Background: Endothelin receptor antagonists (ERA) improve the prognosis of patients with pulmonary arterial hypertension (PAH). However, only limited data are available on the effect of treatment with the ERA bosentan on exercise capacity assessed with cardiopulmonary exercise testing (CPX) in patients with PAH or inoperable chronic thromboembolic pulmonary hypertension (CTEPH). Purpose: To investigate the effect of the oral, dual-ERA bosentan on exercise capacity in patients with PAH or inoperable CTEPH by means of CPX. Methods: Fifteen consecutive PAH (mean age, 47 ± 21 years) and 9 consecutive inoperable CTEPH patients (mean age, 49 ± 12 years) with World Health Organization Functional Class II to IV were treated with bosentan. All patients underwent cardiac catheterization, echocardiography, and CPX at baseline. CPX was performed both prior to initiation of bosentan therapy and after 6 months. Results: In PAH patients, peak VO₂ significantly increased from 13.8 ± 6.8 mL/kg/min at baseline to 16.8 ± 7.2 mL/kg/min after 6 months (P < 0.01). Similarly, VE/VCO₂ slope also significantly decreased from 56.8 ± 22.5 to 48.9 ± 17.5 (P < 0.05). However, in CTEPH patients, there were no significant differences in peak VO₂ or VE/VCO₂ slope between the before and after bosentan therapy values (P = 0.35, P = 0.67, respectively). The medication was well tolerated by all patients, and there was no evidence of drug-related liver dysfunction. Conclusions: Bosentan therapy improves exercise capacity in patients with PAH within a relatively short period. However, the effect is not seen in patients with CTEPH.


Short-term drug interaction of bosentan and sildenafil under the long-term use in patients with pulmonary arterial hypertension
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Background: Bosentan and sildenafil are often administered together for the treatment of PAH. Bosentan is a known inducer of CYP3A4 in chronic use and therefore, the plasma concentration of sildenafil is decreased almost by half when co-administered. In the course of daily life, patients tend to take these medicines at the same time in the morning and the evening. We investigated how the plasma concentration of sildenafil changed when bosentan/sildenafil was taken beforehand with the other. Methods: A randomized, open-label crossover study was conducted in PAH patients of WHO functional class III, who chronically received both bosentan and sildenafil. Patients were randomly assigned to either Pattern 1 or 2, both of which consisted of three phases as follows: phase S: patients take sildenafil 3 h prior to bosentan, phase B: patients take bosentan 3 h prior to sildenafil, and phase C: patients take sildenafil and bosentan simultaneously (control). We collected blood samples on the last day of each phase and measured the plasma concentration of sildenafil using liquid chromatography-tandem mass spectrometry. Results: Six patients entered the study. In sildenafil Cmax, phase S was 72.9 ± 40.9 (ng/ml, mean ± S.D) and it was significantly lower than phase C (P = 0.0215). Phase B was 99.6 ± 33.9 with no significant difference with phase C (P = 0.6173). In sildenafil AU0C0-8, phase S was 108.2 ± 126.4 (h*ng/ml, mean ± S.D) and phase B was 240.7 ± 121.8. Neither phase proved significant difference with that of phase C (203.5 ± 81.3, P = 0.3213 and 0.1999, respectively). Conclusion: It is indicated that there is a short-term drug interaction between bosentan and sildenafil which may be relevant to CYP3A4 metabolism.


Ambrisentan and tadalafil synergistically attenuate chronic hypoxia-induced PAH in rats
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