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Sustained long term benefit of sildenafil in primary pulmonary hypertension

Sildenafilin primer pulmoner hipertansiyonda kalıcı uzun dönem yararlı etkisi

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Primary pulmonary hypertension is a rare disease with an ominous prognosis for which new therapeutic options are being developed. Recently, there have been case reports indicating that sildenafil may be of benefit in short to midterm follow up. However, long term clinical data of sildenafil in primary pulmonary hypertension patients is lacking. We report a patient with primary pulmonary hypertension treated with sildenafil 200 mg/day for 50 months with a sustained clinical response.

Key words: ***sildenafil, pulmonary hypertension***

Primer pulmoner hipertansiyon, nadir, kötü seyirli tedavisi için yeni ilaçların geliştirilmeye çalışıldığı bir hastalıktır. Son zamanlarda tedavide kısa ve orta dönemde sildenafilin olumlu etkilerini bildiren yayınlar çıkmaya başlamıştır. Ancak primer pulmoner hipertansiyonda sildenafilin uzun dönem etkinliğine dair veri bulunmamaktadır. Primer pulmoner hipertansiyon tanısıyla 200 mg/gün sildenafil ile 50 ay boyunca başarılı bir şekilde tedavi ettiğimiz hastamızı takdim ediyoruz.

Anahtar sözcükler: ***sildenafil, pulmoner hipertansiyon***

Primary pulmonary hypertension (PPH) is a rare disease with poor prognosis. Despite improvements in treatment, mortality remains high and research for newer therapies is on going.

Sildenafil (Viagra, Pfizer), a phosphodiesterase type 5 inhibitor (PDE5) that is approved for erectile dysfunction, has recently been reported in case reports and small series to be beneficial in patients with PPH (1-3). However, long term efficacy data and controlled studies are lacking. We report a patient with PPH who has maintained sustained improvement with sildenafil for 50 months.

Case report

In January 2001, a 31 year old male patient was referred to our clinic for evaluation of progressively worsening effort intolerance for 2 years and recent presyncope while driving. He complained of severe effort intolerance and cyanosis on exertion. The patient did not use illicit drugs or anorexic medications to treat obesity known to cause pulmonary hypertension. His physical examination revealed slight jugular venous distention, a markedly accentuated P2, a right ventricular S4, a grade 2/6 systolic murmur best heard over the tricuspid area, tender hepatomegaly that was palpable 3-4 centimeters below the costal arch, and clubbing. Chest X-ray (CXR) demonstrated marked dilation of the pulmonary conus. An echo-doppler study revealed a dilated right ventricle (RV), moderate to severe tricuspid regurgitation with an estimated systolic pulmonary artery pressure of 90 mmHg, normal left ventricular size and function, and no

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Table 1. Initial, intermediate and long term follow-up echocardiographic data of the patient

Date	*Estimated PASP (mmHg)*	*Tricuspid regurgitation*	*RV dimension (cm)*
January 2001(Initial hospitalisation)	90	Moderate to severe	3.2
January 2002 (10th month of therapy)	65	Mild to moderate	3.0
May 2003 (26th month of therapy)	60	Mild	2.8

PASP: Pulmonary artery systolic pressure **RV:** Right ventricle

Table 2. Hemodynamic data: Initial and after 4 months of sildenafil treatment

	PCWP (mmHg)	*PAP (mmHg)*	*RVP (mmHg)*	*RAP (mmHg)*	*CO (L/min)*	*PVR (dynes/sec/cm $^{-5}$)*
Initial	10	72/38/50	72/0/3	3	4.3	744
Fourth month	9	63/33/45	63/0/2	2	4.6	626

PCWP: Pulmonary capillary wedge pressure, **PAP:** Pulmonary artery pressure, **RVP:** Right ventricular pressure, **RAP:** Right atrium pressure, **CO:** Cardiac output, **PVR:** Pulmonary vascular resistance.

left to right shunt. A thorough diagnostic work-up was performed to exclude secondary etiologies of pulmonary hypertension, including arterial blood gas (ABG) analysis, spirometric tests, V/Q scan, computed tomography of the thorax, pulmonary artery computed tomography angiography, HIV test, and immunological profile. Right heart catheterisation coupled with oximetric analysis and an adenosine reversibility test demonstrated no shunt, a pulmonary capillary wedge pressure of 10 mmHg, a mean pulmonary artery pressure of 50 mmHg, and no reversibility with adenosine. Based on this evaluation he was diagnosed with PPH and was felt to be New York Heart Association (NYHA) Class III. Since epoprostenol is not marketed in Turkey and recent case reports suggested beneficial clinical outcomes (1) with sildenafil, it was elected to initiate therapy with this drug. In March 2001, therapy was begun with warfarin, digoxin (0.125 mg/daily), low dose nifedipine (30 mg qd), and sildenafil up-titrated to an empirical dosage of 200 mg/daily, in addition to furosemide 40 mg/daily and 25 mg of spironalactone daily. The patient's clinical status improved to Class II over the ensuing several months.

In July 2001, the patient was sent to the University of California San Diego for further evaluation. The distance walked in six minutes was 600 meters. Right heart catheterisation demonstrated a mean pulmonary artery pressure of 45 mmHg with a further reduction to 38 mmHg in response to inhaled nitric oxide.

The patient remains stable with the following regimen : Sildenafil 50 mg four times a day, spiranolactone 25 mg daily, warfarin adjusted to maintain an INR 2-3, nifedipine 30 mg daily. Arterial blood gases have also improved during follow-up: His initial pO_2 was in the range of 55-62 mmHg, and O_2 saturation was in the range of 89-92 % before treatment, at the end of 1 year therapy pO_2 increased to the range of 65-70 mmHg and saturations increased to 94-97 % range and remained stable thereafter. Echo-doppler studies markedly improved during the follow up (Table1). A slight improvement was noted in the right heart catheterisation data after 4 months of treatment (Table 2). Repeat 6-minute walk was 590 meters in December 2003. He has not reported any side effects that are attributable to his medications.

Discussion

In recent years, reports indicating beneficial effect of sildenafil in treating PPH has increased significantly, demonstrating a clinical or hemodynamic benefit mainly due to relatively selective pulmonary vasodilatory properties. Moreover, in a recent study sildenafil proved to be valuable to further lower pulmonary artery pressure in PPH patients when added to inhaled iloprost (3). Another recent study demonstrated sildenafil to be beneficial, as an adjunct therapy, for patients with pulmonary arterial hypertension who deteriorated while on inhaled iloprost therapy (4). In that study follow-up was up to 9-12 months and 9 of 14 patients received 25 mg sildenafil 3 times daily while 5 of 14 patients used 50 mg three times daily (4).

Sildenafil is proposed to have relatively selective pulmonary vasodilator properties via the inhibition of phosphodiseterase type 5, an enzyme that is abundant in lung tissue (5). The inhibition of phosphodiesterase type 5 causes increased levels of cyclic guanosine monophosphate (cGMP), which modulates pulmonary vasodilation.

One might argue that the beneficial effect might be due to nifedipine. However, a major benefit of nifedipine would be unlikely since the patient was minimally responsive to acute vasodilator testing. Moreover the dosages of calcium antagonists that would be effective in PPH patients are higher than those generally used in treating hypertension (6).

There have been several prior publications demonstrating sildenafil to be beneficial in PPH (1-4). However, they generally report short to intermediate term follow-up. To the best of our knowledge, the present case report is the only one indicating sustained long term (50 months by end of May 2005) benefit of sildenafil in treating PPH with excellent tolerability. Randomized large scale studies to further evaluate the efficacy and safety of sildenafil in

treating PPH are needed to determine whether this response is consistent and to identify those characteristics that may be helpful in selecting patients who are most likely to benefit from sildenafil therapy.

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