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Successful therapy of bosentan-refractory pulmonary arterial hypertension (PAH) with inhalative iloprost

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a severe complication of systemic sclerosis. High vascular resistance in PAH arises from an imbalance between vasodilatory mediators (prostacyclin, NO) and vasoconstrictive mediators (endothelin, thromboxane A-2). Inhaled iloprost and the dual endothelin receptor antagonist bosentan have recently been shown to be effective in controlled clinical trials. Our case report demonstrates that patients with bosentan-refractory PAH can be successfully treated with iloprost inhalation.

Introduction

Pulmonary arterial hypertension (PAH) is a severe complication of systemic sclerosis. The main pathophysiological factors in PAH are vasoconstriction, *in situ* thrombosis and remodeling of pulmonary vessels. Inhaled iloprost and the dual endothelin receptor antagonist bosentan have been shown to be effective in controlled clinical trials recently (1-5). However, sufficient data to establish a stage- and individual-risk adopted treatment is still lacking as demonstrated by our as report of bosentan-refractory PAH which finally responded to inhalative iloprost.

Case report

A 64-year-old female patient presented in February 2002 in our department with dyspnoea at rest. Physical examination showed dermatosclerosis, Raynaud-phenomenon and edemas of the lower legs. Crackling sounds were heard on both lungs. ANA was 1:2560 with centriole pattern. SCl 70 and CENP were positive. Both chest X-ray and HR-CT-scan of the thorax showed discrete signs of minor interstitial fibrosis. Lung function was impaired by pulmonal restriction (vital capacity: 79.6%) and reduced diffusion capacity (60.1%). FEV1 was 73.9%. Analysis of arterial blood gases disclosed partial respiratory insufficiency (PaO_2: 54 mmHg $PaCO_2$: 31 mmHg, SO_2: 95%). Arterial blood pressure was 120/80 mmHg. Bronchoalveolar lavage showed signs of a neutrophil alveolitis (neutrophil granulocytes 7%, normal< 5%). Catheter examination of the right heart disclosed an elevated pulmonary arterial pressure (mean 68 mmHg) and pulmonary artery resistance (1298 dyn x s x cm^{-5}) and cardiac index of 3.7 l/min/m^2. A coronary angiography excluded coronary heart disease. Diffuse cutaneous systemic sclerosis according to ACR criteria was diagnosed and severe pulmonary hypertension (WHO class III).

PAH was progressive under conventional therapy with calcium antagonists and O2 therapy >15 hours/day. Conventional therapy was continued and bosentan treatment started (4 weeks on 2 x 62.5 mg followed by 2 x 125 mg p.o./day). However, after 28 weeks of treatment with bosentan there was a significant decrease in the 6-minute walking range and a further increase in PAP. Arterial blood gas analysis remained unchanged. Bosentan therapy was stopped and inhalation with the prostacyclin analogue iloprost (mean daily dosage of 30 µg, 6-9 times daily with an ultrasonic atomizer) was started. After 8 weeks of this treatment there was an increase in the 6-minute walking (18 meters) The PAP did not rise any further under iloprost (Fig. 1). During the period of observation pulmonary hemodynamic parameters were assessed four times by means of right heart catheterisation (after patient's agreement). These parameters corresponded well to the results evaluated by echocardiography.

Discussion

Severe pulmonary hypertension has a bad prognosis (median survival time 3 years). Conventional treatment with oxygen or digitalis glycosides has limited effects on PAH. Anticoagulation may slow disease progression. Calcium antagonists may have a positive effect on patients with primary PAH but not on other forms of PAH (6).

High vascular resistance in PAH is based on an imbalance between vasodilatory mediators (prostacyclin, NO) and vasconstrictive mediators (endothelin, thromboxane A-2). Recently, the dual endothelin receptor antagonist bosentan was approved by the European Agency (EMEA) for treatment of PAH patients in WHO class III. In our pa-

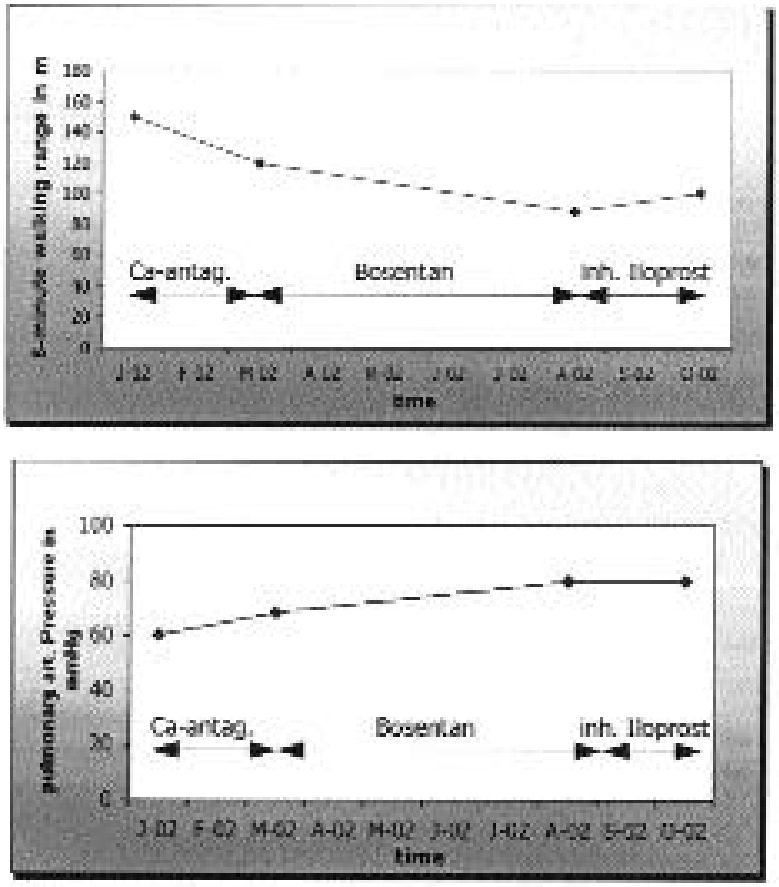

Fig. 1. Improvement of 6-minute walking range and stagnation of PAH with inhalative iloprost in a patient with bosentan-refractory PAH. The 6-minute walking distance has been used as primary endpoint in studies of bosentan in PAH (1, 2).

tient bosentan did not slow progression of the PAH. Prostanoids have demonstrated efficacy in controlled trials and constitute a therapeutic option for treatment of pulmonary hypertension (3-5, 7). Continuous infusion of epoprostenol has been approved by the FDAand in some European countries for the treatment of advanced PAH (7). Iloprost, a stable prostacyclin analogue, appears to be as effective as epoprostenol for the treatment of PAH. Iloprost also has antiproliferative effects in dermal sclerosis (8) As a result of alveolar deposition iloprost improves the ventilation-perfusion ratio whereas systemic vascular resistance is hardly affected (3-5). Administration of iloprost resulted in improvement of the 6-minute walking range and a stagnation of PAH in our patient. The therapeutic effect can be attributed to the administration of iloprost since bosentan was stopped. However, a lasting or late evolving effect of bosentan after it's withdrawal can not totally be excluded although it seems less likely.

Our case report demonstrates that patients with bosentan-refractory PAH can be treated successfully with iloprost inhalation. Future studies should disclose risk factors for primary bosentan-resistance and identify patients in need of other treatment options (iloprost, sildenafil) or combined treatment strategies.

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