Journal of Critical Care (2006) **21**, 217–223

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Journal of Critical Care

Clinical Research—Pediatric

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

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

**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.



## 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

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doi:10.1016/j.jcrc.2006.01.001

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: [OI = MAP × $F_{IO_2}$/$Pa_{O_2}$ × 100] where MAP is the mean airway pressure (cm $H_2O$), $F_{IO_2}$ is the fraction of inspired oxygen, and $Pa_{O_2}$ 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 $F_{IO_2}$) 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