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EFFECT OF NEBULIZED NITROGLYCERIN ON CHILDREN WITH VENTRICULAR SEPTAL DEFECT AND PULMONARY HYPERTENSION

GONG Fang-qi(龚方戚), KANG Man-li(康曼丽), XIA Cheng-sen(夏呈森)

(*Children's Hospital, Medical College Zhejiang University, Hangzhou 310003, China*)

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Abstract: In order to find a safe, simple, effective and selective pulmonary vasodilator, we tested the effectiveness and safety of inhalation of nebulized nitroglycerin (Neb-NTG) by children with ventricular septal defect and pulmonary hypertension (VSD-PH). Twenty μg/kg Neb-NTG was inhaled by seven children with VSD-PH using face mask during cardiac catheterization. The pulmonary artery pressure (PAP), systemic arterial pressure (SAP) and methemoglobin (MetHb) concentration were measured before and after inhalation of Neb-NTG. After inhalation of Neb-NTG, the PAP and pulmonary-to-systemic pressure ratio (Pp/Ps) decreased significantly; There was no significant decrease in SAP. The systolic and diastolic PAP decreased respectively 13±4% and 9±7% in 5 min, 21±3% and 13±17% in 10 min, 24±3% and 16±19% in 15 min. The Pp/Ps decreased 12±4% in 5 min, 21±9% in 10 min and 24±6% in 15 min. There was no significant increase in the MetHb level after inhalation of 20 μg/kg of Neb-NTG. The MetHb level was below 1.5%. Neb-NTG is a safe, simple, effective and selective pulmonary vasodilator.

Key words: vasodilator, nitroglycerin, inhalation, pulmonary hypertension
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INTRODUCTION

Pulmonary hypertension (PH) is very common and a primary cause of mortality in children with some congenital and acquired heart and lung diseases (Hoffman et al., 1981; Bush et al., 1988). However, up to now, no safe, simple, effective and selective pulmonary vasodilator has been identified. Since the Endothelial Derived Relaxing Factor (EDRF) was discovered in the early 1980s and identified as nitric oxide (NO) (Furchtgott et al., 1980; Palmer et al., 1987; Moncada et al., 1988), many studies showed that inhaled NO can decrease PAP but does not significantly decrease SAP in animals and humans with PH. However, inhalation of NO gas requires complicated and expensive instruments and elaborate preparations to avoid administration of toxic gas (Warren et al., 1996).

Under normal physiological conditions, the endothelium maintains low pulmonary vascular resistance by producing two potent vasodilators, EDRF and prostacyclin. The EDRF stimulates cytoplasmic guanylate cyclase and increases the cyclic guanosine monophosphate (cGMP) concentration, which is the second messenger that relaxes the vascular smooth muscle, after activation of cGMP-dependent protein kinase (Ignarro et al., 1981; Feelisch 1991; Chung et al., 1990). It was reported that the production of endogenous vasodilator NO decreases in animals and patients with PH caused by endothelial dysfunction (Loscalzo 1992; Perez-Vizcaino et al., 1997; Dinh-Xuan et al., 1990; Celermajer et al., 1993).

Nitroglycerin (NTG) is a safe and effective drug that has been used for many years to treat heart diseases. It is also common to treat PH by intravenous infusion of NTG. But the use of intravenous nitrovasodilators for PH is, however, often limited by the systemic effect (Van-Obbergh et al., 1996; Troncy et al., 1996). It was proved that NTG can be metabolized to produce NO (Ignarro et al., 1981; Feelisch 1991; Chung et al., 1990; Salvemini et al., 1993), thus it is possible to reproduce the effects of inhaled NO gas by inhalation of Neb-NTG by animals and humans with PH, which is simpler than inhalation of NO gas.

A review of the English literature did not reveal previous reports of inhalation of NTG liquid to treat PH in human. Therefore, in order to find a safe, simple, effective and selective pulmonary vasodilator, we determined to test the effectiveness and safety of inhalation of NTG in children with VSD-PH.

METHODS

Seven children with VSD, aged 6 months to 6 years, who were found to have PH during cardiac catheterization, were enrolled in this study approved by the Hospital Committee on Human Research. Table 1 lists their clinical and cardiac catheterization data. In all cases, physical examination revealed accelerated pulmonary second heart sound and a grade Ⅲ-Ⅳ/6 pan-systolic murmur at the 3rd – 4th intercostal space of the left sternal border. Continuous heart murmur was revealed at the second intercostal space of the left sternal border in case 2. In all cases, chest X-rays revealed pulmonary artery segment prominence and increased pulmonary vasculature; the cardiothoracic ratio was 0.61 to 0.65 (0.63 ± 0.02). The electrocardiogram showed right and left ventricular hypertrophy.

Left and right cardiac catheters were inserted respectively through the femoral artery and vein with the children under intravenous and sacral anesthesia, and routine cardiac catheterization was performed. All cases whose Pp/Ps was more than 0.5 initially inhaled 60% oxygen for 15 min using a face mask. Then 20μg/kg NTG diluted by normal saline to a total volume of 3 ml and nebulized with 60% oxygen was inhaled by all children for 15 min using the same face mask. The PAP was measured continuously with fluid-filled transducers. The SAP was measured intermittently (once per minute) using an automated cuff (Dynamap). The MetHb concentration in four children was measured before and after inhalation of Neb – NTG by them.

Table 1 Clinical and cardiac catheterization data.

Patient [No]	Sex	Age	Wt [kg]	Diagnosis	Qp [L/min]	Qs [L/min]	Qp/Qs	SAP[S/D(M)] [mm Hg]*	PAP[S/D(M)] [mm Hg]*	SVR [wood U]	PVR [wood U]	R_p/R_s
1	M	6Y	17	VSD	11.8	3.6	3.3	84/51(64)	80/32(58)	17.8	4.9	0.28
2	M	3Y	12	VSD,PDA	7.4	2.5	3.0	93/39(63)	85/33(51)	25.2	6.9	0.27
3	M	18M	8	VSD	14.5	5.4	2.7	96/62(74)	56/35(44)	13.7	3.0	0.22
4	M	6M	6	VSD	4.7	1.8	2.6	64/34(44)	50/20(38)	24.4	8.1	0.33
5	F	2Y	10	VSD	6.4	2.4	2.7	90/62(74)	64/30(48)	30.8	7.5	0.24
6	F	18M	8	VSD	7.8	2.8	2.8	84/52(65)	58/28(42)	23.2	5.4	0.23
7	F	4Y	14	VSD	8.4	3.3	2.5	88/58(68)	80/38(58)	20.6	6.9	0.33
Mean			10.7		8.7	3.1	2.8	65(M)	48(M)	22.2	6.1	0.27
± SD			±3.9		±3.4	±1.2	±0.3	±10	±8	±5.5	±1.8	±0.05

* mmHg = 0.133kPa

Abbreviations: VSD, ventricular septal defect; PDA, patent ductus arteriosus; Qp, pulmonary artery flow; Qs, systemic flow; Qp/Qs, pulmonary-to-systemic flow ratio; SAP, systemic arterial pressure; PAP, pulmonary artery pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; Rp/Rs, pulmonary-to-systemic resistance ratio.

Hemodynamic changes before and after the inhalation of Neb – NTG were assessed with the paired Student's t test; each child served as his own control. A p value < 0.05 was considered to be significant.

RESULTS

After inhalation of 60% oxygen, the PAP, SAP and Pp/Ps did not change significantly within 15 min in all cases. Baseline hemodynamics and responses of all children to 20 μg/kg Neb – NTG are summarized in Table 2. The data reveals that systolic and diastolic PAP decreased significantly after inhalation of 20μg/kg Neb – NTG. The systolic and diastolic PAP decreased 13 ± 4% and 9 ± 7% in 5 min, 21 ± 3% and 13 ± 17% in 10 min, 24 ± 3% and 16 ± 19% in 15 min, respectively. There was no significant decrease in the systolic and diastolic SAP. The Pp/Ps decreased 12 ± 4% in 5 min, 21 ± 9% in 10 min and 24 ± 6% in 15 min, respectively. There was no significant increase in the MetHb level in four children after their inhalation of 20μg/kg of Neb – NTG. The MetHb level was below 1.5%.

Table 2 The hemodynamic data after inhalation of NTG by seven children with VSD – PH (mean ± SD, n = 7).

	Basal	Neb – NTG 5min	Neb – NTG 10min	Neb – NTG 15min
Systolic PAP (mm Hg)*	68 ± 14	58 ± 11△	53 ± 10△	51 ± 9△
Diastolic PAP (mm Hg)	31 ± 6	28 ± 6△	26 ± 4△	25 ± 4△
Systolic SAP (mm Hg)	86 ± 11	85 ± 8	86 ± 4	86 ± 6
Diastolic SAP (mm Hg)	51 ± 11	50 ± 10	52 ± 8	51 ± 9
Pp/Ps	0.79 ± 0.14	0.69 ± 0.10△	0.62 ± 0.12△	0.59 ± 0.10△
MetHb(%)	★1.05 ± 0.24			★1.13 ± 0.22

△ $P < 0.01$ compared with basal values; ★ $n = 4$; * mmHg = 0.133kPa

Abbreviations: Neb – NTG, nebulized nitroglycerin; PAP, pulmonary artery pressure; SAP, systemic arterial pressure; Pp/Ps, pulmonary-to-systemic pressure ratio; MetHb, methemoglobin.

DISCUSSION

The results of this study showed that inhalation of 20 μg/kg Neb – NTG could decreased PAP, but did not significantly decrease the SAP and increase MetHb in children with VSD – PH. The Pp/Ps was decreased significantly.

PAP-decreasing effects have been reported in patients with PH after they were administered NTG by intravenous infusion. But as intravenous nitrovasodilators usually caused decrease of SAP and PAP simultaneously, the Pp/Ps was not altered (Van-Obbergh et al., 1996; Troncy et al., 1996). Because the direct entry of NTG into the systemic circulation has the simultaneous and same effects on the pulmonary and systemic vasculature, the method of intravenous infusion of NTG cannot be used to treat PH effectively and selectively.

Pulmonary vasodilator therapy in patients with PH may be complicated by systemic hypotension, which can result in coronary ischemia and acute right ventricular failure (Prielipp et al., 1988). A drug with preferential pulmonary (versus systemic) vasodilator effect minimizes the risk of systemic hypotension. In our study, the effectiveness and selectivity of pulmonary vasodilation were assessed by the changes in Pp/Ps with drug therapy. An ideal pulmonary vasodilator for the treatment of PH would decrease PAP more than SAP, or not decrease SAP, thereby decrease Pp/Ps during therapy. In this study, inhalation of 20 μg/kg Neb – NTG significantly decreased the systolic and diastolic PAP in children with VSD – PH. However, there were no significant decreases in the systolic and diastolic SAP. The Pp/Ps decreased significantly. Because NTG is inhaled, it can be metabolized to produce exogenous NO in endothelial cells of the pulmonary vasculature. NO acts on the pulmonary vasculature firstly and directly, and relaxes the vascular smooth muscle cell by stimulating cytoplasmic guanylate cyclase to increase the cGMP concentration (cGMP pathway) (Ignarro et al., 1981; Feelisch, 1991; Chung et al., 1990; Salvemini, et al., 1993). NO is rapidly inactivated in the alveolar capillaries due to the reaction with oxyhemoglobin to form MetHb (Warren et al., 1996; Rimar et al., 1993). This mode of administration produces little, if any, direct effect on the systemic vasculature. Thus, no significant systemic hypotension occurs after inhalation of 20 μg/kg Neb – NTG, which is common after intravenous infusion of NTG.

In the case of left to right shunts associated with congenital heart disease, PH is induced by several mechanisms: the high flow (hyperkinetic) mechanism, the vasoconstriction (reactive) mechanism, and the remodeling (obstructive) mechanism. The significantly increased pulmonary blood flow and progressive structural changes of vessel walls can lead to an irreversible stage where extensive intimal changes, obliteration, adventitial fibrosis, and reduction in the number of intraacinar arteries occur. The overlap in terms of responsible mechanisms is emphasized by the fact that vasoconstriction is an important secondary factor in many forms of PH, in addition to obstruction or obliteration (Hoffman et al., 1981; Weir et al., 1995).

In all cases, the pulmonary-to-systemic flow ratio (Qp/Qs) was more than 2.5, and the PH might be due to high pulmonary flow and vasoconstriction of the pulmonary arterioles. After inhalation of Neb – NTG, the pulmonary arterioles would be quickly dilated, and the PAP significantly decreased. PAP was decreased very rapidly following inhalation of Neb – NTG, often with-

in 10 min of inhalation; and after ten minutes, decreased little. Because the SAP did not decrease simultaneously, the Pp/Ps decreased significantly in the same way as the PAP.

Because the dose of inhaled NTG was very little in this study, the MetHb level did not increase significantly. It is better than the direct inhalation of NO, because it ofter caused methemoglobinaemia after inhalation of NO (Warren et al., 1996).

Our study showed inhalation of Neb – NTG may produce the desired local pulmonary vasodilation by liberating NO without the potential toxic gas contamination and significant systemic hypotension. The risks of inhaled NTG are minimal, as the amount inhaled is less than the routine amount administered by intravenous or sublingual procedures. The method is very simple, and does not require complicated or expensive instruments. Although the study revealed only the acute effects of inhaled NTG on children with VSD – PH, the results showed that in patients with PH, these acute effects are the same as those from inhalation of NO gas. Furthermore, the inhalation of Neb – NTG does not cause significant systemic hypotension or methemoglobinaemia.

The results of this study demonstrated that Neb – NTG is a safe, simple, effective, and selective pulmonary vasodilator and may offer a new method to treat PH.

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