S46-5 Development of NS-304, a selective and long-acting prostacyclin receptor agonist, as a novel drug for pulmonary hypertension

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NS-304 is a novel, orally available and long-acting agonist for the prostacyclin receptor (IP receptor). MRE-269, an active metabolite of NS-304, is a highly selective agonist for the IP receptor, compared with the prostacyclin (PGI_2) analogs, beraprost and iloprost. NS-304 increased femoral skin blood flow in rats in a long-lasting manner without affecting the hemodynamics. These findings indicate that NS-304 acts as a long-acting IP receptor agonist *in vivo*. The continuous vasodilation evoked by NS-304 was not attenuated by repeated treatment in rats. Moreover, a microdose pharmacokinetic study in which NS-304 was orally administered to healthy male volunteers showed a long plasma elimination half-life for MRE-269. In a rat model of pulmonary hypertension (PH) induced by monocrotaline (MCT), NS-304 ameliorated vascular endothelial dysfunction, pulmonary arterial wall hypertrophy, right ventricular hypertrophy, and elevated right ventricular systolic pressure, and improved survival. MRE-269 induced vasodilation equally in large pulmonary arteries (LPA) and small pulmonary arteries (SPA) in rats, whereas beraprost and iloprost induced less vasodilation in SPA than in LPA. Endothelium removal markedly attenuated the vasodilation induced by beraprost, but not that induced by MRE-269 or iloprost. Moreover, the vasodilation induced by beraprost and iloprost, but not that induced by MRE-269, was more strongly attenuated in LPA from MCT-treated rats than from normal rats. Therefore, NS-304 is a promising drug for pulmonary hypertension with good compliance.