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Safety of Adenosine for Acute Pulmonary Vasoreactivity Testing in Pulmonary Hypertension

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Abstract

Background: Acute pulmonary vasoreactivity testing (APVT) is performed during right heart catheterization (RHC) in patients with pulmonary arterial hypertension (PAH) to identify those who may benefit from long-term calcium channel blocker (CCB) therapy. Inhaled nitric oxide (iNO) is the most commonly used agent. However, a few other agents such as intravenous (i.v.) epoprostenol or i.v. adenosine can also be used. At present, intravenous prostaglandins and iNO are expensive and not-easily available in most Iranian medical facilities. Indeed intravenous adenosine is less expensive and available in all hospital settings.
Objectives: We aimed to investigate the safety profile of adenosine in a group of Iranian PAH patients undergoing APVT.
Methods: In this prospective study, a total of 57 consecutive patients with PAH who were scheduled to undergo RHC were enrolled. Acute reactivity testing was performed in 56 patients.
Results: Twenty (36%) patients had positive APVT. In all cases, adenosine administration was limited by the occurrence of drug-induced minor side effects including chest pressure or tightness, flushing and dyspnea. The maximal tolerated dose of adenosine was 225 $\pm$ 25 μg/kh/min (range 200 - 300 μg/kh/min) in the study population. Only 2 patients developed atrioventricular block at doses of 100 μg/kh/min and 150 μg/kh/min, respectively. Both patients spontaneously converted to sinus rhythm within one minute of discontinuation of adenosine infusion.
Conclusions: Intravenous adenosine can be safely used for APVT in Iran.

Keywords: Adenosine, Adverse Effects, Pulmonary Hypertension, Safety

1. Background

Pulmonary arterial hypertension (PAH) is defined by a mean pulmonary arterial pressure higher than 25 mmHg at rest as assessed by right heart catheterization (RHC) (1, 2).

The acute pulmonary vasoreactivity testing (APVT) is performed during RHC in patients with PAH to identify those who may benefit from long-term calcium channel blocker (CCB) therapy (3, 4). Inhaled Nitric oxide (iNO) is the most common used agent for this purpose (4). However, intravenous (i.v.) prostaglandins (epoprostenol) and i.v. adenosine can also be used (5). Adenosine, an intermediate product in the metabolism of adenosine triphosphate, is a potent vasodilator that has a class IIb recommendation by the ESC/ERS guideline for use in acute pulmonary vasoreactivity testing (5). Intravenous adenosine has a very short serum half-life with an acceptable safety profile which makes it a desirable agent for acute pulmonary vasoreactivity testing.

Currently, intravenous prostaglandins and inhaled nitric oxide (iNO) are relatively expensive and are not easily available in most Iranian medical facilities. On the other hand, the adverse effects of i.v. adenosine in the setting of APVT have not been previously investigated in Iranian patients.

2. Objectives

As a result, in the present study, we aimed to assess the safety profile of adenosine in a group of Iranian PAH patients undergoing APVT.

3. Methods

In this prospective study, a total of 56 consecutive patients with idiopathic pulmonary arterial hypertension (iPAH) who were scheduled to undergo diagnostic RHC at Heart Failure and Transplantation department of Rajaei Cardiovascular Medical & Research center enrolled.

A 7F Swan-Ganz catheter was placed in the pulmonary artery and cardiac output was determined by the thermodilution technique.

The pulmonary vascular resistance was calculated as:

Mean pulmonary artery pressure - PCWP/CO

The systemic vascular resistance was calculated as:

Mean systemic blood pressure - right atrial pressure/CO.

After baseline hemodynamic measurements, the acute vasoreactivity was evaluated with adenosine infusion via an antecubital vein. The infusion begun at 50 μg/kg/min with a stepwise increase by 50 μg/kg/min every 2 minutes until either maximum dosage was reached (350 mg/kg/min) or a positive response were observed or adverse effects developed. A positive test is considered when mean pulmonary arterial pressure (mPAP) decreases more than 10 mmHg or a (mPAP) less than 40 mmHg without affection of the cardiac output.

The study protocol was approved by the institutional ethics committee and all participants provided written informed consent.

4. Results

Using ESC/ERS guidelines criteria for responsiveness to vasoreactivity test, 20 (36%) patients had positive acute pulmonary vasoreactivity testing.

During APVT, the hemodynamic changes in pulmonary circulation with adenosine started at 100 $\pm$ 25 μg/kh/min dosage the effect lasted up to 5 minutes.

In all cases, adenosine administration was limited by the occurrence of drug-induced minor side effects including chest pressure or tightness, flushing and dyspnea. The maximal tolerated dose of adenosine was 225 $\pm$ 25 μg/kh/min (range 200 - 300 μg/kh/min) in the study population.

Only 2 patients developed atrioventricular block at doses of 100 μg/kh/min and 150 μg/kh/min, respectively. No cases of hypotension, bradycardia, dizziness or syncope were observed. Patient I was a 40 year old female who developed Mobitz type 1 atrioventricular block with narrow QRS complex and patient II was a 41 year old female who developed complete AV block. Both patients spontaneously converted to sinus rhythm within one minute of discontinuation of adenosine infusion.

5. Discussion

Acute vasodilator testing is performed during the diagnostic right heart catheterization to identify a subset of patients who have a better survival and also will benefit from long-term CCB therapy (3, 4, 6). The optimal vasodilator agent for this purpose has not been established yet. Even though, both ESC/ERS and ACCF/AHA guidelines have introduced iNO as the preferred vasodilator and intravenous epoprostenol and intravenous adenosine as the acceptable alternatives (5, 7). However, iNO is not widely available in all health care facilities, particularly in developing countries. Indeed, intravenous adenosine is much less expensive and is widely available in almost all hospital settings.

The positive vasoreactivity rate varies according to the medication used for the test and the population of interest. We found a 36% positive vasoreactivity in Iranian iPAH patients using adenosine. This is substantially higher than previous reports. A study on Korean PAH patients using iNO showed a positivity rate of 15% (8). A study by Oliveira et al. on 39 Brazilian PAH patients showed 15% vasoreactivity with iNO and zero vasoreactivity with adenosine (9). Another study on Chinese PAH patients showed 13.5% vasoreactivity with iloprost and 10.8% with adenosine (10). A study on German PAH patients demonstrated 8.1% vasoreactivity with iNO 11.6% with sildenafil (11). In another study on Thai patients, acute vasoreactivity occurred in 13% of patients with inhaled iloprost and 25% of patients with oral sildenafil (12).

Adenosine stimulates A2 type endothelial cell and vascular smooth muscle receptors to increase intracellular cyclic adenosine monophosphate (cAMP) level (13). Hence it induces smooth vascular muscle relaxation. As a vasodilator, it acts on various vascular beds of the body systems including coronary, pulmonary and systemic circulations (14-16). However, preferential vasodilatory effect of adenosine on the pulmonary vasculature has been shown previously (10, 17). Adenosine deaminase, presented in erythrocytes and endothelial cells, metabolizes adenosine giving rise to a short half-life of 5 - 10 seconds (18). Following intravenous administration, this short half-life results in a relatively higher plasma concentration of adenosine in the pulmonary rather than the systemic vasculature; thereby reducing systemic side effects (19).

The aim of the present study was to investigate the safety profile of adenosine in a subgroup of Iranian iPAH patients undergoing acute vasodilator testing. Our results demonstrated that adenosine administration is associated with acceptable adverse effects and a good safety in patients with iPAH. The only feared adverse effects seen in our patients was AV block in 2 patients, a Mobitz type I with narrow QRS complex and a complete AV block which both spontaneously reverted to sinus rhythm within one minute of discontinuation of adenosine infusion.

Bush et al. showed that adenosine causes an increase in pulmonary blood flow and a decrease in systemic vascular resistance without inducing reflex tachycardia (15). Adding these effects to its rapid onset and offset of effects makes adenosine a desirable agent for vasodilation testing in pulmonary artery hypertension.

Schrader et al. safely used adenosine for rapid assessment of vasodilator reserve in patients with primary pulmonary hypertension (20). The reported side effects in their study included shortness of breath, abdominal discomfort or nausea, chest pressure, headache and numbness or tingling of the extremities. They reported that all

of these side effects disappeared within 30 seconds of the discontinuation of the adenosine. No arrhythmia was also recorded during adenosine administration in their study.

In the study by Oliveira et al. on 39 patients with pulmonary artery hypertension, adenosine administration during APVT resulted in bronchospasm, thoracic pain and bradycardia in 38%, 28% and 13% of patients respectively; limiting its titration to the maximum dosage (9). In a study done by Jing et al. 47.3% of patients receiving adenosine during APVT experienced an adverse effect including hypotension, palpitations, shortness of breath and abdominal or pharyngeal pain (8).

However, still there is no general consensus regarding the cost-effectiveness of adenosine administration in acute vasodilator testing; therefore physiologic effects of adenosine in pulmonary circulation and its comparison with other agents such as iNO and prostaglandins are yet to be answered and was not discussed in the present investigation.

To better elucidate the cost-effectiveness of adenosine administration during APVT, further studies with larger sample sizes, control arms and extended follow-up to identify responders to CCB therapy are suggested.

5.1. Study Limitations

The main limitation of our study is relatively small sample size. In addition, presence of a control group (placebo arm) would make our result more reliable. We also did not have follow up of our patients to see what percentage of patients with positive APVT responded to CCB therapy. However, the primary aim of this study was measurement of safety profile rather than true validity and prognostic role of APVT with adenosine.

5.2. Conclusion

In conclusion, we showed that intravenous adenosine can be safely used for APVT in Iran.

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