Use of Long-Term Combined Therapy With Inhaled Iloprost and Oral Sildenafil in an Adult Patient With Eisenmenger Syndrome

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Abstract: Eisenmenger syndrome is characterized by elevated pulmonary vascular resistance and right-to-left shunting of blood through a systemic to pulmonary circulation connection. Treatment requires either lung transplantation with intracardiac repair or heart–lung transplantation. There are inadequate data regarding treatment alternatives when the patient is not a candidate for surgery. In this article, we report on the case of a 68-year-old woman with Eisenmenger syndrome related to congenital heart disease who was treated with inhaled iloprost and oral sildenafil for 2 years.

Key Words: Eisenmenger syndrome, inhaled iloprost, oral sildenafil

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This report presents the case of a 68-year-old woman with Eisenmenger syndrome related to congenital heart disease who was treated with inhaled iloprost and oral sildenafil. Also described are our short- and long-term experiences with this combined therapy.

CASE REPORT

A 68-year-old woman was admitted to the emergency room with chest pain and dyspnea at rest. She had a history of pulmonary hypertension (PHT) for 10 years and was treated with angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers. The physical examination revealed jugular vein distension, a grade 2/6 pansystolic murmur over the entire precordium, and coarse rales over lung fields. Her electrocardiogram showed right ventricular hypertrophy. She had considerable hypoxemia in her arterial blood gas analysis (PO_2 50.4 mm Hg, O_2 saturation 85%) and she was cyanotic. Chest radiography revealed a large cardiothoracic ratio resulting from right atrial and ventricular enlargement and dilated central pulmonary arteries. Echocardiography revealed dilatation of both the right ventricle and pulmonary arteries and an ostium primum atrial septal defect (Fig. 1). Systolic pulmonary artery pressure (PAP) estimated through tricuspid regurgitant jet velocity by Doppler echocardiography was 140 mm Hg, whereas the arterial blood pressure was measured as 130/80 mm Hg. The diagnosis of Eisenmenger syndrome was confirmed by right heart catheterization. Coronary angiography was normal. Because of the refractoriness to previous therapy with ACE inhibitors and calcium channel blockers, the patient was treated with inhaled iloprost (10 μg/10 min, 8 inhalations per day) using a nebulizer system. Two weeks later, both the systemic arterial pressure and echocardiographic PAP were measured simultaneously during iloprost inhalation. A decrease in PAP was prominent (Table 1). Her 6-minute walk distance was measured as 192 m with iloprost therapy at 2 weeks, whereas her functional capacity was New York Heart Association (NYHA) class IV. Subsequently, 50 mg oral sildenafil was added to the inhaled therapy by increasing doses. At the sixth week with inhaled iloprost and oral sildenafil, the 6-minute walk distance was 318 m and the arterial blood saturation increased to 90%, whereas the serum hematocrit level decreased from 55% to 50%. No significant adverse event occurred with the combination vasodilatory therapy. The patient was discharged from the hospital with a treatment regimen that included inhaled nitric oxide (NO), oral sildenafil, ACE inhibitor, and calcium channel blocker. Anticoagulation therapy was discontinued because of gastrointestinal bleeding. At hospital discharge, her NYHA functional capacity was class II. During 2 years of follow up with this combination therapy, there were no serious cardiovascular complaints or evidence of clinical deterioration. The clinical, laboratory, echocardiographic, and 6-minute walk parameters during follow up are listed in Table 2.

DISCUSSION

Pulmonary hypertension is defined as an elevation in both pulmonary arterial pressure and pulmonary vascular resistance and is a pathologic end point of a variety of conditions. Treatment of pulmonary hypertension consists of

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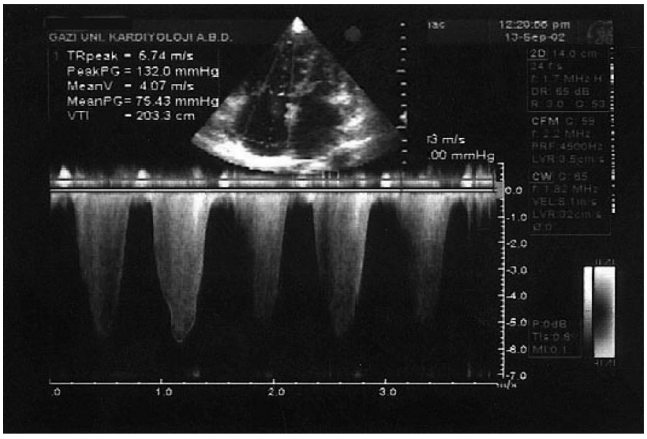

FIGURE 1. Echocardiography of the patient showed right atrial and ventricular dilatation. Systolic pulmonary arterial pressure estimated through tricuspid regurgitant jet velocity is 140 mm Hg.

oxygen, calcium channel blockers, ACE inhibitors, anticoagulant therapy, endothelin antagonists (bosentan), inhaled NO, L-arginine, sildenafil, and prostacyclin. Prostacyclin is a potent pulmonary vasodilatory agent. Continuous intravenous prostacyclin (epoprostenol) improves the functional status, exercise capacity, and pulmonary hemodynamics and reduces mortality in severe primary[1] and secondary[2] pulmonary hypertension. Chronic infusion of prostacyclin has a number of drawbacks such as the development of tolerance, occurrence of systemic side effects, and catheter infections. The use of inhaled iloprost, a stable analog of prostacyclin, resulted in clinical and hemodynamic improvements in patients with severe pulmonary hypertension without the disadvantages of intravenous prostacyclin.[3] A similar effect has been shown with beraprost, an oral prostacyclin analog.[4] Recently, Sastry and colleagues demonstrated that the selective phosphodiesterase inhibitor sildenafil significantly improves exercise tolerance, cardiac index, and quality of life in patients with primary pulmonary hypertension in a randomized, placebo-controlled, double-blind study.[5] Sildenafil also acts synergistically with inhaled iloprost in severe pulmonary hypertension.[6]

Eisenmenger syndrome is characterized by elevated pulmonary vascular resistance and right-to-left shunting of blood through a systemic to pulmonary circulation connection. Once the Eisenmenger syndrome is developed, closure of the systemic to pulmonary connection results in death. Treatment requires either lung transplantation with intracardiac repair or heart–lung transplantation. The patients are commonly diagnosed in childhood/adolescence and survive for 20 to 30 years. Delayed diagnosis until adulthood, reduced systemic blood flow and elevated right atrial pressure are associated with poor prognosis.[7] Our patient was 68-year-old and she had the diagnosis of Eisenmenger syndrome for 10 years.

TABLE 1. The Changes of Systemic and Pulmonary Arterial Pressure During Iloprost Inhalation

	Systemic Arterial Pressure	Systolic Pulmonary Arterial Pressure
At the beginning	155/60 mm Hg	147 mm Hg
3 min later	146/60 mm Hg	132 mm Hg
10 min later	139/59 mm Hg	126 mm Hg
30 min later	145/65 mm Hg	122 mm Hg
60 min later	148/64 mm Hg	130 mm Hg
90 min later	150/60 mm Hg	140 mm Hg

TABLE 2. The Clinical and Testing Parameters Before Combined Vasodilatory Therapy and During Follow Up

Parameter	Before Therapy	At Sixth Week	In Second Year
NYHA class	Class IV	Class II	Class II
Six-minute walk distance	—	318 m	346 m
Oxygen saturation	85%	90%	90%
Hematocrit level	55%	50%	48%
Systolic PAP with echocardiography	147 mm Hg	≈130 mm Hg	≈120 mm Hg

NYHA indicates New York Heart Association; PAP, pulmonary artery pressure.

Despite all developments in the therapy for severe pulmonary hypertension, there are inadequate data about the effects of combined prostacyclin and sildenafil therapy in adult patients with Eisenmenger syndrome. Fernandes and colleagues treated 8 patients with Eisenmenger syndrome as a result of congenital heart diseases (mean age, 37 years) and reported that the use of intravenous prostacyclin resulted in both subjective and objective hemodynamic improvement.[8] However, more prospective trials are needed for patients with Eisenmenger syndrome who do not benefit from conventional therapies and are not candidates for surgery.

Our patient did not benefit from ACE inhibitors and calcium channel blockers, and her NYHA functional capacity was class IV before hospitalization. She was inoperable as a result of her advanced age. She received 2.5 μg iloprost as an initial dose because of the risk of excess systemic hypotension. With an optimal dose of inhaled iloprost (10 μg per inhalation), systolic PAP decreased more than the systemic arterial pressure (Table 1). During combination therapy, no significant adverse event occurred. She was followed for 2 years with repeat clinical examinations, oxygen saturation measurements, echocardiography, and 6-minute walk tests (Table 2). A right heart catheterization was considered but the patient declined. It was interesting that the echocardiographic follow up revealed no progressive decrease in systolic PAP, which remained in the range of 120 to 130 mm Hg at every visit. The patient did not describe any shortness of breath, and there was no decrease in oxygen saturation, NYHA functional capacity, or the 6-minute walk test.

Impaired NO production is strongly related to the development of pulmonary hypertension, and it is a well-known fact that residual pulmonary vasoreactivity strongly predicts success of selective vasodilatory therapy. Moreover, responsiveness to inhaled NO was associated with improved outcome in a study.[9] According to the experiences in pediatric cardiology, chronic ambulatory therapy is not possible as

a result of the need for hospitalization and the insufficiency of dose-adjusting systems. Long-term use of inhaled NO is also associated with the development of methemoglobinemia, and the discontinuation of therapy results in severe rebound pulmonary hypertension. In this aspect, inhaled NO is not preferred in our case. The elevation of plasma L-arginine levels stimulates NO synthesis, but the underlying mechanisms are not clear. It is proposed that L-arginine acts as a NO donor. Lacassie and colleagues reported the case of a pregnant woman with Eisenmenger syndrome who was treated with oral L-arginine and sildenafil during pregnancy and the postpartum period. This combination was found to be associated with clinical and hemodynamic improvement and fetal well-being with minimal side effects.[10] In another study, which includes 9 patients diagnosed with Eisenmenger syndrome, long-term use (median follow-up time was 9.5 months) of oral bosentan, an endothelin-1 antagonist, resulted in clinical improvement.[11] In this case, L-arginine and bosentan are not available in our country. Moreover, significant clinical and hemodynamic improvement was recorded with the combined therapy, including inhaled iloprost and oral sildenafil.

CONCLUSION

According to our long-term experience in this case of Eisenmenger syndrome, combined pulmonary vasodilator therapy with inhaled iloprost and oral sildenafil is both safe and effective. To our knowledge, this is the first report on the long-term use of combined inhaled iloprost and oral sildenafil therapies in an adult patient with Eisenmenger syndrome related to congenital heart disease.

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