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The Pharmacokinetics of Milrinone in Pediatric Patients after Cardiac Surgery

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Background: **Milrinone has been shown to increase cardiac output in children after cardiac surgery, but pharmacokinetic analysis has not been used to identify effective dose regimens. The purpose of this study was to characterize the pharmacokinetics of milrinone in infants and children and to apply the results to the issue of dosing.**

Methods: **Twenty children were studied after they underwent repair of congenital cardiac defects. Control hemodynamic measurement was made after the children were separated from cardiopulmonary bypass, and each patient was given a loading dose of 50 μg/kg progressively in 5 min. Hemodynamic measurements were recorded again at the end of the loading dose and when a blood sample was taken to determine milrinone plasma concentrations. Further blood samples were taken during the next 16 h for milrinone plasma concentration analysis. The pharmacokinetics of milrinone were analyzed using the population pharmacokinetic program NONMEM.**

Results: **The loading dose of milrinone resulted in a mean decrease in mean blood pressure of 12% and a mean increase in cardiac index of 18% at a mean peak plasma concentration of 235 ng/ml. The pharmacokinetics of milrinone were best described by a three-compartment model. In the optimal model, all volumes and distribution clearances were proportional to weight, and weight-normalized elimination clearance was proportional to age; *i.e.*, Cl1 = 2.5 · weight · (1 + 0.058 · age) where Cl1 is expressed as ml/min, and the units of weight and age are kg and months, respectively.**

Conclusions: **A loading dose of 50 μg/kg effectively increases cardiac index in children after cardiac surgery. Simulations indicate that the peak plasma concentration can be maintained by following the loading dose of 50 μg/kg with an infusion of approximately 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 30 min and then a maintenance infusion, which may require adjustment for age. (Key words: Congenital heart disease; pharmacokinetics; phosphodiesterase inhibitors.)**

THE phosphodiesterase inhibitors, amrinone and milrinone, are used to treat congestive heart failure and low cardiac output syndrome, especially after cardiac surgery.[1–5] The hemodynamic effects of these drugs have been studied in some detail in adults. Administration of amrinone or milrinone results increases cardiac output and stroke volume, decreases intracardiac filling pressures, and decreases systemic vascular resistance, with no significant change in heart rate or myocardial oxygen consumption. These actions are attributed to selective phosphodiesterase inhibition, leading to increased levels of cyclic adenosine monophosphate in the myocardium and vascular endothelium with positive inotropic effects and vasodilation.[1–5] In clinical practice, often milrinone is preferred to amrinone because it has shorter context-sensitive elimination half-times and is associated with a lower incidence of thrombocytopenia[6,7] in adults.

The role of phosphodiesterase inhibitors in the treatment of low cardiac output syndrome in children after cardiac surgery has not been evaluated as fully. Amrinone has been shown to enhance cardiac performance in infants and children after cardiac surgery and to increase cardiac output.[8–10] The hemodynamic effects of milrinone in neonates after cardiac surgery have been reported,[11] and its efficacy in conjunction with catecholamines to treat septic shock in children has been shown.[12] Milrinone often is used to treat low cardiac output in infants and children after cardiac surgery. The purposes of this study were to analyze the pharmacokinetics of milrinone in infants and children after cardiac surgery and to use the pharmacokinetic characterization to determine an effective dose regimen in this patient population.

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Table 1. Demographics

Age (mo)	Weight (kg)	Diagnosis	Dopamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)
Patients receiving a single bolus dose of milrinone only			
3	3.2	VSD	—
4	4.4	VSD	—
4	4.7	VSD	—
4	5.1	VSD	—
5	5.7	VSD	—
12	11.5	ALCA	10
14	10.4	VSD	—
17	8.4	VSD	—
Patients receiving a bolus dose of milrinone plus a continuous infusion			
3	3.3	VSD	5
3	5.6	TOF	10
4	4.6	AVC	10
5	3.7	VSD	—
6	5.8	AVC	—
7	4.8	VSD	—
9	6	AVC	10
11	9.5	TOF	—
12	9.7	TOF	5
15	12	TOF	3
16	9.2	VSD, PS	—
22	10.9	VSD, PS	—

VSD = ventricular septal defect; AVC = atrioventricular canal defect; TOF = tetralogy of Fallot; PS = pulmonary stenosis; ALCA = anomalous left coronary artery.

Methods

The study protocol was approved by the Human Investigations Committee of Emory University School of Medicine. After we obtained informed parental consent, we evaluated 20 children after they underwent primary surgical repair of congenital heart defects. Table 1 shows the patient demographics.

Patients were evaluated after surgical repair of the presenting defect, separation from cardiopulmonary bypass, and administration of protamine. All patients were anesthetized with fentanyl (>50 μg/kg) and midazolam (>0.1 mg/kg) after halothane inductions (if an intravenous catheter was available, anesthesia was induced with fentanyl and midazolam), supplemented with isoflurane during the period before cardiopulmonary bypass. No patient in the study had a residual systemic-pulmonary shunt as determined by either transesophageal echocardiography or by measurement of hemoglobin oxygen saturation of samples taken from the superior vena cava, right atrium, and pulmonary artery. After the surgical repair was completed, the patients were weaned from cardiopulmonary bypass using inotropes chosen at the discretion of the attending anesthesiologist. After hemodynamic and hemostatic stability was achieved after separation from cardiopulmonary bypass, a set of baseline hemodynamic measurements was recorded (heart rate and rhythm, systemic blood pressure, left atrial pressure, central venous pressure, and cardiac output). Cardiac output was measured by thermodilution using a 2.5-French thermistor placed in the main pulmonary artery by the surgical team and injection of 3 or 5 ml cold (4°C) saline into the distal port of a double-lumen central venous catheter placed *via* the right internal vein. A loading dose (50 μg/kg) of milrinone was administered progressively in 5 min using an infusion pump. Left atrial pressure was kept constant during milrinone loading by administration of a 50:50 autologous blood–albumin mixture. Immediately after the loading-dose infusion was complete, an arterial sample was drawn to analyze the milrinone plasma concentration, and a second set of hemodynamic measurements was recorded. Hemodynamic variables before and after the loading dose were compared using paired *t* tests.

The original protocol stipulated that the 50 μg/kg dose would be administered to 10 patients and a 50 μg/kg loading dose plus a continuous infusion (*via* an infusion pump) of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ would be given to another 10 patients. Two patients enrolled to receive only the 50 μg/kg loading dose also received the 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ continuous infusion because the attending anesthesiologist deemed it clinically necessary. Finally, the infusion rate was increased to 0.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before completion of the study for three patients at the request of the attending intensivist. For all patients, additional arterial samples were taken at 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360, 600, and 960 min for analyses of milrinone plasma concentrations. All infusions were continued until we drew the last plasma sample, and then the infusion was discontinued at the discretion of the attending intensivist.

Milrinone plasma concentrations were measured by high-performance liquid chromatography as described in a previous study of adult patients from this laboratory[6] except that the sample size was 2 ml.

The pharmacokinetics of milrinone were analyzed using NONMEM, a nonlinear extended least-squares regression program that accounts for interpatient variability.[13] We used the first-order conditional estimation technique because we encountered systematic bias in our initial analysis using the more basic first-order method. Implementation of NONMEM for pharmacokinetic analysis requires a subroutine to predict drug plasma concentrations given pharmacokinetic parameters. We used

NMVCLDRG, a Fortran program written and distributed by Dr. Steven Shafer of the Palo Alto Veteran's Medical Center and the Department of Anesthesiology of the Stanford University School of Medicine (available on the World Wide Web at http://pkpd.icon.palo-alto.med.va-.gov). We evaluated two- and three-compartment models, the parameters of which were compartment volumes (V1, V2, and V3), elimination, or metabolic clearance (Cl1) and intercompartment clearances from the central compartment to the second compartment (Cl2) and from the central compartment to the third compartment (Cl3). These parameters allow us to compare the results with those of our previous study of adult patients. NMVCLDRG assumes that the compartment volumes and clearances have a log-normal distribution; *i.e.,* the parameter of individual I, P_i, is equal to $P_{TV}\exp(\eta_i)$ where η_i is normally distributed around zero and P_{TV} is the typical value for the population. We also assumed that the pharmacokinetic parameters were not correlated. The effect of body mass on the pharmacokinetics of milrinone was evaluated by modeling each parameter as a linear function of either weight or body surface area; *i.e.,* we considered models in which the clearances and volumes were assumed to be proportional to weight or body surface area. The effects of age and dopamine dose were initially considered by plotting the η values for individual patients *versus* age. Values for η are returned by the NONMEM *post hoc* step and represent the variation between the individual patient and the typical patient. Age and dopamine dose were evaluated more formally as covariates by assuming that each parameter is proportional to age or some power of age. These models were compared with a basic model in which it was assumed that the parameter was independent of age. The ability of our model to predict the observed data was measured in terms of performance error, defined as $(C_{measured} - C_{predicted})/C_{predicted}$. Values of the square root of the mean squared performance error and median absolute performance error were calculated for the final model. The optimal model was selected based on the objective function (-2 × logarithm of the likelihood of the results) and the median absolute performance error.[13,14]

Results

Table 2 presents the hemodynamic effects of the 50-μg/kg loading dose of milrinone. These are expressed as the mean percentage change in heart rate, mean blood pressure, left atrial pressure, central venous pressure, and cardiac index. Also shown are the standard errors of the means. This table shows that the 50-μg/kg loading dose resulted in a 12% decrease in mean blood pressure (significant at the $P < 0.05$ level) and an 18% increase in cardiac output (significant at the $P < 0.05$ level). There were insignificant changes in heart rate, left atrial pressure (this was part of the study design), and central venous pressure. The mean milrinone plasma concentration when these hemodynamic effects were observed was 235 ng/ml (with a standard deviation of 104).

Table 2. Hemodynamic Effects of Loading Dose (50 μg/kg)

Variable	Control	Completion of Loading Dose	Percentage Change
HR (bpm)	134 (3.8)	137 (3.4)	2.4 (1.5)
MBP (mmHg)	66.7 (1.4)	58.9 (2.)	−11.7 (2.2)*
CVP (mmHg)	8.3 (0.6)	8.5 (0.6)	3.0 (2.3)
LAP (mmHg)	7.6 (0.6)	7.4 (0.6)	−1.5 (1.9)
CI (L/min-m^2)	2.9 (0.2)	3.4 (0.3)	18.1 (2.8)*

Values are mean (standard error of the mean).

HR = heart rate; MBP = mean blood pressure; CVP = central venous pressure; LAP = left atrial pressure; CI = cardiac index.

* Significantly different from zero ($P < 0.05$).

The basic three-compartment model, in which all volumes and clearances were equal for all patients (not a function of covariates), had a significantly lower (by 93 units) objective function than did the comparable two-compartment model. Modeling each parameter as a linear function of weight ($P = \theta \times$weight) improved the objective function of the three-compartment model by 300 units and decreased the median absolute performance error from 54.3% to 24.5%. After weight correction, the NONMEM *post hoc* step was used to generate values of η for individual patients. Figure 1 presents η for Cl1 *versus* age. This figure suggests that CL1 increases with age. Subsequently, we modeled weight-normalized CL1 as a linear function of age; *i.e.,* we assumed that $Cl1 = \theta(1) \cdot \text{weight} \cdot (1 + \theta(2) \cdot \text{age})$. This improved the objective function by an additional 44 units, with a decrease in median absolute performance error to 23.2%. Inclusion of body surface area or dopamine dose did not improve the objective function or the median absolute performance error compared with the model with all parameters normalized to weight and weight-normalized CL1, which is a linear function of age (our optimal model). Table 3 shows model parameters and standard errors of the parameter estimates and estimates of interindividual variation. The parameters reported in table 3 correspond to a unit disposition function of C =

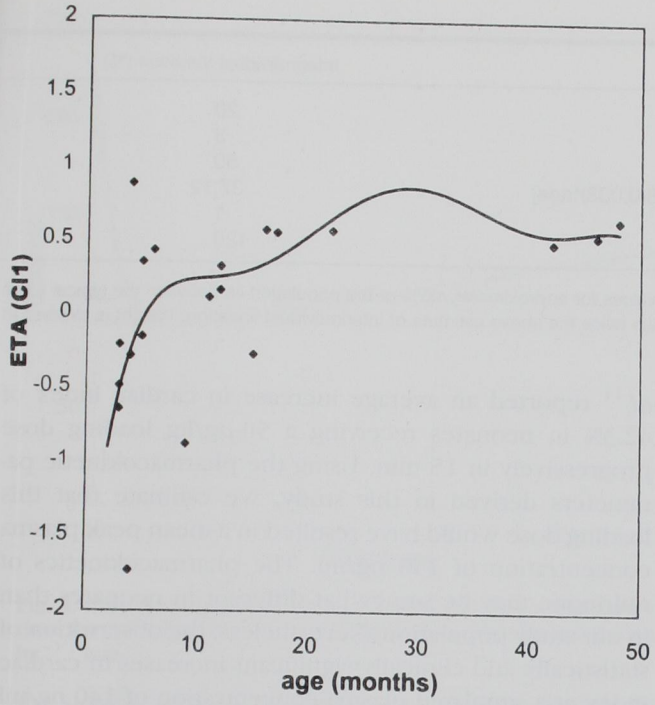

Fig. 1. Individual values for η (determined using the *post hoc* step of NONMEM) plotted against age. The solid line is a loess smoother.

$0.69 \cdot \exp(-0.1352 \cdot t) + 0.15 \cdot \exp(-0.0161 \cdot t) + 0.16 \cdot \exp(-0.0016 \cdot t)$ for a patient with the median age (6.5 months) in this study. This equation predicts the concentration (normalized to unity at time zero) that would result from a instantaneous bolus dose.

The covariance matrix generated by NONMEM allows interindividual variation of parameter estimates to be determined, and these are shown in table 3. The highest Interindividual variation (more than 100%) was observed for Cl3, whereas the lowest was close to zero (V2 and CL2), with intermediate values for the other parameters.

For the optimal model, the square root of the mean squared performance error was 42%, and the median absolute performance error was 23.2%. Figure 2 shows the ratio of predicted to measured concentrations as a function of time. Figure 3 is a plot of measured *versus* predicted concentration.

Discussion

Our optimal pharmacokinetic model adjusted the compartment volumes and distribution clearances for weight and elimination clearance for weight and age. The most obvious difference we noted between the pharmacokinetics of pediatric and adult patients is the increase in elimination clearance with increasing age in the pediatric model. In general, we can expect that elimination clearance will be a function of body mass; *i.e.,* it is intuitive that larger patients will clear more milrinone per unit of time than will smaller patients. However, after we included weight as a covariate, it appeared that elimination clearance also increased with increasing age (fig. 1). In our optimal model, weight-mormalized elimination clearance was expressed as a linear function of age. The youngest patients in this study were aged 3 months. The predicted elimination clearance for these patients is 2.6 $ml \cdot min^{-1} \cdot kg^{-1}$. The oldest patient was aged 22 months, so the predicted elimination clearance is 5.6 $ml \cdot min^{-1} \cdot kg^{-1}$. Of course, it is important not to extrapolate this conclusion beyond the range of ages (3–22 months) and weights (3.2–12 kg) found in this study.

The elimination clearances predicted by our optimal model are slightly smaller than those reported by Ramamoorthy *et al.,*[15] who report elimination clearances of 3.8 $ml \cdot kg^{-1} \cdot min^{-1}$ for infants (younger than 1 yr) and 5.9 $ml \cdot kg^{-1} \cdot min^{-1}$ for children (older than 1 yr). It is possible that the use of a two-compartment model by Ramamoorthy *et al.* led to a higher apparent elimination clearance than we found, with distribution processes contributing to the terminal phase of the biexponential unit disposition function of the two-compartment model. We found that a three compartment model significantly improved the log likelihood of the results compared with a two-compartment model. These authors predict a lower elimination clearance for infants than for children. Ramamoorthy *et al.* included age as a covariate in their analysis but concluded that because weight correlated highly with age in their study, deletion of age from the model did not alter the goodness of fit. The value of volume of distribution at steady state found by Ramamoorthy *et al.* was 900 ml/kg for infants and 700 ml/kg for children, which is comparable to the value of 851 ml/kg we found. Otherwise, it is difficult to compare the results of our study with theirs because they used a two-compartment model. The pharmacokinetic parameters reported in the current study should be considered with the realization that the need for inotropic support was not a criterion for entry into our study. If one accepts the premise that pharmacokinetics will be influenced by patient hemodynamics, then the kinetics of patients requiring inotropic support may differ from those of "healthy" patients.

A primary reason for pharmacokinetic analysis is de-

Table 3. Pharmacokinetic Parameters

Parameter	Typical Value	Interindividual Variation (%)
V1 (ml)	190(19)*weight	20
V2 (ml)	204(14)*weight	3
V3 (ml)	457(124)*weight	50
Cl1 (ml · min^{-1})	2.5(1.4)*weight*[1 + 0.058(0.038)*age]	37,12
CL2 (ml · min^{-1})	14.5(1.7)*weight	1
CL3 (ml · min^{-1})	5(2.5)*weight	120

Values in parentheses are standard errors of the parameter estimates. Parameter values for approximately 95% of the population lie between the typical value minus twice the above estimate of interindividual variation and the typical value plus twice the above estimate of interindividual variation. Weight is expressed as kilograms and age as months.

termination of an effective dosing regimen. To accomplish this goal, a therapeutic plasma concentration must be identified. We found that administration of a 50-μg/kg loading dose of milrinone progressively in 5 min resulted in a mean percentage increase in cardiac index of 18% and a mean percentage decrease in mean blood pressure of 12%. Changes in heart rate, central venous pressure, and left atrial pressure (by study design) were insignificant. From a clinical perspective, cardiac output probably cannot be measured to more than 15% accuracy. The 50-μg/kg loading dose resulted in an increase in cardiac index in excess of this threshold and was associated with a mean peak plasma concentration of 235 ng/ml. The magnitude of therapeutic effect was probably underestimated in this study because the need for inotropic support was not an inclusion criterion. Studies of amrinone in children and of milrinone in adults suggest a greater therapeutic effect in patients who need inotropic support to maintain an adequate cardiac index.[9–11] Chang *et al.*[11] reported an average increase in cardiac index of 42.3% in neonates receiving a 50-μg/kg loading dose progressively in 15 min. Using the pharmacokinetic parameters derived in this study, we estimate that this loading dose would have resulted in a mean peak plasma concentration of 140 ng/ml. The pharmacokinetics of milrinone may be somewhat different in neonates than in our study population. Nevertheless, the observation of statistically and clinically significant increases in cardiac index at a simulated plasma concentration of 140 ng/ml in the study by Chang *et al.*[11] and at an average measured concentration of 235 ng/ml in this study suggests that an approximate therapeutic target would be 200 ng/ml. In short, the 50-μg/kg loading dose achieves the desired therapeutic effect (in this study and that of Chang *et al.*). If we accept the assumption that drug effect correlates with plasma concentration, then a reasonable goal for

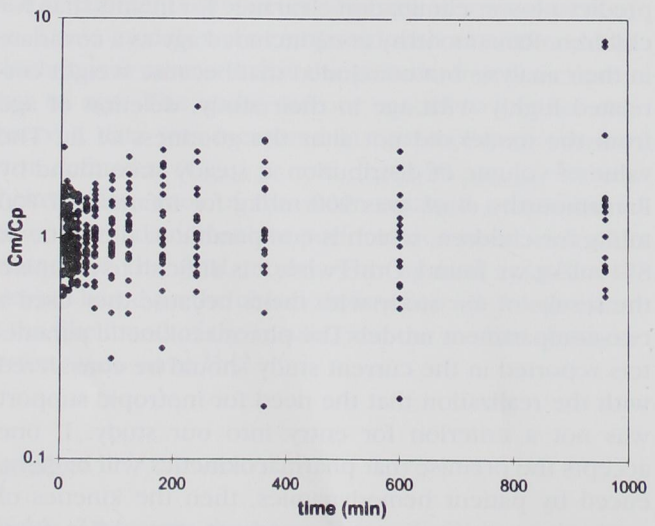

Fig. 2. The ratio of measured milrinone concentration to predicted concentration, using the estimated pharmacokinetic parameters, as a function of time.

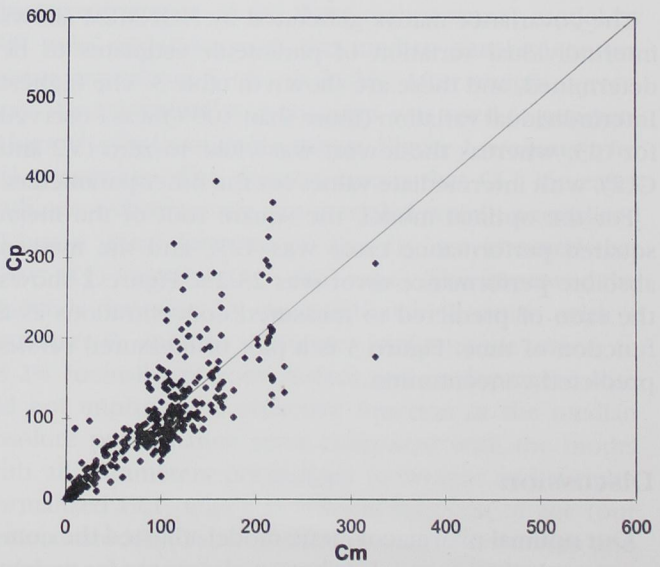

Fig. 3. The relationship between measured milrinone concentrations and those predicted using the estimated pharmacokinetic parameters.

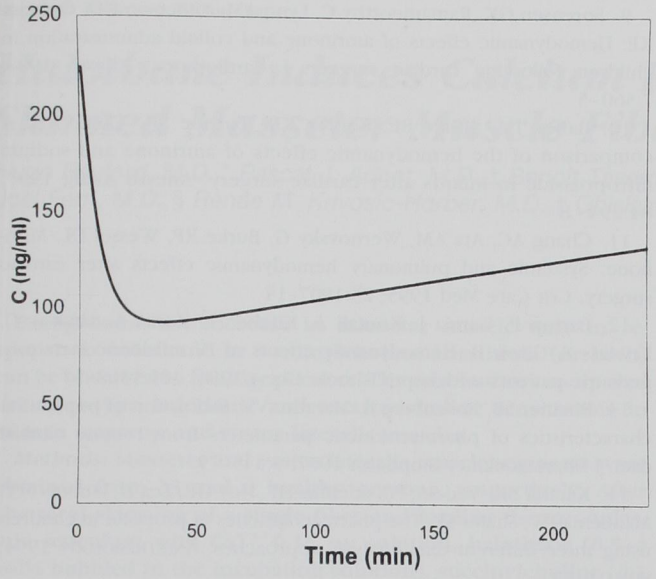

Fig. 4. The predicted milrinone concentration as a function of time for a loading dose of 50 μg/kg plus an infusion of 0.5 μg · kg^{-1} · min^{-1}.

the dosing regimen would be to maintain the plasma levels achieved by this loading dose. However, our data were not adequate to provide a model of the entire concentration–effect relation. Thus, we cannot comment on the effects of lower or higher plasma concentrations. We also should emphasize that assuming that drug effect is proportional to plasma concentration is a major assumption. If there were significant plasma–"effect" site hysteresis, the 200 ng/ml target at steady state could be unnecessarily high. It is our clinical experience that the peak hemodynamic effects of milrinone are noted soon after bolus injection, and this is consistent with presumed effect sites (myocardium and vascular endothelium), which would equilibrate rapidly with plasma.

Figure 4 shows the concentrations one would predict after a loading dose of 50 μg/kg, given as a bolus dose, with the concomitant institution of an infusion of 0.7 μg · kg^{-1} · min^{-1} to a 6.5-month-old infant (the median in this study). It can be seen that the loading dose of 50 μg/kg produces therapeutic levels (> 200 ng/ml), but these levels decrease rapidly. Figure 5 shows the levels predicted for a 50-μg/kg loading dose followed by an infusion of 3.5 μg · kg^{-1} · min^{-1}, which is reduced at 30 min to 0.5 μg · kg^{-1} · min^{-1}. This dosing regimen was derived from the parameters in table 3 using an approximate technique to maintain constant plasma concentrations[16] and consistently maintains therapeutic levels at more than 200 ng/ml. Thus, this dosing regimen is predicted to be effective for the median patient in our study. The kinetic parameters reported in table 3 may be used to derive dosing regimens for patients of other ages and weights.[16] Obviously, because there is significant interpatient variability, dosing guidelines are only approximate. Because the parameters determining distribution kinetics are linear with weight, we can anticipate that a rational dosing regimen would consist of a 50-μg/kg loading dose (because this results in a statistically and clinically significant increase in cardiac index) and a rapid infusion of approximately 3 μg · kg^{-1} · min^{-1} for the first 30 min for all patients, to maintain the therapeutic levels achieved by the loading dose during drug redistribution. This should be followed by a maintenance infusion of approximately 0.5 μg · kg^{-1} · min^{-1}, with the realization that elimination clearance, and thus the necessary maintenance infusion rate, may be lower in infants.

In conclusion, we have found that milrinone significantly increases the cardiac index in children after cardiac surgery in association with plasma levels of 235 ng/ml. The pharmacokinetics of milrinone in this patient population were best described by a three-compartment model with all parameters corrected for weight and with weight-normalized elimination clearance also proportional to age.

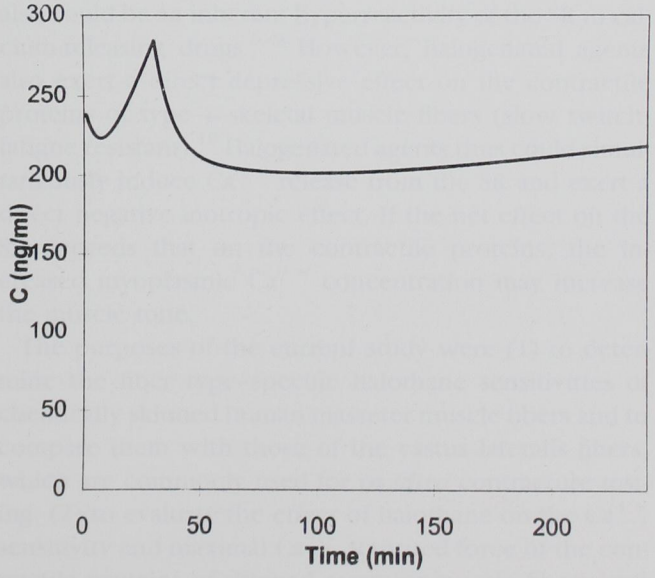

Fig. 5. The predicted milrinone concentration as a function of time for a loading dose of 50 μg/kg plus an infusion of 3.5 μg · kg^{-1} · min^{-1} reduced at 30 min to 0.5 μg · kg^{-1} · min^{-1}.

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