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Safety of milrinone use in neonatal intensive care units

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Abstract

Background—Milrinone use in the neonatal intensive care unit has increased over the last 10 years despite a paucity of published safety data in infants. We sought to determine the safety of milrinone therapy among infants in the neonatal intensive care unit.

Methods—We conducted a retrospective data analysis, identifying all infants exposed to milrinone discharged from 322 neonatal intensive care units managed by the Pediatric Medical Group from 1997–2010. We identified adverse events (AEs) during milrinone exposure. The unit

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Conflict-of-interest statement

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of observation for clinical AEs was the first course of milrinone and for laboratory AEs was an infant-day of exposure to milrinone.

Results—Overall, 1446 of 716,821 (0.2%) infants received milrinone for a total of 6894 infant-days. The proportion of infants exposed to milrinone increased from 0 in 1997 to 4/1000 infant cases in 2010. Persistent pulmonary hypertension (40%) was the most commonly reported diagnosis at the start of milrinone administration. Overall, 606/1446 (42%) of infants had at least 1 clinical AE recorded during milrinone therapy. Hypotension requiring pressors and thrombocytopenia ($<100,000/\text{mm}^3$) were the most commonly reported clinical and laboratory AEs, respectively. Death was reported in 8% of infants during the first course of milrinone therapy.

Conclusion—Among infants hospitalized in the neonatal intensive care unit, there was an increase in the use of milrinone over the past 13 years. The safety, dosing, and efficacy of milrinone in infants should be determined in prospective clinical trials.

Keywords

milrinone; infants; safety; adverse events; neonatal intensive care unit; persistent pulmonary hypertension

1. Introduction

Milrinone, a derivative of amrinone, belongs to the bipyridine compounds group of drugs that selectively inhibit cyclic nucleotide phosphodiesterase (PDE) enzymes and exert their hemodynamic effect through a change in intracellular calcium, independently of beta-adrenergic receptors [1–7]. Milrinone is approved by the U.S. Food and Drug Administration for short-term treatment of acute decompensated heart failure in adult patients, but its use in children remains off-label [8]. The first reported use of milrinone in infants was in those with low cardiac output following cardiac surgery [9]. Milrinone use has increased in the neonatal intensive care unit (NICU) and has been the focus of studies on the treatment of persistent pulmonary hypertension (PPHN), post patent ductus arteriosus (PDA) ligation syndrome, low cardiac output syndrome after corrective surgery for congenital heart defect, and low blood pressure of extremely preterm infants [9–11]. Recent pediatric studies investigating the efficacy of milrinone therapy in the pediatric and infant population resulted in the European Medicines Agency approval for the short-term (<35 hours) use of milrinone for children with severe congestive heart failure in 2011 [12].

Milrinone is used in hospitalized infants despite a paucity of safety data in this population. There is also lack of consensus about the appropriate indication and dosing of milrinone for infants. Milrinone clearance is higher in term infants relative to preterm infants [13–15]. Despite reports of adverse events (AEs) in small cohorts of infants, the safety of milrinone has not been investigated in a large cohort of exposed infants [16, 17]. Considering this lack of safety data and the increased use of this medication, we sought to describe the safety of milrinone therapy among infants in the NICU.

2. Methods

2.1. Data source

We identified all infants exposed to milrinone in the first 365 days of life discharged from 322 NICUs in North America managed by the Pediatrix Medical Group from 1997–2010. Data were obtained from an administrative database that prospectively captures information from daily progress notes generated by clinicians. Data on multiple aspects of care are entered into the system to generate admission notes, daily progress notes, procedure notes, and discharge summaries.

We defined a milrinone day as each day of exposure to milrinone. We counted an AE if it occurred on a milrinone day. Clinical AEs were only counted if they occurred during the first course of milrinone therapy. Daily laboratory results, medications, and diagnoses occurring during milrinone exposure were recorded. Adverse outcomes were classified as clinical AEs or laboratory AEs. Clinical AEs included: cardiovascular (hypotension requiring inotropic support, tachycardia, arrhythmia, and PDA requiring medical or surgical treatment), neurological (intraventricular hemorrhage [IVH] of any grade, seizure, and tremor), gastrointestinal (medical or surgical necrotizing enterocolitis [NEC] and intestinal perforation), hematological (bleeding events, defined as intraventricular, intracranial, cerebral, cerebellar, pulmonary, or gastrointestinal hemorrhage, hemorrhagic gastritis, hematuria, hematochezia, petechia, disseminated intravascular coagulation, or hemorrhage not otherwise specified), dermatological (rash), and death. Laboratory AEs identified included hypokalemia, renal dysfunction (elevated blood urea nitrogen [BUN] or creatinine [Cr]), liver dysfunction (elevated liver enzymes or direct bilirubin), and thrombocytopenia. Only the first episode of each clinical AE was counted. Laboratory AEs were categorized as AEs or serious adverse events (SAEs) based on pre-specified laboratory cut-off values. Each day of a laboratory abnormality was counted as a separate AE and reported per 1000 infant-days.

The study was approved by the Duke University Institutional Review Board without the need for written informed consent as the data were collected without individual identifiers.

2.2. Statistical analysis

The unit of observation was the first course of milrinone therapy for each infant for clinical AEs and an infant-day of exposure to milrinone during any course of milrinone therapy for laboratory AEs. We used standard summary statistics to describe the study variables. Analyses were performed using SAS 9.3 software (SAS institute, Cary NC).

3. Results

3.1. Demographics

During the study period, 716,821 infants were discharged from 322 NICUs. Of those, 1446 infants (0.2%) were exposed to milrinone for a total of 6894 infant-days (Table 1). The median gestational age (GA) and birth weight were 36 weeks (interquartile range; 31, 39) and 2700 g (1500, 3300), respectively. Of the infants exposed to milrinone, 365 (25%) died prior to discharge.

3.2. Milrinone therapy

The median age at first exposure to milrinone was 2 days (1, 7). The majority of infants received only 1 course of milrinone—1399/1446 (97%). The proportion of infants exposed to milrinone increased during the study period from 0 in 1997 to 4/1000 infants in 2010, with a more prominent increase from 2006–2010 (Figure 1). There was no significant difference in GA between infants exposed to milrinone from 1997–2005 (n=163) and those exposed from 2006–2010 (n=1283)—mean 33.8 vs. 34.6, $p = 0.70$. PPHN (40%) followed by hypoperfusion (9%) were the most commonly reported diagnoses on the first day of milrinone exposure (Table 2). Dopamine was the most commonly administered medication at time of milrinone exposure (Table 3). Milrinone-exposed infants who died prior to discharge were less likely to have PPHN on the first day of milrinone exposure and more likely to experience laboratory AEs (41% vs. 31%, $p = 0.03$, and 298 vs. 360 per 1000 infant-days, $p = 0.02$, respectively) (Table 4).

Forty-two percent (n=606) of infants had at least 1 clinical AE recorded during milrinone therapy. Hypotension requiring pressors and PDA requiring treatment were the most commonly reported AEs while on milrinone (20% and 13%, respectively). The majority of hypotension events occurred on the start day of milrinone therapy—243/288 (84%). Hypotension was also more frequent among infants with an underlying diagnosis of PPHN—179/405 (31%)—vs. infants without PPHN—109/694 (14%), $p < 0.0001$. Arrhythmia, NEC, and intestinal perforation were each reported in <2% of patients (Table 5).

The overall incidence of laboratory AEs and SAEs was 301 and 161 per 1000 infant-days, respectively. Thrombocytopenia ($<100,000/\text{mm}^3$) was the most common laboratory AE (238/1000 infant-days), followed by hypokalemia (39/1000 infant-days) (Table 6). Cardiovascular, neurological, and hematological AEs were more commonly reported in preterm infants of ≤ 32 weeks GA relative to term infants ($p < 0.01$) (Figure 2). Laboratory AEs were more commonly reported in infants of <26 weeks GA as compared with infants ≥ 37 weeks GA ($p < 0.01$).

4. Discussion

This is the first report of milrinone safety in a large multicenter cohort of hospitalized infants. PPHN followed by hypoperfusion was the most common diagnosis reported at initiation of milrinone therapy. This result is consistent with existing reports on use of milrinone, which are mainly focused on infants with PPHN or low cardiac output syndrome [9,11,13–15]. We found that over 40% of infants on milrinone therapy experienced at least 1 clinical AE and that a laboratory AE occurred on approximately one third of infant-days.

Hypotension requiring pressors (20%) and PDAs requiring treatment (13%) were the most commonly reported clinical AEs during milrinone therapy. Hemodynamic effects of milrinone therapy in infants are reported in 2 randomized, double-blind, placebo-controlled trials. The first study examined milrinone therapy in postoperative children and infants of >36 weeks GA and 2 kg with congenital heart defect (PRIMACORP), and the second trial was on the use of 18-hour milrinone therapy in preterm infants <30 weeks GA for the prevention of low blood pressure in the transitional period [13,14]. The PRIMACORP trial

showed a significant reduction in systolic blood pressure at 1, 4, and 8 hours after initiation of treatment in patients receiving milrinone [13]. In the recent open-label study of milrinone in infants with PPHN, a transient reduction in systolic arterial pressure was observed following co-administration of milrinone and 15 ml/kg of normal saline bolus [15]. When used prophylactically for low systemic blood flow of preterm infants in the transitional period, hypotension was observed in 50% of newborns randomized to milrinone vs. 38% in the placebo group ($p = 0.2$) [14]. Milrinone also appeared to slow the closure of the ductus arteriosus. Late treatment with indomethacin was needed in 15/44 (44%) infants on milrinone vs. 11/44 (33%) in the placebo group after the start of milrinone therapy ($p = 0.2$). Surgical ligation was required in 4/42 (9%) infants from the milrinone group vs. 2/44 (4%) in the placebo group ($p = 0.7$) [14]. This adverse outcome is physiologically relevant in view of augmenting effects of PDE inhibitors on biological dilators of the ductus arteriosus muscle and the vasodilatory effect of milrinone on the vascular smooth muscles [14,18,19].

In a prospective observational study of pediatric patients undergoing congenital heart surgery, milrinone use was found to be an independent risk factor for clinically significant tachyarrhythmia in the early postoperative period of 724 procedures, with an estimated odds ratio (95% confidence interval) of 4.5 (3.0–6.9). Newborns <1 month of age accounted for 175 (24%) of these procedures, and age <1 month was identified as an independent risk factor for the development of a tachyarrhythmia [16]. In our study, only 0.5% of the patients experienced arrhythmia while receiving milrinone therapy. This lower rate might, in part, be explained by the difference in the setting and in the number of congenital heart surgeries between the 2 studies.

Of the few existing reports on the use of milrinone in infants, none have examined the risk of bleeding events secondary to milrinone. PDE III enzymes are not only present in cardiac and vascular muscles but also in platelets [20]. As a potent PDE III inhibitor, the potential effect of milrinone on platelet aggregation and hemostasis needs further investigation. We observed a bleeding event in >10% of the infants in our cohort during milrinone therapy.

The incidence of IVH in our cohort was 4%, with grade III or IV accounting for half of the ventricular bleeds. Although a report of 4 infants with severe PPHN treated concomitantly with nitric oxide and milrinone described development of serious IVHs in 2 of the infants and a small IVH in 1 infant, the 42 preterm newborns who received prophylactic milrinone for the prevention of the low systemic blood flow did not show a significant increase in the risk of high-grade hemorrhage during the 28 days of follow-up [14,17]. In our study, preterm infants accounted for the majority of infants with high-grade IVH with median GA of 27 weeks (27, 32).

Thrombocytopenia was the most commonly reported laboratory AE during milrinone therapy in our cohort. A prospective, open-label study of the pharmacokinetics and side effects of milrinone in infants and children after open-heart surgery showed a significant decrease in platelet count during milrinone therapy, with up to 58% of patients experiencing thrombocytopenia ($<100,000$ cells/mm³). The risk increased significantly with duration of infusion [20]. In contrast, no significant increased risk of thrombocytopenia was observed in the PRIMACORP study or in the only randomized controlled trial of milrinone therapy in

preterm newborns [13,14]. Both of these studies, however, had limitations in their patient characteristics, sample size, or duration of therapy, thus limiting the generalizability of their results to the infant population.

Infants on milrinone had elevated BUN or Cr on 50/1000 infant-days. As the renal clearance of milrinone is age-dependent, infants experience a lower clearance and longer half-life compared with children. The potential impairing effect of milrinone on renal function can further decrease the clearance and leads to higher steady-state concentration, which can result in SAEs [10,21,22]. This finding is particularly concerning considering the susceptibility of hospitalized infants in the NICU to renal impairment [23].

Our study has some limitations. The data used are derived from electronic documentation of clinical care and not collected primarily for research purposes. In the absence of a known drug of the same class or a drug with similar pharmacodynamic effects that is used frequently in infants, we were unable to identify a control group with which to compare the incidence of AEs. The most common clinical AEs were cardiovascular, and we were not able to control for the potential bias of the increased rate of underlying cardiovascular conditions among the infants treated with milrinone. We were unable to differentiate if clinical AEs occurring on the start day of milrinone started prior to or after the initiation of milrinone. The clinical significance of hypotension as the most commonly reported AE also remains unknown in our population as it could have potentially been associated with enhancement of the left heart preload and cardiac output [15]. Laboratory AEs may be affected by the frequency of blood draws, which occur at the discretion of the clinician. The study was performed over a 13-year period, and changes in practice during the study period may have affected incidence of AEs associated with the use of milrinone. Although the current recommended dosing of milrinone therapy in infants supports the use of a loading dose followed by maintenance infusion, loading doses are frequently avoided due to the fear of potential AEs [11,15,24]. We were unable to delineate the details of milrinone dosing in our dataset.

This study—the first to report on the safety of milrinone in a large multi-center cohort of hospitalized infants—also has several strengths, including the relatively large patient population. We also were able to examine a wide range of clinical and laboratory AEs, previously reported in relation to the use of milrinone, for the first time in infants. The large sample size and the broad range of clinical data used helped to determine preliminary measures of potential associations between previously reported AEs in adults and older children and the use of milrinone in sick infants.

In this study, we identified a large relative increase in the use of milrinone since the first report of its use in 1998. This substantial increase, along with the report of most commonly identified clinical and laboratory AEs during milrinone exposure, underscore the urgent need for a prospective clinical trial to explore the safety of this medication in newborns and infants.

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Highlights

- This retrospective analysis identified infants exposed to milrinone from 1997–2010.
- We identified AEs during milrinone exposure.
- Hypotension requiring pressors was the most commonly reported clinical AE.
- Thrombocytopenia was the most commonly reported laboratory AE.
- Milrinone use has increased over the past 13 years.

Figure 1.
Infants exposed to milrinone by year.

Figure 2. Frequency and type of adverse events by gestational age. (A) Laboratory adverse event per 1000 infant-days by weeks gestational age. (B) Clinical adverse event by weeks gestational age. AE, adverse event; SAE, serious adverse event; CVS, cardiovascular; neuro, neurological; GI, gastrointestinal; hem, hematological.

Table 1

Patient characteristics

	N=1446
Gestational age (weeks)	
<26	133 (9%)
26–28	127 (9%)
29–32	174 (12%)
33–36	289 (20%)
37	722 (50%)
Birth weight (g)	
<1000	221 (15%)
1000–1499	122 (8%)
1500–2499	292 (20%)
2500–3499	557 (38%)
3500	254 (17%)
Male	854 (59%)
Race/ethnicity	
White	649 (45%)
Black	248 (17%)
Hispanic	426 (29%)
Other	74 (5%)
Antenatal antibiotics	357 (25%)
Antenatal steroids	372 (26%)
Vaginal delivery	480 (33%)
Outborn	668 (46%)
Duration of milrinone therapy (days) *	3 (1, 6)

* Median (interquartile range).

Table 2

Diagnosis reported on the first day of milrinone therapy

	N=1446
Persistent pulmonary hypertension	584 (40%)
Hypoperfusion	127 (9%)
Cardiac dysfunction	74 (5%)
Cardiomyopathy	72 (5%)
Congestive heart failure	42 (3%)
Perinatal depression	47 (3%)
Right ventricular hypertrophy	22 (2%)
Cardiogenic shock	20 (1%)
Myocarditis	5 (0.3%)

Table 3

Concomitant medications per milrinone course

	N=1497
Dopamine	636 (42%)
Furosemide	474 (32%)
Fentanyl	440 (30%)
Gentamycin	419 (28%)
Midazolam	378 (25%)
Ampicillin	376 (25%)
Dobutamine	360 (24%)
Inhaled nitric oxide	299 (20%)
Epinephrine	286 (19%)
Vancomycin	286 (19%)

Table 4

Characteristics and adverse event frequencies by survival

	Survived (N=1081)	Died (N=365)	P value
Diagnosis on the first day of milrinone therapy			
Persistent pulmonary hypertension	547 (41%)	37 (31%)	0.03
Hypoperfusion	112 (8%)	15 (13%)	0.13
Clinical adverse events			
Cardiovascular	399(30%)	39(33%)	0.58
Neurological	98(7%)	6(5%)	0.33
Gastrointestinal	12(1%)	3(3%)	0.10
Hematological	136(10%)	9(8%)	0.34
Laboratory adverse events*			
Serious adverse event	159	191	0.10
Adverse event	298	360	0.02

*
Per 1000 infant-days.

Table 5

Clinical adverse events during the first course of milrinone therapy

	N=1446
Cardiovascular	
Hypotension requiring pressors	288 (20%)
Tachycardia	16 (1%)
Arrhythmia	8 (0.5%)
PDA	194 (13%)
Neurologic	
IVH, grade I or II	37 (3%)
IVH, grade III or IV	38 (3%)
Seizure	39 (3%)
Gastrointestinal	
NEC, surgical	5 (0.3%)
NEC, medical	5 (0.3%)
Intestinal perforation	6 (0.4%)
Hematological	
Bleeding events	145 (10%)
Dermatologic	
Rash	1 (0.1%)
Death	120 (8%)

Table 6

Laboratory adverse events

	Adverse events		Serious adverse events	
		AE/1000 infant days		SAE/1000 infant days
Serum electrolytes				
Hypokalemia	<3 mmol/L	39	<2.5 mmol/L	9
Renal dysfunction				
Elevated BUN	>70 mg/dL	25	>100 mg/dL	5
Elevated creatinine	>1.7 mg/dL	36	>3.0 mg/dL	12
Liver dysfunction				
Elevated AST	>500 U/L	8	>1000 U/L	4
Elevated ALT	>500 U/L	4	>1000 U/L	1
Direct bilirubin	>5 mg/dL	23	>10 mg/dL	7
Complete blood count				
Thrombocytopenia	<100,000/mm ³	238	<30,000/mm ³	133
Any laboratory AE		301		161

AST, aspartate aminotransferase; ALT, alanine transaminase.