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Case report

Combined Usage of Inhaled and Intravenous Milrinone in Pulmonary Hypertension after Heart Valve Surgery

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A B S T R A C T

Secondary pulmonary hypertension is a frequent condition after heart valve surgery. It may significantly complicate the perioperative management and increase patients' morbidity and mortality. The treatment has not been yet completely defined principally because of lack of the selectivity of drugs for the pulmonary vasculature. The usage of inhaled milrinone could be the possible therapeutic option. Inodilator milrinone is commonly used intravenously for patients with pulmonary hypertension and ventricular dysfunction in cardiac surgery. The decrease in systemic vascular resistance frequently necessitates concomitant use of norepinephrine. Pulmonary vasodilators might be more effective and also devoid of potentially dangerous systemic side effects if applied by inhalation, thus acting predominantly on pulmonary circulation. There are only few reports of inhaled milrinone usage in adult post cardiac surgical patients. We reported 2 patients with severe pulmonary hypertension after valve surgery. Because of desperate clinical situation, we decided to use the combination of inhaled and intravenous milrinone. Inhaled milrinone was delivered by means of pneumatic medication nebulizer dissolved with saline in final concentration of 0.5 mg/ml. The nebulizer was attached to the inspiratory limb of the ventilator circuit, just before the Y-piece. We obtained satisfactory reduction in mean pulmonary artery pressure in both patients, and they were successfully extubated and discharged. Although it is a very small sample of patients, we conclude that the combination of inhaled and intravenous milrinone could be an effective treatment of secondary pulmonary hypertension in high-risk cardiac valve surgery patient. The exact indications for inhaled milrinone usage, optimal concentrations for this route, and the beginning and duration of treatment are yet to be determined.

Key words: *milrinone, heart surgery, aerosol drug therapy, nebulizers, pulmonary hypertension*

Introduction

Pulmonary hypertension is defined as a systolic pulmonary artery pressure (PAP) of 35 mm Hg, or, alternatively, as a mean PAP of 25 mm Hg at rest or 30 mm Hg with exertion[1].

Secondary pulmonary hypertension (PH) is a frequent condition after heart valve surgery with the incidence of severe PH in the range of 16–21 per cent[2–4]. It may significantly complicate the perioperative management and increase patients' morbidity and mortality[5].

The development of PH has long been considered an important risk factor for poor outcome in patients undergoing valve replacement surgery. In patients with mitral valve replacement (MVR) and severe PH the operative mortality was in range from 15 to 31 per cent, reaching even 61 per cent, when PAP was at systemic levels[6]. Recently, several reports have demonstrated improved outcome in patients with PH undergoing MVR, that was attributed to better myocardial preservation, and improved postoperative care. Nevertheless, this perioperative mortality is still around 10 per cent. Almost all deaths were attributed to persistent low cardiac output (CO) syndrome due to right ventricular failure[3,4,7]. However, the mortality rate in patients with supra-systemic PAP was as high as 28.5 per cent[3].

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Regarding perioperative morbidity, about 40 per cent of patients developed major complications including reoperation for hemorrhage, stroke, respiratory failure, myocardial infarction or >30 day hospitalization[2,3,6].

All these facts emphasize the need for the effective treatment of secondary PH after heart valve surgery. The treatment of secondary PH has not been yet completely defined, principally because of lack of selectivity of drugs for the pulmonary vasculature[4,8,9]. The conventional therapy consists of intravenous vasodilators (nitrates or prostaglandins), but associated systemic hypotension with increasing dosage, is obvious limiting factor[10].

The possible therapeutic option could be the usage of inhaled milrinone. Milrinone is an inodilator drug, i.e. it is a non-sympathomimetic drug that increases myocardial and vascular smooth muscle cyclic AMP concentrations by inhibiting phosphodiesterase III enzymes, thus modulating intracellular calcium levels and producing increased myocardial contractility and systemic vasodilatation. It is commonly used intravenously for patients with PH and ventricular dysfunction after cardiac surgery[11]. The decrease in systemic vascular resistance frequently necessitates use of norepinephrine together with milrinone[12].

Inhaled milrinone may be more effective and also devoid of troublesome systemic side effects by acting predominantly on the pulmonary circulation. There are only few reports of use of inhaled milrinone in adult post cardiac surgical patients, with many unresolved questions – strict indications for its usage, optimal drug concentration for this route, as well as time of beginning and duration of treatment[10,13].

Methods

We reported 2 patients with severe PH after heart valve surgery treated with inhaled milrinone, following local Ethics Committee approval.

The patients were orotracheally intubated and ventilated by Evita XL ventilator (Draeger Medical, Luebeck, Germany) in intermittent positive-pressure ventilation (IPPV) mode. Tidal volumes and respiratory rates were set to achieve end-tidal CO_2 values between 4.0 and 4.5 kPa. Milrinone (Corotrope 10 mg/10 mL, Sanofi Aventis, Paris, France) was delivered by means of pneumatic medication nebulizer (Draeger Medical, Luebeck, Germany), dissolved with 10 mililiters of saline, having final concentration of 0.5 mg/mL. The nebulizer was attached to the inspiratory limb of the ventilator circuit, just before the Y-piece. The use of nebulizer is possible in all ventilation modes of Evita XL ventilator. The mean mass diameter of droplets delivered was 6.2 μm, as stated by the manufacturer, and they were delivered at a rate of 0.3 mL/min[14,15]. The duration of such treatment was approximately 70 minutes. The minimal period between 2 milrinone inhalations was set arbitrarily to 4 hours.

Intravenous vasoactive drugs were administered via perfusors (Space, B. Braun Melsungen AG, Melsungen, Germany), with following dose ranges (milrinone 0.5–0.75 μg/kg/min, nitroglycerine 1–3 μg/kg/min, dobutamine 2.5–10 μg/kg/min and amiodarone 900 mg/day).

The mean arterial pressure (MAP), systolic PAP, diastolic PAP, mean pulmonary artery pressure (MPAP), pulmonary artery wedge pressure (PAWP) and pulmonary vascular resistance (PVR) values were analyzed at four time points: before the beginning of the inhaled milrinone treatment, at the end of inhaled milrinone treatment, as well as 12 and 24 hours after the termination of inhaled milrinone. The hemodynamic values were collected according to stored critical care charts data (intervals of 60 minutes). CO was assessed before the inhaled milrinone treatment and at the end of each predetermined period by a thermodilution technique using 5% dextrose as an indicator, and the PVR values were automatically derived.

Case Reports

Case 1

63-year old female underwent mitral and aortic valve replacement (MVR+AVR), because of mitral and aortic stenosis and insufficiency. Preoperatively, she had persistent atrial fibrillation and chronic obstructive pulmonary disease (Table 1). Her postoperative course was complicated with severe PH. She was mechanically ventilated 3 days and could not be weaned. Her medications were intravenous milrinone, nitroglycerine, and amiodarone. Despite high dosages of aforementioned drugs, her

TABLE 1
CHARACTERISTICS OF PATIENTS RECEIVING COMBINED INHALED AND INTRAVENOUS MILRINONE

Patient	1	2
Diagnosis	AS + AI, MS + MI	endocarditis, AI + MI + TI
EuroSCORE†	7 (6.55%)	20 (89.83%)
Surgery	AVR + MVR	AVR + MVR
Ventilator days	5	4
Imil	4	1
Inh (n)	3	3
Intravenous drugs	MIL, NTGL, AMI	D, MIL
Remarks	COPD, AF	preoperative heart failure, endocarditis, CVVHDF

MS – mitral valve stenosis, MI – mitral valve insufficiency, AS – aortic valve stenosis, AI – aortic valve insufficiency, TI – tricuspid valve insufficiency, †EuroSCORE = EUROpean System for Cardiac Operative Risk Evaluation[23], standard and logistic value, AVR – aortic valve replacement, MVR – mitral valve replacement, Imil – day (postoperative) of beginning the treatment with inhaled milrinone, Inh (n) = number of applied inhalations of milrinone, D – dobutamine, MIL – intravenous milrinone, AMI – amiodarone, COPD – chronic obstructive pulmonary disease, AF – atrial fibrillation, CVVHDF – continuous veno-venous hemodiafiltration

PH was severe with systolic PAP reaching 80 mmHg and MPAP in the range of 40–50 mmHg. Inhaled milrinone was started on postoperative day 3, and repeated on postoperative day 4. The hemodynamic values were improving, as shown in Table 2. During inhaled milrinone treatment, there was a slight decrease in MPAP (–7.6 per cent), but significant decrease of PVR (–42.5 per cent). The hemodynamic data after the completion of inhaled milrinone treatment were also favorable (Table 2). Twenty four hours after the completion of the inhaled milrinone treatment, there was no change in MPAP value regarding baseline values, but there was a decrease in PVR (–31.9 per cent) and increase in MAP (+16.2 per cent), resulting in increase of MAP/MPAP ratio (+15.6 per cent). On postoperative day 5 she was successfully weaned from ventilator and extubated on postoperative day 6. The systolic PAP after extubation was in range of 55–60 mmHg, and MPAP of 30–35 mmHg. During the following days, she was hemodinamically stable and was discharged from the intensive care unit (ICU) on postoperative day 10 in good clinical condition.

Case 2

49-year old female was admitted to the cardiac surgery ICU pre-operatively in very bad condition. She had dyspnea, heart and renal failure, severe aortic insufficiency, as well as mitral and tricuspid insufficiency. Fifteen days before she had been admitted to the Cardiology Department because of progressive dyspnea. Heart failure and endocarditis of aortic and mitral valve had been found. Despite of desperate clinical conditions, the surgery (AVR+MVR) was planned, after short pre-operative stabilization in the ICU. Dobutamine and continous veno-venous hemodiafiltration (CVVHDF) were started pre-operatively (Table 1). On the day 5, she underwent surgery. Despite high dosages of intravenous milrinone and dobutamine after the surgery, she was unstable with severe PH (systolic PAP occasionally reaching 90 mmHg and MPAP >50 mmHg). Inhaled milrinone was started as early as 6 hours postoperatively. The hemodynamic data before, during and after the completion of the inhaled milrinone treatment are shown in Table 2. During inhaled milrinone treatment, PVR decreased by 40 per cent, with minimal changes of other hemodynamic parameters. Twelve and 24 hours after the end of the inhaled milrinone treatment, the pulmonary artery pressures were significantly lower (–15.9 and –24.6 per cent, respectively), but we were able to wean and extubate the patient as late as on postoperative day 4. The systolic PAP after extubation was in range of 48–55 mmHg, and MPAP of 28–31 mmHg. On the following days inotropes were gradually tapered, the patient was hemodinamically stable. On postoperative day 10, the patient was transferred to the Department of Cardiac Surgery in good condition.

Discussion

We reported 2 patients with severe pulmonary hypertension after heart valve surgery (Table 1). Because of desperate clinical situation, we decided to use inhalation milrinone. Although it is a very small sample of patients, by combining multiple inhalations of milrinone (10 mg milrinone per inhalation, concentration –0.5 mg/mL, rate –0.15 mg/min) with intravenous milrinone (0.5–0.75

TABLE 2
HEMODYNAMIC PARAMETERS OF PATIENTS RECEIVING COMBINED INHALED AND INTRAVENOUS MILRINONE*

		Time Periods			
	Hemodynamic Parameters†	Before IM	During IM	12 h after IM	24 h after IM
Patient 1‡	MAP	71.7	73.5 (+2.5%)	81.3 (+13.4%)	83.3 (+16.2%)
	MPAP	38.0	35.1 (–7.6%)	38.0 (0%)	37.4 (–1.6%)
	MAP/MPAP	1.9	2.1 (+10.5%)	2.1 (+10.5%)	2.2 (+15.6%)
	D-W	9	5	5	6
	PVR	623	358 (–42.5%)	420 (–32.6%)	424 (–31.9%)
Patient 2‡	MAP	70.1	64.9 (–7.4%)	69.2 (–1.3%)	72.0 (+2.7%)
	MPAP	40.3	37.8 (–6.2%)	33.9 (–15.9%)	30.4 (–24.6%)
	MAP/MPAP	1.7	1.7 (0%)	2.0 (+17.6%)	2.4 (+41.2%)
	D-W	8	5	3	4
	PVR	640	384 (–40%)	340 (–46.4%)	390 (–39.1%)

* values are expressed in mmHg (MAP, MPAP, D-W) and dynes/s/cm^5 (PVR), †average values for given time period (except D-W gradient, and PVR, measured immediately before the start of the inhaled milrinone treatment and furthermore once at the end of time period),
‡ numbers in parentheses refer to percent change regarding baseline values of MAP, MPAP, MAP/MPAP ratio, and PVR, IM – inhaled milrinone treatment, MAP – mean arterial pressure, MPAP – mean pulmonary arterial pressure, MAP/MPAP – ratio between mean arterial and mean pulmonary pressure, D-W = gradient between pulmonary artery diastolic and wedge pressure, PVR = pulmonary vascular resistance

μg/kg/min) we managed to reduce pulmonary artery pressures, PVR, and to increase MAP/MPAP ratio.

Secondary PH after heart valve surgery is undoubtedly still a considerable problem in the ICU, with the average mortality of 10 per cent and reaching almost 30 per cent in the most severe cases. After preliminary reports of d'Ambra and co-workers more than 20 years ago[16], numerous pulmonary vasodilators were applied, and recently new guidelines have been adopted from the American College of Chest Physicians[17]. Despite these achievements, however, PH remains a serious, life-threatening condition[18].

There is only one article regarding inhaled milrinone usage on intubated patients in the ICUs after adult cardiac surgery. Haraldsson et co-workers conducted the study in patients with pulmonary hypertension after coronary artery bypass grafting (CABG) and orthotopic heart transplantation, immediately after admittance to the ICU. They used 3 different concentrations of milrinone (0.25, 0.5 and 1 mg/mL), which were stepwise increased in 10-minutes period. During the first part of the study (9 patients) a decrease in pulmonary vascular resistance (PVR) was found with a maximal effect (20%) at the largest administered concentration without associated systemic effects. During the second part of the study (11 patients), the inhaled milrinone was administered concomitantly with inhaled prostaglandin I2 (iPGI2) and there was an additional (8%) decrease in PVR. Interestingly, 20 minutes after milrinone inhalation all patients' values returned to baseline regarding all measured hemodynamic values. They concluded that inhaled milrinone alone or in combination with iPGI2 may present a therapeutic option for marginal patients with pulmonary hypertension and severe right-ventricular failure after cardiac surgery[10]. Unlike our report, although the authors had excellent protocol and included significant number of patients, the duration of the impact of milrinone on pulmonary hypertension was transient. Besides, this cohort did not include patients after heart valve surgery.

There are some other uses of inhaled milrinone in the perioperative setting of cardiac surgery. Lamarche and co-workers retrospectively analyzed 73 patients in 3-year period receiving inhaled milrinone before or after cardiopulmonary bypass (CPB). In this high-risk cohort they found that inhaled milrinone was well tolerated, and if administered pre-CPB it could help weaning from CPB[19]. According to our opinion, it is difficult to predict the onset of pulmonary hypertension after heart surgery and we consider preventive use of inhaled milrinone as a doubtful one.

In another study, inhaled aerosolized milrinone, given for a short period (10 minutes) selectively dilated the pulmonary vasculature in 18 heart transplant candidates with elevated PAP, without producing systemic side effects. But, these patients were not mechanically ventilated and the dosage of milrinone was 2 mg dissolved in 3 mililiters of saline. Also, as distinguished from our case reports, the authors used ultrasonic nebulizer and the particle size ranges from 3 to 5 μm with this device[20].

Inhaled milrinone is easy to deliver with modern ventilators in the ICUs. It could be applied in every mode of ventilation. The aerosol is derived synchronously with the inspiration phase of flow and respiratory minute volume is kept constant, as well as inspired oxygen fraction[14].

In our patients the beginning of the treatment with inhaled milrinone was as early as in the first postoperative hours (case 2), and in case 1 on postoperative day 3, after the failure of conventional therapies. Regarding the hemodynamic variables after discontinuation of inhaled milrinone, in patient 2 there was decrease of MPAP, while in patient 1 there was a minimal change in MPAP values, but MAP values were higher. As a result, the improved MAP/MPAP ratio and considerably more favorable hemodynamic conditions were achieved. Besides, we observed the decrease in gradient between diastolic PAP and PAWP in both patients (Table 2). Namely, in persons with severe PH, diastolic PAP is often substantially higher than PAWP, while in normal circumstances they are usually within 5 mmHg of one another[21,22].

Along with small sample of patients, another limitation of these reports could be the lack of comparison of individual effects of either inhaled or intravenous milrinone on pulmonary pressures, but it is not disputable that combination of inhaled and intravenous milrinone proved effective in these 2 patients. This beneficial hemodynamic effect lasted even after the discontinuation of inhaled milrinone, and the patients were successfully extubated and discharged.

Although it is a very small sample of patients, we conclude that the combination of repeated inhaled (0.05 per cent milrinone, at a nebulization rate of 0.15 mg/min) and continuous intravenous milrinone (dose range 0.5–0.75 μg/kg/min) could be an effective treatment of secondary pulmonary hypertension in high-risk cardiac valve surgery patient. Optimal concentration for this route, the time of beginning and duration of treatment are yet to be determined.

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KOMBINACIJA INHALIRAJUĆEG I INTRAVENSKOG MILRINONA U LIJEČENJU PLUĆNE HIPERTENZIJE NAKON KIRURGIJE SRČANIH ZALISTAKA

S A Ž E T A K

Sekundarna plućna hipertenzija je relativno česta nakon kirurškog zahvata na srčanim zaliscima. Ona može znakovito kompliciratiperioperacijski period, te povećati pobol i smrtnost operiranih bolesnika. Način liječenja ovog stanja nije posve definiran, poglavito zbog manjka selektivnih lijekova za plućni krvožilni sustav. Uporaba inhalirajućeg milrinona mogla bi biti jedna od terapijskih mogućnosti. Milrinon, lijek iz skupine inodilatatora, uglavnom se koristi intravenski kod bolesnika s plućnom hipertenzijom i poremećenom funkcijom klijetki nakon kardiokirurških zahvata. Pad sustavnog vaskularnog otpora, a koji izaziva ovaj učinkoviti lijek, obično zahtijeva istodobnu uporabu noradrenalina. Smatra se da bi plućni vazodilatatori bili učinkovitiji, a samim tim i bez potencijalno opasnih sustavnih nuspojava, kad bi se primjenjivali inhalacijom, a na taj način bi mogli djelovati poglavito na plućni krvotok. U literaturi postoji svega nekoliko izvješća o uporabi inhalirajućeg milrinona u poslijeoperacijskoj skrbi kardiokirurškog bolesnika, a uz još uvijek veliki broj neriješenih pitanja – točno definirane indikacije, vrijeme početka i trajanja liječenja, te optimalne koncentracije lijeka za ovaj način davanja. Ovdje smo opisali tijek liječenja 2 bolesnika s teškom plućnom hipertenzijom nakon zahvata na srčanim zaliscima. Zbog uznapredovalog pogoršanja kliničkog stanja bolesnika, odlučili smo se u liječenje uključiti kombinaciju inhalirajućeg i intravenskog milrinona. Milrinon, otopljen u fiziološkoj otopini 0,5 mg/mL, je davan pomoću pneumatskog raspršivača. Raspršivač je bio priključen na inspiracijski krak ventilacijskog kruga, neposredno do Y-završetka. Postigli smo zadovoljavajuće smanjenje plućnog tlaka u oba bolesnika, te su oba uspješno ekstubirana i otpuštena iz Jedinice intenzivnog liječenja. Iako se radi o vrlo malom uzorku bolesnika, naš je zaključak da bi kombinacija inhalirajućeg i intravenskog milrinona mogla biti učinkovita u visokorizičnih bolesnika sa sekundarnom plućnom hipertenzijom nakon kardiokirurških zahvata na srčanim zaliscima. Točno definirane indikacije, optimalnu koncentraciju za ovaj način dopreme lijeka, te početak i trajanje liječenja treba utvrditi u kontroliranim randomiziranim eksperimentima.