and the clinical effectiveness of the drug is probably due to the vasodilating, antithrombotic, and platelet disaggregating effects. The biological half-life of the drug administered orally to healthy volunteers is 60 min, which is much longer than intravenous PGI_2. Accordingly, beraprost appears to be an effective and available substitute for oral vasodilators and continuous intravenous infusion of PGI_2 in the treatment of primary pulmonary hypertension for both short- and long-term management[19]. In this study, beraprost produced an approximately equivalent effect of pulmonary vasodilation to NO, and combined administra-

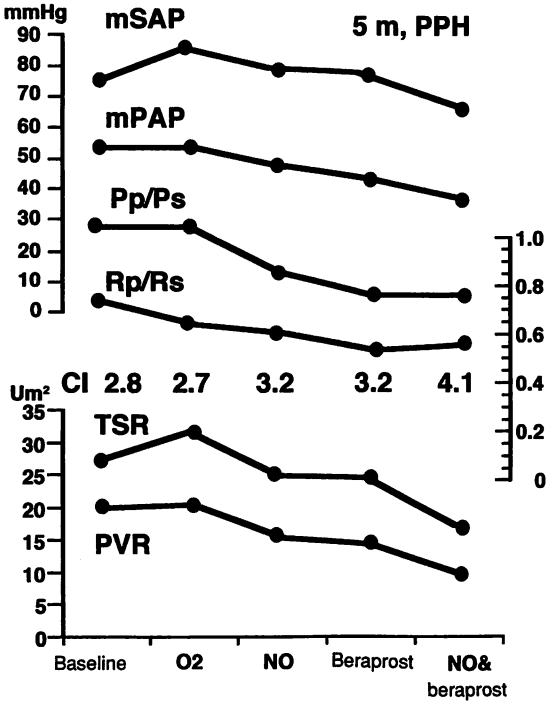

Fig. 6 Hemodynamic effects of combined administration of beraprost and NO in a representative patient with primary pulmonary hypertension

Hemodynamic variables were recorded at baseline after administration of 100% oxygen, NO alone, beraprost alone, and both NO and beraprost administered simultaneously. The maximum reduction of mPAP and PVR was achieved by combined administration of NO and beraprost with the maximum cardiac index of 4.1 *l*/min/m².

tion of beraprost and NO showed the maximum efficacy in reduction of PVR and mPAP with sufficient increase of cardiac index. Although we have shown that combined therapy with beraprost and NO is superior to prostacyclin alone or NO alone, no comparative data of combined therapy have been reported.

In this study, NO did not elicit reduction of total systemic resistance, whereas modest reduction of TSR was recognized after administration of beraprost, so NO is a more selective pulmonary vasodilator than beraprost. However, no serious systemic hypotension was observed during administration of beraprost even in this study group of infants and children, which has been frequently reported in the treatment of intravenous infusion of PGI_2.

The conventional management of pulmonary hypertensive crisis includes administration of tolazoline, and which has been widely used in infants and children[20,21]. However, due to the prevalence and severity of side-effects and its prolonged duration of action, tolazoline is not considered the ideal agent[22]. Our study shows that NO may offer more than a pharmacologic alternative to increased tolazoline dosage if tolazoline proves to be insufficient.

In one of the three patients defined as nonresponders, vasodilation was observed in response only to NO. This implies that there is endothelial dysfunction or that the diminished reponse to beraprost is due to increased background PGI_2 released by the endothelium stimulated by high flow, leading to maximal relaxation of the underlying smooth muscle[23]. Furthermore, in the nonresponder both to NO and beraprost, endothelial cell injury and a more advanced stage of pulmonary vascular disease may have been present. Two of the three nonresponders had 21 trisomy. Morphological study of the pulmonary artery in pulmonary hypertension indicated that intimal changes developed at an earlier age in patients with 21 trisomy, and were more severe than in those without 21 trisomy[24]. These results imply that nonresponders to vasodilators may be frequently found in patients with 21 trisomy because of the characteristic morphological differences in pulmonary arteries.

CONCLUSION

The acute effect of beraprost to relieve pulmonary vasoconstriction compares favourably with that of inhaled NO, which appears to be an effective and available substitute for tolazoline and NO in screening for pulmonary vasodilator responsiveness in children. In addition, the combined use of beraprost and NO may serve as an alternative treatment for pulmonary hypertension in children.

要　約

小児期肺高血圧症における経口 prostacyclin と一酸化窒素吸入の効果

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肺高血圧症を有する先天性心疾患および原発性肺高血圧症の 17 例 (平均年齢 1 歳 9 ヵ月) において，経口 prostacyclin (PGI_2) および一酸化窒素 (NO) 吸入の効果と血行動態に及ぼす影響を比較検討した．心臓カテーテル検査時に tolazolin 静注 (1 mg/kg)，経口 PGI_2 (1–2 μg/kg)，NO 吸入 (20 ppm) を行い，肺動脈圧，肺血管抵抗などに及ぼす変化を比較検討した．

経口 PGI_2，NO 吸入，tolazolin により，おのおのの平均肺動脈圧は低下傾向が認められ，肺血管抵抗はおのおの 20%, 26%, 18% 低下した ($p<0.05$)．肺体血管抵抗比は NO 吸入後に最も低下した (33%, $p<0.05$)．更に，経口 PGI_2 と NO 吸入の併用により，体血圧低下をきたすことなく，肺血管拡張の最大効果が認められた (49%)．

経口 PGI_2 は NO 吸入や tolazolin 同様，先天性心疾患における肺高血圧の術前評価において有用であった．術後の肺高血圧発作には即効性の NO 吸入が有用であり，残存する肺高血圧には経口 PGI_2 の投与が有用であることが示唆された．

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