Study on relationship between right heart echocardiographic parameters and pulmonary artery pressure, and pharmacokinetics / pharmacodynamics of oral sildenafil in a canine model of chronic embolic pulmonary hypertension

Abstract of Doctoral Thesis

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Pulmonary hypertension (PH) is a progressive disorder characterized by the elevation of pulmonary artery pressure (PAP). Evaluation of pathological conditions via echocardiography related to right heart, and basic information regarding the pharmacokinetics and pharmacodynamics of oral sildenafil in dogs with PH have not been investigated fully. Therefore, the present study aimed to investigate the relatinoship between right heart echocardiographic parameters and pulmonary artery pressure, and examine the pharmacokinetics and pharmacodynamics of oral sildenafil.

Firstly, we investigated the relatinoship between right heart echocardiographic parameters and invasive pulmonary artery pressure using a canine model of chronic embolic pulmonary hypertension (CEPH). As it turned out that the normalized right ventricular internal diameter in diastole, the ratio of the pulmonary artery and aortic diameter in diastole (PA/Ao), the acceleration time to ejection time ratio in pulmonary artery flow profile (AT/ET), and the normalized tricuspid annular plane systolic excursion were correlated with the PAP. In addition, AT/ET and PA/Ao had sufficient sensitivity and specificity for predicting CEPH. Therefore, alterations in these echocardiographic parameters enable us to evaluate pathological condition related to elevated PAP.

Secondly, we aimed to describe the pharmacokinetic properties of oral sildenafil, and determine the effect of feeding and dose proportionality in healthy dogs. As a result, feeding reduced the absorption of sildenafil. For dose proportionality, nonproportional increases in the plasma concentration and absorbed amount of sildenafil were detected by a power model analysis.

Thirdly, we examined the pharmacokinetics of oral sildenafil in a canine model of CEPH. As a consequence, it is likely that the non-proportionality of sildenafil observed in healthy dogs disappeared in dogs with CEPH showing increased PAP and decreased cardiac output (CO). The disappearance of non-proportionality for sildenafil in CEPH models appears attributable to impaired drug absorption due to hypoperfusion of the gastrointestinal tract resulting from reduced CO. In addition, the decrement in the elimination rate was detected when 4 mg/kg sildenafil were administered compared to 1 mg/kg. However, the extent of the decrement in the elimination rate is mild and it is regarded pharmacokinetically and clinically insignificant.

Finally, we evaluated the short-term effects of oral sildenafil on pulmonary and systemic

hemodynamics in a canine model of CEPH. As a result, sildenafil decreased PAP and pulmonary vascular resistance in a dose-dependent manner without notable changes in systemic artery pressure and systemic vascular resistance. Therefore, oral sildenafil at high dose is able to enhance the effect of treatment.

In conclusion, alterations in echocardiographic parameters of right-sided heart enable us to evaluate pathological conditions related to elevated PAP. In addition, the effect of feeding and altered pharamcokinetics of oral sildenafil in dogs with PH should be considered for providing maximal therapeutic effects.