Treatment of Severe Pulmonary Hypertension Secondary to Scleroderma: A Three-Drug Approach

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Abstract

We present a case of scleroderma complicated by severe pulmonary hypertension. The use of a three-drug (bosentan, iloprost, and sildenafil) approach contributed to significant improvement of both the clinical conditions and the pulmonary hemodynamics. Combining three pulmonary vasodilators with different mechanisms of action could benefit patients with severe pulmonary hypertension resistant to conventional therapy.

Key words: pulmonary hypertension, scleroderma, iloprost, bosentan, sildenafil

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Introduction

Pulmonary arterial hypertension (PH) is an important cause of mortality and worsening health status in interstitial lung disease. It occurs in up to 27% of patients with scleroderma, and earlier treatment is associated with better treatment outcomes (1). Different vasodilators have been proven to be effective, but only combinations of two drugs have hitherto been tested (2-4). We describe the efficacy and safety of triple-drug vasodilator therapy in a patient with severe PH secondary to scleroderma.

Case Report

A 55-year-old woman with a 25-year history of CREST variant scleroderma was admitted to our cardiology unit for dyspnea at rest. Three years previously she was recognized to be affected by severe secondary PH. At the time of admission she was taking bosentan 125 mg/day, prednisone 5 mg/day, domperidone 10 mg tid, calcium carbonate 1,250 mg + vitamin D3 400 UI/day, omeprazol 20 mg/day, and O2 therapy 3 l/min for at least 15 hours/day.

On admission the patient was unable to walk because of severe dyspnea, asthenia and hypotension (80/50 mm Hg). She had diffuse thickening of the skin of arms, legs, neck and face, and teleangiectasia on the face, lips, and hands. At the time of our observation digital ulcers were absent. Routine laboratory analyses were normal except for a slight reduction in hemoglobin levels (11.8 g/dl), and an increased platelet count (505,000/mm3). The patient had anti-nuclear (1 : 160) and anti-Scl70 antibodies.

Her electrocardiogram showed right p wave and right ventricular hypertrophy (Fig. 1A). Arterial blood gases were: PaO2=35.5 mmHg, PaCO2=50.6 mmHg, pH=7.37, and SaO2=64.9%. Chest X-ray revealed diffuse bilateral interstitial thickening, and a restrictive pattern (FEV1=41% of predicted; FVC=38%) characterized spirometry. Echocardiography revealed severe PH (PAP=124 mmHg), right ventricular dilatation (42 mm), normal left ventricular function (EF=50%) and interventricular delay (37 msec at the tissue doppler imaging measurement). The d-dimer value was 158 ng/ml.

The following treatment was started: bosentan 125 mg/day, iloprost 50 mg diluted in 250 ml of saline solution i.v. (starting at 7.5 ml/h and progressively increasing of 7.5 ml/h the infusion rate at 30 minutes intervals until the rate of 30 ml/h was reached) for 5 days followed by inhaled iloprost 6 times/day, sildenafil 25 mg tid, and warfarin. PAP decreased to 105 mmHg after the first administration of bosentan and iloprost i.v., and to 95 mmHg after the addition of sildenafil.

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Clinical conditions rapidly improved and at day 2 her blood pressure was 100/60 mmHg and heart rate 111 bpm. On day 12, both echocardiographic measures (PAP=75 mmHg; interventricular delay=28 msec) and arterial blood gases (PaO₂=49.2 mmHg; PaCO₂=42.3 mmHg; pH=7.39; SaO₂=82.6%) improved. A cycloergometric test before discharge was interrupted after 30 seconds at 50 W for dyspnea; SaO₂ fell from 94 to 69%, and PAP rose from 70 to 118 mmHg. The patient could not perform a six-minute walking test. On day 13 she was discharged and was prescribed sildenafil, bosentan, and inhaled iloprost. Two further in-hospital cycles of i.v. iloprost were performed 30 and 60 days later.

At the end of the third i.v. iloprost cycle PAP was 75 mmHg, and ECG had dramatically improved (Fig. 1B). The cycloergometric test was interrupted after 1 minute at 50 W for muscle fatigue; SaO₂ fell from 94 to 80%, and PAP rose from 75 to 96 mmHg. The six-minute walking test was interrupted after 138 m because of dyspnea. The patient was discharged and is still continuing triple therapy. At the time of the last follow-up visit (6 months) she had no side effect.

**Discussion**

PH complicating connective tissue diseases variably depends upon parenchimal and pulmonary arterial changes (5). Relieving the hypoxemia is the mainstay of therapy, but lately PH resists this measure. At this stage, selected pulmonary vasodilators could be effective (2). Previous experience shows that the addition of bosentan to inhaled iloprost or oral beraprost has additive effects, at least in primary PH (6). The present case suggests that combining three drugs with different mechanisms of action can be both effective and safe. Indeed, although these drugs also are systemic vasodilators, arterial blood pressure increased during treatment. This favourable result suggests that even severe hypotension coexisting with pulmonary hypertension does not exclude such an aggressive therapeutic approach in critical patients, because relieving the pulmonary vascular barrage could improve left ventricular filling and, then, the arterial pressure. Furthermore, health status and physical performance improved and the ECG showed a dramatic regression of signs of right heart overload/hypertrophy. The only study investigating such a combination therapy showed that none of the patients showed signs or symptoms suggestive of additive toxicity of the medications used, as side effects were usually attributed to a single drug (liver transaminase elevation, headache, hypotension, syncope) (7).

Sildenafil was added shortly after the first administration of iloprost i.v. with bosentan. Thus, we can not completely exclude that a two drug regimen (iloprost and bosentan) may have produced a clinical improvement comparable to that observed with three drugs. However, after the addition of sildenafil PAP decreased appreciably with regard to values observed after the administration of iloprost i.v. and
bosentan. Furthermore, the administration of oral sildenafil plus inhaled iloprost is known to produce a much greater pulmonary vasodilatory response than each single agent (8). This evidence and the dramatic clinical conditions of our patient were the rationale for such an aggressive approach to pulmonary hypertension.

In conclusion, combining three pulmonary vasodilators with different mechanisms of action could benefit patients with severe PH resistant to conventional therapy. While these drugs cannot slow the progression of the main disease, they can relieve symptoms and, possibly, bridge towards heart-lung transplantation.

References


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