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A Population Pharmacokinetic Analysis of Milrinone in Pediatric Patients after Cardiac Surgery[1]

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The purpose of this study was to ascertain the optimal pharmacokinetic model for milrinone in pediatric patients after cardiac surgery when milrinone was administered as a slow loading dose followed by a constant-rate infusion. The data used for pharmacokinetic analysis were collected in a prospective, randomized, placebo-controlled multi-center trial of milrinone as prophylaxis for the development of low cardiac output syndrome after surgery for repair of complex congenital cardiac defects. Two blood samples were randomly collected from each patient for determination of plasma milrinone concentrations with subsequent population pharmacokinetic modeling. The pharmacokinetics of milrinone in pediatric patients under 6 year's age were best described by a weight-normalized one compartment model after a slow loading dose followed by a constant-rate infusion. The volume of distribution was 482 ml kg^{-1}, and was independent of age. Clearance was a linear function of age given by $Cl = 2.42$ ml kg^{-1} $min^{-1}[1 + 0.0396*age]$.

KEY WORDS: congenital heart disease; phosphodiesterase inhibitors; milrinone; pharmacokinetics; mixed-effects modeling.

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INTRODUCTION

More than 300,000 children under the age of 21 have congenital cardiovascular disease, and 38% will undergo at least one surgical procedure. Advances in cardiac surgery have increasingly made repair early in life more feasible. However, even with advances, there is a predictable and reproducible decrease in cardiac output, low cardiac output syndrome (LCOS), after cardiac surgery (1–3). LCOS occurs even if there are no residual cardiac lesions. The causes of LCOS are multifactorial and include myocardial ischemia due to aortic cross-clamping, the residual effects of cardioplegia, and activation of inflammatory pathways from exposure of blood to foreign surfaces during cardiopulmonary bypass (CPB). LCOS is associated with increased mortality and morbidity and is seldom left untreated (1,2). Standard therapy for LCOS has included catecholamines, but catecholamines may exacerbate tachycardia and the risk of dysrhythmias, and may increase afterload. Because of these adverse effects, the phosphodiesterase inhibitors are being increasingly used for the treatment of LCOS. Rational use of any drug requires an understanding of the drug's pharmacokinetics. While the pharmacokinetics of the phosphodiesterase inhibitor, milrinone, has been described in two studies, the numbers of patients in both studies were small (4,5).

Furthermore, pharmacokinetic models are often a reflection of how the drug is dosed and the previous studies were initiated in the operating room with loading doses of the study drug. The pharmacokinetics of milrinone, in pediatric patients after biventricular repair, is discussed in this report. This analysis is based on data derived from a multi-center randomized double-blind study of milrinone for the prevention of LCOS in pediatric patients after cardiac surgery, the PRIMACORP study (6,7). The objectives of this analysis were (1) to determine the best population pharmacokinetic model for milrinone in pediatric patients using the study dose regimen and (2) to determine whether the covariates of weight, age, hepatic function, and renal function, influenced drug disposition. Patients in this study were randomly administered either placebo, low-dose milrinone, or highdose milrinone, as described below, and followed for 36 hr. During this period blood samples were taken randomly from each patient for determination of milrinone plasma concentration. The number of blood samples was limited to two per patient and, consequently, population pharmacokinetic methods were used for the analysis.

METHODS

The PRIMACORP trial was a randomized double-blind multi-center trial of milrinone as prophylaxis for the development of LCOS (6,7). The Institutional Review Boards of each of the participating institutions approved the protocol and informed consent. A total of 242 patients in 31 institutions were enrolled after obtaining informed consent from parents or guardians.

The protocol stipulated the administration of placebo or one of two doses of milrinone, in a randomized, double-blind manner, to pediatric patients at high risk of developing LCOS after cardiac surgery. The inclusion criteria stipulated patients 6 years or younger who required surgery for anatomic repair of certain congential defects: transposition of the great arteries with or without a ventricular septal defect (VSD), VSD with an arch anomaly, complete atrioventricular canal, tetralogy of Fallot, total anomalous pulmonary venous repair, truncus arteriosus, double-outlet right ventricle (biventricular repair), anomalous left coronary from the pulmonary artery, and congenital mitral or aortic valve defects. Eligible patients who were deemed stable and not experiencing LCOS were enrolled within 90 min after arrival in the intensive care unit. Enrolled patients were randomized to either placebo, low dose milrinone (25 μg kg^{-1} over 60 min followed by a 0.25 μg kg^{-1} min^{-1} infusion) or high dose (75 μg kg^{-1} over 60 min followed by a 0.75 μg kg^{-1} min^{-1} infusion). Milrinone was continued for up to 36 hr during which time patients were evaluated for the primary endpoint of the study, a composite of death or the development of LCOS, requiring one or more of the following: (1) initiation of mechanical support of the circulation, (2) administration of new, open-label positive inotropic agents or other pharmacological support, or (3) an increased need ($\geq$100% over baseline) for existing pharmacological support. Patients were diagnosed with LCOS if they demonstrated clinical signs of the syndrome-tachycardia, oliguria, cold extremities or cardiac arrest-with or without a $\geq$30% difference in arterial-mixed venous oxygen saturation or metabolic acidosis (an increase in the base deficit of >4 or an increase in lactate of >2 mg dl^{-1}) on two successive blood gas measurements. Study drug (placebo or milrinone) was discontinued when LCOS was diagnosed.

Two blood samples were drawn from each patient for determination of milrinone plasma concentrations. The sampling times were randomly selected from the following schedule: 15, 30, 45, 60, 90, 120, 180, 240, 360, or 480 min after initiating study drug, with the proviso that samples were at least 2 hr apart in any one patient. If the primary endpoint was

reached, study drug was stopped and a sample was obtained at that time point if two previous samples were not already obtained. These samples provided the data base for the pharmacokinetic analysis. Other data collected for the pharmacokinetic analysis included the following information: study site, patient identification number, sampling times, study drug concentration, infusion pump rates, infusion duration, and the covariates weight, age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine clearance (CrCl), development of LCOS, and presence of serious adverse event (SAE).

Blood samples were collected into vacutainer tubes containing sodium heparin. Tubes were inverted 10–15 times to assure mixing and then were centrifuged for 15 min at 3500 rpm. Plasma was separated and transferred to pre-labeled plastic storage tubes. Samples were frozen and shipped to Covance Laboratories (Indianapolis, IN) for temporary storage until shipment to Emory University. Samples were shipped frozen, on dry ice overnight, to Emory University in Atlanta, Ga. Upon arrival, samples were inspected and immediately placed in a −70 °C freezer and kept frozen until analysis time. A high performance liquid chromatographic (HPLC) validated method was used for the determination of milrinone in human plasma (8). For the analysis, samples were thawed at room temperature, and aliquots of patients' samples were mixed with internal standard (IS-SW041417), and after addition of ammonium sulfate, were extracted into ethyl acetate and back-extracted into 0.1 N hydrochloric acid. Traces of ethyl acetate were removed at 45 °C under nitrogen and after pH adjustment, samples were chromatographed on a C18 column at 25 °C using mobile phase consisting of a mixture of phosphate buffer and acetonitrile. Detection of milrinone and the internal standard was achieved by UV detection at 340 nm. Signals from the detector were collected and stored on a Vectra VL computer equipped with Chem Station software (part of the HPLC system).

The relationship between peak area ratio (drug/IS) and amount ratio (drug/IS) was found to be linear within 5–500 ng ml^{-1} for milrinone in plasma with an average correlation coefficient of 0.999. Inter-day precision of the method ranged from 9.54% at 5 ng ml^{-1} to 4.24% at 500 ng ml^{-1} and accuracy of the method ranged from 98% to 104%. The limit of quantitation (LOQ) from 1 ml of plasma was 5 ng ml^{-1}.

Because there were, at most, two samples for each patient, the data were analyzed using population pharmacokinetic methods. This was done using NONMEM, Version 5 (9). One, two, and three compartment models were considered, assuming intravenous dosing into a central compartment. The pharmacokinetic parameters were the compartment volumes, elimination clearance, and inter-compartmental distribution clearances. We assumed that each structural parameter had a log normal distribution, i.e.,

$$P_{\mathrm{i}} = P_{\mathrm{tv}} \exp(\eta_i)$$

where P_i is the parameter for individual i, P_{tv} is the "typical value" for the population, and η_i is a random variable from a distribution with a mean of zero and variance denoted by $\langle \eta^2 \rangle$. We considered models in which the η values for different parameters (volumes and clearances) could be correlated, as well as models in which we assumed that different parameters were not correlated. We assumed that the residual error, the difference between predicted and measured milrinone concentrations, could be described by a log normal plus additive model, i.e.,

$$C_{\mathrm{m}} = C_{\mathrm{p}} + C_{\mathrm{p}} \exp(\epsilon_1) + e_2$$

where C_{m} is the measured concentration, C_{p} is the predicted concentration, and ε_1 and ε_2 have normal distributions with means of zero.

NONMEM estimates pharmacokinetic parameters by determining the parameter values that minimize the "objective function", which is minus two times the logarithm of the likelihood of the observed results (9). In general, the integrals needed to evaluate the objective function are too complicated to solve without approximation. In the first order estimation approximation, the log likelihood is expanded to first order around the mean values of the ηs (which are zero by assumption), simplifying the objective function (9,10). In the conditional estimation techniques, it is recognized that expansion around $\eta = 0$ may be a poor approximation and, instead, the log likelihood is expanded to first order around conditional estimates of the η, derived from the prior iteration (9,10). We used the first order estimation technique for initial model building. This is in line with the recommendations of the NONMEM Project Group (9). However, final models were compared using the first order conditional estimation technique.

The optimal compartment model was selected using the Aikake Information Criterion (9), which stipulates that the optimal model is that which minimizes the sum of the objective function plus two time the total number of parameters. We compared one, two, and three compartment models without inclusion of weight as a covariate. However, it was recognized that weight may be an important pharmacokinetic covariate in a pediatric population and that clinicians dose drugs on a per kilogram basis. Consequently, it was considered impossible to select an optimal compartment model without consideration of body mass. Therefore, comparisons were made of one, two, and three compartment models in which

it was assumed that each parameter was directly proportional to body weight, i.e., we assumed that $P = \Theta^* W$, where P_i is the pharmacokinetic parameter (compartment volume or clearance), Θ is estimated, and W is weight. We also considered a more sophisticated method of incorporating weight as a covariate, in which both volumes and clearance were assumed to be given by $P = \Theta 1^* W^{\Theta 2}$ where both $\Theta 1$ and $\Theta 2$ are estimated. The optimal compartment model was identified by the Aikake Information Criterion for both weight-corrected and weight-independent models.

Following identification of the optimal compartment model (including weight-dependence), the conditional (non-Laplace) estimation method was used to estimate η values for individual patients for each parameter. These were plotted vs. the covariates age, AST, ALT, CRT. These plots were evaluated for significant correlations between η (which is a measure of the deviation of the patient's pharmacokinetic parameter from the "typical value") and the covariate in question, for further development of the model. For both clearance and volume of distribution, a two-tailed t-test (assuming equal variances) was used to compare estimates in patients with and without LCOS and to compare estimates in patients with and without SAEs.

RESULTS

The data set was comprised of 462 plasma samples collected from 235 patients at 29 clinical sites. There were 78 patients each in the placebo and high dose groups and 79 patients in the low dose group. There were 46 neonates (0–1 month), 93 infants (1–24 months), and 18 children (>24 months) who received either the high or low dose. The mean age of patients receiving milrinone was 7.2 months and the mean weight was 5.8 kg. The three most common operations were repair of tetralogy of Fallot ($n = 54$), repair of complete atrioventricular canal defects ($n = 45$), and the arterial switch procedure ($n = 36$). Figure 1 is a histogram of the sampling times. Figure 2 is a plot of the observed milrinone concentrations as a function of time.

The various pharmacokinetic models considered are described in Table I, which also summarizes the results of non-linear regression function for the model. Model identification was begun by considering the simplest, a one compartment model, and comparing models in which the parameters (volume of distribution and clearance) were independent of weight and in which the parameters were directly proportional to weight. Assuming that volume of distribution and clearance were directly proportional to weight (and ignoring interparameter correlation) resulted in a significant decrease of the objective function from 2835 to 2660.

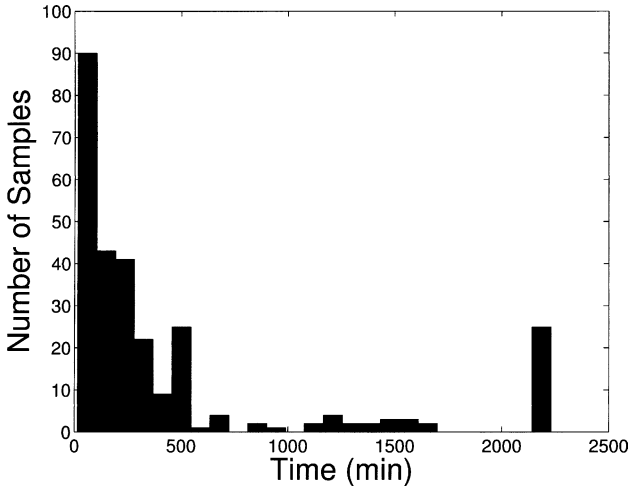

Fig. 1. A histogram of sampling times.

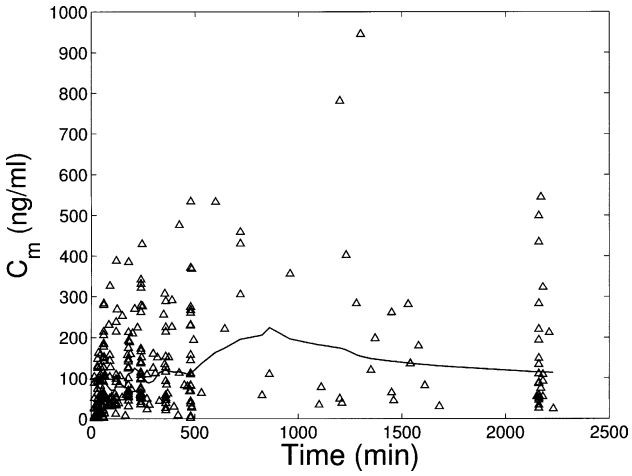

Fig. 2. Measured milrinone concentration as a function of time. The solid line is a LOESS smoother.

Minimization of the objective function for a two compartment model in which parameters were independent of weight and which assumed no correlation between parameters terminated in a rounding error with a value of 2840. Assuming that the parameters were directly proportional to weight led to a significantly improved objective function of 2667.

Table I. Model Development

Data Set	Model	Results of regression
Full	1 compartment, no weight correction	obj = 2835
Full	1 compartment, $P=\Theta*W$	obj = 2660
Full	2 compartment, no weight correction	obj = 2840
Full	2 compartment, $P=\Theta*W$	obj = 2667
Full	3 compartment, no weight correction	obj = 2840 re
Full	3 compartment, $P=\Theta*W$	obj = 2667 re
High dose	1 compartment, $P=\Theta*W$	obj = 1441
High dose	2 compartment, $P=\Theta*W$	obj = 1441
Low dose	1 compartment, $P=\Theta*W$	obj = 1196
Low dose	2 compartment, $P=\Theta*W$	obj = 1195
Neonates	1 compartment, $P=\Theta*W$	obj = 808
Neonates	2 compartment, $P=\Theta*W$	obj = 812
Infants	1 compartment, $P=\Theta*W$	obj = 1600
Infants	2 compartment, $P=\Theta*W$	obj = 1602
Children	1 compartment, $P=\Theta*W$	obj = 944
Children	2 compartment, $P=\Theta*W$	obj = 943
Full	1 compartment, $P=\Theta*W$, CE	obj = 2636
Full	1 compartment, $P=\Theta*W$/age-corrected, CE	obj = 2616
Full	1 compartment, $P = \Theta1*W^{\Theta2}$/age-corrected, CE	obj = 2619

Data set refers to patients used for the analysis, with stratification on the basis of dose and age group (neonate 0–1 month, infant 1–24 months, children >24 months). Regression results are expressed in terms of the objective function (obj) with a lower value indicating a superior fit. The model with the smallest Aikake information criterion was chosen as the superior model. Note that the objective function is smaller for smaller data sets. $P = \Theta*W$ indicates that each pharmacokinetic parameter is assumed to be directly proportional to weight. Age correction indicates that clearance is assumed to be a linear function of age, as discussed in the text. $P = \Theta1*W^{\Theta2}$ indicates that we allowed pharmacokinetic parameters to be proportional to weight raised to variable powers, estimated by NONMEM. CE denotes first order conditional estimation.

The three compartment model failed to converge with or without normalization of parameters by weight due to rounding errors, although the objective function at the point of termination was significantly lower (2667 vs. 2840) for the weight-normalized model. Because the assumption of weight-proportional parameters significantly improved the objective function for both one and two compartment models, this assumption was utilized in further model identification.

Since the three compartment weight-normalized model failed to converge due to rounding errors with an objective function no lower than the two compartment model, it was not given further consideration. Weight-normalized one and two compartment models were further investigated.

The objective function for the weight-normalized one compartment model was 2660 while the objective function for the weight-normalized

two compartment model was 2667, using the first order estimation technique. This indicated that the one compartment model is preferable. Furthermore, the median absolute prediction error for both models was essentially identical (0.39 to two significant digits) and the two models were almost functionally identical. The estimate of volume of distribution was 481 ml kg^{-1} for the one compartment model and 528 ml kg^{-1} for the two compartment model ($V_1 = 174$ ml kg^{-1}, $V_2 = 354$ ml kg^{-1}). The estimate of elimination clearance was 3.00 ml kg^{-1} min^{-1} for the one compartment model and 3.04 for the two. More importantly, the estimate of distribution clearance for the two compartment model was 102 ml kg^{-1} min^{-1}, indicating very rapid distribution into the total volume of distribution and functional equivalence to a one compartment model.

The one and two compartment models were compared for several patient subgroups. When stratified by age, neonates (1 month or less), infants (1 month to 2 years) and children (age 2–6 years), the one compartment model was superior to the two compartment model in each age group. As observed for the full data set, in neonates and infants the two compartment model was functionally equivalent to a one compartment model due to very rapid distribution clearances ($Q = 103$ and 226 ml kg^{-1} min^{-1} respectively). In children, the parameter estimates for the two compartment model were functionally distinct from the one compartment model ($V_1 = 166$ ml kg^{-1}, $V_2 = 269$ ml kg^{-1}, $Cl = 6.29$ ml kg^{-1} min^{-1}, $Q = 4.75$ ml kg^{-1} min^{-1}). However, the objective functions were virtually identical. We also considered the possibility that dose influenced the optimal model. The two dose groups were analyzed separately. Again, the one compartment model was optimal.

In summary, the weight-normalized two compartment model did not significantly improve the quality of the fit, the predictive accuracy was no different and it was no different functionally than the one compartment model. Furthermore, the one compartment model was superior in each of the patient age subgroups. The weight-normalized one compartment model was adopted for further analysis.

Using the weight-normalized one compartment model, values of η for individual patients (the deviation of the estimate of either clearance or volume of distribution for the individual patient from the mean) were estimated using the first order conditional estimation technique. The estimates were plotted vs. the covariates of age, ALT, AST, and CrCl. There were no significant correlations between either η and AST, ALT, or CrCl. There were significant correlations between age and individual η values for Cl. This is illustrated in Fig. 3. There was no correlation between η values for Vd and age.

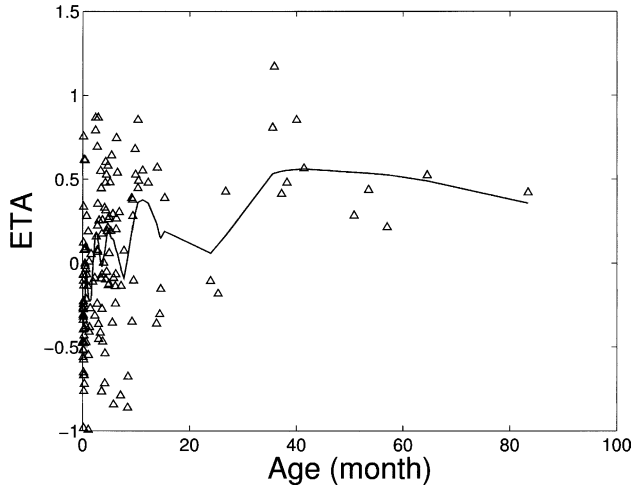

Fig. 3. Values of η_{Cl} vs. age where η_{Cl} is the deviation of the estimate of clearance for an individual from the mean estimate. The solid line is a LOESS smoother.

Since the η value for clearance was correlated with age, a model was considered in which clearance was modeled as a linear function of age, i.e.,

$$C_l = \Theta(1) * \text{Weight} * [1 + \Theta(2) * \text{Age}]$$

in which $\Theta(1)$ is the baseline clearance for a newborn and $\Theta(2)$ represents the increment in clearance with increasing age. This improved the objective function by 20 units when first order conditional estimation was used. The estimates of $\Theta(1)$ and $\Theta(2)$ (with standard error in parentheses) were 2.42(0.288) and 0.0396(0.0139).

We also considered the possibility that the relationship between pharmacokinetic parameters and weight was more complex than simple direct proportionality. However, a model that allowed both volume of distribution and clearance to be proportional to variable powers of weight actually resulted in a slight increase in the objective function despite the addition of two parameters and was not given further consideration.

Cl was lower in those patients having SAE (mean η value of–0.11) compared to those who did not (mean η of 0.05), using a two-tailed t-test assuming equal variances ($p = 0.038$) (Fig. 4). The individual values of Vd tended to be lower in patients who experienced a SAE (mean η of −0.12) than in patients who did not (mean η of 0.035) but this was not significant

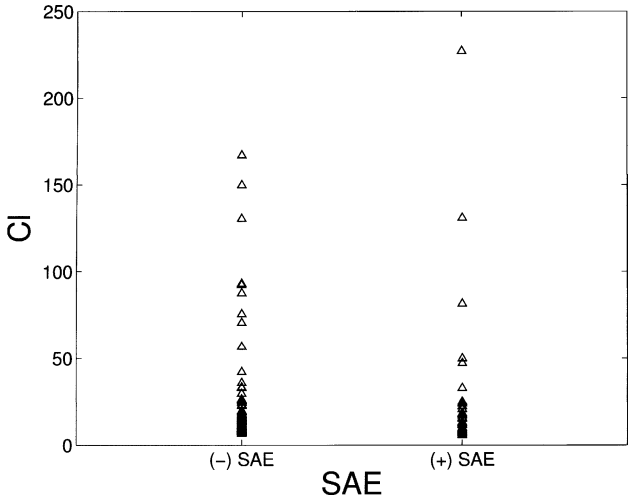

Fig. 4. Individual clearance values for patients who experienced a SAE vs. those who did not.

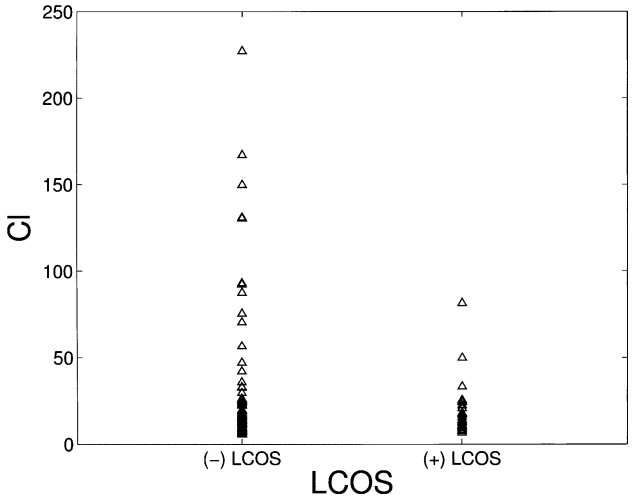

Fig. 5. Individual clearance values for patients who experienced LCOS vs. those who did not.

($p = 0.084$). The individual values of Cl tended to be lower in patients who experienced LCOS (mean η of -0.12) compared to those who did not (mean η of 0.03), but it was not significant at the 0.05 level ($p = 0.081$) (Fig. 5).

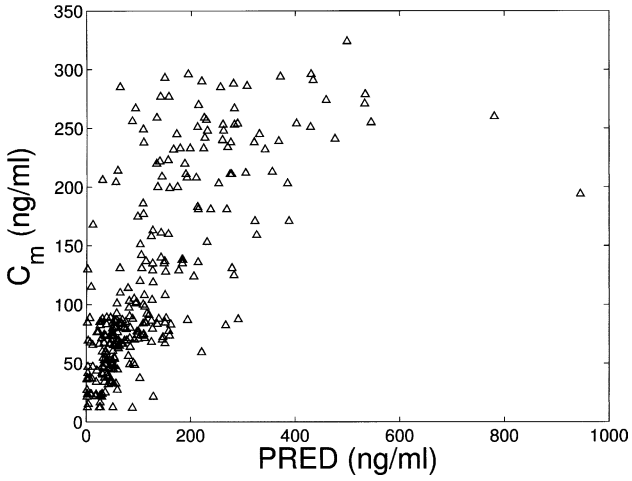

Fig. 6. The relationship between the milrinone concentration predicted by the final model without using conditional estimation (PRED) and the measured concentration (C_m).

The weight-normalized one compartment model with clearance as a linear function of age was adopted as the final model for the total patient population. The volume of distribution was 482 ml kg^{-1} and clearance was given by the relationship

$$C_l = 2.42\,\mathrm{ml\,min^{-1}kg^{-1}}(1 + 0.0396^{*}\mathrm{age})$$

A plot of measured concentration vs. the predicted concentration without *post hoc* conditional estimation (denoted PRED) for this model is shown as Fig. 6. Figure 7 presents measured concentration vs. predicted concentration with conditional estimates (denoted IPRED). Figure 8 shows the ratio, C_m/C_p (PRED), as function of time. Figure 9 presents weighted residuals (WRES) as a function of time.

Table II presents parameter estimates (with standard errors) for the final model as well as estimates for the following patient subgroups: neonates, infants, children, patients receiving the high dose and patients receiving the low dose. It should be noted that when the patients are stratified by age the estimates of clearance increase with age.

DISCUSSION

The primary finding of this study was that the optimal pharmacokinetic model is a single compartment. The data were quite "noisy" with an

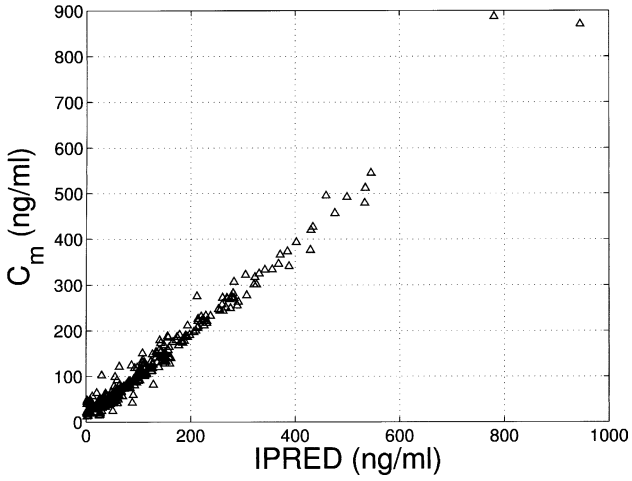

Fig. 7. The relationship between the milrinone concentration predicted by the final model using conditional estimation (IPRED) and the measured concentration (C_m).

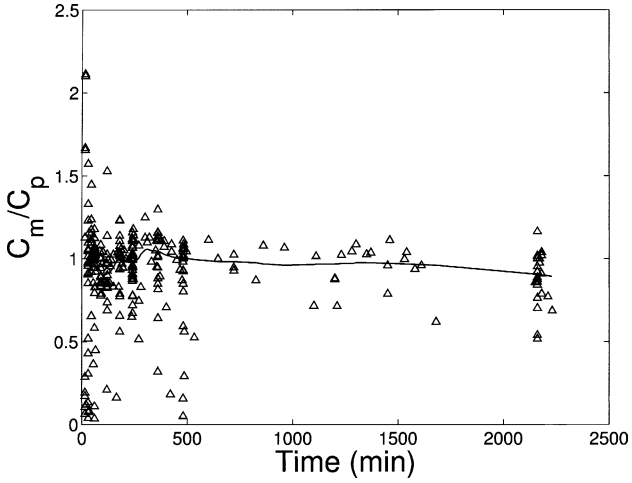

Fig. 8. The ratio of measured concentration, C_m, to predicted concentration, C_p (without conditional estimation), as function of time. The solid line is a LOESS smoother.

absolute median prediction error of 0.39. The estimates of volume of distribution and clearance are not remarkably different from previously reported values in pediatric patients. However, the two previous studies of milrinone used two and three compartment models (4,5). There are

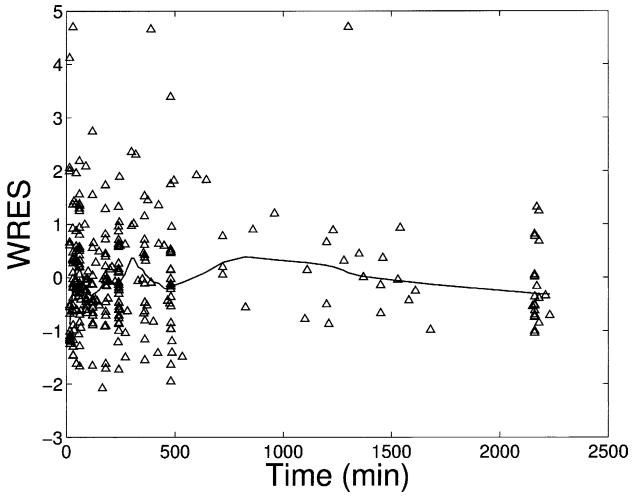

Fig. 9. Weighted residuals (WRES) as a function of time. The solid line is a LOESS smoother.

certainly differences between these earlier studies and the current one. The prior studies enrolled far fewer patients and had older age distributions. The current study is the only study of the pharmacokinetics of milrinone that enrolled large numbers of neonates. This difference in typical patient age may explain why the one compartment model was optimal in the current study. However, much more plausible explanations are the dosing schedule and the sampling schedule. The pharmacokinetic component of the PRIMACORP trial was an "add-on" study, and the primary objective of the trial was to determine whether milrinone was an effective prophylaxis for development of LCOS (6,7). Because of safety concerns in this prophylaxis trial, it was deemed essential for patient enrollment and successful completion of the study to give the loading dose over 1 hr. In contrast, in the prior pharmacokinetic studies of milrinone the loading doses were given much more quickly. It is notable that the study that identified a three compartment model (5) as optimal gave the loading dose over 5 min and the study which identified a two compartment model as optimal gave the initial loading dose over 10 min (4). It is believed that when the loading dose is given over 60 min, distribution processes are no longer the rate-limiting step for equilibration of drug among body stores. Instead, the infusion rate is the rate-limiting factor for drug disposition. This makes it impossible to analyze the kinetics of distribution processes. Furthermore, and most significantly for model development, only two samples were taken from each patient. This was necessitated by the age

Table II. Estimates of Pharmacokinetic Parameters for the One Compartment Weight-Corrected Model

Vd (ml kg^{-1})		Cl (ml kg^{-1} min^{-1})
Group		
Total (n = 157)	482 (39.3)	2.42(0.228)*[1 + age*0.0396(0.0139)]
High (n = 78)	466 (17.1)	2.21(0.184)*[1 + age*0.0379(0.0166)]
Low (n = 79)	505 (57)	2.55(0.396)*[1 + age*0.0491(0.032)]
Neonates (0–1 m) (n = 48)	523 (28.5)	1.64 (0.373)
Infants (1–24 m) (n = 94)	461 (40.2)	3.38 (0.2)
Children (24–72 m) (n = 12)	353	6.68

Parameter estimates with standard errors in parentheses are shown. The covariance step was unsuccessful for children so standard errors are not shown for this group. Use of age as a covariate on Cl was not used for age-stratified groups (neonates, infants, children).

distribution of our study population and the "add-on" aspect of this multi-center trial. Since multiple blood samples were needed for the evaluation of the clinical end-point and since most of the patients were infants or neonates, extensive sampling for pharmacokinetic purposes would have been unethical. We elected to use random sampling times. We are unaware of any evidence that this leads to excessive bias and it is certainly preferable to using the same fixed sampling schedule in every patient. Given the sparse data available to us, the latter strategy would have had no chance of identifying multiple compartments.

It should be noted that, given the positive clinical outcome of the trial (7), the dosing schedule used for the study is likely to be adopted by practitioners, and the pharmacokinetic model reported herein will be relevant to how the drug is likely to be given.

As would be expected, we found that both volume of distribution and clearance increased with increasing body weight. In our final model, both volume of distribution and clearance were *directly* proportional to weight. A weight-proportional model certainly simplifies dosing recommendations for the clinician. However, there are plausible theoretical reasons to believe that while volume of distribution may be directly proportional to weight, clearance should be proportional to weight raised to a power of 0.7 (11). Despite these theoretical considerations, a model in which both parameters were proportional to a variable power of weight did not improve the quality of the fit and was not further explored.

The most notable finding from this analysis of the influence of covariates is that clearance, but not volume of distribution, increases linearly with patient age. This suggests that the metabolic processes that eliminate milrinone are functions of age. This could reflect a delayed maturation of drug clearance processes. The clearance of milrinone in neonates was less

than 25% of that in children, when analyzed by age stratification. This indicates that a constant-rate infusion will take much longer to approach steady-state levels in neonates. However, for the same infusion rate, the steady-state concentration will be higher in neonates than older patients. The clinical significance of this will obviously depend on the relative pharmacodynamics of milrinone in different age groups. For example, consider a 1 day old neonate and a 4 year old child. It is very easy to demonstrate by simulation that if therapy is initiated with a constant-rate infusion of 0.75 μg kg^{-1} min^{-1}, the plasma levels will always be higher in the neonate, although it will take far longer to approach the steady-state concentration in the neonate. The neonate will take 2 hr to reach 50% of the steady-state concentration in comparison to 45 min for the older child. Use of a loading dose infusion, as utilized in this study, reduces the time to approach steady-state significantly (the time needed to reach 50% of steady-state is now only 70 min for the neonate). If the pharmacodynamics of milrinone is similar in the various age groups we can anticipate that the onset of effect will be very similar in each group but the infusion rate may need reduction in younger patients.

No relationship was found between either pharmacokinetic parameter and hepatic function (as measured by AST and ALT) or renal function (as measured by creatinine clearance).

Patients who had a SAE had significantly lower values of clearance and a trend toward lower volumes of distribution. Patients who experienced LCOS had a trend toward lower values of clearance. The clinical significance of this is quite unclear, although clearance is an exposure measure and lower values imply greater drug exposure.

In conclusion, the results of this study have clinical implications for the pediatric intensivist using milrinone. The decrease in clearance with age implies that a constant-rate infusion will eventually result in higher blood levels in younger patients. However, the longer half-life of milrinone in younger patients also implies that it will take longer to approach steady-state, *underscoring the necessity of a loading dose for the rapid achievement of a therapeutic blood concentration*. The intensivist should also be aware that with longer duration of administration, dose reductions may be appropriate and can be done without lowering the plasma concentration below therapeutic levels.

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