PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the Children's Medical Center at the University of Virginia

Volume 9 Number 2 February 2003

The Use of Milrinone in Infants and Children

Marcia L. Buck, Pharm.D., FCCP

Traditionally, catecholamines such as dopamine, dobutamine, epinephrine, and norepinephrine have been used for their positive inotropic effect in children with low cardiac output. These agents, however, produce several undesirable effects, including an increase in heart rate and myocardial oxygen consumption, down-regulation of beta-adrenergic receptors, and an increase in systemic vascular resistance. Unlike the catecholamines, milrinone produces a positive inotropic effect with concurrent vasodilation and little chronotropic effect. As a result of these differences, milrinone has become a valuable tool in the treatment of children following cardiac surgery and in the management of shock.

Mechanism of Action

Milrinone, like its predecessor inamrinone (formerly called amrinone), is a bipyridine inotrope/vasodilator. It is a selective inhibitor of peak III cyclic adenosine monophosphate (cAMP) phosphodiesterase in cardiac and vascular muscle. Inhibition of this enzyme results in an accumulation of cAMP, producing an increase in intracellular ionized calcium in cardiac muscle which increases contractile force. Increasing cAMP also produces relaxation of vascular smooth muscle. Milrinone exhibits a concentration-dependent response, with optimal effects occurring between 100 and 300 ng/ml.[1-3]

Use After Cardiac Surgery

Several investigators have studied the effects of milrinone in reversing the low cardiac output frequently observed in infants and children after cardiac surgery.[4-8] In 1995, Chang and colleagues conducted a prospective study of milrinone in ten neonates (3 to 27 days of age) with low cardiac output following surgical repair of congenital heart defects.[4] Patients were given a loading dose of 50 mcg/kg intravenously (IV) over 15 minutes, followed by an infusion of 0.5 mcg/kg/min for 30 minutes. The doses used were based on standard dosing for adults. Administration of milrinone produced a significant increase in cardiac index, from 2.1 ± 0.5 at baseline to 3.0 ± 0.8 L/min/m^2 during treatment, with a decrease in mean atrial pressure from 66 ± 12 to 57 ± 10 mm Hg. Systemic vascular resistance decreased by an average of 37% ($2,136\pm432$ to $1,336\pm400$ dyne·sec/cm^5·m^2) and pulmonary vascular resistance decreased by 27% (488 ± 160 to 360 ± 120 dyne·sec/cm^5·m^2). Heart rate increased transiently during the loading dose, but slowed during the infusion. Myocardial oxygen consumption was unchanged.

In 1999, Bailey and colleagues studied the effects of milrinone in 20 children between 3 and 22 months of age with low cardiac output after surgery.[6] All patients received a 50 mcg/kg loading dose. In 12 of the children, the loading dose was followed by an infusion of 0.5 to 0.7 mcg/kg/min. The loading dose produced an average increase in cardiac index of 18% (mean$\pm$SE 2.0 ± 0.2 to 3.4 ± 0.3 L/min/m^2) at a mean serum concentration of 235 ng/ml. Mean blood pressure decreased by an average of 12%, from 66.7 ± 1.4 to 58.9 ± 2 mm Hg. Heart rate, left atrial pressure, and central venous pressure were unchanged. Based on pharmacokinetic simulations performed with the data from this study, the authors suggest that a short-term, high-dose infusion of 3 mcg/kg/min for 30 minutes may be beneficial prior to initiation of a 0.5 mcg/kg/min maintenance infusion to account for the larger volume of distribution observed in children.

Since publication of these initial reports, milrinone has gained acceptance as an alternative or supplement to catecholamines in the management of pediatric patients with low cardiac output following repair of congenital heart defects. Although the data available to date have been promising, questions about the optimal timing for initiation of therapy, dosing, and monitoring remain. A prospective

multicenter, randomized, double-blind, placebo-controlled study is currently under development to address these questions.[7] The Prophylactic Intravenous Use of Milrinone After Cardiac Operation in Pediatrics (PRIMACORP) study will compare a low-dose milrinone regimen consisting of a 25 mcg/kg loading dose followed by an infusion of 0.25 mcg/kg/min, a high-dose regimen with a 75 mcg/kg loading dose followed by an infusion of 0.75 mcg/kg/min, and placebo for up to 36 hours. Study end points will include mortality, cardiac indices, and length of hospital stay. A pharmacokinetic assessment will also be done.

While the PRIMACORP study addresses the optimal use of IV milrinone, other routes of administration are also being considered for the postoperative patient population. In a recent study of adults with pulmonary hypertension following cardiac surgery, inhaled milrinone was shown to produce additive pulmonary vasodilation when administered with inhaled prostacyclin.[9] Compared with prostacyclin alone, inhaled milrinone in concentrations of 0.25, 0.5, and 1 mg/ml given with prostacyclin produced a significantly greater and longer reduction in pulmonary vascular resistance and an increase in stroke volume. Systemic vascular resistance and mean arterial pressure were unchanged. While this route of administration has not yet been studied in children, it may offer an alternative to current therapies for pulmonary hypertension following cardiac surgery.

Use in Septic Shock

In addition to its use after cardiac surgery, milrinone may also be beneficial in the management of low cardiac output resulting from septic shock.[10,11] Barton and colleagues studied the effects of milrinone in 12 children with septic shock (ages 9 months to 15 years) already receiving catecholamine infusions.[10] In this prospective, double-blind trial, patients were randomized to receive either a loading dose of 50 mcg/kg milrinone followed by an infusion of 0.5 mcg/kg/min or placebo. After two hours, the patients were crossed over to the other arm and treated for an additional two hours. At the end of this phase, patients could continue to receive milrinone at their physician's discretion.

Milrinone significantly increased cardiac index, from an average of 3.7 ± 0.8 L/min/m^2 at baseline to 5.5 ± 1.6 L/min/m^2 at 2 hours, while values in the placebo group remained unchanged. Stroke volume index and oxygen delivery were also significantly increased during the active treatment phase, while systemic vascular resistance, pulmonary vascular resistance, and mean pulmonary artery pressure were decreased. No significant changes were noted in heart rate, systolic or diastolic blood pressure, mean systemic arterial pressure, or pulmonary capillary wedge pressure. All patients continued on milrinone after the 4-hour trial, for a mean duration of 48 hours. The authors concluded that in volume-resuscitated pediatric patients with septic shock, milrinone, used in conjunction with traditional catecholamines, improves cardiovascular function.

Pharmacokinetics

In adults, milrinone has a volume of distribution of 0.3 to 0.4 L/kg, a terminal elimination half-life of 1.5 to 2.3 hours, and a clearance of approximately 2 ml/kg/min. It is excreted in the urine, as unchanged drug (83% of a dose) and the glucuronide conjugate (12%).[2,3,5]

As shown in the previous studies, the pharmacokinetics of milrinone are altered in infants and children. In 1998, Ramamoorthy and colleagues studied the pharmacokinetics of milrinone after cardiac surgery in 19 children between 1 month and 11 years of age.[5] Eleven of the children were enrolled into a low-dose protocol: two 25 mcg/kg bolus doses were given, followed by an infusion titrated to a final rate of 0.5 mcg/kg/min. The remaining eight children were placed on a high-dose protocol and given a 50 mcg/kg bolus dose followed by a 25 mcg/kg bolus dose and an infusion titrated to a final rate of 0.75 mcg/kg/min. Blood samples were obtained over 24 hours. Pharmacokinetic parameters were evaluated using traditional and non-linear mixed effects modeling techniques.

The milrinone concentration data were best fit to a two-compartment pharmacokinetic model in this trial. At steady-state, both groups had milrinone concentrations above the desired level of 100 ng/ml, with a mean of 113 ± 39 ng/ml in the low-dose group and 206 ± 74 ng/ml in the high-dose group. The volume of distribution was significantly higher in these patients than reported in adults, with mean values of 0.9 ± 0.4 and 0.7 ± 0.2 L/kg in patients < 1 year and ≥ 1 year of age, respectively. Likewise, clearance was increased, with values of 3.8 ± 1 and 5.9 ± 2 ml/kg/min in the two groups. Terminal elimination half-life was prolonged in the infants (mean 3.15 ± 2 hrs), but similar to adult values in the older children (mean 1.86 ± 2 hrs).

In conjunction with their study of the efficacy of milrinone in children with septic shock, Lindsay, Barton, and colleagues also conducted a pharmacokinetic evaluation.[11] Using a one-compartment model, the authors calculated an

average volume of distribution at steady-state for milrinone of 1.47±1.03 L/kg, a clearance of 11±9.6 ml/kg/min, and a terminal elimination half-life of 2.88±3.21 hours. Like the data from Ramamoorthy[5], this study documented a larger volume of distribution in children than reported in adults. These studies, together with the paper by Bailey[6], suggest that a larger loading dose, and perhaps a greater initial infusion rate, may be necessary in children to achieve serum concentrations within the desired range and produce an optimal cardiovascular response.

Adverse Effects

As with other positive inotropes, the phosphodiesterase inhibitors have the potential to produce arrhythmias. Milrinone produces a slight shortening of atrioventricular node conduction time, which may result in an increased ventricular response rate in patients with atrial flutter or fibrillation. In Phase II and III clinical trials of adults, ventricular arrhythmias were reported in 12% of patients. In these patients, 8.5% experienced ventricular ectopic activity, 2.8% had nonsustained ventricular tachycardia, 1% had sustained ventricular tachycardia, and 0.2% had ventricular fibrillation (some patients had more than one type of arrhythmia). Supraventricular arrhythmias occurred in 3.8% of patients. Hypokalemia has been reported in 0.6% of patients receiving milrinone and may predispose them to the development of arrhythmias.[1-3]

Other adverse effects associated with milrinone use in adult clinical trials include: hypotension (2.9%) seen most often with rapid administration of the loading dose, headaches (2.9%), angina (1.2%), tremor (0.4%), and thrombocytopenia (0.4%). The incidence of thrombocytopenia is substantially less than that seen with inamrinone (2.4%). Post-marketing surveillance has included case reports of bronchospasm and elevations in liver function tests in patients receiving milrinone.[1-3]

While only a small number of pediatric patients have been evaluated in clinical trials, the adverse effect profile of milrinone in children appears similar to that of adults. In the pharmacokinetic study by Ramamoorthy, 2 of the 19 children (11%) developed arrhythmias.[5] Both patients were infants; one underwent repair for tetralogy of Fallot and the other for an atrioventricular canal defect. Both developed junctional ectopic tachycardia requiring discontinuation of milrinone. Eleven patients (58%) developed thrombocytopenia; however, the authors suggest that this adverse effect may be more the result of surgery than milrinone. In a comparison group of children undergoing cardiac surgery without milrinone, 25% developed thrombocytopenia. Liver function tests, BUN, and creatinine in the milrinone patients were within normal limits.

Other pediatric milrinone studies reported no significant adverse effects. In the study by Chang[4], one child had occasional premature atrial beats, but there were no sustained tachyarrhythmias. No patients in the studies by Bailey[6] and Barton[10] exhibited arrhythmias.

Dosing Recommendations

Milrinone (Primacor®; Sanofi-Synthelabo) is available in a 1 mg/ml concentration in 10, 20, and 50 ml single-dose vials, 5 mg/5ml Carpuject® sterile cartridges, and in 200 mcg/ml premixed 100 and 200 ml bags.[3]

Based on the studies presented, the recommended loading dose of milrinone in infants and children is 50 to 75 mcg/kg given IV over 15 to 60 minutes. The loading dose may be reduced to 25 mcg/kg or omitted in patients at risk for hypotension. Immediately after the load, a continuous infusion of 0.375 to 0.75 mcg/kg/min may be started. Administration of milrinone within this range should produce serum concentrations above the minimum desired concentration of 100 ng/ml. The maintenance infusion rate should be titrated to patient response. Serum concentration monitoring is not routinely available in most institutions.

Infusion rates should be decreased in patients with renal impairment.[1-3] Although no specific recommendations have been published for children with renal dysfunction, the following table of recommendations for adults may be used as a general reference.

Table 1. Dose Adjustment for Renal Impairment

Creatinine Clearance	*Milrinone Rate*
50 ml/min/1.73m^2	0.43 mcg/kg/min
40 ml/min/1.73m^2	0.38 mcg/kg/min
30 ml/min/1.73m^2	0.33 mcg/kg/min
20 ml/min/1.73m^2	0.28 mcg/kg/min
10 ml/min/1.73m^2	0.23 mcg/kg/min
5 ml/min/1.73m^2	0.2 mcg/kg/min

Drug Interactions and Compatibility

The loading dose of milrinone may be given undiluted or diluted to 10 to 20 ml. For infusion, milrinone should be diluted to a concentration of 200 to 400 mcg/ml with D_5W, 0.9% sodium chloride, 0.45% sodium chloride, or lactated Ringer's solution. Milrinone is compatible with many other drugs commonly used in the intensive care setting. The following table lists

drugs physically compatible with milrinone for a period of 4 hours.[12,13]

Table 2. Drugs Compatible with Milrinone

acyclovir[a]	magnesium sulfate[b]
amikacin[a]	meropenem[a]
ampicillin[a]	methylprednisolone[a]
atracurium[b]	metronidazole[a]
bumetanide[b]	midazolam[b]
calcium chloride[a]	morphine[a,b]
calcium gluconate[a,b]	nitroglycerin[b]
cefazolin[a]	norepinephrine[b]
cefepime[a]	oxacillin[a]
cefotaxime[a]	pancuronium[b]
ceftazidime[a]	parenteral nutrition[a,b]
cefuroxime[a]	piperacillin[a]
cimetidine[b]	piperacill./tazobactam[a]
ciprofloxacin[a]	potassium chloride[b]
clindamycin[a]	propofol[b]
dexamethasone[a]	ranitidine[b]
diltiazem[b]	rocuronium[b]
dobutamine[b]	sodium bicarbonate[b]
dopamine[b]	sodium nitroprusside[b]
epinephrine[b]	theophylline[b]
fentanyl[b]	ticarcillin[a]
gentamicin[a]	ticarcillin/clavulanate[a]
heparin[b]	tobramycin[a]
insulin, human regular[b]	torsemide[b]
isoproterenol[b]	vancomycin[a]
lorazepam[a,b]	vecuronium[b]

[a] tested with milrinone 200 mcg/ml[13]
[b]tested with milrinone 400 mcg/ml[12]

Milrinone should not be infused with furosemide. A chemical interaction occurs between these drugs resulting in formation of a precipitate. Mixing of milrinone and imipenem-cilastatin results in a change in the color of the solution from light to dark yellow. While the clinical significance of this color change has not been assessed, it may indicate drug inactivation.[2,13]

Summary

With its combined inotropic and vasodilatory effects, milrinone provides a useful alternative to traditional catecholamines in children with low cardiac output. Although several small-scale studies in children are available, more research is needed to evaluate long-term effects, better define the adverse effect profile, and determine an optimal dosing strategy.

References

1. Levy JH, Bailey JM, Deeb GM. Intravenous milrinone in cardiac surgery. Ann Thorac Surg 2002;73:325-30.
2. Burnham TH, ed. Drug Facts and Comparisons. 2003. St. Louis: Facts and Comparisons, Inc. : 403-4.
3. Primacor® product information. Sanofi-Synthelabo, Inc. October 2000. Available at www.sanofi-synthelabous.com/products/pi_primacor/pi_primacor.html
4. Chang AC, Atz AM, Wernovsky G, et al. Milrinone: systemic and pulmonary hemodynamic effects in neonates after cardiac surgery. Crit Care Med 1995;23:1907-14.
5. Ramamoorthy C, Anderson GD, Williams GD, et al. Pharmacokinetics and side effects of milrinone in infants and children after open heart surgery. Anesth Analg 1998;86:283-9.
6. Bailey JM, Miller BE, Lu W, et al. The pharmacokinetics of milrinone in pediatric patients after cardiac surgery. Anesthesiology 1999;90:1012-8.
7. Chu CC, Lin SM, New SH, et al. Effect of milrinone on postbypass pulmonary hypertension in children after tetralogy of Fallot repair. Chung Hua I Hsueh Tsa Chih 2000;63:294-300.
8. Hoffman TM, Wernovsky G, Atz AM, et al. Prophylactic intravenous use of milrinone after cardiac operation in pediatrics study. Am Heart J 2002;143:15-21.
9. Haraldsson A, Kieler-Jensen N, Ricksten S. The additive pulmonary vasodilatory effects of inhaled prostacyclin and inhaled milrinone in postcardiac surgical patients with pulmonary hypertension. Anesth Analg 2001;93:1439-45.
10. Barton P, Garcia J, Kouatli A, et al. Hemodynamic effects of IV milrinone lactate in pediatric patients with septic shock. Chest 1996;109:1302-12.
11. Lindsay CA, Barton P, Lawless S, et al. Pharmacokinetics and pharmacodynamics of milrinone lactate in pediatric patients with septic shock. J Pediatr 1998;132:329-34.
12. Akkerman SR, Zhang H, Mullins RE, et al. Stability of milrinone lactate in the presence of 29 critical care drugs and 4 IV solutions. Am J Health-Syst Pharm 1999;56:63-8.
13. Veltri MA, Conner KG. Physical compatibility of milrinone lactate injection with intravenous drugs commonly used in the pediatric intensive care unit. Am J Health-Syst Pharm 2002;59:452-4.

Pharmacology Literature Review

Once-daily aminoglycosides in children

Although frequently used in adults, once-daily aminoglycoside dosing has failed to become a standard practice in pediatrics. The authors of this review provide reasons for this resistance and suggest areas for future study. Knoderer CA, Everett JA, Buss WF. Clinical issues surrounding once-daily aminoglycoside dosing in children. **Pharmacotherapy 2003;23:44-56.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 1/31/03:

1. Secretin (SecreFlo®) was added to the Formulary to aid in the diagnosis of pancreatic dysfunction or gastrinoma and to facilitate cholangiopancreatography.
2. Two chemotherapeutic agents, oxaliplatin (Eloxatin®) and yttrium^{90} ibritumomab tiuxetan (Zevalin®), were added to the Formulary.

Contributing Editor:Marcia L. Buck, Pharm.D.
Editorial Board: Anne E. Hendrick, Pharm.D.
Michelle W. McCarthy, Pharm.D.
Kristi N. Hofer, Pharm.D.
If you have comments or suggestions for future issues, please contact us at Box 800674, UVA

Health System, Charlottesville, VA 22908 or by e-mail to mlb3u@virginia.edu. This newsletter is also available at www.hsc.virginia.edu/medicine/clinical/pediatrics/CMC/pedpharm/pedpharm.html