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Acute hemodynamic response of infused fasudil in patients with pulmonary arterial hypertension: A randomized, controlled, crossover study

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ABSTRACT

Background: The Rho-kinase pathway has been shown to be involved in the pathogenesis of PAH. As yet, however, the acute effects of the Rho-kinase inhibitor fasudil have not been compared with established pulmonary selective vasodilators in patients with PAH. We compared the acute effects of intravenous fasudil with inhaled iloprost in patients with pulmonary arterial hypertension (PAH).
Methods: Using a crossover design, 50 patients with PAH (idiopathic PAH, PAH associated with repaired left-to-right cardiac shunts, or connective tissue disease) were randomized to iloprost inhalation (5 μg) and intravenous fasudil (30 mg over 30 min). Hemodynamic data were collected at baseline and during acute drug exposure.
Results: Comparable decreases were observed in mean pulmonary artery pressure (−4.6 ± 4.3 mm Hg vs. −4.8 ± 4.2 mm Hg) and pulmonary vascular resistance (−3.0 ± 3.0 Wood U vs. −2.2 ± 2.7 Wood U) with fasudil infusion and iloprost inhalation, respectively, during acute challenge. However, fasudil infusion resulted in a more pronounced increase in mean cardiac output and mixed venous oxygen saturation compared with iloprost inhalation (13.7 ± 17.1% vs. 6.9 ± 15.0%; $p = 0.044$ and 4.5 ± 5.3% vs. 2.7 ± 8.2%; $p = 0.044$, respectively). Whereas inhaled iloprost resulted in a non-significant increase in mean systemic arterial oxygen saturation (0.8 ± 3.6%), infused fasudil resulted in a non-significant reduction (−0.6 ± 1.1%).
Conclusion: Infused fasudil improved pulmonary hemodynamics in patients with PAH without significant toxicity.

1. Introduction

Pulmonary arterial hypertension (PAH) is a rare progressive disease without a cure, although current therapies have improved the outlook for patients. Pathobiological changes in PAH include vascular endothelial dysfunction, vascular smooth muscle hypertrophy, and proliferative changes in the pulmonary arteries [1,2]. All of the currently available therapies act on one of three pathways identified to play a role in the development of PAH [3]. Prostanoids act to increase cyclic AMP [4], phosphodiesterase type 5 inhibitors increase cyclic GMP [5], and endothelin receptor antagonists block either the endothelin A receptor or both the A and B receptors [6].

In the past few years, there has been a paradigm shift as newer drugs that target alternative pathways have been studied. The importance of dysregulated cell growth and failure to inhibit vascular proliferation has become a target of therapy. In this regard, the tyrosine kinase inhibitor imatinib is currently in phase III clinical trials in patients with very advanced PAH [7–9].

The central role of kinase-mediated signaling has also focused attention on the Rho-kinase pathway. A variety of preclinical and clinical studies suggest that the Rho-kinase pathway is involved in vascular signaling in cardiovascular disease [10,11] and pulmonary hypertension [12–17]. Do et al. have shown that Rho-kinase activity is upregulated in circulating neutrophils and in the pulmonary vasculature of patients with PAH [18]. Most recently, a pilot double-blind, placebo-controlled study performed in 23 PAH patients to examine the clinical effects of mid-term oral treatment with an extended release formulation of fasudil hydrochloride [19]. Despite the primary efficacy endpoint (6-min walk distance, 6MWD) did not reach significant differences between the 2 groups, pulmonary hemodynamics tended to be improved in the fasudil group [19]. In The Rho-kinase inhibitor fasudil is currently

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approved in Japan and China as a treatment to prevent cerebral vasospasm in aneurysmal subarachnoid hemorrhage.

In this study, we report on the acute effects of intravenous fasudil compared with inhaled iloprost in a cohort of 50 patients with either idiopathic PAH (IPAH), PAH associated with congenital heart disease (CHD-PAH), or PAH associated with connective tissue disease (CTD-PAH).

2. Methods

2.1. Patient population

Between March 2009 and December 2010, 50 patients with IPAH or PAH associated with connective tissue disease or repaired congenital heart disease (at least 3 years previously) were enrolled consecutively into a randomized, controlled, crossover study. PAH was established by right heart catheterization, a mean pulmonary arterial pressure (mPAP) > 25 mm Hg, and pulmonary vascular resistance (PVR) >3 Wood U. Patients were between 18 and 65 years of age, clinically stable for 30 days, and had World Health Organization (WHO) functional class II or III symptoms. No PAH-specific drugs were used within 3 months prior to enrollment. Patients had to be able to provide written informed consent to participate in the study.

To exclude other forms of pulmonary hypertension, patients underwent scintigraphy and/or spiral computed tomography (to exclude chronic thromboembolic pulmonary hypertension), high-resolution computed tomography (lung disease), serologic testing (HIV infection), and comprehensive pulmonary and liver function studies (lung or liver disease). In addition to clinical features, evaluations undertaken in all patients included an electrocardiogram (ECG), chest radiography, Doppler echocardiography, measurement of the 6MWD, and measurement of plasma level of brain natriuretic peptide (BNP). Patients with significant medical comorbidities such as advanced renal failure, uncontrolled diabetes, and poorly controlled asthma were excluded.

The study protocol was reviewed and approved by the Ethics Committee of Shanghai Pulmonary Hospital, Tongji University.

2.2. Hemodynamic measurements

All patients were admitted to the catheterization laboratory at Shanghai Pulmonary Hospital, where they were in room air and without additional oxygen supply. Despite needing to stay in the catheterization laboratory for over 2 h, none of the enrolled patients received any sedation due to uncomfortable events. An 8 F introducer sheet was placed in the left antecubital vein or left subclavian vein, and a 7 F Swan-Ganz catheter (Edwards Lifesciences Co., Ltd, USA) was advanced into the pulmonary artery. Correct positioning of the catheter was verified by fluoroscopy. Transducers were positioned at the mid-axillary line and zeroed at atmospheric pressure. mPAP, systemic arterial pressure (SAP), right atrial pressure (RAP), and pulmonary artery wedge pressure (PAWP) were measured at baseline and after study drug administration, along with mixed venous saturation and systemic arterial oxygen saturation. Cardiac output (CO) was measured in triplicate by the thermodilution technique (Cardiac Output Computer; GE, USA) with iced normal saline. The cardiac index (CI) was calculated by dividing CO by body surface area (BSA). Pulmonary vascular resistance (PVR) was calculated as mPAP minus PAWP divided by CO. Systemic vascular resistance (SVR) was calculated as SAP minus RAP divided by CO. The heart rate and the transcutaneous arterial oxygen saturation were monitored continuously.

2.3. Administration of vasodilator drugs

After baseline hemodynamic parameters had been established (baseline 1), patients were randomized to either iloprost inhalation ($n = 25$) or fasudil infusion ($n = 25$) as the first vasodilator drug. Randomization was performed via computer-generated random numbers. On the basis of previous studies showing that the pulmonary vasodilator effects of iloprost inhalation or fasudil infusion are likely to end within 1 h [14,20], we set a 1-hour interval after administration of the first drug for hemodynamic parameters to return to baseline. After a second baseline set of hemodynamic data had been established (baseline 2), patients were then given the crossover study medication. Iloprost (Ventavis, Bayer, Germany) 5 μg was given via a jet nebulizer (PARI TurboBOY-N type, PARI GmbH, Germany) for 15 min, and the maximal responses during the iloprost inhalation were recorded. Fasudil (Chuanwei, Chasesun Pharmaceutical Co., Ltd, Tianjin, China) was delivered by continuous intravenous infusion at a rate of 1 mg/min for 30 min. Hemodynamic data were measured continuously for up to 60 min after drug administration. Blood samples were obtained from the main pulmonary artery and radial arteries for gas tension analysis before and after vasodilator administration. Any adverse events that occurred during administration of the vasodilator drugs were recorded. Particularly, renal function was monitored before the study, then 24 and 72 h after the study.

2.4. Statistical analysis

Baseline hemodynamic data were expressed as means ± standard deviation (SD). Changes in hemodynamic parameters before and after each intervention were analyzed by Student's 2-sided, paired *t*-test. To compare the acute hemodynamic effects of the two interventions, the Mann–Whitney non-parametric test was used. The significance level was set at $p < 0.05$. Statistics were performed using SPSS software (version 15.0).

3. Results

3.1. Study population

Fifty patients (mean age 39 years; range 18 to 64 years; 41 women and 9 men) with PAH (Table 1) were prospectively enrolled in the study to examine the acute effects of inhaled iloprost and infused fasudil hydrochloride on pulmonary hemodynamics. Twenty-nine patients had IPAH, 18 patients had CTD-PAH (12 with systemic lupus erythematosus, 2 with Sjögren's syndrome, 1 with mixed connective tissue disease, 1 with systemic sclerosis, and 1 with rheumatoid arthritis), and 3 had PAH associated with repaired congenital heart disease (2 with ventricular septal defects and 1 with patent ductus arteriosus). Thirty-five patients were WHO functional class III, and 15 were class II. The patients' demographic and clinical characteristics are shown in Table 1.

3.2. Inhaled iloprost administration

The hemodynamic parameters and the oxygen saturations at baseline and at the end of the inhalations of iloprost and infusions of fasudil are shown in Table 2 and Fig. 1. During iloprost inhalation, mPAP declined by −4.8 ± 4.2 mm Hg (95% confidence interval (CI), −6.0 to −3.6 mm Hg; $p < 0.001$ vs. baseline 1), whereas the heart rate and RAP remained unchanged. The CO increased by 0.2 ± 0.5 L/min (95% CI, 0.1 to 0.4 L/min; $p = 0.004$ vs. baseline 1), and mixed venous oxygen saturation (SvO_2) increased by 1.1 ± 4.1% (95% CI, 0.2 to 0.6%; $p = 0.062$ vs. baseline 1). PVR declined by −2.2 ± 2.7 Wood U (95% CI, −5.6 to −2.9 Wood U; $p < 0.001$ vs. baseline 1) and SAP and SVR were also significantly decreased by −3.1 ± 8.0 mm Hg (95% CI, −5.3 to −0.8 mm Hg; $p = 0.009$ vs. baseline 1) and −1.9 ± 4.4 Wood U (95% CI, −3.2 to 0.7 Wood U; $p = 0.003$ vs. baseline 1), respectively. There was a non-significant increase in PaO_2 during inhalation of iloprost of 0.6% (95% CI, −0.3 to 1.6%; $p = 0.157$ vs. baseline 1).

3.3. Infused fasudil administration

Infused fasudil caused a significant decline in mPAP of −4.6 ± 4.3 mm Hg (95% CI, −5.8 to −3.4 mm Hg; $p < 0.001$ vs. baseline 2) and a significant reduction in PVR of −3.0 ± 3.0 Wood U (95% CI, −3.9 to −2.2 Wood U; $p < 0.001$ vs. baseline 2). SAP and SVR were also significantly decreased by −3.2 ± 5.5 mm Hg (95% CI, −4.7 to −1.6 mm Hg; $p < 0.001$ vs. baseline 2) and −3.2 ± 3.2 Wood U (95% CI, −4.1 to −2.3 Wood U; $p < 0.001$ vs. baseline 2), respectively. CO was significantly increased by 0.45 ± 0.59 L/min (95% CI, 0.28 to

Table 1
Characteristics of the study population.

Characteristics	Number or mean value
Female/male, *n*	41/9
Age, years	39 ± 13
BSA, kg/m^2	1.6 ± 0.1
Etiologies, *n*:	
IPAH	29
CTD-PAH	18
Repaired CHD-PAH	3
WHO FC II/III, *n*	15/35
BNP, pg/mL	353 ± 397
6MWD, m	377 ± 69

Data are shown as mean values ± SD, or frequency.
BNP = brain natriuretic peptide; BSA = body surface area; CTD-PAH = connective tissue disease-associated PAH; CHD-PAH = congenital heart disease-associated PAH; FC = functional class; IPAH = idiopathic PAH; 6MWD = 6-minute walk distance; PAH = pulmonary arterial hypertension; WHO = World Health Organization.