Acute Vasoreactivity Testing with Nicardipine in Patients with Pulmonary Arterial Hypertension

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Short running title: Nicardipine Challenge in PAH

Abstract: Acute vasoreactivity testing for patients with pulmonary arterial hypertension (PAH) has been reported to be useful to identify patients with sustained beneficial response to oral calcium channel blockers (CCBs), but there is a risk of exacerbation during the testing with oral CCBs. Therefore, we developed a testing method utilizing intravenous nicardipine, a short-acting CCB, and examined the safety and usefulness of acute vasoreactivity testing with nicardipine in PAH patients. Acute vasoreactivity testing with nicardipine was performed in 65 PAH patients. Nicardipine was administered by short-time continuous infusion (1 μg/kg/min for 5 min and 2 μg/kg/min for 5 min) followed by bolus injection (5 μg/kg). Hemodynamic responses were continuously measured using a right heart catheter. Acute responders were defined as patients who showed a decrease in mean pulmonary artery pressure of at least 10 mmHg to an absolute level below 40 mmHg with preserved or increased cardiac output. Two acute responders and sixty-three non-acute responders were identified. There was no hemodynamic instability requiring additional inotropic agents or death during the testing. Acute responders had good responses to long-term oral CCBs. The acute vasoreactivity testing with nicardipine is safe and might be useful for identifying CCB responders in PAH patients.

Key words: calcium channel blockers, acute vasoreactivity testing, pulmonary arterial hypertension

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Abbreviations

BP = blood pressure; **BNP** = brain natriuretic peptide; **$[Ca^{2+}]_{cyt}$** = free Ca^{2+} concentration in the cytosol; **CCB** = calcium channel blocker; **CO** = cardiac output; **CI** = cardiac index; **GPCR** = G protein-coupled receptors; **HR** = heart rate; **iNO** = inhaled nitric oxide; **IP_3R** = inositol 1,4,5-trisphosphate receptors; **NO** = nitric oxide; **PAH =** pulmonary arterial hypertension; **PAP** = pulmonary artery pressure; **PCWP** = pulmonary capillary wedge pressure; **PVR** = pulmonary vascular resistance; **RAP** = right atrial pressure; **RHC** = right heart catheterization; **ROC =** receptor-operated Ca^{2+} channel; **S_aO_2** = saturation of arterial blood; **SOC** = store-operated Ca^{2+} channel; **$S_{PA}O_2$** = saturation of pulmonary arterial blood; **$S_{RA}O_2$** = saturation of right atrial blood; **SVR** = systemic vascular resistance; **TRPC** = transient receptor potential cation channels; **TPR** = Total pulmonary resistance; **TRPG** = tricuspid regurgitation pressure gradient; **VDCC** = voltage-dependent calcium channel

Introduction

Pulmonary arterial hypertension (PAH) is a condition characterized by elevated mean pulmonary artery pressure, and the prognosis is poor in most cases (1, 2). Although we and other investigators have reported that a small proportion of patients with PAH respond to long-term calcium channel blockers (CCBs) and have a better prognosis (3-6), the empiric use of CCBs in PAH is not recommended because of the risk of exacerbation (7, 8).

Acute vasoreactivity testing is usually performed to predict a better prognosis and identify acute responders who are more likely to have a sustained beneficial response to oral CCBs and can be treated with these less-expensive drugs (6, 9). Although acute vasoreactivity testing is most commonly performed using inhaled nitric oxide (iNO) (10), intravenous epoprostenol (11), or intravenous adenosine (12), there are uncertainties regarding the choice of vasodilator (13).

In pulmonary arterial smooth muscle cells (PASMCs), the free Ca^{2+} concentration in the cytosol ($[Ca^{2+}]_{cyt}$) is an important determinant of contraction, migration and proliferation. $[Ca^{2+}]_{cyt}$ in PASMCs can be increased by Ca^{2+} influx through voltage-dependent calcium channels (VDCC), receptor-operated Ca^{2+} channels (ROC) and store-operated Ca^{2+} channels (SOC) and by Ca^{2+} release from intracellular stores via inositol 1,4,5-trisphosphate receptors (IP$_3$Rs) and ryanodine receptors. NO, epoprostenol and adenosine suppress elevation of $[Ca^{2+}]_{cyt}$ through inhibition of ROC and SOC, which are associated with G protein-coupled receptor (GPCR), IP$_3$R and transient receptor potential cation channels (TRPCs); however, CCBs suppress the elevation through inhibition of VDCCs (14).

Acute vasoreactivity testing using CCBs appears to be a reasonable method for predicting response to long-term CCBs, however, the safety and efficacy of oral and intravenous CCBs for the testing have not been established in PAH patients. Occurrence of

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life-threatening hemodynamic compromise has often been documented in nifedipine and verapamil testing (7, 15, 16).   Therefore, it is now accepted that CCBs should not be used for acute testing (17, 18).

Since oral CCBs have a long half-life, there is a risk of exacerbation due to instability of pharmacokinetics when they are used for testing (7, 16).   Therefore, the development of a testing method using a short-acting intravenous CCB is needed.

Nicardipine chloride, a hypotensor available in most countries in the world, is administered to patients with hypertensive emergency, to those with acute heart failure associated with hypertension, and to those with hypertension during an operation by continuous infusion at 0.5 to 6 μg/kg/min, at 0.5 to 2 μg/kg/min, and at 0.5 to 10 μg/kg/min or bolus injection at 10 to 30 μg/kg respectively, by reference to Japanese package insert.   The half-life of nicardipine after intravenous injection at 10 μg/kg to a healthy adult is about 1 h, which is shorter than that of nifedipine at 10 mg per os (about 2.6 hours).   Therefore, we developed a testing method using short-acting intravenous nicardipine and examined the safety and usefulness of the test.

Materials and Methods

Subjects

We performed acute vasoreactivity testing using intravenous nicardipine for adult patients diagnosed as having PAH without left heart disease who had been hospitalized in our hospital from April 1999 to October 2011.

Pulmonary hypertension was defined by a resting mean pulmonary artery pressure (PAP) ≥25 mmHg during right heart catheterization (RHC) with a mean pulmonary capillary wedge pressure (PCWP) ≤15 mmHg (19).

Exclusion criteria were as follows: thromboembolic pulmonary hypertension, hemodynamic instability including cardiac index less than 2.2 L/min/m^2 and systolic blood pressure less than 80mmHg, or having symptoms associated with low cardiac output at rest.

All of the studies were approved by the Ethics Committee of Okayama University Graduate School of Medicine, Density, and Pharmaceutical Sciences, and written informed consent was obtained from all patients before the procedure. The investigation also conformed to the principles outlined in the Declaration of Helsinki.

Baseline Evaluation

Baseline evaluation included medical history, WHO functional class, physical examination, 6-minute walk test and brain natriuretic peptide (BNP). Baseline hemodynamic evaluations were performed in all patients with RHC as previously described ([1, 20]). Baseline hemodynamic measurements included heart rate (HR), blood pressure (BP), right atrial pressure (RAP), mean PAP, PCWP, and CO determined by the Fick method. Cardiac index (CI) was calculated as CO/body surface area. Total pulmonary resistance (TPR) was calculated as (mean PAP/CO) × 80.

Acute Vasoreactivity Testing

Acute vasoreactivity testing was performed at the time of absence of hemodynamic instability. Acute pulmonary vasodilator responsiveness was assessed by administration of nicardipine (Astellas Pharma Inc, Tokyo, Japan) with short-time continuous infusion (1 μg/kg/min for 5 min and 2 μg/kg/min for 5 min) followed by bolus injection (5 μg/kg) (Figure 1). We used continuous infusion at a low dose for a short time before bolus injection to ensure PH patients' safety.

Hemodynamic responses were continuously measured before, during and after administration of nicardipine using an RHC. S_aO_2 (saturation of arterial blood) and $S_{PA}O_2$ (saturation of pulmonary arterial blood) were measured to calculate CO every 5 minutes.   A significant acute response to nicardipine was defined as a reduction in mean PAP of at least 10 mmHg to an absolute mean PAP of less than 40 mmHg without a decrease in CO according to the American College of Chest Physicians developed guidelines (21). Discontinuance criteria were systemic BP less than 70 mmHg, HR elevation more than 50 bpm from baseline, and/or appearance of any other constitutional symptoms.

Chronic Treatment with CCB

Chronic oral CCB therapy was initiated in patients who showed significant acute pulmonary vasoreactivity as defined above.

Statistical Analysis

All values are expressed as mean ± standard deviation.

Results

Study group

Sixty-five patients met the criteria of PAH and were included in the analysis.   The clinical characteristics and baseline hemodynamic parameters of these 65 patients are shown in Table 1.

Responses to intravenous nicardipine and long-term CCB in acute responders

Hemodynamic changes during the testing are shown in Table 2.   The values after

administration shown in Table 2 were measured when maximum variation of mPAP was detected.   There was no hemodynamic instability requiring additional inotropic agents or death during the testing.   Two acute responders were identified.

Responder 1

A 26-year-old woman with idiopathic PAH was admitted to our hospital 4 years after diagnosis at another hospital.   Beraprost sodium at a daily dose of 60 μg had been prescribed for 2 years, but shortness of breath became exacerbated and recurrent episodes of syncope during activity occurred.   She was therefore referred to our hospital for treatment. Pretherapeutic hemodynamic data were as follows: HR, 65 bpm; systemic BP, 108/66/85 mmHg; PCWP, 7 mmHg; PAP, 84/35/55 mmHg; RAP, 5 mmHg; CO, 3.3 L/min; CI, 2.2 L/min/m^2; systemic vascular resistance (SVR), 1939 dynes·sec·cm^{-5}; pulmonary vascular resistance (PVR), 1163 dynes·sec·cm^{-5}; and TPR, 1333 dynes·sec·cm^{-5}.

Unfortunately, her hemodynamic data were incomplete because the right heart catheter tip had moved down to the right ventricle from the pulmonary artery and could not be recovered.   Systolic right ventricular pressure (sRVP) and saturation of right atrial blood ($S_{RA}O_{2)}$ were therefore assessed as alternatives to systolic PAP and saturation of pulmonary arterial blood ($S_{PA}O_{2)}$, respectively.   Her sRVP decreased to 41 mmHg from 69 mmHg and CO increased to 3.0 L/min from 2.0 L/min after administration of nicardipine, and she was therefore considered to be an acute responder.

Treatment with oral nifedipine at a daily dose of 10 mg was started, and then the daily dose was titrated up to 90 mg.   Two years after starting the drug treatment, her data were as follows: HR, 64 bpm; systemic BP, 135/85/102 mmHg; PCWP, 5 mmHg; PAP, 35/10/22 mmHg; RAP, 0 mmHg; CO, 4.1 L/min; CI, 2.8 L/min/m^2; SVR, 1990

dynes·sec·cm^{-5}; PVR, 331 dynes·sec·cm^{-5}; and TPR, 429 dynes·sec·cm^{-5}.   Figure 2 shows improvement of right ventricular overload on an electrocardiogram and improvement in enlargement of cardiothoracic ratio and main pulmonary trunk on a chest X-ray.   She has now achieved remission without PAH.

Responder 2

A 37-year-old woman with IPAH was admitted to our hospital with the chief complaint of shortness of breath.

Pretherapeutic hemodynamic data were as follows: HR, 65 bpm; systemic BP, 117/67/89 mmHg; PAP, 62/25/37 mmHg; RAP, 2 mmHg; CO, 6.1 L/min; CI, 3.6 L/min/m^2; SVR, 1135 dynes/sec/cm^5; and TPR, 482 dynes/sec/cm^5.

Hemodynamic changes in this acute responder were as follows: HR, 65 bpm; systemic BP, 111/60/79 mmHg; PAP, 39/15/24 mmHg; RAP, 2 mmHg; CO, 6.7 L/min; CI, 4.0 L/min/m^2; SVR, 923 dynes·sec·cm^{-5}; TPR, 288 dynes·sec·cm^{-5}; variation in mPAP, -13 mmHg; and variation in CO: +0.6 L/min.

Treatment with oral amlodipine at a daily dose of 2.5 mg was started.   Four days after starting the drug treatment, tricuspid regurgitation pressure gradient (TRPG) had decreased to 41 mmHg from 70 mmHg as shown by ultrasonography.   Now she takes amlodipine at a daily dose of 5 mg and TRPG is 53 mmHg.   Figure 3 shows improvement of septal flattening during systole and TRPG by an echocardiogram.

Non-responders

Data for the 63 non-responders were as follows: baseline mPAP, 54±18 mmHg; variation in mPAP, 0.9±4.4 mmHg; and variation in CO, 0.4±0.9 L/min.

Discussion

We performed acute vasoreactivity testing using intravenous nicardipine. The test was safe and two responders were identified in the 65 patients.

It has been demonstrated that long-term CCB responders have better prognosis than that of CCB non-responders, and CCBs are less expensive than other vasodilators (6, 22). Therefore, vasoreactivity testing to find responders is important and is required in clinical settings.

According to the ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2009), vasodilator challenge should only be performed with short-acting, safe, and easy-to-administer drugs with no or limited systemic effects (23). Acute vasoreactivity testing is most commonly performed using inhaled nitric oxide (iNO) (10), intravenous epoprostenol (11), or intravenous adenosine (12). However, several investigators have also pointed out a problem with these agents: it is important to consider that these agents have different mechanisms of action and diverse hemodynamic effects, and their use may therefore not be interchangeable (13, 24). Since iNO vasodilates the pulmonary artery selectively and its half-life is very short (3 minutes) it has minimal systemic side effects (25). However, the duration of inhalation and the concentration for testing have not been standardized. Although adverse effects of iNO are very rare, to prevent leakage of NO, a delivery system, a gas cylinder and respiratory therapy are required.

Intravenous epoprostenol revealed the patients most likely to benefit from CCB therapy; however, a favorable response to epoprostenol does not indicate that all patients will have a long-term response to CCBs (22). Epoprostenol causes frequent adverse reactions, such as flushing, headache and hypotension (25). In addition, this drug is ten-times more expensive in Japan than in America.

Adenosine is an easily available, stable and inexpensive medication that has pulmonary vasodilatory properties.   Its half-life is 5-10 seconds.   When given intravenously, the short half-life allows a relatively higher plasma concentration of the agent in the pulmonary circulation rather than the systemic circulation, thus reducing systemic side effects (26).   Adverse effects are palpitation, bronchospasm, hypotension, bradycardia and atrioventricular block (27).

Acute vasoreactivity testing with the above-described drugs still fails to identify all of the patients who will have a long-term CCB response (6, 9), and it is unclear why some patients have an initial positive vasoreactivity testing but do not respond to CCBs after some time.

Furthermore, according to the ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2009) , the use of CCBs given orally or i.v. as an acute test is discouraged, due to the risk of potentially life-threatening complications, however, the statement was based on the reports in which oral nifedipine, intravenous/oral verapamil, or intravenous diltiazem was used for acute vasoreactivity testing (23, 28-31). We performed acute vasoreactivity testing using intravenous nicardipine.   The test was safe in the 65 patients.

Nicardipine is an intravenous CCB, available not only in Japan but also in other countries, and is administrated as a hypotensor.   This drug inhibits uptake of Ca^{2+} to vascular smooth muscle cells to dilate blood vessels (32).   It has been reported that nicardipine has more powerful antagonism in vascular smooth muscle cells than in cardiomyocytes and is more vasoselective than other CCBs (nifedipine, verapamil, diltiazem) (33).   Nicardipine, an intravenous CCB, is short-acting compared to oral CCBs.   Therefore, it appeared that acute vasoreactivity testing using nicardipine could be carried out safely and might be useful

for identifying long-term CCB responders more specifically than other vasodilators. Since our study was carried out in a small population, further controlled studies in larger populations are needed to confirm our results of testing including safety.

Since nicardipine was reported to induce reflex tachycardia and palpitation, we used low dosage by reference to that for patients with acute heart failure (34-36), and marked elevation in HR during testing was not observed in our study (Table 2). Fortunately, there were no critical hypotensive effects, and the testing could be carried out safely. However, it is often difficult to restore a patient's condition, when the condition has deteriorated. Therefore, PAH patients should be closely monitored in the intensive care unit during acute vasoreactivity testing.

We did not compare this testing with other conventional vasodilator approaches and an active control group. Therefore, appropriate dosage for testing and usefulness were not adequately established. However, the mechanisms by which elevation of $[Ca^{2+}]_{cyt}$ are suppressed by nicardipine and by other drugs (NO, epoprostenol and adenosine) are different, and addition of nicardipine testing with other vasodilator approaches might therefore raise the precision of acute vasoreactivity testing.

A positive test is observed in about 10-15% of patients with IPAH. Approximately half of these patients will experience long-term benefits of CCBs (24). As stated above,n only a small number of patients benefit from CCBs. However, survival rate of long-term CCB responders was 97% in an average follow-up period of 7 years in a large retrospective study (**n**=557) in which IPAH patients were treated with CCBs after demonstrating acute pulmonary vasoreactivity (6). Therefore, treatment with a CCB is one of the favorable and possible treatment options.

In conclusion, acute vasoreactivity testing with nicardipine is safe for PAH patients

and might be useful for identifying long-term CCB responders in PAH patients.

Acknowledgments

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Figure Legends

Figure 1: Protocol of acute vasoreactivity testing with nicardipine.

Figure 2: Improvements in electrocardiogram and chest X-ray of responder 1. **(A)** is before administration of nifedipine in April 1999. **(B)** is at three years after starting administration, March 2003.

Figure 3: Improvement in transthoracic echocardiogram of responder 2. Upper panels are parasternal short-axis view images in diastole and end-systole, and lower panels are tricuspid regurgitation velocity images. **(A)** Before administration of amlodipine in October 2009, septal flattening at end-systole was observed (upper panel). Tricuspid regurgitation (TR) velocity was 422 cm/s (lower panel) and TR pressure gradient (TRPG) , which is used for estimation of systolic PAP, was 71 mmHg. **(B)** At six days after starting administration of amlodipine at 2.5 mg in November 2009, septal flattening at end-systole was improved (upper panel). TR velocity was 319.4 cm/s (lower panel) and TRPG was 41 mmHg. **(C)** With administration of amlodipine at 5 mg in January 2011, septal flattening at end-systole was improved (upper panel). TR velocity was 364.3 cm/s (lower panel) and TRPG was 53 mmHg.