Effects of the Rho-Kinase Inhibitor, Fasudil, on Pulmonary Hypertension
Keiichi Odagiri, MD, PhD; Hiroshi Watanabe, MD, PhD

Pulmonary hypertension (PH) is a progressive, life-threatening disease characterized by vasoconstriction, thrombosis, and vascular remodeling, leading to elevated pulmonary arterial pressure (PAP), right heart failure and death. Vasorelaxant agents, including prostanoids, phosphodiesterase-5 (PDE-5) inhibitors, and endothelin receptor antagonists (ERAs), have been shown to improve symptoms, exercise tolerance, and mortality in PH patients. It is well recognized that the RhoA/ROCK pathway is involved in several cell functions, such as cell contraction, motility, migration, proliferation, differentiation, and apoptosis. Activation of Rho/ROCK is considered to play a major role in the pathogenesis of several cardiovascular diseases, including PH, and thus is a new therapeutic target for PH (Figure). Fasudil is one of the most frequently used ROCK inhibitors, and was approved as a therapeutic agent for vasospasm after arachnoid hemorrhage.

Several studies reported that fasudil ameliorated PH in various animal models, including PH induced by monocrotaline (MCT), Sugen5416/hypoxia, and bleomycin. Oka et al demonstrated the effects of acute ROCK inhibition by intravenous administration of fasudil on Sugen5416/hypoxia-induced PH in rats. Intravenous fasudil was more effective in reducing right ventricular systolic pressure (RVSP) compared with...
inhaled NO or intravenous iloprost. Bei et al evaluated the effects of fasudil on bleomycin-induced pulmonary fibrosis and PH in mice. Long-term intraperitoneal administration of fasudil attenuated the increase in RVSP, right ventricular hypertrophy (RVH), pulmonary vascular remodeling, and lung fibrosis by reducing lung inflammation and decreasing lung collagen content. Abe et al reported the beneficial effects of long-term oral administration of fasudil on MCT-induced PH in rats. Fasudil significantly and dose-dependently reduced the mortality rate. Furthermore, fasudil reduced RVSP, improved RVH, and suppressed vascular remodeling. Several studies have revealed that monotherapy with fasudil may induce not only functional but also histological improvements in various animal PH models. Because the target molecule of fasudil is different from those of PDE-5 inhibitors and ERAs, the efficacy of combined therapies with fasudil and other PH drugs was expected to be greater. One study showed that monotherapy with fasudil or sildenafil improved RVSP and RVH, and a combination of the 2 drugs reduced RVSP to a greater degree than either drug alone. In contrast, another study showed that combined therapy with fasudil and either sildenafil or bosentan did not show any additional effects in ameliorating hemodynamics and vascular remodeling. Thus, the efficacy of combination therapy is still controversial.

The acute clinical effect of fasudil on PH patients was demonstrated for the first time by Fukumoto et al in 2005. Intravenous fasudil significantly reduced pulmonary arterial resistance by 17% in severe PH patients, and tended to improve the PAP and cardiac index (CI). Importantly, there were no serious side effects of fasudil in that study. In the past decade, there have been several further studies on the effects of fasudil in PH patients. Ishikawa et al confirmed the beneficial acute effects of intravenous fasudil in pulmonary arterial hypertension (PAH) patients. Intravenous administration of fasudil significantly reduced total pulmonary resistance and mean PAP, and increased CI. Fujita et al revealed that inhaled fasudil also reduced mean PAP, without changing the ratio of pulmonary to systemic vascular resistance in PAH patients. Recently, the results of a phase IIa clinical trial of oral fasudil in PAH patients indicated that the rate of improved CI was significantly higher in the fasudil group than in the placebo group, and that fasudil showed a tendency to improve pulmonary vascular resistance (PVR) and mean PAP. In this issue of the Journal, Xiao et al report the acute effects of intravenous fasudil in patients with a congenital heart defect and severe PH. Their results are consistent with previous studies that have shown the beneficial acute effects of intravenous fasudil in PH patients. They demonstrate that intravenous fasudil markedly decreased mean PAP, PVR, and total pulmonary resistance. The mean pulmonary-systemic pressure (mPp/Ps) ratio was also significantly reduced, and the pulmonary-systemic blood flow (Qp/Qs) ratio was increased. These results suggest that fasudil dilates pulmonary arteries more selectively than systemic arteries and can be a useful drug for management of inoperable patients with a congenital heart defect and severe PH.

PH-specific drugs targeting endothelial dysfunction (ie, PDE-5 inhibitors, ERAs, and prostanoids) are well-established first-line treatments. Combinations of these 3 classes of drugs are also considered standard treatment strategies, because monotherapy with PH-specific drugs is not sufficient for severe PH patients. Although these treatment strategies have contributed to an improvement in the mortality rate of PH patients, they are not able to reverse the remodeling of the pulmonary artery. Fasudil has shown therapeutic potential to prevent and reverse pulmonary arterial remodeling in animal models, and is considered a promising therapeutic agent for PH patients. Several clinical studies have shown the superior effects of fasudil in PH patients. However, most clinical studies have evaluated the acute effects of fasudil, and the long-term efficacy and safety of fasudil should be examined in a large-scale prospective randomized study.

Disclosures
K.O. has received lecture fees from Pfizer and GlaxoSmithKline. H.W. has received research funding from the Ministry of Health, Labour and Welfare of Japan, Teikai Seiyaku, Nippon Shinyaku, Pfizer, Acterion and Daiichi Sankyo, and lecture fees from Pfizer, Acterion, Astellas Pharmaceuticals, GlaxoSmithKline and MSD. These funders had no role in the preparation of the manuscript or the decision to publish it.

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