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/cm², and cardiac index (CI) at 2.63 L/min/m². Following inhaled nitric oxide (NO) test, he had significantly decreased his PVR to 74 dynes s/cm², mPAP dropped to 26 mmHg, and CI increased to 3.39 L/min/m².

Although considered as nonresponsive but 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/cm², and CI of 3.4 L/min/m². 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/cm², and CI of 4.06 L/min/m².

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/m²) |
|------------|---------------|------------|-------------|----------|-------------|-------------------------|
| April 2009 | At diagnosis  | 5          | 31          | 242 dynes s/cm² | 13         | 2.65                    |
| July 2009  | Nifedipine (40 mg/day) | 1          | 24          | 145 dynes s/cm² | 10         | 3.40                    |
| December 2010 | Nifedipine (40 mg/day) | 8          | 29          | 153 dynes s/cm² | 14         | 3.45                    |
| November 2012 | Nifedipine (40 mg/day) | 3          | 22          | 97 dynes s/cm²  | 11         | 4.06                    |
| May 2015   | Nifedipine (40 mg/day) | 12         | 32          | 106 dynes s/cm² | 20         | 3.98                    |
| March 2016 | Nifedipine (60 mg/day) | 5          | 25          | 128 dynes s/cm² | 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. 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. 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.

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.

Mouhamad Nasser¹, Julie Traclet¹, Jean-François Mornex¹²

RECEIVED
1. Department of Respiratory Medicine, National Reference Centre for Rare Pulmonary Diseases, Regional Competence Centre for Severe Pulmonary Arterial Hypertension, Louis Pradel Hospital,
2. Claude Bernard University Lyon 1, Lyon, France
E-mail: jean-francois.mornex@univ-lyon1.fr

REFERENCES
1. Natarajan R. Recent trends in pulmonary arterial hypertension. Lung India 2011;28:39-48.
2. Galéï N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPc), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
3. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327:76-81.
4. Sitbon O, Humbert M, Jais X, loos V, Hamid AM, Provencher S, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005;111:3105-11.
5. Traclet J, Khouatra C, Piégay F, Turquier S, Zeghmar S, Mornex JF, et al. Pulmonary arterial hypertension in heroin users. J Heart Lung Transplant 2016;35:932-4.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Access this article online
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.

© 2018 Indian Chest Society | Published by Wolters Kluwer - Medknow