Inhaled iloprost as a long-term additional therapy to oral sildenafil in severe idiopathic pulmonary arterial hypertension

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ÖZET

Ağır idiyopatik pulmoner arteryel hipertansiyonda oral sildenafil tedavisine eklenen inhale iloprost tedavisinin uzun dönem sonuçları

İdiyopatik pulmoner arteryel hipertansiyon (İPAH) oldukça nadir görülen ve tedavi edilmediğinde hızlı bir seyirle sağ kalp yetmezliği ve ölüme kadar giden morbidite ve mortalitesi yüksek bir hastalıktır. Son yıllarda tedavi alanındaki gelişmelerle hastalığın seyri değiştirilebilmektedir. Ancak alternatif tedavi protokollerinin uzun dönem sonuçları ve hastaların bu tedavilere olan yanıtları ile ilgili yeterli veri bulunmamaktadır. Daha önce geçici olarak konvansiyonel tedavi ve oral kalsiyum blokerine yanıt veren İPAH olgusunda sildenafil monoterapisinin uzun dönem klinik ve fizyolojik etkilerini, inhale sildenafil tedavisi eklenmesi sonrasındaki değişikliklerle karşılaştırdık. İPAH olgularında vazodilatör tedavilere kısa süreli ve geçici yanıtlar verilebilmektedir. Ancak uzun dönem sonuçları ile ilgili yeterli veri olmayıp, mutlaka takip edilmelidirler ve bu hastalarda kombinasyon tedavileri daha etkili olabilmektedir.

Anahtar Kelimeler: *İdiyopatik pulmoner arteryel hipertansiyon, sildenafil, inhale iloprost, kombinasyon tedavisi, uzun dönem tedavi.*

SUMMARY

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Idiopathic pulmonary arterial hypertension (IPAH) is an uncommon and devastating disease which, if untreated, progresses rapidly and leads to right heart failure and death. The course of the disease has been altered by advances in medical therapies. However, the effects of long-term alternative therapies and responses to each treatment protocols are not definite. We want to define an IPAH case, which had long-term temporary responses to the conventional therapy plus calcium channel blockers treatment and moreover compared the long-term clinical and physiologic effects of oral sildenafil mono therapy and additional inhaled iloprost therapy. Patients with IPAH may have response to a short-term vasodilatation therapy but they have to follow for the long-term results and may be of benefit from combination treatments.

Key Words: *Idiopathic pulmonary arterial hypertension, sildenafil, inhaled iloprost, combination treatment, long-term treatment.*

Idiopathic pulmonary arterial hypertension (IPAH) is an uncommon disease (with an annual incidence of 1 to 2 per million) which causes severe limitations on exercise capacity, with an increase in pulmonary vascular resistance and leading to right ventricular failure (1,2). Although IPAH is a progressive disease with high mortality, the recent outcomes are heterogeneous, with some patients dying within months of diagnosis and others living for decades. The course of the disease has also been altered by advances in medical therapies (3).

Conventional treatment, including warfarin, diuretics, digoxin respectively; improved survival in retrospective and prospective studies, used to reduce the fluid overload state for hemodynamic optimization, used in right ventricular dysfunction but the long term benefit is uncertain (4-6). To reduce potential component of hypoxic vasoconstriction home oxygen therapy is recommended. Furthermore, chronic administration of oral calcium channel blockers (CCB) is beneficial in less than 10% of IPAH patients and real responders have high rates of tolerance in long-term follow up (5,7).

Phosphodiesterases are a super family of enzymes that inactivate cyclic adenosine monophosphate and cyclic guanosine monophosphate, which are the second messengers of prostacyclin and nitric oxide. Phosphodiesterases also have different tissue distributions and substrate affinities and phosphodiesterase-5 is abundantly expressed in lung tissue (8,9). Sildenafil is a selective vasodilator that enhances and prolongs the action of cyclic guanosine monophosphate (a primary mediator of vasodilatation) with selective inhibition of the cyclic guanosine monophosphate specific phosphodiesterase-5 isoenzyme (10).

Inhalation of iloprost, a stable prostacyclin analogue, causes pulmonary vasodilatation matched to ventilation but avoids vasodilatation in non ventilated lung areas. Long-term use of inhaled iloprost has been shown to improve exercise capacity and hemodynamic variables in patients with IPAH (11).

We reported a case of IPAH who respectively benefited from long-term conventional therapy plus oral sildenafil monotherapy and additional inhaled iloprost therapy for 18 months.

CASE REPORT

A fourty-one years old male patient was admitted to our hospital with the diagnosis of IPAH. He had previous three years for ruling out collagen vascular disease, pulmonary disease and/or pulmonary thromboembolic disease, left heart abnormality and other systemic disorders by; blood tests, pulmonary function tests, perfusion lung scan, pulmonary high resolution CT, Doppler echocardiography and right-left heart catheterization respectively as defined by World Health Organization World Symposium on pulmonary hypertension. Afterwards he had received long-term conventional therapy plus oral calcium channel antagonist. At the time of diagnosis, echocardiographic systolic pulmonary arterial pressure (sPAP) was 95 mmHg, after 1 year treatment sPAP decreased to 65 mmHg, which is 31% and exercise dyspnea was also improved,

however in the second and third year due to clinical and hemodynamic deterioration he received too much oral calcium channel antagonist because of the initial response but just side effects were reported instead of improvement. At the admission to our clinics, right heart failure signs were manifest; dyspnea and fatigue were also present in any physical activity, New York Heart Association (NYHA) functional class was IV. Echocardiographic sPAP was 125 mmHg and the other baseline data is shown in Table 1. Systemic mean arterial blood pressure was measured and a six minute walking test (6MWT) with modified Borg dyspnea scale was performed before and after sildenafil monotherapy. Also we tried to perform symptom limited cardiopulmonary exercise testing but the patient could not complete the test. After patient gave written informed consent, a 100 mg/day oral dose of sildenafil was given additionally to the warfarin and diuretic treatment. Medication was well tolerated without any side effect and the patient continued to receive same dose. After two weeks he reported an improvement in dyspnea on exertion and at the 3rd month 20% decrease was reported in sPAP without significant changes in systemic blood pressure. Besides, NYHA functional class improved from IV to II with an arterial oxygen increase, six-minute walk distance (6MWD) increased from 302 meters to 580 meters and Borg dyspnea index reduced from 8 to 1 after 6MWT. At the 6th month controls, although the sPAP was stable, exercise dyspnea deteriorated and 6MWD decreased from 580 m to 440 m with leg discomfort and fatigue. Additionally NYHA functional class increased from II to III (Table 1). Because of this condition and according to guidelines patient received additional inhaled iloprost 100 µg/day with 6 inhalations per day. The conventional treatment and oral sildenafil regimen were unchanged. Also every measurement were repeated as same as sildenafil monotherapy protocol (Table 1). Flushing was the only side effect during combination treatment. After six months of combination therapy NYHA functional class reduced from III to I and stable at the 12th month also sPAP is reduced 36% from the baseline sPAP and 48% at the 6th and 12th month, respectively. 6MWD increased from 302 m to 600 m. Symptom-limited cardiopulmonary exercise testing was performed successfully at the 6th and 12th month, VO_2 peak were 1.05 L/min and 1.20 L/min respectively, the increase was 15% (Table 1). Patient has still receiving combination therapy and ongoing his usual life.

DISCUSSION

We want to define an IPAH case, which had long-term temporary response to the conventional therapy plus CCB treatment and compared the long-term clinical and physiologic effects of oral sildenafil monotherapy and additional inhaled iloprost therapy.

Table 1. Patient data during treatment protocols.

	NYHA/ WHO Class	sPAP (mmHg)	6MWD (m)	Systemic mean arterial blood pressure	SaO_2 (%)	Borg dyspnea	Symptom limited cardiopulmonary exercise testing
Baseline (admission)	IV	125	302	70	86	8	Not completed
Sildenafil 100 mg/d 3rd month	II	100	580	85	91	1	
Sildenafil 100 mg/d 6th month	III	100	440	80	88	6	
Sildenafil 100 mg/d + Inh. Iloprost 100 µg/d 6th month	I	80	580	75	92	0.5	VO_2 peak= 1.05 L/min Peak work= 140 watt SaO_2 peak= 86%
Sildenafil 100 mg/d + Inh. Iloprost 100 µg/d 12th month	I	65	600	75	92	0	VO_2 peak= 1.20 L/min Peak work= 160 watt SaO_2 peak= 86%

Chronic administration of CCB is beneficial who demonstrate acute vasoreactivity. Patient with true vasoreactive response, demonstrate a reduction in the mean PAP more than 10 mmHg to reach lower than 40 mmHg in the absence of decrease in systemic arterial pressure. Our patient was responder at the first year but in time course received CCB for another two years and deteriorated. In the IPAH treatment, common opinion with the patients who initially respond to CCB therapy but subsequently develop disease progression should be treated with alternative agents and calcium channel blocker should be discontinued (12). Because of this agreement we decided to change the treatment protocol.

Histological microthrombosis of the small vessels is often seen with IPAH. Likely benefit from anticoagulation in IPAH is related to the effect on the in-situ thrombosis and possibly occurs by counteracting the effects of thrombin activation and associated with prolonged survival in IPAH (4). Diuretics prevent sodium and water retention and have great impact on physical capacity and quality of life in many patients. Also remain the gold standard for relieving the symptoms of fluid overload in right heart failure (6). In 1993 Ogata et al. reported the five year survival was significantly higher in the group treated with anticoagulants and vasodilators (13). There was no contraindication for the conventional therapy so we prefer to continue warfarin and diuretics in our patient.

Sildenafil is a recently developed vasodilator and a specific inhibitor of phosphodiesterase-5. So far there are only small numbers of reports about long-term treatment with sildenafil monotherapy. In our case, medication doses were well tolerated without any side effect. Also the 6MWD, Borg dyspnea index, echocardiographic sPAP improved at the second week of treatment and maintained at the 3rd month but symptoms and functional clinical status changed at the 6th month of mono therapy. Bharani and associates treated 10 patient with sildenafil after two weeks the 6MWT and dyspnea index significantly improved, with a decrease in echocardiographic sPAP levels (14). Ghofrani and colleagues found that the phosphodiesterase-5-selective inhibitor sildenafil caused strong dose dependent pulmonary vasodilatation, even in the absence of exogenous nitric oxide administration in patients with PAH as early as in the second week and remained at the 3rd month (15). In these studies acute effects were seen in the second week as we reported and the long term treatment time was three months but we treated our patient with sildenafil monotherapy for six months and the results at the 3rd and 6th months were not similar. We did not prefer to increase the treatment doses because sildenafil is a systemic drug so side effects can be occur dose dependently. Also our patient had a transient response to another vasodilator for long-term treatment; we preferred to add another vasodilator to the sildenafil treatment.

Addition of inhaled iloprost to the long-term therapy with sildenafil monotherapy improved Borg dyspnea index, 6MWD, NYHA functional class, sPAP without significant decrease in systemic mean arterial blood pressure and oxygen saturation at the reported doses. This improvement was similar with the 3rd month sildenafil monotherapy results and also the results were maintained at the 6th and the 12th month with combination therapy. Wilkens and Ghofrani reported additional improvement with combination therapy but the results were just for three months time (7,16).

There are a range of non-invasive and invasive parameters used to monitor disease progression in IPAH. Worsening the exercise dyspnea is the most obvious and probably most sensitive marker of the underlying disease progression associated with IPAH, NYHA functional class has proven to be the most practical parameter which shows the clinical status of affected patients, 6MWT can also be combined with that from commonly used Borg dyspnea index a self measure of perceived breathlessness (17). The echocardiogram is an important non-invasive tool both in terms of diagnosis and prognosis in IPAH (18). That's why we preferred to diagnose and monitor our patient with Doppler echocardiography, NYHA functional class and six-minute walk test with Borg dyspnea index. These non invasive diagnostic and screening methods

have been used to demonstrate the responses to each treatment successfully and objectively in our case.

Idiopathic pulmonary arterial hypertension is characterized by extensive remodeling of the pulmonary vasculature. During the last decade some advances in the treatment have been achieved. However, the appropriate therapies are limited because of poor efficacy or high costs. Potentially new treatment options such as oral sildenafil offer patients effective therapies. On the other hand response to the treatment may be transient because of this remodeling and need appropriate follow up time to decide the treatment protocols require additional therapies. In conclusion, combination treatments seems to allow to reverse remodeling and entire disease process better than monotherapy but still there is not enough long-term outcomes with combination therapies.

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