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Research Article

Clinical pharmacology of Milrinone in paediatric patients

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Abstract

Milrinone inhibits human heart phosphodiesterase 3 and phosphodiesterase 4 with similar potency. By increasing cAMP concentration, they have similar actions as the β receptor agonists dobutamine and epinephrine, but tend to lower systematic and pulmonary vascular resistance more than do the catecholamines. The vasodilation due to milrinone is related to increased levels of cAMP in vascular smooth muscle. Milrinone is used for short term treatment of acute low cardiac output after cardiac surgery due to septic shock. Milrinone is administered by continuous intravenous infusion and its dosage consists in a loading dose followed by a maintenance infusion in infants and children. Milrinone is efficacy and safe in infants and children but it may induce adverse-effects. The effects of milrinone in infants and children have been extensively studied: milrinone improves oxygenation and myocardial performance, milrinone is used to treat pulmonary, ventricular dysfunction, and tachyarrhythmias. The pharmacokinetics of milrinone have been studied in infants and children and the elimination half-life is 3.1 hours in infants aged < 1 year and 1.9 hours in children. The treatment of infants and children with milrinone has been extensively studied: milrinone treats hypoxemic respiratory failure and reduces diastolic arterial pressure, milrinone has been successfully used in infants and children undergoing heart surgery, and milrinone prevents death or low cardiac output syndrome in children undergoing surgery for congenital heart disease. The aim of this study is to review the milrinone dosing, efficacy and safety, effects, adverse-effects, pharmacokinetics, and treatment in infants and children.

INTRODUCTION

Mechanism of milrinone action

Parenteral formulation of milrinone is used for short term circulation support in advanced congestive heart failure. Milrinone inhibits human heart phosphodiesterase 3 and phosphodiesterase 4 with similar potency. By increasing intracellular cAMP concentrations, they have similar actions as the β receptor agonists dobutamine and epinephrine, but tend to lower systemic and pulmonary vascular resistance more than do the catecholamines it should be kept in mind that the phosphodiesterase inhibitors potentiate the action of β receptor agonists, both beneficial and detrimental. In adults, the loading dose of milrinone is ordinarily 25 to 75 μg/kg, and the continuous infusion rate ranges from 0.375 to 0.75 μg/kg per min, and the elimination half-life of milrinone is 0.5 to 1 hour but it can be increased in patients with severe congestive heart failure [1].

Clinical use of milrinone

Milrinone lactate has been most commonly used in the postoperative care of infants with congenital heart disease to treat low cardiac output state and in near-tern and term infants with persistent pulmonary hypertension of the newborn infant as an adjunct to, or sometimes in place of nitric oxide [2]. Milrinone improves cardiac output by enhancing myocardial contractility, enhancing myocardial diastolic relaxation and decreasing vascular resistance. It acts via selective phosphodiesterase 3 inhibition that leads to increased intracellular cAMP, increased myocardial intracellular calcium, and increased reuptake of calcium after systole. Vasodilatation is related to increased levels of cAMP in vascular smooth muscle. Unlike catecholamines, myocardial oxygen consumption is not increased. Elimination is primarily via renal mechanisms. The half-life is quite variable, ranging from approximately 10 hours in extremely-low-birthweight infants to approximately 3 hours in older and more mature infants. Milrinone is used for short term (< 72 hours) treatment of acute low cardiac output after cardiac surgery or due to septic shock. It is recommended the continuous monitoring of the blood pressure and the heart rate rhythm. It should be assessed the sign of cardiac output. In addition, it should be monitored carefully the fluid and electrolyte changes, the renal function during therapy, and the platelet counts. Milrinone is incompatible with furosemide, imipenem-cilastatin, and procainamide [3]. (Figure 1)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "milrinone dosing infants, children", "milrinone efficacy, safety, infants, children", "milrinone effects infants, children", "milrinone adverse-effects infants, children", "milrinone pharmacokinetics infants, children", and "milrinone treatment infants, children". In addition, the books: The pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by

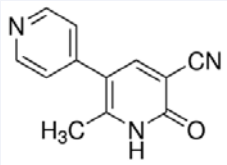

Figure 1 Milrinone molecular structure (molecular weight = 211.22 grams/mole).

Young and Mangum [3], and The British National Formulary for Children [4] are consulted.

RESULTS

Administration schedules of milrinone to infants and children

Administration by intravenous infusion to infants [2]:

1. **Preterm infants.** Give a loading dose of 0.75 μg/kg per min for 3 hours, and then a maintenance infusion of 0.2 μg/kg per min for 18 hours.
2. **Term infants and older infants.** Give a loading dose of 50 to 75 μg/kg over 30 to 60 min, and then a continuous intravenous infusion of 30 to 45 μg/kg per hour for 2 to 3 days (usually for 12 hours after cardiac surgery). Hypotension may occur while the loading dose is being given because the drug causes some vasodilation. Volume expansion and/or low-dose dopamine will usually counteract this.
3. **Administration by intravenous infusion to children [4]:** Give initially 50 to 75 μg/kg over 30 to 60 min, reduce or omit the initial dose if there is the risk of hypotension, and then (by continuous infusion) give 30 to 45 μg/kg per hour for 2 to 3 days (usually for 12 hours after cardiac surgery).

Efficacy and safety of milrinone in infants and children: Preterm infants undergoing a post-ligation cardiac syndrome were treated with milrinone as a bolus infusion of 0.75 μg/kg per min for 3 hours followed by a 0.16 μg/kg per min maintenance infusion and this treatment is efficacy and safe [5]. Milrinone is found safe in hospitalized infants [6]. Milrinone is found efficacy and safe in children undergoing low cardiac output syndrome [7]. The use of milrinone for ≥ 3 days is effective and safe in preventing low cardiac output in children after cardiac surgery [8].

Effects of milrinone in infants and children: Milrinone improves both oxygenation and myocardial performance in preterm infants with pulmonary hypertension [9]. Milrinone is a useful therapy for preterm infants with echocardiography findings of pulmonary hypertension and/or ventricular dysfunction [10]. Administration of milrinone to infants with low cardiac output leads to improved postoperative stability [11]. Intravenous milrinone produces early improvements in oxygenation in infants without compromising systemic blood pressure [12]. Administration of milrinone in infants with low cardiac output after cardiac surgery lowers filling pressures, systemic and pulmonary arterial pressures, and systemic and pulmonary vascular resistances, while improving cardiac index [13]. Perioperative milrinone infusion improved the mortality after the Norwood-Sano procedure in children [14]. Milrinone is found to have several beneficial hemodynamic effects in children during critical illness when used at usual clinical doses [15]. Milrinone is used by the vast majority of caregivers following congenital heart surgery in children [16]. Milrinone use is an independent risk factor for clinically significant tachyarrhythmias in the early postoperative period after congenital heart surgery in children [17]. Milrinone is beneficial in the optimization of cardiovascular function after cardiac surgery and in children with septic shock [18]. Low dose of milrinone has anti-inflammatory properties and potentially can improve splanchnic perfusion in children [19]. Bolus milrinone consistently decreases pulmonary vascular resistance in children with pulmonary hypertension secondary to severe heart failure [20].

Adverse-effects which are common or very common in infants and children [4]: Arrhythmia supraventricular (increased risk in patients with pre-existing arrhythmias), arrhythmias, headache, and hypotension.

Adverse-effects which are uncommon in infants and children [4]: Angina pectoris, chest pain, hypokalaemia, thrombocytopenia, and tremor.

Adverse-effects which are rare or very rare in infants and children [4]: Anaphylactic shock, bronchospasm, and skin eruption.

Adverse-effects whose frequency is not known in infants and children [4]: Intraventricular haemorrhage and renal failure.

Contra-indications [4]: Severe hypovolaemia.

Cautions [4]: Correct hypokalaemia, heart failure associated with hypertrophic cardiomyopathy, stenosis or obstructive valvular disease or other outlet obstruction.

Pregnancy [4]: The manufactory advises the use of milrinone only the potential benefit outweighs the risk.

Pharmacokinetics of milrinone in infants and children: Hornik et al. [21] studied the pharmacokinetics of milrinone in 74 infants, children, and adolescents whose demographic characteristics are reported in table 1. The subjects received milrinone by continuous intravenous infusion at median dose of 0.5 μg/kg per min (range, 0.1 to 41) for a median duration of 12 hours (range, 0.02 to 2,647) (Table 1& 2).

This table shows that the distribution volume is similar to the water volume and there is a remarkable interindividual variability in the total body clearance and in the distribution volume. Such variability is accounted by the wide variability of the subject characteristics.

Ramamoorthy et al. [22] investigated the pharmacokinetics of milrinone in 19 infants and children after open heart surgery. Table 3 summarizes the demographic characteristics of the subject included in the study. (Table 3)

Subjects were divided in two groups to receive milrinone as follows: 11 subjects were treated with an initial bolus dose of

Table 1: Demographic characteristics of subjects included in the study. Figures are the number and (%), by Hornik et al. [21].

Characteristic	Median (range) or number (%)
Age (years)	2.9 (0.04, 18)
≤ 28 days	13 (8%)
>28 days to ≤ 2 years	19 (26%)
>2 years to ≤ 12 years	29 (39%)
>12 years	13 (18%)
Gestational age (weeks)	39 (37 - 41)
Postmenstrual age (weeks)	192 (37 - 977)
Body-weight	13.1 (2.6 - 158)
Male	39 (53%)
Serum creatinine (mg/dl)	0.5 (0.1 - 3.1)
Creatinine clearance (ml/min/1.73 m²)	118 (1.1 - 261)

25 μg/kg followed by a maintenance infusion dose of 0.25 μg/kg per min started at the end of the first dose. Thirty min later, a second 25 μg/kg bolus was given, and the infusion was increased to 0.5 μg/kg per min (small dose). Eight subjects received a 50 μg/kg bolus administered over 10 min, and an infusion of 0.5 μg/kg per min was started at the end of the bolus. A 25 μg/kg bolus was given 30 min after the first bolus, and the final rate infusion was increased to 0.75 μg/kg per min (large dose). In addition, the subjects in both groups received a third bolus dose of milrinone of 25 μg/kg. (Table 4)

This table shows that the distribution volume is similar to the water volume, milrinone is rapidly eliminated and there is a remarkable variability in the pharmacokinetic parameters. Such variability accounts for the wide variability of the demographic characteristics and also for the heart disease. (Table 5)

This table shows that the distribution volume is larger in infants and the total body clearance is higher in children. Milrinone is mainly eliminated by the renal route and the renal function increases with the infant maturation and child development.

Treatment of infants and children with milrinone: Milrinone treats infants with hypoxemic respiratory failure and hypoxic ischemic encephalopathy and develops profound reduction in diastolic arterial pressure [23]. Dobutamine and milrinone, two primary medicines that can be used in the treatment of cases with postligation cardiac syndrome in infants, possess similar therapeutic efficacy on this pathology [24]. Intravenous milrinone used in conjunction with infants treated with nitric oxide will result in a reduction in the time spent on infants treated with nitric oxide only [25]. Intravenous milrinone is a commonly used medication in neonatal/paediatric intensive care units and is currently used in 17% of patients with congenital diaphragmatic hernia [26]. Milrinone treatment is effective in children with cardiac dysfunction and in the therapy for cardiac transplant, or as palliative therapy for cardiomyopathy [27]. Milrinone treatment prevents death or low cardiac output syndrome in children undergoing surgery for congenital heart disease [28]. Milrinone, epinephrine, dopamine, and dobutamine are mostly used, and should be prioritised for future research on low cardiac output syndrome treatment in children [29]. A loading dose of 75 μg/kg milrinone lactate and starting infusion rates of 0.75 to 1.0 μg/kg per min for children with normal renal function should be used and the infusion rate should then be titrated to effect [30]. Intravenous administration of milrinone is used in paediatric patients with non-hyperdynamic septic shock [31].

Table 2: Parameter estimates and bootstrap results for the final population pharmacokinetic model, by Hornik et al. [21].

Parameter	Estimate (RSE)	Bootstrap median (5th, 95th percentile)
Total body clearance$_{70kg}$ (L/h)	15.9 (23%)	15.9 (12.2, 33.5)
Distribution volume$_{70kg}$ (L)	32.2 (30%)	31.6 (12.4, 154)
Exponent for power function characterizing the effect of CrCl on TBC)	0.522 (27%)	0.54 (0.30, 0.82)
TM$_{50}$ (weeks PMA)	67.7 (64%)	68.4 (39.5, 1,159)
Hill Coefficient	1.12 (70%)	1.1 (0.44, 24.7)
Interindividual variation of TBC (CV%)	70 (27%)	67 (48, 83)
Residual proportional error (%)	32 (29%)	26 (20, 30)

TBC = total body clearance. %RSE = %relative standard error. CrCl = creatinine clearance. PMA = postmenstrual age in weeks. CV = coefficient of variation. The total body clearance and the distribution volume are standardized to a body-weight of 70 kg.

Table 3: Demographic characteristics of the subjects included in the study. Figures are the minimum, maximum, mean, and standard deviation (±SD), by Ramamoorthy et al. [22].

Value	Age (year)	Body-weight (kg)	CPB	ICU (arrival to milrinone start (min)	Duration of infusion (h)
Minimum	0.36	4.4	52	55	16
Maximum	11.8	42.0	164	192	91
Mean	3.0	12	120	107	40
SD	±3.7	±12	±24	±34	±20

ICU = intensive care unit.

Table 4: Pharmacokinetic parameters of milrinone which are obtained in 19 infants and children. Figures are the mean and standard deviation (±SD), by Ramamoorthy et al. [22].

Parameter	Mean±SD
$Conc_{ss}$ (Small dose)	113±39
$Conc_{ss}$ (Large dose)	206±74
Total body clearance (L/h)	4.0±4.9
Total body clearance (ml/kg/min)	4.5±1.8
β (h)	0.45±0.34
Elimination half-life (h)	2.7±2.1
DVβ (L)	8.4±7.2
DVβ (L/kg)	0.83±0.40

$Conc_{ss}$ = steady-state plasma milrinone concentration. β = terminal elimination rate constant. DV = distribution volume.

Table 5: Comparison of the pharmacokinetic parameters which are obtained in 12 infants and 7 children. Figures are the mean and the standard deviation (±SD), by Ramamoorthy et al. [22].

Parameter	Infants aged < 1 year (N = 12)	Children aged > 1 year (N = 7)
Distribution volumeβ (L/kg)	0.9±0.4	0.7±0.2*
TBL (ml/kg/min)	3.8±1.0	5.9±2.0*
Elimination half-life (h)	3.1±2.0	1.9±2.0*

β = terminal elimination rate-constant. *P-value (Student test) < 0.05.

DISCUSSION

Parenteral formulation of milrinone is used for term circulation support in advanced congestive heart failure. Milrinone inhibits human heart phosphodiesterases 3 and 4 with similar potency. By increasing intracellular cAMP concentrations, they have similar actions as the β receptor agonists dobutamine and epinephrine, but tend to lower systemic pulmonary vascular resistance more than do the catecholamines and the phosphodiesterase inhibitors potentiate the action of β receptor agonists, both beneficial and detrimental [1] and the vasodilatation is related to increased levels of cAMP in vascular smooth muscle [3]. Milrinone is administered by continuous intravenous infusion and the dosage of milrinone consists in a loading dose followed by a maintenance infusion in infants [2] and children [4]. The efficacy and safety of milrinone have been described in infants and in children [5-8]. Preterm infants undergoing post-ligation cardiac syndrome were treated with milrinone and this treatment is efficacy and safe [5]. Milrinone has been found safe in hospitalized infants [6] and in children undergoing low cardiac output syndrome [7]. Milrinone is efficacy and safe in preventing low cardiac output in children after cardiac surgery [8]. The effects of milrinone have been reported in infants and children [9-20]. Milrinone improves both oxygenation and myocardial performance in preterm infants with pulmonary hypertension [9], milrinone is a useful therapy for preterm infants with pulmonary hypertension and/or ventricular dysfunction [10], and milrinone improves postoperative stability in infants with low cardiac output [11]. Administration of milrinone improves oxygenation in infants without compromising systemic blood pressure [12], and administration of milrinone in infants with low cardiac output after cardiac surgery lowers filling pleasures, systemic and pulmonary arterial, and systemic and pulmonary vascular resistances [13]. Milrinone improves the mortality-rate after Norwood-Sano procedure in children [14], milrinone has beneficial hemodynamic effect in children during critical illness [15], milrinone is used in children following congenital heart surgery [16], milrinone treats tachyarrhythmias in children during early postoperative period after cardiac surgery and in children with septic shock [17], and milrinone optimizes cardiovascular function in children after cardiac surgery and in children with septic shock [18]. Low dose of milrinone has anti-inflammatory properties [19], and milrinone decreases vascular resistance in children with pulmonary hypertension [20]. Milrinone may cause adverse effects in infants and children [4]. The pharmacokinetics of milrinone have been studied in infants and children [21-22]. The elimination half-life of milrinone is 3.1 hours in infants aged < 1 year and 1.9 hours in children [22] and the distribution volume is similar to the water volume [21-22]. Milrinone is mainly eliminated by renal route and the renal function increases with infant maturation and child development. This consideration explains the longer elimination half-life of milrinone in infants than in children. The total body clearance, the distribution volume, and the elimination half-life range in a wide interindividual variability and this variability is accounted by the wide variation in the demographic characteristics of subjects and by the heart disease. The treatment of infants and children with milrinone has been extensively reported [23-31]. Milrinone treats infants with hypoxemic respiratory failure and hypoxic ischemic encephalopathy and reduces the diastolic arterial pressure [23]. Dobutamine and milrinone can be used in the treatment of infants with postligation cardiac syndrome and possess similar therapeutic efficacy on this pathology [24]. Intravenous milrinone is used in combination with nitric oxide and reduces the time spent on infants treated with nitric oxide only [25], and intravenous milrinone is used in infants and children with congenital diaphragmatic hernia [26]. Treatment with milrinone is effective in children with cardiac dysfunction or as palliative therapy for cardiomyopathy [27]. Milrinone treatment prevents death or low cardiac output syndrome in children undergoing surgery for congenital heart disease [28]. Milrinone, epinephrine, dopamine, and dobutamine are used for the treatment of low cardiac output syndrome in children undergoing surgery for congenital heart disease [29]. The treatment of children with milrinone lactate requires a loading dose of 75 μg/kg followed by an infusion of 0.75 to 1.0 μg/kg per min [30], and intravenous milrinone is used in paediatric patients with non-hyperdynamic septic shock [31].

In conclusion, milrinone inhibits human heart phosphodiesterases 3 and phosphodiesterases 4 with similar potency. By increasing intracellular cAMP concentrations, they have similar actions as the β receptor agonists dobutamine and epinephrine, but tend to lower systematic and pulmonary vascular resistance more than do the catecholamines. The phosphodiesterase inhibitors potentiate the action of β receptor agonists, both beneficial and detrimental. The vasodilatation induced by milrinone is related to increased levels of cAMP in vascular smooth muscle. Milrinone is used for short term (<

72 hours) treatment of acute low cardiac output after cardiac surgery or due to septic shock. Milrinone is administered by continuous intravenous infusion and it is administered by a loading dose followed by a maintenance infusion in infants and children. Milrinone has been found efficacy and safe in infants and children but it may induce adverse-effects. The effects operated by milrinone and the pharmacokinetics of milrinone have been extensively studied in infants and children. In infants aged < 1 year, the elimination half-life of milrinone is 3.1 hours and it is 1.9 hours in children. Milrinone is mainly eliminated by renal route and the renal function increases with infant maturation and child development. The treatment of infants and children with milrinone has been extensively studied. The aim of this study is to review the clinical pharmacology of milrinone in infants and children.

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