Prophylactic Intravenous Use of Milrinone After Cardiac Operation in Pediatrics (PRIMACORP) study

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Background Many pediatric patients undergoing cardiac surgery involving cardiopulmonary bypass have a predictable fall in the cardiac index 6 to18 hours after surgery, the so-called low cardiac output syndrome (LCOS). Because patients who have LCOS require more monitoring and support and have a prolonged stay in the intensive care unit, the syndrome is associated with a costly morbidity. Milrinone, a phosphodiesterase III inhibitor, improves cardiac muscle contractile force and vascular muscle relaxation through positive inotropic and vasodilatory effects. The purpose of the Prophylactic Intravenous Use of Milrinone After Cardiac Operation in Pediatrics (PRIMACORP) study is to evaluate the safety and efficacy of the prophylactic use of milrinone in pediatric patients at high risk for development of LCOS after undergoing cardiac surgery.

Methods Patients in the multicenter, randomized, double-blind, placebo-controlled, parallel treatment study will be randomized to 1 of 3 treatment arms: (1) low-dose milrinone (25 μg/kg intravenous bolus over 60 minutes followed by a 0.25 μg/kg/min infusion for 35 hours), (2) high-dose milrinone (75 μg/kg intravenous bolus over 60 minutes followed by a 0.75 μg/kg/min infusion for 35 hours), or (3) placebo.

Results The primary end point for efficacy evaluation will be based on a composite variable consisting of death or development of LCOS requiring additional mechanical or pharmacologic support, up to 36 hours after randomization. A 2-sided test with a 0.025 type I error will be used for the primary end point analysis. The PRIMACORP study will enroll a total of 240 patients. Six additional secondary end points will be analyzed.

Conclusions The PRIMACORP study will address several questions regarding the safety and efficacy of prophylactic milrinone use in pediatric patients at high risk for development of LCOS after cardiac surgery. (Am Heart J 2002;143:15-21.)

Congenital cardiovascular defects, which affect approximately 32,000 infants each year in the United States,[1] can cause abnormal patterns of blood flow and influence structural and functional circulatory development.[2] Advances in cardiac surgery—including improved cardiopulmonary bypass (CPB), postoperative care, and repair of complex cardiac defects—have made surgical repair a primary therapy for an increasing number of pediatric patients with cardiovascular disease.[3] More than 300,000 children and adults have congenital cardiovascular disease, and 38% will undergo one or more surgical procedures during their lifetimes.

Congenital cardiac malformations often cause severe pressure or volume overload; moreover, the primary treatment modality for congenital heart disease (CHD) is surgery, commonly much more complex than adult cardiac surgery. Although some cases of low cardiac output syndrome (LCOS) after congenital heart surgery are the result of residual hemodynamic burdens of the underlying defect, even when all anatomic defects are repaired there remains the possibility of depressed myocardial performance, which may be associated with increased mortality.[4]

The causes of low cardiac output after cardiac surgery are multifactorial. After surgery, there are acute changes in the loading conditions of the myocardium. Surgical repair of cardiac malformation exposes the myocardial tissue to prolonged periods of myocardial ischemia[3] and cardioplegia.[5] Residual lesions, even if minor (eg, tricuspid regurgitation) may complicate the physiologic mechanisms. Finally, some repairs require a ventriculotomy for adequate surgical exposure and repair, which may result in myocardial dysfunction. CPB causes activation of the inflammatory cascade, with secondary elevations of systemic and pulmonary vascular resistance, capillary leak, and pulmonary dysfunction.[6]

Several recent studies have documented the pre-

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dictable and reproducible fall in cardiac output that occurs after congenital heart surgery, particularly in neonates, infants, and young children. In 1975, Parr et al[4] reported that nearly 25% of young children had a cardiac index (measured by dye dilution) of <2.0 L/min/m^2 and concluded that low cardiac index was a strong predictor of acute cardiac death. Similarly, Wernovsky et al[7] reported in 1995 that 25% of neonates with transposition of the great arteries who underwent an arterial switch operation had a cardiac index of <2.0 L/min/m^2 (measured by thermodilution techniques), typically occurring between 6 and 18 hours after surgery. This predictable fall in cardiac index was associated with an elevation of systemic vascular resistance of approximately 25% over baseline with a concomitant rise in pulmonary vascular resistance of about 40% over baseline. Other recent reports have documented similar, predictable falls in cardiac index and elevations in systemic and pulmonary vascular resistance after surgery in neonates.[8,9]

The diagnosis of LCOS after cardiac surgery may be problematic. Quantitative measurements of cardiac index may not be reliable in patients with residual intracardiac shunts, and technical considerations may limit the use of thermodilution techniques in small neonates and infants. Alternative objective assessments include the measurement of mixed venous oxygen saturations and serum lactate levels. Parr et al[4] showed a close correlation of low mixed venous oxygen saturations with low cardiac index in young patients after cardiac surgery. In addition, serum lactate measurements have been increasingly used in predicting LCOS after neonatal cardiac surgery. Recent studies have shown that a rising lactate predicts mortality or the need for extracorporeal membrane oxygenation (ECMO) with 89% sensitivity, 100% specificity, and 100% positive predictive value.[10]

The postoperative course for many pediatric patients with CHD who undergo cardiac surgery involving CPB is associated with significant, yet predictable, hemodynamic instability.[5,8,9,11-14] The etiology of this postoperative LCOS is impaired myocardial contractility and the peripheral effects of ischemia/reperfusion injury on the endothelium.[5,15] Postoperative management strategies for pediatric cardiac patients therefore aim to, in part, optimize contractility, improve diastolic dysfunction, maintain adequate preload, and reduce afterload.

Traditionally, pediatric cardiac critical care physicians have used inotropic agents[11-14,16] and vasodilators to facilitate the intraoperative or postoperative re-establishment of adequate myocardial function. The use of catecholamines to provide inotropic support exhibits several drawbacks, including increased myocardial oxygen consumption, tachycardia, proarrhythmic effects, increased afterload, and depressed myocardial response as a result of down-regulation of β-adrenergic receptors. To avoid these potential problems and to improve diastolic function, increase cardiac index, and decrease systemic and pulmonary vascular resistance, the use of the phosphodiesterase (PDE) inhibitor milrinone has increased considerably in the past few years.

The ability to achieve a rapid hemodynamic response after intravenous administration of milrinone is extremely important after separation from CPB where uncompensated LCOS can soon result in deterioration of the patient's hemodynamic status and subsequent secondary organ dysfunction. Distinctly different from digitalis glycosides or catecholamines, milrinone is a bipyridine compound that selectively inhibits PDE III cyclic adenosine monophosphate (cAMP) isozyme, causing cAMP-mediated increases in cardiac muscle contractile force and vascular muscle relaxation.[13,14,17] The clinical utility of milrinone in the pediatric population, therefore, is similar to that of milrinone in adult patients with heart failure. Milrinone effectively improves cardiac index in adult patients with congestive heart failure[18] or LCOS occurring after cardiac surgery.[11,16] In adult heart disease, myocardial recovery is much more variable and frequently irreversible. However, in the pediatric population with congenital heart disease, after interventions, although transient LCOS is common, relief of cyanosis, pressure, or volume overload results in an eventual expected improvement in ventricular function. Few studies involving the pediatric population have been published.

Two studies have observed the hemodynamic effects of milrinone in a young pediatric population with established LCOS. In a prospective cohort study, Chang et al[13] evaluated the hemodynamic effects of intravenous milrinone in 10 neonates, aged 3 to 27 days, with low cardiac output (mean cardiac index 2.1 L/min/m^2) but adequate filling pressures (left atrial pressure ≥8 mm Hg) after cardiac surgery. An initial 50 μg/kg bolus of milrinone was administered over 15 minutes and followed by an infusion of 0.5 μg/kg/min for 30 minutes. Compared with effects seen at baseline, milrinone demonstrated significant increases in heart rate (149 ± 13 to 163 ± 12 beats/min, $P < .01$), cardiac index (2.1 ± 0.5 to 3.0 ± 0.8 L/min/m^2, $P < .01$), right ventricular stroke work index (2.9 ± 1.5 to 3.5 ± 1.7 g · m/m^2, $P < .05$), and left ventricular stroke work index (10.8 ± 4.1 to 12.3 ± 4.9 g · m/m^2, $P < .01$), along with significant decreases in right atrial pressure (11 ± 3 to 9 ± 3 mm Hg, $P < .01$), left atrial pressure (12 ± 2 to 10 ± 1 mm Hg, $P < .01$), mean systemic arterial pressure (66 ± 12 to 57 ± 10 mm Hg, $P < .01$), pulmonary arterial pressure (26 ± 5 to 23 ± 5 mm Hg, $P < .05$), systemic vascular resistance index (2136 ± 432 to 1336 ± 400 dyne · s/cm^5 · m^2, $P < .01$), and pulmonary vascular resistance (488 ± 160 to 360 ± 120 dyne · s/cm^5 · m^2. $P < .01$). The effects of milrinone were evident after the bolus

dose and were maintained during the infusion. No change in the rate pressure index, an indicator of myocardial oxygen consumption, was observed. Similarly, Bailey et al[14] also reported an 18% mean increase in the cardiac index (2.9 ± 0.2 to 3.4 ± 0.3 L/min/m^2, $P < .05$) in 20 children aged 3 to 22 months who received milrinone after surgical repair of congenital cardiac defects. Both studies demonstrate hemodynamic effects similar to those seen in adults administered milrinone after undergoing cardiac surgery.[11,16]

The pharmacokinetics of milrinone have been studied in a limited number of pediatric patients after cardiac surgery.[12,14] In one study by Ramamoorthy et al,[12] milrinone was administered to 19 children, aged ≤12 years, after open heart surgery. Low-dose intravenous milrinone, administered to 11 patients, consisted of a 25 μg/kg bolus over 5 minutes, continued at 0.25 μg/kg per minute and followed 30 minutes later by another 25 μg/kg dose, continued at an infusion rate of 0.5 μg/kg per minute. High-dose intravenous milrinone, administered to 8 patients, consisted of a 50 μg/kg bolus over 10 minutes, continued at 0.5 μg/kg per minute, and followed 30 minutes later by another 25 μg/kg dose, continued at an increased infusion rate of 0.75 μg/kg per minute. Patients in both groups also received a third 25 μg/kg dose if the clinical response of the patient indicated a need. In a study by Bailey et al,[14] 20 hemodynamically stable children aged 3 to 22 months undergoing primary surgical repair of a congenital heart defect received milrinone after being weaned from CPB. The protocol stipulated that patients would either receive a 50 μg/kg bolus or a 50 μg/kg bolus followed by continuous intravenous infusion of 0.5 μg/kg per minute. In the study by Ramamoorthy et al,[12] steady-state plasma concentrations were 113 ± 39 ng/mL in the low-dose groups and 206 ± 74 ng/mL in the high-dose groups. The mean milrinone plasma concentration in the study by Bailey et al[14] was 235 ± 104 ng/mL. The plasma concentrations of milrinone observed in these studies were also consistent with the therapeutic range observed in the adult population (100-300 ng/mL).[17]

Although data are limited in pediatric patients, especially neonates, milrinone demonstrates beneficial hemodynamic effects in the pediatric population with LCOS and provides therapeutic plasma concentrations. Because pediatric patients undergoing cardiac surgery involving CPB may have LCOS, use of a positive inotropic and vasodilatory agent, such as milrinone, is most likely to improve cardiac function and prevent the morbidity and mortality associated with LCOS. The purpose of the Prophylactic Intravenous Use of Milrinone After Cardiac Operation in Pediatrics (PRIMACORP) study is to evaluate the safety and efficacy of milrinone to prevent LCOS from developing in pediatric patients after cardiac surgery.

Methods

Study organization

The study design and supervision of the PRIMACORP trial is the responsibility of the Steering Committee, Clinical Endpoint Committee, and Data Safety Monitoring Board (DSMB). In addition to the protocol development, the role of the Steering Committee is to provide academic leadership for the overall conduct of the trial, which includes interpreting and disseminating the results. The DSMB is responsible for overseeing the safety of PRIMACORP participants. The Clinical Endpoint Committee, a blinded committee, mediates and validates the investigators' evaluation of primary and secondary end points by using a standard method to ensure that all data potentially related to the end point are reviewed. The committee reviews all end point–related data early in the conduct of the trial and adjudicates the end points as established and approved by the Steering Committee.

Study design

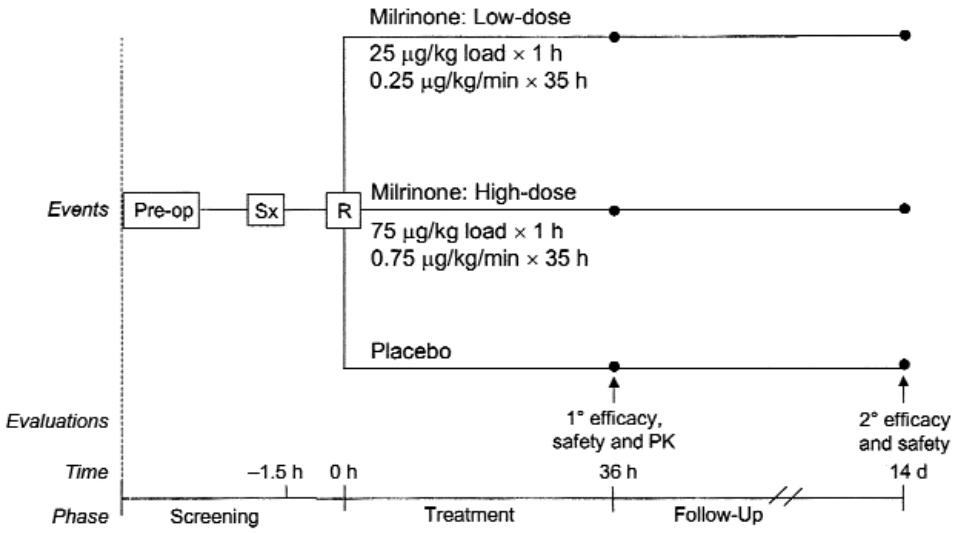
This is a multicenter, randomized, double-blind, placebo-controlled study using 3 parallel treatment groups in pediatric patients undergoing cardiac surgery. The PRIMACORP protocol will receive ethics approval from all investigator sites. Eligible patients who are stable after surgery are randomized within 90 minutes after arrival in the intensive care unit (ICU) to either low-dose intravenous milrinone (25 μg/kg bolus over 60 minutes followed by a 0.25 μg/kg/min infusion for 35 hours), high-dose intravenous milrinone (75 μg/kg bolus over 60 minutes followed by a 0.75 μg/kg/min infusion for 35 hours), or placebo (Figure 1). The patient must be deemed "stable" according to the following criteria before randomization: (1) no ongoing cardiopulmonary resuscitation, (2) no initiation of a cardiovascular assist device, and (3) no ongoing pulmonary resuscitation that prevents placement on the ventilator. All patients are followed up for at least 14 days after randomization. Patients may receive baseline catecholamines, at the discretion of the attending physician, if additional circulatory support is needed before randomization.

Study participants

Inclusion criteria. Male and female patients ≤6 years old who are undergoing cardiac surgery involving CPB and who do not have preoperative LCOS are eligible for PRIMACORP study entry. All patients must require biventricular repair for congenital defects as listed in Table I. The parents or legal guardians of all patients must give written informed consent before randomization.

Exclusion criteria. Patients weighing ≤2 kg, who are ≤36 weeks postconceptual age, who demonstrate creatinine levels >1.5 mg/dL within 48 hours of surgery, who have LCOS immediately before surgery, or who have hypotension immediately before study drug administration are excluded from the study. Hypotension is defined as a systolic blood pressure (SBP) <50 mm Hg in patients <1 month old, SBP <60 mm Hg in patients 1 to 12 months old, or SBP <65 mm Hg in patients ≥12 months old. In addition, patients receiving milrinone or amrinone within 48 hours of randomization, patients currently participating in other research studies with investigational drugs or devices, or newborn infants having surgery for

Figure 1



PRIMACORP study design. *PK,* Pharmacokinetic; *R,* randomization; *Sx,* surgery.

Table I. Inclusion criteria: eligible surgical procedures

Ventricular septal defect with
Interrupted aortic arch
Arch hypoplasia
Coarctation of the aorta
Repair of transposition of the great arteries by the arterial switch operation
Complete atrioventricular canal
Tetralogy of Fallot
Total anomalous pulmonary venous return
Truncus arteriosus
Double outlet right ventricle (biventricular repair)
Anomalous left coronary from the pulmonary artery
Congenital mitral valve anomaly (may be reoperation)
Aortic valve disease using the Ross operation with or without a Konno procedure

a single ventricle causing intercirculatory mixing are excluded from the study.

Study end points

The primary end point is a composite variable consisting of death or development of LCOS, which requires mechanical support, increased need for existing pharmacologic support (≥100% over baseline), or administration of new, open-label positive inotropic agents or other pharmacologic interventions to treat LCOS. This end point is evaluated 36 hours after patients are randomized to their respective study groups. Patients are diagnosed with LCOS if they demonstrate clinical signs and symptoms of the syndrome—such as tachycardia, oliguria, cold extremities, or cardiac arrest—with or without a ≥30% difference in arterial-mixed venous oxygen saturation or metabolic acidosis (an increase in the base deficit of >4 or an increase in the lactate of >2 mg/dL) on 2 successive blood gas measurements.

Six secondary end points are also being evaluated. These include (1) primary composite end point 14 days after randomization, (2) individual components of the primary composite end point 14 days after randomization, (3) total urine output (milliliters per kilogram per hour) in the first 36 hours after initiation of study medication, (4) creatinine clearance at 36 hours after initiation of study medication, (5) duration of initial hospital stay, and (6) pharmacokinetic assessment of milrinone within 36 hours after initiation of study medication.

Pharmacokinetics. Concentration at steady state (C_{ss}) and plasma clearance are determined by obtaining 2 blood samples (3-4 mL) and using nonlinear mixed effects modeling (NONMEM). Blood samples are collected at least 2 hours apart and are drawn from the indwelling arterial catheter at 2 of 11 time points (15, 30, 45, 60, 90, 120, 180, 240, 360, or 480 minutes or 36 hours) after initiating study drug administration. Blood samples are centrifuged for 15 minutes, and the resultant plasma is maintained in a frozen state at −70°C until chemical assay by high-pressure liquid chromatography.

Patient safety

Guidelines for the characterization of adverse events were established by the Steering Committee. In the case of a serious adverse event, the patient will be followed up until clinical recovery is complete or until progression has been stabilized. Patients may be discontinued from the study for the occurrence of adverse clinical circumstances, including development of a serious adverse event or development of a significant comorbid condition that, in the opinion of the study investigator, makes study continuation medically undesirable.

The DSMB is responsible for overseeing the safety of PRIMACORP participants. The DSMB will review safety-related data

(including end points), evaluate the treatments for excess adverse events according to treatment group, and judge whether the overall integrity of the study remains acceptable throughout the conduct of the trial. The DSMB chairperson will receive, on an ongoing basis, all case report forms for serious adverse events that are unexpected and considered to be related to the study drug by the investigator or sponsor's drug safety surveillance reviewer. The chairperson will then assess the unexpectedness of the serious adverse event. In addition, the chairperson will review monthly the blinded safety reports containing data summaries. If the chairperson deems it necessary, a full DSMB meeting will be held to discuss the contents of the report. Such a meeting will be in addition to the regularly scheduled meetings of the DSMB, to be held after the first 30, 100, and 170 patients have completed the hospitalization phase of the study. After reviewing at each meeting the blinded DSMB reports, the DSMB will recommend to the Steering Committee to continue, modify, or discontinue the study.

The trial will not be stopped because of efficacy or superiority of the treatment arm over the placebo arm. In this study, the O'Brien-Fleming α-spending function[19,20] will be used, which allows the type I error rate to be kept fixed at .025 (for each primary end point) with an unspecified number of interim analyses. With this procedure, a portion of the α of .025 will be spent for each interim analysis according to the stage of the trial (ie, percentage of data collected). The critical value for each interim analysis will be determined at the time of analysis with use of the a priori α of .025 and the percentage of data collected at the time of the analysis.

In the adult population, the long-term use of oral milrinone, which is not commercially available, was associated with an increase in mortality.[21] However, the short-term administration of intravenous milrinone is not associated with an increase in mortality; it has been demonstrated to be safe and effective therapy, improving hemodynamics in adult patients treated for acute uncompensated heart failure[18,22] and LCOS occurring after cardiac surgery.[11,16] The short-term administration of milrinone has been evaluated in clinical trials in excess of 1600 patients with congestive heart failure and heart failure associated with cardiac surgery or with myocardial infarction. The total number of deaths, either on therapy or shortly thereafter (24 hours), was 15 (<0.9%); few of these were thought to be drug-related.[17]

There are no data with intravenous milrinone demonstrating a positive effect on mortality, as has been demonstrated with long-term heart failure therapies such as angiotensin-converting enzyme inhibitors and β-adrenergic blocking agents. This is expected because the drug, with its inotropic and vasodilatory actions, is administered in the short term and has a relatively short half-life.

In the pediatric population, on the basis of the published literature regarding the clinical evaluation of milrinone in the settings of cardiac surgery[12-14,23] and septic shock,[24,25] there have been no reported deaths. The doses of milrinone used in the PRIMACORP trial have been based on the available literature on the use of milrinone in the pediatric population, the experience of the Steering Committee with the drug, the recommended doses for adults as described in the package insert,[17] and a request from the US Food and Drug Administration.

Surgery-related mortality in this population is expected to be approximately 5% to 10%.[26,27] To detect a 20% reduction in mortality with the lowest estimate control event rate of 5% would require 14,000 patients (2-sided test, $P < .05$ and 80% power). Therefore, given the large cohort required, the study will not be powered to draw any conclusions regarding the effect of milrinone on mortality.

Therefore, on the basis of the statistical power of the study and the available knowledge of the drug, no definite conclusion regarding intravenous milrinone and mortality can be drawn from the PRIMACORP trial. Nevertheless, the number of drug-related deaths in this study may provide some insights on the effect of milrinone in the pediatric population.

All patients who receive any amount of study medication will be included in the safety analyses. Analyzed safety variables will include reported adverse events, study drug discontinuations, and clinically significant changes in vital signs and laboratory parameters.

Statistical analysis

A .025 type I error rate, or α level, was used to calculate sample size to allow for both the high-dose milrinone versus placebo and the low-dose milrinone versus placebo comparisons of the primary end point. A total enrollment of 240 patients, allowing for 80 patients in each treatment group, is needed to reach 80% power with a maximum 10% dropout rate. This sample size will differentiate a 20% change between placebo and treated patients with a .025 type I error rate in analysis with use of a 2-sided test.

The intent-to-treat population, which includes all randomized patients, will be analyzed for the primary end point. In addition, an analysis will be performed on the per-protocol population—randomized patients receiving study medication for any period of time with no major protocol violation. Analysis of all end points will be performed with use of a 2-sided test; the type I error rate applied will be .025 for the primary end point and .05 for all other end points. A Student *t* test will be used to evaluate the response rates for high-dose versus placebo and low-dose versus placebo. The Fisher exact test will be used for analysis of all categorical variables in which there are few observations. Analysis of covariance will be used for continuous variables, with baseline serving as the covariate.

Discussion

Because of the strong relationship between a drop in cardiac index and the possibility of cardiac death, it is imperative that LCOS be identified and treated.[3] Parr et al[4] evaluated 139 infants and small children ≤48 months old for 72 hours after intracardiac surgery. The mortality rate was 19.4% (n = 27), and more than half the deaths were caused by acute cardiac failure and were associated with a low cardiac index (<2.0 L/min/m^2). Wernovsky et al[7] evaluated 171 pediatric patients <3 months old who underwent an arterial switch operation for transposed great arteries. A predictable drop in cardiac index occurred between 6 and 18 hours after surgery as patients received moderate and consistent inotropic support. A total of 24% of their population had a cardiac index <2.0 L/min/m^2, and the average fall in cardiac index was 30% during the first night after surgery. Both studies demonstrate a

consistent drop in cardiac index after surgery. Other useful measurements of predicting mortality after cardiac surgery include reduced mixed venous oxygen partial pressure and serum lactate levels.[4,10]

Catecholamines are the mainstay of therapy to augment cardiac output in pediatric patients with low cardiac output after surgery.[13] Adverse effects of catecholamines include arrhythmogenesis, excessive chronotropy, increased myocardial oxygen consumption, down-regulation of β-adrenergic receptors, and increased afterload, which can raise impedance and decrease cardiac output.[13] Avoiding chronotropy is important because tachycardia often correlates with postoperative ischemia after cardiac surgery.[13] Down-regulation of β-adrenergic receptors may compromise the cardiac response to pharmacologic interventions.[13] Catecholamine administration may even result in direct injury or apoptosis of cardiomyocytes, although it is unclear whether this in an acute or chronic consequence of adrenergic stimulation.

Milrinone is a bipyridine compound that improves inotropic and vasodilator properties with little or none of the chronotropic activity, associated alterations in myocardial oxygen consumption, or agonist effect on the β-adrenergic receptors, characteristic with use of other catecholamines.[14,17] Milrinone selectively inhibits phosphodiesterase III cAMP isozyme and causes cAMP-mediated increases in cardiac muscle contractile force and vascular muscle relaxation.[13,17] Administration of milrinone increases cardiac output and stroke volume, decreases intracardiac filling pressures, and decreases systemic vascular resistance.[14] Although data are limited, milrinone administered at 0.25 to 0.75 μg/kg per minute demonstrates beneficial hemodynamic effects and therapeutic plasma concentrations without safety compromise in the pediatric population.[12-14]

One of the important objectives of the study is to characterize the renal clearance of study drug in this patient population—volume of distribution is increased in neonates and postoperative glomerular filtration rate is variable. One of the secondary study end points is creatinine clearance at 36 hours after initiation of study medication. Patient creatinine clearance as well as associated pharmacokinetics will be detailed.

Clinical research has undergone remarkable and beneficial expansions over the past 2 decades. Well-designed, multicenter, randomized clinical trials are commonly organized in adult cardiovascular medicine to clarify the value of pharmacologic and mechanical interventions. Childhood cardiovascular diseases, however, are relatively infrequent and heterogeneous, therefore impairing the recruitment of large numbers of subjects, thus rendering clinical trials of the same extent difficult in pediatric cardiology. PRIMACORP, the first prophylactic trial to prevent LCOS in pediatric patients, is the largest multicenter clinical trial in pediatric cardiac surgery to date and the first study in a large group of neonates and infants for the efficacy, safety, and pharmacokinetic analyses of milrinone. The postoperative course for this patient population will be extensively characterized.

Conclusion

The results from PRIMACORP will address several study questions regarding the safety and efficacy of the prophylactic use of milrinone in pediatric patients at high risk for development of LCOS after cardiac surgery. If a benefit is observed in this and future investigations, the use of milrinone may significantly decrease the mortality and morbidity associated with the development of LCOS.

References

1. American Heart Association. Cardiac disease in children. American Heart Association Web site. Available at: http://www.americanheart.org/Heart_and_Stroke_A_Z_Guide/cardk.html. Accessed 2000.
2. Friedman WF. Congenital heart disease in infancy and childhood. In: Braunwald E, editor. Heart disease: a textbook of cardiovascular medicine. 5th ed. Philadelphia: WB Saunders; 1997. p. 877-962.
3. Antman EM. Medical management of the patient undergoing cardiac surgery. In: Braunwald E, editor. Heart disease: a textbook of cardiovascular medicine. 5th ed. Philadelphia: WB Saunders; 1997. p. 1715-40.
4. Parr GVS, Blackstone EH, Kirklin JW. Cardiac performance and mortality early after intracardiac surgery in infants and young children. Circulation 1975;51:867-74.
5. Burrows FA, Williams WG, Teoh KH, et al. Myocardial performance after repair of congenital cardiac defects in infants and children: response to volume loading. J Thorac Cardiovasc Surg 1988;96:548-56.
6. Nagashima M, Imai Y, Seo K, et al. Effect of hemofiltrated whole blood pump priming on hemodynamics and respiratory function after the arterial switch operation in neonates. Ann Thorac Surg 2000;70:1901-6.
7. Wernovsky G, Wypij D, Jonas RA, et al. Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants: a comparison of low-flow cardiopulmonary bypass and circulatory arrest. Circulation 1995;92:2226-35.
8. Pesonen EJ, Peltola KI, Korpela RE, et al. Delayed impairment of cerebral oxygenation after deep hypothermic circulatory arrest in children. Ann Thorac Surg 1999;67:1765-70.
9. du Plessis AJ, Jonas RA, Wypij D, et al. Perioperative effects of alpha-stat versus pH-stat strategies for deep hypothermic cardiopulmonary bypass in infants. J Thorac Cardiovasc Surg 1997;114: 991-1000.
10. Charpie JR, Dekeon MK, Goldberg CS, et al. Serial blood lactate measurements predict early outcome after neonatal repair or palliation for complex congenital heart disease. J Thorac Cardiovasc Surg 2000;120:73-80.
11. Wright EM, Skoyles J, Sherry KM. Milrinone in the treatment of low output states following cardiac surgery. Eur J Anaesthesiol 1992; (5 Suppl):21-6.
12. Ramamoorthy C, Anderson GD, Williams GD, et al. Pharmacokinet-

ics and side effects of milrinone in infants and children after open heart surgery. Anesth Analg 1998;86:283-9.
13. 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.
14. Bailey JM, Miller BE, Lu W, et al. The pharmacokinetics of milrinone in pediatric patients after cardiac surgery. Anesthesiology 1999; 90:1012-8.
15. Asimakopoulos G, Taylor KM. Effects of cardiopulmonary bypass on leukocyte and endothelial adhesion molecules. Ann Thorac Surg 1998;66:2135-44.
16. Feneck RO. Intravenous milrinone following cardiac surgery, I: effects of bolus infusion followed by variable dose maintenance infusion. The European Milrinone Multicentre Trial Group. J Cardiothorac Vasc Anesth 1992;6:554-62.
17. Primacor. In: Physicans' desk reference. Montvale (NJ): Medical Economics; 1999. p. 2802-4.
18. Monrad ES, Baim DS, Smith HS, et al. Effects of milrinone on coronary hemodynamics and myocardial energetics in patients with congestive heart failure. Circulation 1985;71:972-9.
19. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
20. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659-63.
21. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. N Engl J Med 1991;325: 1468-75.
22. Anderson JL, Baim DS, Fein SA, et al. Efficacy and safety of sustained (48 hour) intravenous infusions of milrinone in patients with severe congestive heart failure: a multicenter study. J Am Coll Cardiol 1987;9:711-22.
23. 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 (Taipei) 2000;63:294-300.
24. Barton P, Garcia J, Kouatli A, et al. Hemodynamic effects of iv milrinone lactate in pediatric patients with septic shock: a prospective, double-blinded, randomized, placebo- controlled, interventional study. Chest 1996;109:1302-12.
25. 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.
26. Jenkins KJ, Gauvreau K, Newburger JW, et al. Validation of relative value scale for congenital heart operations. Ann Thorac Surg 1998; 66:860-9.
27. Mavroudis C, Gevitz M, Ring WS, et al. The Society of Thoracic Surgeons National Congenital Heart Surgery Database Report: analysis of the first harvest (1994-1997). Ann Thorac Surg 1999; 68:601-24.

Correction

A typographical error appeared in the article by D'Agostino RB, Russell MW, Huse DM, et al, Primary and subsequent coronary risk appraisal: New results from the Framingham Study (Am Heart J 2000;139:272-81). In Table III. Health risk appraisal functions, initial CHD events. Under the column Women, With triglycerides, Coeff, the coefficient for the Variable Antihypertensive therapy/SBP interaction, the coefficient is given as –0.098. This coefficient should be –0.0098.