Hemodynamic Effect of Iloprost Inhalation and Oral Sildenafil during Acute Vasoreactivity Test in Pulmonary Arterial Hypertension

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Background: *The vasoreactivity test is usually performed to identify pulmonary arterial hypertension (PAH) patients who may benefit from long-term calcium channel blocker (CCB). The first and most commonly used agent is intravenous epoprostenol. A few other agents such as intravenous adenosine and inhaled nitric oxide are also used. In Thailand, epoprostenol is not available and the others are costly. Therefore, inhaled iloprost or oral sildenafil may be alternatives to test vasoreactivity.*

Objective: *To evaluate the hemodynamic effect and response rate of inhaled iloprost and oral sildenafil during acute vasoreactivity test in PAH patients.*

Material and Method: *In this retrospective descriptive study, the authors recruited patients with idiopathic PAH (IPAH) or PAH associated with connective tissue disease (PAH-CNT) seen at the Medicine department Siriraj Hospital between January 2005 and December 2011 for whom acute vasoreactivity test was indicated. All patients used 20 microgram of inhaled iloprost via Delphinus® nebulizer for the test. Hemodynamic parameters were recorded before and after iloprost administration. Eight of those patients subsequently had a repeated test using 100 mg of oral sildenafil.*

Results: *Fifteen patients had acute vasoreactivity testing. Eleven patients were IPAH and four were PAH-CNT. Using ESC/ERS guidelines criteria for responsiveness to vasoreactivity test, the response rate was 13% (2 out of 15 patients) using inhaled iloprost. Hemodynamic change was seen as early as five minutes after the inhalation and the effect lasted up to 35 minutes. The response rate was 25% (2 out of 8 patients) using oral sildenafil. Hemodynamic change was seen as early as 30 minutes after sildenafil ingestion and lasted up to 480 minutes.*

Conclusion: *Inhaled iloprost can be used for acute vasoreactivity test in Thailand. The hemodynamic parameters should be recorded immediately after iloprost inhalation. Oral sildenafil, however, is not a suitable agent for acute vasoreactivity test due to its extended effect.*

Keywords: *Acute vasoreactivity test, Pulmonary hypertension, Inhaled iloprost, Sildenafil*

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The disease of pulmonary arteries that results in elevated pulmonary arterial pressure called pulmonary arterial hypertension (PAH). Mean pulmonary arterial hypertension over or equal to 25 mmHg is the definition of pulmonary arterial hypertension (PAH). The pathological findings of pulmonary arteries in PAH were characterized by endothelial hyperplasia, medial hypertrophy, and adventitious proliferation. Decreased endothelial production of pulmonary vasodilators such as prostacyclin and nitric oxide and increase of pulmonary vasoconstrictor such as endothelin were found to be PAH pathogenesis[1,2].

The world health organization (WHO) classify pulmonary hypertension into five categories[5]; pulmonary arterial hypertension (PAH), which is subdivided into five subgroups, idiopathic pulmonary hypertension (IPAH), heritable PAH, drugs and toxins induced PAH, associated with PAH (APAH) which include PAH associated with connective tissue disease (CNT), congenital heart disease, portal hypertension, HIV infection, schistosomiasis, chronic hemolytic anemia, and persistent pulmonary hypertension of the newborn. Patients with IPAH had poor prognosis. The one, three, and five-year survival rates after symptom onset were 68%, 48%, and 34%, respectively. One of

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the prognostic indicators of IPAH is response to acute vasodilator test. This vasoreactivity test is also the test for identifying the IPAH patients who may benefit from long-term use of calcium channel blocker (CCB) therapy, which can increase the survival and quality of the life of IPAH patient[3,4]. Thus, all PAH patients who may benefit from CCB should have an acute vasoreactivity test performed. After administration of pulmonary vasodilator, a decrease in the mPAP by at least 10 mmHg to reach an absolute value of 40 mmHg or less without a decrease in cardiac output is currently considered a positive vasoreactivity test or being a responder[5]. International guidelines have recommended a variety of pulmonary vasodilators for acute vasoreactivity testing. The agents with fast onset, short duration of action, and minimal adverse effect should be used. Intravenous epoprostenol, intravenous adenosine, and inhaled nitric oxide are the three commonly used agents for acute vasoreactivity test worldwide[5]. However, intravenous epoprostenol is not available in Thailand. The high dose of adenosine required for the test leads to higher cost and adverse effect. Nitric oxide is also expensive and not widely available. Inhaled iloprost and oral sildenafil are available in Thailand. They may be good candidates for use in acute vasoreactivity test.

Iloprost is a stable, short-acting carbacyclin analogue of prostacyclin (prostaglandin I2) with a plasma half-life of 20 to 30 minutes[9]. Aerosolized iloprost is a more potent pulmonary vasodilator than nitric oxide[6,7]. Compared with intravenous adenosine, inhaled iloprost by specific ultrasonic nebulizer is as effective in the vasoreactivity test and is better tolerated[8]. Since there were no specific types of nebulizers recommended to be used with inhaled iloprost and no detailed guides for using this agent in an acute vasoreactivity test, we thus performed this study to determine its effect and hemodynamic response in an acute vasoreactivity test.

Sildenafil is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase 5 (PDE-5) that can cause relaxation of pulmonary vascular smooth muscle. Recent studies showed that sildenafil could be used for long-term treatment of PAH from many etiologies. Sildenafil is absorbed rapidly, reaching peak plasma concentration after one hour and has plasma half-life of three to four hours[10]. The authors postulated that sildenafil might be used as an alternative agent for acute vasoreactivity test.

Material and Method

Patient population

Patients with PAH, seen at Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University between January 2005 and December 2011, who had indication for acute vasoreactivity test (including diagnosis with IPAH or APAH, in New York Heart Association (NYHA) functional class II-IV, had stable hemodynamics and might benefit from long-term CCB use) were recruited. All subjects signed informed consent prior to the studies.

Hemodynamic measurement

All patients were admitted to respiratory critical care unit (RCU) at Siriraj Hospital. An 8.5 F vascular sheet was placed in the right internal jugular vein. Swan-Ganz catheter with continuous cardiac output monitoring tip (CCOmboV 7.5 F, Edwards Lifesciences®) was advanced via the vascular sheet into the pulmonary artery until it sat in the proper position. The hemodynamic values set, which included mean pulmonary arterial pressure (mPAP), systolic pulmonary pressure (SPAP), diastolic pulmonary pressure (DPAP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistances (PVR), systemic vascular resistance (SVR), and cardiac output (CO) were measured at baseline and after vasodilator administration at a regular preset timetable. Blood pressure, oxygen saturation, and heart rate were also recorded at the same time with hemodynamic value set.

Vasodilator drug administration

Step I: After baseline hemodynamic values set and blood pressure recording, 20 microgram (μg) of iloprost inhalation (ventavis®) were administered via Delphinus® jet nebulizer for 15 minutes (Delphinus® jet nebulizer used in this study gave aerosolized particles with mass median aerodynamic diameter of 2.9 μm and the percentage of particles smaller than 5 μm is 77%). After inhalation of iloprost, the hemodynamic values and blood pressure recorded every five minutes for four times, every 30 minutes for four times and then every one hour. The total duration of the step I test was four hours twenty minutes.

Step II: On the next day, the baseline hemodynamic values set and blood pressure were again recorded. One-hundred milligram (mg) of sildenafil (Viagra®) was ingested. After sildenafil

ingestion, the hemodynamic values set were recorded every 10 minutes for three times, every 15 minutes for six times, every 30 minutes for eight times and every hour for six times. The total duration of the step II test was 12 hours.

Acute vasoreactivity response criteria

A positive acute vasoreactivity test or responder was defined as a fall in mPAP of at least 10 mmHg to reach an absolute mPAP value of 40 mmHg or less without a decreasing of cardiac output (this followed the criteria from the European Society of Cardiology/European Respiratory Society guideline)[5].

Statistical analysis

Quantitative data are presented as mean ± SEM. A positive acute vasoreactivity test or responder was showed as percentage.

Results

Fifteen patients with PAH (11 had idiopathic pulmonary arterial hypertension (IPAH) and four had PAH associated with CNT) were enrolled in our study. Mean age was 41±11 years old; male: female ratio was 1:14. Eleven patients were in NYHA functional class III and four were in NYHA functional class IV. Average mean pulmonary arterial pressures (mPAP) was 54.1±11.2 mmHg. All 15 patients had step I test with inhaled iloprost; eight patients also had step II test with oral sildenafil. The patient baseline clinical characteristics were shown in Table 1.

Acute vasoreactivity responses in step I test using inhaled iloprost

The response rate was 13% (2 out of 15 patients). mPAP change was seen as early as five minutes after the inhalation of iloprost. Its effect lasted up to 20 minutes. mPAP and PVR change were all back to baseline at 50 minutes after inhalation (as shown in Fig. 1). The PVR was decreased and the cardiac output was increased or unchanged during the hemodynamic response. All patients developed facial flushing during iloprost inhalation. This symptom improved after inhalation withdrawal. None of patients developed hypotension.

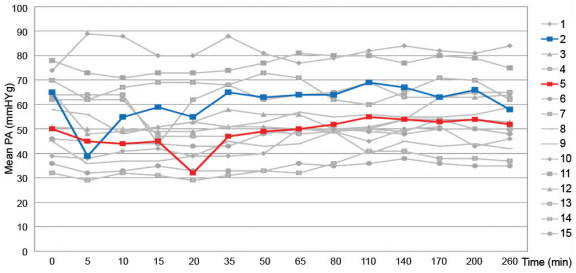
Acute vasoreactivity responses in step II test using oral sildenafil

The response rate was 25% (2 out of 8 patients) mPAP change was seen as early as 30 minutes after sildenafil ingestion. Its effect lasted up to 120 minutes mPAP and PVR change were all back to baseline at 480 minutes after sildenafil ingestion (as shown in Fig. 2). The PVR was decreased and the cardiac output was increased or unchanged during the hemodynamic response. No adverse event was observed with oral sildenafil use.

Table 1. Subject baseline clinical characteristics (n = 15)

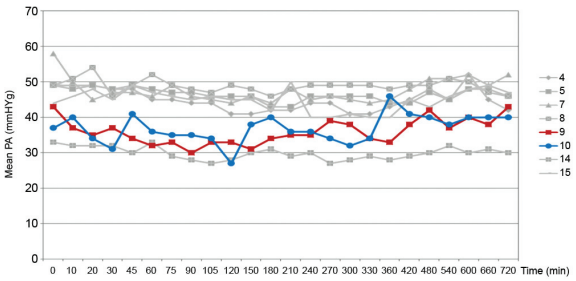
	Mean ± SD
Age (year)	41±11
Male:female (n)	1:14
NYHA (n)	
III	11
IV	4
Etiology (n)	
IPAH	11
CNT disease	4
Mean PAP (mmHg)	54.1±11.2
PVR (dyne.sec.cm^{-5})	967.0±550.7

NYHA = New York Heart Association; IPAH = idiopathic pulmonary arterial hypertension; CNT = connective tissue; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistances



Remarks: Dense line represent the 2 subjects with acute vasoreactivity response

Fig. 1 Mean pulmonary pressure after inhaled iloprost during acute vasoreactivity test.



Remark: Dense line represent the 2 subjects with acute vasoreactivity response

Fig. 2 Mean pulmonary artery pressure after oral sildenafil during acute vasoreactivity test.

Discussion

The reported response rate of acute vasoreactivity test in IPAH patients ranged from 4.5 to 14%[8-10]. Thenappan et al had shown the acute vasoreactivity response rate of 4.5% when using intravenous adenosine in IPAH patient[10]. Jing et al reported the vasoreactive response rate of 11% using intravenous adenosine and 14% using iloprost inhalation[8]. The present study using inhaled iloprost at the dose of 20 microgram via Delphinus® jet nebulizer for acute vasoreactivity test in IPAH patients demonstrated the response rate of 13%, which is comparable to previously reported response rates. Even though we used Delphinus® jet nebulizer, which had not been used for acute vasoreactivity test in other studies, the response rate from the present study did not differ from others. This assured us that Delphinus® jet nebulizer can be used for this testing. In addition, Gessler et al had compared hemodynamic change between Ultrasonic versus jet nebulized of iloprost; they found no significant change in mPAP, PVR, and cardiac index between those two nebulizers. The Ultrasonic nebulizer may provide shorter duration for inhalation and less wastage of drug[11]. Thus, 20 µg of inhaled iloprost via Delphinus® jet nebulizer can be used as an alternative for acute vasoreactivity test in Thailand.

The present study has shown that the mPAP started to decrease as early as five minutes after inhalation of iloprost. Hemodynamic change in all patients lasted up to 50 minutes after inhalation. We recommend that hemodynamic recording for acute vasoreactivity test using inhaled iloprost should be started as early as five minutes after inhalation and continued up to 60 minutes. The frequency of hemodynamic measurement recording can be followed our step I protocol.

From the present study result, the effect of oral sildenafil on hemodynamic change in PAH patients lasted up to eight hours. Though we did not find any adverse effects in the group using oral sildenafil, we do not recommend using oral sildenafil for acute vasoreactivity test due to its longer duration of action. Interestingly, two patients who responded to inhaled iloprost did not respond to oral sildenafil. This indicates that, in each individual IPAH patient, different predominated pathological pathways may play roles in its pathogenesis and may lead to different responses to different therapeutic interventions. The authors followed all eight patients who had oral sildenafil acute vasoreactivity test. All of them received low dose (25 mg every eight hours) of sildenafil for long-term treatment. Two patients who responded to oral sildenafil in the acute vasoreactivity test showed better improvement in their NYHA functional class from class III to I. Six patients who did not respond to oral sildenafil had improved their NYHA functional class from III to II. The response to high dose oral sildenafil during an acute vasoreactivity test may predict better outcome from long-term sildenafil treatment.

In conclusion, inhaled iloprost at the dose of 20 microgram via Deiphinus® jet nebulizer can be used for acute vasoreactivity testing in Thailand. Our protocol can be used as a prototype for testing and it can be modified for proper use in other centers. Oral sildenafil is, however, not suitable for acute vasoreactivity testing.

What is already known on this topic?

Aerosalized iloprost using specific type of ultrasonic nebulizer can be used for acute vasoreactivity test.

What this study adds?

Deiphinus® jet nebulizer can also be used to deliver aerosolized iloprost in acute vasoreactivity test in Thailand. The hemodynamic recording during the test should be started as early as five minutes, and continue up to 60 minutes.

Potential conflicts of interest

None.

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ผลของการพ่นสูด iloprost และยารับประทาน sildenafil ต่อการไหลเวียนเลือดในการทดสอบความไวของหลอดเลือดผู้ป่วยความดันหลอดเลือดแดงปอดสูง

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ภูมิหลัง: *การทดสอบความไวของหลอดเลือดผู้ป่วยความดันหลอดเลือดแดงปอดสูงช่วยคัดกรองผู้ป่วย ซึ่งอาจจะได้ประโยชน์จากการรักษาด้วยยากลุ่ม calcium channel blocker (CCB) ในระยะยาว สารที่ได้ความนิยมใช้มากเป็นอันดับต้นคือ epoprostenol ฉีดเข้าหลอดเลือดดำซึ่งยานี้ไม่มีใช้ในประเทศไทย ส่วนการฉีด adenosine เข้าหลอดเลือดดำหรือการสูดก๊าซไนตริกออกไซด์ (nitric oxide) มีราคาค่อนข้างสูง จึงมีการใช้ยาสูดพ่น iloprost หรือ ยารับประทาน sildenafil แทนในการทดสอบความไวของหลอดเลือดผู้ป่วยความดันหลอดเลือดแดงปอดสูง*

วัตถุประสงค์: *ประเมินอัตราการตอบสนองและการเปลี่ยนแปลงการไหลเวียนเลือดหลังการสูดพ่น iloprost และรับประทาน sildenafil ในการทดสอบความไวของหลอดเลือดผู้ป่วยความดันหลอดเลือดแดงปอดสูง*

วัสดุและวิธีการ: *Retrospective descriptive study ผู้ป่วยความดันหลอดเลือดแดงปอดสูงไม่ทราบสาเหตุ (idiopathic pulmonary arterial hypertension, IPAH) และจากโรคเนื้อเยื่อเกี่ยวพัน (connective tissue disease, PAH-CNT) ที่เข้ารับการรักษา ณ ภาควิชาอายุรศาสตร์ โรงพยาบาลศิริราชในช่วงเดือนมกราคม พ.ศ. 2548 ถึง ธันวาคม พ.ศ. 2554 ซึ่งมีข้อบ่งชี้การทดสอบความไวหลอดเลือดจะได้รับการทดสอบด้วยยาสูดพ่น iloprost ขนาด 20 ไมโครกรัม โดยเครื่อง Delphinus® nebulizer ค่าตัวแปรการเปลี่ยนแปลงการไหลเวียนเลือด ทั้งก่อนและหลังให้ยาจะถูกบันทึกเป็นระยะ จากนั้นผู้ป่วยจำนวน 8 ราย จะได้รับการทดสอบซ้ำต่อด้วยยารับประทาน sildenafil 100 มิลลิกรัม*

ผลการศึกษา: *ผู้ป่วย 15 ราย ที่ได้รับการทดสอบความไวของหลอดเลือด มีภาวะ IPAH 11 ราย ส่วนอีก 4 ราย มีภาวะ PAH-CNT อัตราตอบสนองต่อยาสูดพ่น Iloprost คือ 13% (2 ใน 15 ราย) การเปลี่ยนแปลงปัจจัยเกี่ยวกับการไหลเวียนเลือดเริ่มปรากฏภายใน 5 นาที หลังการสูดพ่นยาและผลดังกล่าวคงอยู่นานถึง 35 นาที ในขณะที่อัตราตอบสนองต่อยารับประทาน sildenafil คือ 25% (2 ใน 8 ราย) การเปลี่ยนแปลงของปัจจัยเกี่ยวกับการไหลเวียนเริ่มปรากฏภายใน 30 นาที หลังรับประทานยาและผลดังกล่าวคงอยู่นาน 480 นาที*

สรุป: *ยาสูดพ่น iloprost เป็นอีกทางเลือกหนึ่งที่ใช้ในการตรวจทดสอบความไวของหลอดเลือดผู้ป่วยความดันหลอดเลือดแดงปอดสูงในประเทศไทยได้ โดยการบันทึกการเปลี่ยนแปลงการไหลเวียนและการตอบสนองควรทำหลังการสูดยาทันที ส่วนการรับประทาน sildenafil ซึ่งออกฤทธิ์นาน ไม่เหมาะที่จะใช้ในการตรวจทดสอบความไวของหลอดเลือด*