Clinical Research—Pediatric

Milrinone improves oxygenation in neonates with severe persistent pulmonary hypertension of the newborn

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Abstract

Background: Many neonates with severe persistent pulmonary hypertension of the newborn (PPHN) are nonresponders to inhaled nitric oxide (iNO). Milrinone is a promising adjunctive therapy because of its pulmonary vasodilator properties and cardiotropic effects.

Design: Case series of neonates with severe PPHN (defined as oxygenation index [OI] ≥20, failure of iNO therapy, and echocardiographic confirmation of PPHN).

Setting: Tertiary neonatal intensive care unit.

Subjects: Full-term (≥37 weeks) neonates with severe PPHN who received intravenous milrinone.

Measurements: The primary end point was the effect of intravenous milrinone on OI and hemodynamic stability over a 72-hour study period. Secondary end points examined included duration of iNO and degree of cardiorespiratory support.

Results: Nine neonates at a mean gestation of 39.25 ± 2.76 weeks, birth weight of 3668 ± 649.1 g, and baseline OI of 28.1 ± 5.9 received milrinone treatment after a poor initial response to iNO treatment. Intravenous milrinone was commenced at a median age of 21 hours (range, 18-49 hours), and patients were treated for median of 70 hours (range, 23-136). Oxygenation index was significantly reduced after milrinone treatment, particularly in the immediate 24 hours of treatment (8.0 ± 6.6, P < .001). There was a significant improvement in heart rate (179 ± 15.2 vs 149.6 ± 22.4, P < .001) over the same period. Infants who received milrinone did not develop systemic hypotension; in fact, there was a nonsignificant trend toward improved blood pressure.

Conclusions: Intravenous milrinone produces early improvements in oxygenation without compromising systemic blood pressure.

Keywords:
Milrinone; Oxygenation failure; Persistent pulmonary hypertension of the newborn; Myocardial dysfunction

1. Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is failure of systemic oxygenation because of marked pulmonary arterial hypertension secondary to elevated pulmonary vascular resistance (PVR) or altered pulmonary vasoreactivity [1,2]. This may lead to extrapulmonary shunting (right to left) of blood across foramen ovale and the patent ductus arteriosus. Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator and widely accepted as the gold standard treatment in PPHN [3]. Its usage has contributed to reduced rates of extracorporeal membrane oxygenation (ECMO) [4]. Nevertheless, 30% of patients with PPHN are iNO nonresponders, and alternative treatment...
options are required [5]. Milrinone, a selective inhibitor of phosphodiesterase (PDE) III in cardiac myocytes and vascular smooth muscle has been shown to reduce PVR and pulmonary artery pressure (PAP) in experimental models of pulmonary hypertension [6-8], adult humans [9,10], and neonates post cardiac surgery [11]. The effect of milrinone therapy has not been studied in neonates with oxygenation failure secondary to pulmonary hypertension.

2. Materials and methods

This retrospective study was conducted at the neonatal intensive care unit at the Hospital for Sick Children, Toronto, Canada, after approval by the local institutional review ethics board. Between January 2002 and April 2004, neonates with severe PPHN who responded poorly to inhaled nitric oxide (iNO) were treated with an alternative vasodilator therapy, intravenous milrinone. We hypothesized that coadministration of intravenous milrinone resulted in improved oxygenation without inducing systemic hypotension, thus minimizing the risk of ECMO. All neonates who received intravenous milrinone for resistant PPHN were identified from the neonatal database. Milrinone was only prescribed after consultation with the neonatal cardiologist when the patient satisfied the following clinical criteria:

1. Treatment with at least 20 ppm iNO for the preceding 4 hours;
2. Poor response to iNO was defined by an oxygenation index (OI) >20 on at least 2 consecutive arterial blood gas samples, at least 20 minutes apart during this period. Oxygenation index was calculated using arterial blood gas specimens according to the formula: \[ \text{OI} = \frac{\text{MAP} \times \text{FiO}_2/\text{PaO}_2}{100} \] where MAP is the mean airway pressure (cm H2O), FiO2 is the fraction of inspired oxygen, and PaO2 is the partial pressure of oxygen (mm Hg);
3. Evidence of a structurally normal heart and suprasystemic PAP from a 2-dimensional echocardiogram (severe tricuspid regurgitation, dilated right heart with bowing of the interatrial or interventricular septum, and right to left shunting at the ductal or atrial level).

Inhaled nitric oxide treatment was initiated according to unit guidelines once the following criteria were met:

1. Severe oxygenation difficulty defined by an OI >20 on 2 consecutive arterial blood gas samples, at least 20 minutes apart;
2. Gestational age >34 weeks and weight >1.5 kg.

If the patient did not respond to 20 ppm of iNO, the dosage could be increased to 80 ppm. If there was no response to the higher dose, the amount was weaned aggressively. If the patient responded to at least 20 ppm, weaning was left to the discretion of the attending neonatologist.

Newborns with congenital heart disease, diaphragmatic hernia, and congenital or lethal malformations (including developmental lung disorders) were excluded.

2.1. Outcomes

The primary outcome was the effect of milrinone on oxygenation and blood pressure over a 72-hour period after commencement of treatment. Secondary outcomes examined included the duration of ventilatory support, duration of iNO therapy, and degree of inotropic support.

2.2. Study drug

Intravenous milrinone (milrinone lactate injection, 10 mg/10 mL, Novopharm) was started at a dose of 0.33 \(\mu\)g/kg per minute. A loading dose was not administered because of illness severity and the potential risk of profound hypotension. The dose was titrated according to the clinical response and increased in increments of 0.33 to a maximum of 0.99 \(\mu\)g/kg per minute.

2.3. Measurements

Data were extracted from the electronic patient charting system and the patients’ medical records over a 72-hour period. The time of milrinone commencement, maximum dose, and duration of treatment were documented. Indices of respiratory (OI, iNO dose, ventilation settings, and FiO2) and cardiovascular stability (heart rate [HR] and blood pressure [systolic, diastolic, and mean]) were documented at 2 hours before; on initiation; and at 2, 6, 12, 24, 48, and 72 hours after commencement of milrinone therapy. Blood pressure readings were obtained from indwelling peripheral or umbilical arterial catheters in all cases. Hypotension was defined as a mean blood pressure less than the current gestational age of the patient [12]. Decisions to commence or adjust alternative inotropes or vasopressors were left to the discretion of the attending neonatologist. The amount of cardiovascular support before and 12 hours after the commencement of the infusion was recorded. The time to successful extubation (defined by a period >12 hours), duration of assisted ventilation (defined by assisted positive pressure ventilation and/or continuous positive pressure ventilation), and duration of supplemental oxygen were also recorded. The decision to wean assisted ventilation or supplemental oxygen treatment was made by the attending neonatologist.

2.4. Statistical analysis

Neonatal data were characterized using descriptive statistics where appropriate (ie, mean [±SD] and median [range] for continuous variables and frequency for categorical variables). Continuous data were analyzed using Student t test and Mann-Whitney U test for respective parametric and nonparametric data sets. Categorical data
were analyzed using $\chi^2$ or Fisher exact test. Analysis of variance testing was used to investigate the effects of milrinone (post hoc Tukey or Dunnett method) on each end point (ie, OI and blood pressure). Level of significance was set at $P < .05$.

3. Results

Seventy-two neonates were admitted to the neonatal intensive care unit with a diagnosis of PPHN during this period. Forty-eight (67%) neonates received iNO therapy. One neonate, with severe meconium aspiration syndrome, who did not receive milrinone, was referred for ECMO treatment. Nine full-term newborns, who received intravenous milrinone combination therapy in severe PPHN, were identified after a poor initial response to iNO. Their mean gestational age was 39.2 ± 2.8 weeks and birth weight, 3668 ± 649.1 g. The etiology of the PPHN was meconium aspiration syndrome (n = 5), birth asphyxia (n = 1), diabetic cardiomyopathy and birth asphyxia (n = 1), transient tachypnea of the newborn (n = 1) and sepsis (n = 1). Baseline OI was 28.7 ± 6.01, and dosage of iNO was 28.1 ± 14.1 at the time of milrinone commencement. The mode of ventilation was high frequency oscillation in 62.5% (5/8) and intermittent positive pressure ventilation in the remaining cases. All neonates had a structurally normal heart and evidence of suprasystemic pulmonary hypertension, with right-to-left intracardiac shunting, on echocardiographic assessment. Overall survival rate was 87.5% (7/8). The patient who died was not referred for ECMO because intensive care support was withdrawn on the grounds of severe asphyxia and poor neurodevelopmental prognosis.

Intravenous milrinone treatment was initiated at a median time of 21 hours (range, 18-49 hours). The median milrinone dose was 0.66 μg/kg per minute (range, 0.33-0.99 μg/kg), and patients were treated for a median of 70 hours (range, 23-136 hours). There was a significant improvement in oxygenation after commencement of milrinone (Fig. 1A and B, $P < .001$), particularly in the immediate 24 hours of treatment ($-20.0 ± 8.7, P < .001$). There was no change in the mode of ventilation during this period, and surfactant was not administered. The delivered mean airway pressure remained unchanged (17.1 ± 3.1 vs 16.4 ± 3.2, $P = .65$), and there were no significant differences in arterial pH and $P_{CO_2}$ after the commencement of milrinone. There was a significant improvement in HR (179 ± 15.2 vs 149.6 ± 22.4, $P < .001$) over the same period (Fig. 2). Infants who received milrinone did not
become hypotensive or receive additional inotropic support; in fact, they demonstrated a nonsignificant trend toward improved blood pressure (Fig. 3). The duration of inotropic support (2.1 days [range, 1-4 days]), maximum and duration of iNO treatment (80 hours [range, 23-187 hours]), time to successful extubation (73 hours [range, 36-240 hours]), and duration of supplemental oxygen (118 hours [range, 70-336 hours]) are consistent with iNO responders at our institution (unpresented data) and in several published reports[2,13,14].

Fig. 3 Blood pressure. Mean, systolic, and diastolic blood pressure after iNO and milrinone treatment. *P < .05 at baseline. SBP, systolic blood pressure. DBP, diastolic blood pressure. MBP, mean blood pressure.

4. Discussion

The ideal agent for the treatment of PPHN should primarily decrease PVR and right ventricular (RV) afterload, minimizing extrapulmonary and intrapulmonary shunt and improving cardiac output and vital organ perfusion without increasing myocardial oxygen demand. Inhaled nitric oxide is widely accepted as the agent of choice because of its selective vasodilator effects on the pulmonary vascular bed[14]. It decreases PAP, improves ventilation-perfusion mismatch, and has been shown to decrease ECMO usage[13,15]. Nevertheless, an alternative to iNO therapy is required for several reasons. Firstly, up to 30% of neonates are nonresponders and require an alternate treatment[5]. Secondly, prolonged high-dose iNO therapy is associated with the development of methemoglobinemia[16], organ injury from higher oxides[17], and cell membrane damage from peroxinitrites[18]. Finally, patient care is often compromised by flight restrictions in many regions (including our own region in Central Eastern Ontario), which limit iNO administration to critically ill patients transported by land vehicles only. In this case series, we present 9 neonates who failed to respond to iNO but demonstrated improved oxygenation after the addition of intravenous milrinone, thus avoiding ECMO.

4.1. Role of phosphodiesterase inhibitors in PPHN

Phosphodiesterase inhibitors increase intracellular levels of cyclic adenosine monophosphate (cAMP), improving myocardial performance without raising myocardial oxygen consumption[19]. The predominant isoenzymes in pulmonary arteries are PDE III and PDE V, suggesting that these enzymes are potential pharmacologic targets for pulmonary vasodilation[20]. Specific effects include vasorelaxation secondary to improved calcium uptake into the sarcoplasmic reticulum[21], inotropy (myocyte contraction) due to cAMP-mediated trans-sarcolemmal calcium flux[22], and lusitropy (myocyte relaxation) possibly due to improved actin-myosin complex dissociation[23]. Milrinone is a bipyridine compound that selectively inhibits PDE III. In a pediatric rodent model of hypoxia-induced pulmonary hypertension, the expression of PDE IIIa is up-regulated, and pulmonary artery relaxation is increased with milrinone treatment[24]. Experience with this drug in neonates is limited. Early studies of milrinone suggested that it was a relatively ineffective inotrope in a neonatal rabbit experimental model[25] and speculated that postnatal maturation of affinity occurred; however, in neonatal canine and porcine models, positive inotropy was demonstrated in the neonatal heart[26,27]. In the setting of postoperative cardiac surgery, prophylactic milrinone is highly effective in reversing the low cardiac output syndrome and improving pulmonary hemodynamics in infants and children[11,28].

4.2. Cyclic adenosine monophosphate–cyclic guanosine monophosphate signaling and pulmonary hypertension

The increased PVR in PPHN is secondary to endothelial dysfunction, leading to imbalances in endogenous vaso-dilators and vasoconstrictors such as endothelin-1, thromboxane A2, and nitric oxide (NO) production. Theoretically, a combination of agents that stimulate cAMP and cyclic guanosine monophosphate (cGMP)–mediated signaling pathways may produce greater improvements in oxygenation because they act synergistically on the pulmonary vascular bed. The addition of milrinone to iNO therapy in both canine and porcine adult experimental models of pulmonary hypertension led to reductions in PVR, PAP, and systemic vascular resistance (SVR) as well as improved RV compliance and cardiac output[7,8,29], compared with iNO alone. In children with pulmonary hypertension after cardiopulmonary bypass, combined milrinone and iNO produced a more pronounced decrease in PAP than either drug alone[30]. In a recent case series, neonates who were poor responders to iNO with severe PPHN, the addition of inhaled prostacyclin,
which also acts through cAMP signaling mechanisms, led to improvements in oxygenation [31].

4.3. Cyclic adenosine monophosphate–cyclic guanosine monophosphate signaling and myocardial function

The physiological roles and interactions of cGMP and cAMP in cardiac myocytes have also been characterized. Hartzell and Fischmeister [32] demonstrated a decrease in trans-sarcolemmal calcium uptake (ICa) after the administration of cGMP that is mediated by cAMP hydrolysis via a cGMP-stimulated cyclic nucleotide PDE. This may antagonize the positive inotropic effects of catecholamines and cAMP. The effects of iNO and cGMP were further characterized by examining the effects of NO donors on ICa and guanylyl cyclase activity in frog ventricular cells [33]. They noted both stimulatory and inhibitory effects on ICa that were mediated by the liberation of NO and accumulation of intracellular cGMP via divergent pathways. The stimulatory effects were mediated by blockade of cGMP-inhibited cAMP-PDE, which interestingly is also the receptor for milrinone. The inhibitory effects were mediated through stimulation of the cGMP-stimulated cAMP-PDE. The clinical implications of these competing effects in iNO-treated neonates is not well understood; however, to date, negative inotropic effects have not been reported in neonates. In an adult porcine model of pulmonary hypertension, increasing doses of iNO (range, 20-80 ppm) does not impair left ventricular contractility [34].

4.4. Implications for clinical practice in the management of PPHN

Traditionally, physicians are reluctant to treat PPHN with afterload-reducing agents because of concerns of systemic hypotension and a desire to maintain supranormal systemic arterial pressures in an attempt to reverse ductal shunting. This approach does not focus on the primary physiological disturbance of the pulmonary vascular bed, leading to increased RV afterload, and may result in harm for several reasons. Firstly, the pulmonary hypertension may be so severe that attempts to superecede it require very high-dose vasopressors. Commonly used agents such as dopamine or epinephrine cause both peripheral and pulmonary vasoconstriction at a dose ranges, which may exacerbate the pulmonary hypertension; secondly, they induce tachycardia and alter the balance of cellular metabolism, in particular, increasing myocardial oxygen demand, potentially increasing the likelihood of apoptosis and myocardial cell necrosis [35,36]. Finally, in some patients, the ductus may not be even be patent [37].

We have shown that the coadministration of intravenous milrinone in severe PPHN (iNO nonresponsiveness) leads to an early improvement in oxygenation and HR while maintaining a satisfactory blood pressure. It is impossible to tease out whether this is a direct effect of milrinone on the pulmonary vascular bed, its potential synergism with iNO, or secondary to improvements in myocardial performance, as outlined above. Theoretically, by reducing pulmonary afterload, improving RV compliance, and increasing myocardial contractility, milrinone improves passive left ventricular filling, hence increased cardiac output and blood pressure stability.

5. Limitations

This is a small retrospective pilot study, which limits study power and increases the likelihood of confounders. Because the study is not controlled, the effect of confounders need also to be considered. There is currently no consensus as to the duration beyond which a patient becomes a nonresponder. Variation in the oxygenation response due to delayed iNO responsiveness has been suggested. Turbow et al [38] studied the response to iNO in 13 neonates with severe PPHN and defined a response to be a 20% reduction in AaDO2 or a 40% reduction in OI. Using this definition, 3 of 12 neonates had an intermediate response (within 8 hours), and 3 of 12 had a delayed response (within 12 hours). It is possible that the intermediate responders in their study were already iNO-responsive by 4 hours of treatment, unlike our patients who demonstrated 4 hours of sustained nonresponsiveness. The authors do concede, however, that patients with delayed improvement in oxygenation were more likely to be responding to multifactorial therapy and concurrent interventions rather than iNO alone. Although there were no significant changes in ventilation, coexisting inotropic support, or addition of new treatments in our patients, changes in acid-base status or alterations in the biochemical milieu may influence oxygenation and myocardial performance. Finally, the improvements in oxygenation did not translate into improvements in the clinical outcomes studied (ie, duration of iNO and time to extubation). This should not be interpreted as a negative result because the study was not designed and was insufficiently powered to answer this question. In addition, it is clinically relevant that although the risk for ECMO was high, this intervention was avoided in all survivors.

In conclusion the addition of intravenous milrinone to neonates with severe PPHN with poor iNO responsiveness may lead to early and sustained improvements in oxygenation without compromising hemodynamic status. It is important to exhaust all medical options and make a decision regarding ECMO in nonresponders within a short time frame, either before the situation becomes irreversible or the patient suffers the consequences of tissue hypoxia. Prospective evaluation of the acute clinical and physiological effects and long-term outcome of intravenous milrinone therapy as an alternative cardiotropic agent or as combination therapy with iNO in neonates with PPHN is required.
References


