Sustained response to low-dose nifedipine in a patient with idiopathic pulmonary arterial hypertension

Sir,

Calcium channel blockers (CCBs) are an effective treatment for patients with idiopathic pulmonary arterial hypertension (IPAH) who have positive acute vasoreactivity (AVR) testing. However, less than

half of responders experience long-term clinical and hemodynamic benefit. Moderate-to-high dose CCBs are usually needed to reach and retain response. Here, we present a case of IPAH treated with low-dose CCBs for 6 years with durable and remarkable clinical and hemodynamic improvement.

A 30-year-old male patient, ex-heroin and cocaine addict, presented to our hospital with presyncope at exertion. He reported also dyspnea of 2-week duration, preceded by lower limb edema, and weight gain of 10 kg during the past 6 months. The patient had been treated with Subutex, an opioid antidote for heroin addiction, for 5 years. He was an active smoker and drunken eight units of beer/day.

On presentation, he denied chest pain, syncope, palpitations, or other cardiac signs. His physical examination revealed normal cardiac and lung auscultation. He had distended jugular veins with bilateral lower limb edema. There were no signs of decompensated liver cirrhosis.

The electrocardiogram showed first-degree atrioventricular (AV) block. Transthoracic echocardiography revealed signs of pulmonary hypertension with dilated right heart cavities.

Computed tomography angiography of the chest as well as ventilation-perfusion scintigraphy excluded pulmonary embolism. Pulmonary function tests were normal. He walked a distance of 520 m on the 6 min walking test, without desaturation at the end of the test.

Human immunodeficiency virus serology, thyroid function tests, and autoimmune studies were negatives.

Right heart catheterization (RHC) revealed an elevated mean pulmonary artery pressure (mPAP) of 31 mmHg, pulmonary vascular resistance (PVR) of 242 dynes s/cm^5, and cardiac index (CI) at 2.63 L/min/m^2. Following inhaled nitric oxide (NO) test, he had significantly decreased his PVR to 74 dynes s/cm^5, mPAP dropped to 26 mmHg, and CI increased to 3.39 L/min/m^2.

Although considered as nonresponsive but giving to the marked improvement of PVR following the NO test, we elected to challenge him with CCBs' treatment trial. The patient was deemed to have IPAH, and anticoagulation treatment was initiated accordingly.

Giving to the presence of first-degree AV block, nifedipine seemed more rational than diltiazem. It was started at a dose of 10 mg three times daily (TID) to be increased to 20 mg TID in the following weeks and to the maximum tolerated dose thereafter.

Three months later, he had improved pulmonary hemodynamic with mPAP of 24 mmHg, PVR of 145 dynes s/cm^5, and CI of 3.4 L/min/m^2. This striking amelioration leads us to stop increasing the dose of nifedipine.

Two years later, he had maintained improvement on the RHC with mPAP of 22 mmHg, PVR of 97 dynes s/cm^5, and CI of 4.06 L/min/m^2.

Finally, 6 years following diagnosis, the patient has a persistent improvement of his IPAH with a little dose of nifedipine. However, in May 2015, we observed an increase in mPAP, right atrial pressure, and pulmonary capillary wedge pressure reflecting volume overload [Table 1].

This breakdown necessitated diuretic and nifedipine dosage optimization. To the best of our knowledge, there was no reported case of IPAH with notable and prolonged clinical and hemodynamic response to low-dose nifedipine.

The European Society of Cardiology and the European Respiratory Society recommend that CCBs should be initiated in patients with IPAH who have positive AVR testing. A reduction in mPAP of ≥10 mmHg to reach an absolute value below 40 mmHg with an increased or unchanged cardiac output.[1,2] It has been shown that CCBs give a survival benefit in IPAH or drug-associated pulmonary hypertension with 100% survival rate at 5 years.[3,4]

Long-term response to CCBs, defined as New York Heart Association-Functional Class I or II with maintained hemodynamic improvement after at least 1 year of treatment and without adding another PAH-specific therapy, is observed in only half of the patients with positive AVR testing. The sustained response is seen in IPAH or anorexigen-associated PAH. The CCBs' dose used to achieve a hemodynamic benefit is considered as much higher than the dose used to control systemic hypertension (diltiazem 240–920 mg/day or nifedipine 60–120 mg/day).[2,3]

Table 1: Hemodynamic measurements of the index case during seven-year follow-up

Date	Treatment	RAP (mmHg)	mPAP (mmHg)	PVR	PAWP (mmHg)	Cardiac index (l/min/m^2)
April 2009	At diagnosis	5	31	242 dynes s/cm^5	13	2.65
July 2009	Nifedipine (40 mg/day)	1	24	145 dynes s/cm^5	10	3.40
December 2010	Nifedipine (40 mg/day)	8	29	153 dynes s/cm^5	14	3.45
November 2012	Nifedipine (40 mg/day)	3	22	97 dynes s/cm^5	11	4.06
May 2015	Nifedipine (40 mg/day)	12	32	106 dynes s/cm^5	20	3.98
March 2016	Nifedipine (60 mg/day)	5	25	128 dynes s/cm^5	11	3.66

RAP: Right atrial pressure, mPAP: Mean pulmonary artery pressure, PVR: Pulmonary vascular resistances, PAWP: Pulmonary artery wedge pressure

In 1992, Rich *et al*. published the first report of a survival benefit of IPAH patients treated with CCBs. Although a small number of patients were studied, it demonstrated a 5-year survival of 100% among responders treated with high-dose CCBs.[3,4] Longer survival has been observed. Nonresponders group had a 5-year survival rate of 48%. However, all but one CCBs, responders were alive after 7 ± 4, 1 year. The mean daily dose of diltiazem and nifedipine used was 180–720 mg and 60–120 mg, respectively. Long-term responders had a lower mPAP and PVR at baseline.[3] This finding may reflect milder disease phenotype in those who sustain hemodynamic and clinical benefit following treatment with CCBs.

This case is unique; it demonstrates a conspicuous and sustained response to conventional dose of nifedipine. It is noteworthy that current definition of positive AVR was absent. Although a reduction of 20% of mPAP and PVR is considered positive and indicative of CCBs treatment, our patient does not fulfill the current criteria of positive AVR, the marked reduction of PVR following NO test and mild pulmonary hypertension incited us toward CCBs therapy. This may reflect different responder's phenotype with lower mPAP and PVR. Of note the patient is a former drug user, we recently reported PAH in this group, and we found that they presented earlier than IPAH or other types of PAH.[5]

IPAH may represent a heterogeneous group with distinct CCBs response. Conventional CCBs dose may be sufficient to maintain long-term response in moderate IPAH patients with positive AVR testing.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/lungindia.lungindia_12_18

How to cite this article: Nasser M, Traclet J, Mornex JF. Sustained response to low-dose nifedipine in a patient with idiopathic pulmonary arterial hypertension. Lung India 2018;35:358-60.