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Effects of fasudil on pulmonary hypertension in clinical practice

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ABSTRACT

Pulmonary hypertension (PH) is a pathophysiologic disorder that may involve multiple clinical conditions and can complicate the majority of cardiovascular and respiratory diseases. The presence of PH is associated with worse outcomes, but the efficacy of current therapy is still unsatisfactory. Because Rho-kinase (ROCK) plays an important role in the pathogenesis of PH, the ROCK inhibitor fasudil is expected to contribute to PH treatment. In animal models of PH, fasudil reduced pulmonary artery pressure (PAP) and improved survival. Furthermore, the short-term efficacy and safety of fasudil in the treatment of PH are demonstrated in clinical trials. Both PAP and pulmonary vascular resistance in patients with PH are significantly decreased by intravenous or inhaled fasudil without apparent side effect. However, no clinical trial has assessed the long-term efficacy of fasudil in the treatment of PH. Limited data suggest that the mid-term use of fasudil could improve exercise capacity and reduce in-hospital mortality. We also discuss the combined use of fasudil and other drugs for PH treatment. However, these combinations have not yet been evaluated in a clinical trial. According to animal studies, the combination of fasudil with beraprost or sildenafil shows synergistic effects, whereas the combination of fasudil with bosentan has no additional ameliorating effects on PH development.

Contents

Abbreviations: CHD, congenital heart diseases; CI, cardiac index; CO, cardiac output; CTD, connective tissue diseases; CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin receptor antagonists; ET, endothelin; IPAH, idiopathic pulmonary arterial hypertension; MCT, monocrotaline; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PASMC, pulmonary artery smooth muscle cells; PDEI, phosphodiesterase-5 inhibitors; PH, Pulmonary hypertension; PVR, pulmonary vascular resistance; PVR/SVR, pulmonary to systemic vascular resistance; Qp/Qs, pulmonary to systemic blood flow; RHC, right heart catheterization; ROCK, Rho-kinase; SAP, systemic artery pressure; SaO_2, arterial oxygen saturation; SVR, systemic vascular resistance; SvO_2, mixed venous oxygen saturation; TPR, total pulmonary resistance; 6MWD, 6-minute walk distance.

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1. Introduction

Pulmonary hypertension (PH), defined as an increase in mean pulmonary artery pressure (PAP) ≥25 mm Hg at rest assessed by right heart catheterization (RHC) [1], is a general term defining a wide spectrum of conditions with different aetiologies and similar clinical presentation. It represents an independent predictive factor of poor prognosis in patients with various primary diseases [2–6]. Based on pathological, haemodynamic and clinical characteristics and treatment strategy, PH can be classified into five groups [1,7].

Group 1 PH, also known as pulmonary arterial hypertension (PAH), includes idiopathic PAH (IPAH), heritable PAH, PAH induced by drugs and toxins and PAH associated with a group of diseases such as connective tissue diseases (CTDs), human immunodeficiency virus infection, portal hypertension, congenital heart diseases (CHDs) and schistosomiasis. Additionally, PH due to pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis is designated as Group 1′, while persistent pulmonary hypertension of the newborn is designated as Group 1''. Group 2 PH is related to left heart disease. Group 3 PH is related to lung disease and/or hypoxia. Group 4 PH includes chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions. Group 5 PH is due to unclear and/or multifactorial mechanisms such as hematologic disorders, systemic disorders and metabolic disorders.

Irrespective of different aetiologies and pathological patterns, the most common characteristic of PH is pulmonary vascular remodelling due to increased vasoconstriction, increased cell proliferation, decreased cell apoptosis, increased clotting and inflammation [8,9]. Vascular remodelling loss of cross-sectional lumen area occurs in all vessel layers, including intima, media and adventitia [9–11]. Many mediators and signalling pathways such as endothelin (ET), nitric oxide (NO), prostacyclin as well as transforming growth factor β family have been demonstrated to be involved in the process of pulmonary vascular remodelling [12,13]. With the research on pathogenesis of PH, some specific drugs for PH have been introduced into clinical practice [14].

Treatment of patients with PAH is characterized by a complex strategy [1,14]. Supportive therapy should be given initially, including oral anticoagulants, diuretics, oxygen and digoxin. Additionally, a high-dose calcium channel blocker is suitable merely for vasoreactive patients in acute vasoreactivity testing. Furthermore, specific drugs alone or in combination should be administered according to the prognostic risk of the patients. Three classes of specific drugs are currently approved and recommended for clinical use [1,14]. First, endothelin receptor antagonists (ERAs) include selective ET_A antagonists ambrisentan and dual ET_A and ET_B receptors antagonists bosentan and macitentan. Second, phosphodiesterase-5 inhibitors (PDEI) include typical drugs sildenafil and tadalafil, and guanylate cyclase stimulators riociguat. Third, prostacyclin includes its analogues epoprostenol, beraprost, treprostinil and iloprost and its receptor agonist selexipag. However, these drugs may be approved in only some countries–for example, beraprost is available in Japan for PAH [15] but not approved by the European Medicines Agency.

These specific drugs could bring about a significant improvement in signs and symptoms and a slower rate of clinical deterioration in patients [14]. A meta-analysis indicates an even greater improvement in survival [16]. Despite such developments in the current therapy of PAH, the estimate of survival is still unsatisfactory [17–20]. PAH is seriously in need of new treatments that could better reduce mortality and ameliorate functional deficits associated with it. Fasudil, a Rho-kinase (ROCK) inhibitor, is one of the promising drugs for PH. In this review, we analyse and summarise clinical trials of the short-term and mid-term use of fasudil in the treatment of PAH, as well as animal studies of the combination fasudil with other PH drugs, to evaluate the prospect of fasudil in clinical practice.

2. ROCK activation in PH

ROCK, as a main downstream effector of a small monomeric G-protein RhoA, is ubiquitously expressed acting as serine/threonine kinases [21,22]. ROCK has two different isoforms [23]: ROCK1 prominent in the lung, liver, spleen, kidney and testes, and ROCK2 prominent in the heart, brain, vascular smooth muscle and skeletal muscle [24]. After activation by the GTP-bound active form of RhoA, ROCK could induce conformational changes within itself and result in relief of autoinhibitory blockage of kinase activity [25]. The activated ROCK could phosphorylate downstream proteins such as the myosin-binding subunit of myosin light chain phosphatase [26], LIM kinases [27] and ezrin/radixin/moesin [28]. Thus, ROCK is implicated in various essential cellular functions, including contraction, motility, migration and proliferation [29–31]. Because of its effects on smooth muscle cell contraction and proliferation, endothelial cell damage and inflammation, ROCK plays an important role in pathogenesis of various cardiovascular diseases such as hypertension, stable and vasospastic angina, ischemic stroke, cerebral vasospasm and PH [32,33].

As a convergence point of a variety of different signals linked to various mediators and pathways contributing to the pathogenesis of PH [34–37], ROCK plays a substantial role in the development of PH. Many studies show that ROCK is hyperactive in patients with PAH [38,39]. Doe et al. found that both ROCK1 and ROCK2 activation in circulating neutrophils from patients with PAH were significantly increased compared to those from controls [38]. Guilluy et al. revealed a significant increase in ROCK activities in the lungs, platelets and pulmonary artery smooth muscle cells (PASMC) in patients with IPAH [39]. In the thickened intima and media of small pulmonary arteries from patients with IPAH, both the expression and the activity of ROCK were significantly elevated [38]. In addition, many animal studies demonstrate that ROCK plays an important role in the pathogenesis of PH, regardless of hypoxia-induced [40,41], monocrotaline (MCT)-induced [42] or other PH models [43–47].

As an important target, ROCK has been observed to be involved in a variety of diseases [48]. The benefit of ROCK inhibition might extend to the treatment of these diseases. Over 170 ROCK inhibitors have been developed in the past two decades [49]. However, only two ROCK inhibitors have been approved for clinical use. Fasudil was approved for treatment of cerebral vasospasm complicating intracranial haemorrhage in Japan and China [50], and ripasudil was approved for the treatment of glaucoma in Japan [51]. According to their chemical characteristics, the ROCK inhibitors could be classified into isoquinolines, pyridines, indazoles, pyrazoles and others [52]. It has been reported that four ROCK inhibitors were investigated in the treatment of PH. Fasudil, a moderate ROCK inhibitor with isoquinoline ring, has been clinically trialled in the treatment of many cardiovascular diseases. Despite the first clinically available ROCK inhibitor, fasudil is not yet approved for the treatment of PH. However, clinical trials have already shown fasudil's effectiveness for treating PAH [53–61]. Y-27632, a ROCK inhibitor with pyridine ring, has been studied in many animal models of PH [40,46,62,63]. Y-27632 could decrease pulmonary vasoconstriction and attenuate the risk of developing PH and vascular remodelling, but it has not been clinically trialled. Azaindole-1, a novel highly selective ROCK inhibitor with pyrazole ring, has also provided therapeutic benefit in MCT-induced and hypoxia-induced