

Aerosolised iloprost improves pulmonary haemodynamics in patients with primary pulmonary hypertension receiving continuous epoprostenol treatment

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Abstract

Background—Continuous intravenous treatment with epoprostenol significantly improves pulmonary haemodynamics and survival in patients with primary pulmonary hypertension (PPH). Its beneficial effect, however, may be blunted due to adverse effects such as catheter sepsis and systemic hypotension. Recent investigations have shown that inhaled iloprost is effective in the treatment of PPH. Based on their different pharmacokinetics, we hypothesised that the combination of intravenous epoprostenol and inhaled iloprost would be more efficacious than epoprostenol alone during acute testing in patients with PPH.

Methods—The effect of a single dose of inhaled iloprost (30 µg total over 15 minutes) on pulmonary haemodynamics was examined in eight patients with PPH (initial non-responders to nitric oxide) who had considerable adverse effects during treatment with epoprostenol.

Results—The combination of inhaled iloprost and intravenous epoprostenol significantly improved mean pulmonary artery pressure (MPAP), cardiac index (CI), mixed venous oxygen saturation (Svo₂), and systemic arterial oxygen pressure (Pao₂) compared with epoprostenol treatment alone. Mean systemic arterial pressure (MSAP) and pulmonary capillary wedge pressure (PCWP) remained unchanged.

Conclusions—The pulmonary vasoreactivity shown by additional iloprost inhalation during effective epoprostenol treatment suggests that an improvement of treatment for pulmonary hypertension may be possible by combining vasoactive substances.

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Keywords: epoprostenol; iloprost; primary pulmonary hypertension

Primary pulmonary hypertension (PPH) is a fatal disease causing progressive right heart failure within three years of diagnosis.¹ Impairment of vascular and endothelial homeostasis is evidenced by a reduced synthesis of prostacyclin, increased thromboxane production, decreased formation of nitric oxide, and increased synthesis of endothelin-1.^{2,3} Prostacyclins such as epoprostenol, a potent vasodilator and inhibitor of both platelet aggregation and smooth muscle cell proliferation, are effective in the treatment of PPH. Although stereochemically different, the prostacyclin analogue iloprost and epoprostenol act via a prostacyclin receptor present in pulmonary artery smooth muscle cells.⁴ Pharmacokinetically, iloprost is more stable than epoprostenol with half lives of 30 minutes and 2 minutes, respectively. Both substances have been shown to improve pulmonary haemodynamics and survival in PPH when administered intravenously.⁵

The continuous intravenous administration of epoprostenol is associated with therapeutic problems such as systemic hypotension, catheter sepsis, gastrointestinal upsets, jaw pain, and headache. We have shown that epoprostenol treatment reverts initial non-responsiveness to nitric oxide (NO),⁶ which suggests that pulmonary vasodilation may be incomplete in patients with PPH during treatment with epoprostenol. We have therefore examined whether additional inhalation of iloprost improves the pulmonary haemodynamics during continuous infusion of epoprostenol, given in a moderate to medium dose, in patients with stable PPH with side effects to the epoprostenol treatment such as systemic hypotension and severe headache.

Methods

PATIENTS

Eight patients with PPH were investigated after a mean treatment period with epoprostenol (Flolan, GlaxoWellcome Ltd, Uxbridge, UK) of 18 months (range 4–28 months). Epoprostenol had been given as a result of non-responsiveness to acute testing with NO (table 1). Each patient gave written informed consent

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Table 1 Haemodynamic values in patients with PPH at baseline and after treatment with epoprostenol and iloprost

Patient no.	MPAP (mm Hg)			MSAP (mm Hg)			PCWP (mm Hg)			CI (l/min/m ²)			CO (l/min)			PVR (dynes/cm ⁵ /m ²)			Svo ₂ (%)			Pao ₂ (mm Hg)			Sao ₂ (%)				
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2
1	63	54	35	87	83	87	10	6	5	2.6	2.7	3.5	5.4	5.5	7.1	785	702	340	60	62	65	66	67.0	86	92	93	97		
2	61	74	65	71	78	75	7	9	8	2.0	1.7	1.8	4.1	3.6	4.2	1053	1448	1086	60	58	62	69	64.3	73	91	92	95		
3	38	57	51	71	73	74	10	9	9	1.9	1.9	2.7	2.5	2.6	3.8	878	1506	873	52	52	55	69	70.6	77	91	92	94		
4	54	87	44	74	73	75	7	8	6	2.4	2.0	3.4	4.5	3.7	6.3	836	1717	486	63	62	63	70	69.8	79	92	91	96		
5	57	63	48	73	72	77	8	11	10	2.9	1.9	2.4	5.2	3.4	4.2	754	1224	724	62	61	63	73	70.1	85	94	94	96		
6	57	50	43	72	61	67	10	11	11	2.1	2.2	2.1	3.2	3.5	3.3	1175	881	783	60	61	60	61	62.1	75	91	92	92		
7	71	67	61	76	74	75	9	10	7	2.0	2.1	2.5	3.1	3.3	3.9	1600	1399	1099	54	55	59	59	60.2	79	89	88	93		
8	55	51	41	68	65	64	8	8	7	1.6	1.7	2.2	2.5	2.6	3.5	1504	1303	771	51	51	54	66	68.1	75	91	92	95		
Mean	57	63	49	74	72	74	9	9	8	2.2	2.0	2.6	3.8	3.5	4.5	1073	1274	770	58	58	60	67	67	78	91	92	95		
SD	9	13	10	6	7	7	1	2	2	0.4	0.3	0.6	1.1	0.9	1.4	328	332	264	5	5	4	5	4	5	2	2	2	p<0.01	

1 = haemodynamic values at baseline; 2 = haemodynamic values after treatment with epoprostenol; 3 = haemodynamic values after treatment with epoprostenol and inhalation of 30 µg iloprost. MPAP = mean pulmonary artery pressure; MSAP = mean systemic arterial pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; CO = cardiac output; PVR = pulmonary vascular resistance; Svo₂, Sao₂ = venous and arterial oxygen saturation; Pao₂ = systemic arterial oxygen pressure.

to participate in the study which was approved by the ethical committee of the University of Vienna. The diagnosis of PPH was based on a raised MPAP of >30 mm Hg and the diagnostic criteria published by Rich *et al.*⁷ In contrast to the initial lack of vasoreactivity to NO, after treatment with epoprostenol all patients had a positive vasodilator response to NO (>10%, 20 ppm NO). The patients had stable pulmonary haemodynamics, although maximum doses were not achieved due to adverse effects such as systemic hypotension and severe headache.

Iloprost (Ilomedin, Schering AG, Berlin, Germany; 30 µg) was inhaled for 15 minutes via the MicroDrop Master Jet (MPV, Truma, Germany) using a particle size of 3 µm to provide alveolar deposition of the substance. Pulmonary haemodynamics and gas exchange were measured before and 15 minutes after inhalation of iloprost while permanently delivering epoprostenol into the subclavian vein as described previously⁸ using a portable pump system (CADD-1, Pharmacia-Upjohn, Vienna, Austria). Right heart catheterisation was performed as previously reported.⁹

STATISTICAL ANALYSIS

Data were analysed descriptively using the IDV-Module Report 6.0.08 and statistically with the IDV-Module Testimate 5.2a. Baseline demographic and haemodynamic variables were recorded and are presented as mean (SD). Intraindividual comparison of the haemodynamic variables measured at baseline and after inhalation with iloprost was made using the two sided Wilcoxon U test for paired data. p values below 0.05 were considered statistically significant.

Results

The effect of simultaneous inhalation of iloprost (30 µg within 15 minutes) on pulmonary haemodynamics was tested in eight patients (two men) with a proven diagnosis of PPH continuously receiving intravenous epoprostenol (dose range 12–30 ng/min/kg, mean 20 ng/min/kg) for a mean period of 18 months. Before inhalation of iloprost the mean (SD) pulmonary artery pressure (MPAP) was 63 (13) mm Hg, cardiac index (CI) 2.0 (0.3) l/min/m², pulmonary vascular resistance (PVR) 1274 (332) dyne/s/cm⁵, pulmonary capillary wedge pressure (PCWP) 9 (2) mm Hg, systemic arterial oxygen tension (Pao₂) 67 (4) mm Hg, and mixed venous oxygen saturation (Svo₂%) 58 (5)%. Addition of 30 µg inhaled iloprost to continuous epoprostenol improved pulmonary haemodynamics in all patients. MPAP decreased to 49 (10) mm Hg (p<0.01) and PVR to 770 (264) dyne/s/cm⁵ (p<0.01). CI increased to 2.5 l/min/m² (p<0.05), Pao₂ to 78 (5) mm Hg (p<0.01), and Svo₂ to 60 (4)% (p<0.05) compared with epoprostenol alone. Systemic blood pressure and PCWP did not change significantly (table 1).

Discussion

The combination of continuous intravenous treatment with epoprostenol and a 15 minute

inhalation of aerosolised iloprost significantly improved pulmonary haemodynamics in eight patients with severe PPH. More importantly, the combination of both drugs improved parameters closely linked to long term effectiveness of treatment and survival in PPH such as SvO_2 , MPAP, and CI.⁵⁻⁹ The addition of iloprost to a continuous infusion of epoprostenol did not result in systemic hypotension or local undesired effects.

These results suggest that epoprostenol at a submaximal dose allows for stable treatment of PPH. Moreover, it provides additional evidence for the fact that continuous epoprostenol treatment regains, at least in part, pulmonary vasodilatation. In addition, this study shows that the increased vasodilatory effect can be achieved by adding a substance with comparable pharmacology, but different pharmacokinetics and a different route of application. Furthermore, it raises the possibility that the combination of prostacyclin treatment with vasodilators representing a different pharmacological approach (such as PDE5 inhibitors) may circumvent the

need for maximum dosing of epoprostenol with its undesirable side effects.

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