CASE REPORTS

Iloprost for Chronic Thromboembolic Pulmonary Hypertension

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Chronic thromboembolic pulmonary hypertension (CTPH) is an uncommon complication of pulmonary embolism. The treatment of choice is thromboendarterectomy, a safe and effective surgical procedure in expert hands. However, a fair number of patients are not considered candidates for thromboendarterectomy or do not accept the risk involved. Such patients may respond well to prostacyclin or its derivatives. In recent years new vasodilator drugs administered by a variety of routes have appeared on the market. These drugs have been studied mainly for their effects on primary pulmonary hypertension or hypertension associated with connective-tissue diseases. Few trials have assessed their efficacy in patients with CTPH, however.

We report 2 cases of CTPH in which thromboendarterectomy was rejected. Neither of the patients responded to the conventional treatment of anticoagulants, diuretics, calcium antagonists, and angiotensin-converting enzyme inhibitors, but they did respond very well clinically, hemodynamically, and functionally to an inhaled prostacyclin analog, iloprost. We discuss the effects of iloprost in patients with CTPH, its mechanism of action, and its use as a potential pharmacological alternative to thromboendarterectomy. We also discuss new pulmonary vasodilators in general.

Key words: *Iloprost. Chronic thromboembolic pulmonary hypertension. Thromboendarterectomy.*

Iloprost en la hipertensión pulmonar tromboembólica crónica

La hipertensión pulmonar tromboembólica crónica (HTPTC) es una complicación infrecuente de la embolia pulmonar. El tratamiento de elección es la tromboendarterectomía, proceder quirúrgico seguro y eficaz en manos expertas. Un número no despreciable de pacientes, sin embargo, no se consideran candidatos a tromboendarterectomía o no aceptan los riesgos de la intervención. Estos pacientes pueden presentar una evolución favorable con prostaciclina o sus derivados. En los últimos años han aparecido nuevos fármacos vasodilatadores que actúan por diversas vías y cuyos efectos se han estudiado fundamentalmente en la hipertensión pulmonar arterial primaria o asociada a conectivopatías; sin embargo, son escasas las referencias en cuanto a su eficacia en la HTPTC.

Se presentan 2 casos de HTPTC en los que se desestimó la tromboendarterectomía y que no respondieron al tratamiento convencional con anticoagulantes, diuréticos, antagonistas del calcio e inhibidores de la enzima de conversión de la angiotensina; en cambio, presentaron una excelente respuesta clínica, hemodinámica y funcional al análogo de la prostaciclina iloprost por vía inhalatoria. Se comentan los efectos de los nuevos fármacos vasodilatadores pulmonares en general y del iloprost en particular en la HTPTC, su mecanismo de acción y su papel como posible alternativa farmacológica a la tromboendarterectomía.

Palabras clave: *Iloprost. Hipertensión pulmonar tromboembólica crónica. Tromboendarterectomía.*

Introduction

Chronic thromboembolic pulmonary hypertension (CTPH) caused by unresolved pulmonary embolism is a potentially treatable cause of pulmonary hypertension[1] and accounts for between 0.1% and 0.5% of patients who survive an acute episode of pulmonary embolism. Thromboendarterectomy is the treatment of choice whenever the thrombi are accessible and there is no serious concomitant lung disease.[2] Otherwise, various medical treatments may be considered, such as intravenous prostacyclin (epoprostenol) and its analogs through inhaled, subcutaneous, or oral endothelin receptor antagonists or nitric oxide releasing and potentiating drugs. We report 2 cases of CTPH with good clinical and hemodynamic responses to treatment with a stable analog of inhaled prostacyclin (iloprost).

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Case Description

Case 1

A 76-year-old woman with a history of primary antiphospholipid syndrome came to our clinic in May of 2000 complaining of a 3-year history of progressive dyspnea and with evidence of edema in both lower legs and orthopnea. At

that time she was in New York Heart Association class III-IV. Lung function tests indicated hypercapnic respiratory failure with PaO_2 of 44 mm Hg, $PaCO_2$ of 50 mm Hg, mild restrictive impairment (total lung capacity, 65%), and major reduction of carbon monoxide transfer—with carbon monoxide diffusing capacity (DLCO) at 44% and the ratio of DLCO to alveolar volume (KCO) at 53%. Doppler ultrasound revealed right atrial dilation with ventricular function intact and functional tricuspid regurgitation with pulmonary artery systolic pressure (PAS) estimated at 62 mm Hg. A lung perfusion scan showed absence of radioisotope uptake in both lower lobes. A spiral computed tomography angiogram of the lung and a magnetic resonance angiogram of the chest revealed complete obstruction of both lower lobe arteries confirmed by angiography. Venography of the lower extremities showed residual thrombosis in the left femoral vein. Right heart catheterization showed a PAS of 67 mm Hg, a mean pulmonary artery pressure of 38 mm Hg, right atrial pressure of 10 mm Hg, and a mean pulmonary capillary pressure of 13 mm Hg with a cardiac index of 3.96 L/min/m^2, and some pulmonary vascular resistance (4.5 Wood units).

The patient refused surgical treatment, and therefore anticoagulants, diuretics, irbesartan, amlodipine, nitrates, and home oxygen therapy were started. A filter was inserted into the inferior vena cava. The patient remained in class III-IV, without showing significant changes in the lung function tests, radiographs, and echocardiograms performed 1, 3, and 9 months after treatment began. The patient required hospitalization for heart failure with pulmonary and systemic congestion. Given that the patient did not respond to treatment, in January of 2002, it was decided to initiate treatment with iloprost at 12 μg/d, administered in 6 daily sessions with a nebulizer (Pari Turbo Boy Nebulizer, GmbH, Starnberg, Germany). Echocardiography performed 3 months after the beginning of the treatment showed persistence of right atrial dilation, slight tricuspid regurgitation, and PAS estimated at 22 mm Hg. Respiratory insufficiency likewise persisted, with PaO_2 at 40 mm Hg and $PaCO_2$ at 48 mm Hg. At month 9 after treatment started, an echocardiogram showed that the right atrial dilation had disappeared without affecting tricuspidal or pulmonary valves, and PAS was therefore not calculated. PaO_2 increased to 57.7 mm Hg, and $PaCO_2$ decreased to 42.5 mm Hg. A magnetic resonance angiogram demonstrated an absence of reperfusion in both lower lobe arteries, which were completely occluded due to persistence of impaired filling. Plethysmography and carbon monoxide transfer continued to show a moderate restrictive defect (total lung capacity, 62%) with major reduction of DLCO (47%) and KCO (59%). Currently, the patient is in functional class II and has not needed further hospitalization.

Case 2

The patient was a 71-year-old man with a history of diabetes mellitus, smoking dependence, and stable angina. In 1998 he had been diagnosed with CTPH of the central and peripheral arterial branches and was in functional class III. On diagnosis a lung scan revealed severely altered perfusion and bilateral lung impairment, with more intense involvement in the right lung. The angio computed tomography of the chest showed a 2-cm thrombus in the right branch of the pulmonary artery and in several right and left segmental branches. The pulmonary angiogram showed a thrombus attached to the bifurcation of the right main bronchus as well as complete occlusion of the right segmental branches 6, 7, 8, and 9 and left 6 and 8. The venograms were negative, and the echocardiogram manifested dilation of the right chambers with signs of overload. PAS was estimated at 98 mm Hg. Right heart catheterization showed a PAS of 97 mm Hg, a mean pulmonary artery pressure of 52 mm Hg, a mean pulmonary capillary pressure of 17 mm Hg with a cardiac index of 2.44 L/min/m^2, and pulmonary vascular resistance of 12.6 Wood units. Spirometric values and lung volumes (plethysmography) were normal, and there was a slight reduction of carbon monoxide transfer, with DLCO of 63% and KCO of 67%. PaO_2 was 54 mm Hg and $PaCO_2$, 42 mm Hg. The patient experienced no significant changes in clinical or hemodynamic parameters upon treatment with calcium channel blockers, diuretics, beta-blockers, nitrites, anticoagulation, or oxygen therapy. Subsequently, the patient was hospitalized twice due to exacerbated heart failure. In November of 2001, treatment of iloprost was started initially at a dose of 9 μg/d and later at 12 μg/d (6 nebulizations per day). A marked reduction in dilation of the right chambers was observed in the echocardiograms performed at 3 and 6 months from the start of this treatment, with PAS estimated at 68 and 60 mm Hg, respectively. The angio computed tomography scan showed no significant differences in the size and distribution of the thrombi. The patient was classified as function class II and has not since presented with any exacerbation leading to hospitalization. No significant changes in carbon monoxide transfer have developed (DLCO and KCO at 60% and 70% respectively, in the tests performed). PaO_2 has been sustained at around 65 mm Hg.

Discussion

Thromboendarterectomy is the treatment of choice for CTPH in the absence of significant pulmonary comorbidity, provided that there is surgical accessibility to the thrombi, understood as being in the main, lobar, and segmental pulmonary arteries. In skilled hands, this procedure has a perioperative mortality rate of 7.6%.[3] Thromboendarterectomy yields favorable results with major reduction, even normalization, of pulmonary artery pressure, noticeable improvement in gas exchange and exercise capacity, as well as in the clinical situation with New York Heart Association functional class descending from III or IV to I or II.[1,4,5] For those patients ineligible for surgical treatment, either because of thromboembolic occlusion of the peripheral branches or because of severe comorbidity, for those who reject surgical treatment, or for those with persistent severe pulmonary hypertension in spite of the thromboendarterectomy (accounting for 10% of cases[1]), a therapeutic trial with intravenous prostacyclin or with new drugs for pulmonary hypertension listed below (Table) is recommended.[3] Very little about medical treatment for CTPH, however, is reported in the literature. In a multi-center, randomized, controlled trial on the efficacy of inhaled iloprost for diverse types of pulmonary hypertension, 57 patients with CTPH out of a total population of 203 were enrolled.[6] This study demonstrated a significant improvement in degree of dyspnea, quality of life, hemodynamic parameters, and

TABLE
New Drugs for the Treatment of Pulmonary Hypertension

Prostacyclin analogs with different administration routes
Subcutaneous: treprostinol
Inhaled: iloprost
Oral: beraprost
Endothelin 1 antagonists: bosentan
Nitric oxide releasing and potentiating drugs
L-arginine
Sildenafil

gas exchange in those patients with pulmonary hypertension in general but did not refer specifically to outcomes in the patients with CTPH. In another similar multi-center trial carried out with endothelin receptor antagonist bosentan, patients with CTPH were not enrolled.[7] Uncontrolled or nonrandomized studies on treatment for CTPH with intravenous epoprostenol,[8] oral beraprost,[9] or the combination of iloprost and sildenafil[10] have reported that clinical, hemodynamic, and functional improvement in CTPH is similar to or slightly less than that obtained in primary pulmonary hypertension. Isolated cases of major hemodynamic improvement have also been reported with inhaled prostacyclin,[11] as in the case of our 2 patients.

Iloprost is a stable analog of prostacyclin that can be inhaled or used intravenously. Its vasodilator action is more long-lasting than that of epoprostenol. It has a selective vasodilator effect on pulmonary vasculature thus reducing the adverse systemic effects peculiar to epoprostenol.[12] Its action is not limited to the relaxation of pulmonary vascular smooth muscle; it also improves the pulmonary clearance of endothelin 1 and inhibits platelet aggregation, vascular remodeling, and vascular cell proliferation and migration.[12-14]

Pulmonary hypertension in CTPH is caused by 2 mechanisms: *a)* in thrombosed arteries, the blood flow is obstructed mechanically by previous emboli or formation of local thrombosis, and *b)* in nonthrombosed arteries, an increase in blood flow occurs due to obstruction in other regions. Subsequent friction gives rise to changes in the vascular walls similar to those in primary pulmonary hypertension.[15] The multifactorial action of iloprost, essentially on the nonthrombosed area, may explain the improvement experienced by our patients, as the nuclear magnetic angio resonance and computed tomography angio scans showed no vascular reperfusion, and the thrombotic lesions persisted.

In conclusion, we believe that pulmonary vasodilators can be used for those patients with CTPH who are ineligible for or refuse thromboendarterectomy. Inhaled iloprost is efficacious, safe, and well-tolerated.[12] The availability of drugs with different mechanisms of action allows for additional combinations: a prostanoid and/or an endothelin antagonist and/or metabolically-activated nitric oxides.

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