D/1
2003
2000

筑波大学

博士（医学）学位論文

Combination of Oral Endothelin-A Receptor Antagonist and Oral Prostacyclin Analogue is Superior to Each Drug Alone in Ameliorating Pulmonary Hypertension in Rats

（肺高血圧ラットにおいて、経口エンドセリン受容体拮抗薬と経口プロスタサイクリン製剤との併用療法は各薬剤の単独療法より有効である）

2000年度

筑波大学大学院博士課程
医学研究科

上野　倫彦

寄贈
上野倫彦氏
平成　年　月　日
01301651

ABSTRACT

Background Pulmonary hypertension (PH) is a poor prognostic and drug-resistant disease. Recently, it has been reported that continuous intravenous prostacyclin (PGI_2) administration is effectual for PH; however, its effect is not sufficient to treat PH. We previously reported that chronic treatment with an endothelin (ET)-A receptor antagonist was effective for PH in rats. In this study, we investigated whether the combination of an oral ET-A receptor antagonist and an oral PGI_2 analogue is superior to the single use of each drug alone for treating PH.

Methods and Results We administered the oral ET-A receptor antagonist, TA-0201, and/or the orally active PGI_2 analogue, beraprost sodium (BPS), to monocrotaline (MCT)-induced PH rats. The rats were divided into the following 5 groups: [1] normal rats with vehicle treatment (Control group), [2] PH rats with vehicle treatment (PH group), [3] PH rats with TA-0201 (0.5 mg/kg/day) treatment (PH+TA group), [4] PH rats with BPS (100 μg/kg/day) treatment (PH+BPS group), and [5] PH rats with TA-0201 (0.5 mg/kg/day) and BPS (100 μg/kg/day) treatment (PH+TA+BPS group). Nineteen days after starting the treatment, right ventricular (RV) systolic pressure and Pp/Ps (the ratio of RV systolic pressure to systemic systolic blood pressure) were markedly higher in PH group than in Control group. The increase of RV systolic pressure and Pp/Ps was significantly and comparably depressed in PH+TA group and PH+BPS group; furthermore, it was more greatly depressed in PH+TA+BPS group than in the groups with each drug alone. The value of ratios of RV weight to body weight and RV weight to left ventricular weight, indicators of RV hypertrophy, showed same pattern as RV systolic pressure and Pp/Ps among 5 groups. The expression of β-myosin heavy chain mRNA, a molecular marker for cardiac hypertrophy, in RV was markedly enhanced in PH group and the enhancement was inhibited in PH+TA+BPS group to the greatest degree. The medial wall thickening of pulmonary artery was markedly increased in PH group and the increase was depressed in PH+TA+BPS group.

Conclusion The combination of an oral ET-A receptor antagonist and an oral PGI_2 analogue is superior to the single use of each drug alone in inhibiting the progression of PH, and this combination therapy may become a new therapeutic strategy for PH treatment.

CONDENSED ABSTRACT

We investigated whether the combination of an endothelin-A receptor antagonist and an oral prostacyclin analogue is effective in treatment of pulmonary hypertension (PH). The increase of right ventricular (RV) systolic pressure, the medial wall thickening of pulmonary artery, and RV weight were observed in monocrotaline-induced PH rats, and it was comparably depressed in PH rats treated with each drug alone; furthermore, the greatest inhibition was observed in combined treatment group. The combination of these drugs is superior to the single use of each drug alone in inhibiting the progression of PH, suggesting that this combination therapy may become a new therapeutic strategy for treatment of PH.

KEY WORDS

pulmonary hypertension, endothelin, prostacyclin, remodeling, hypertrophy