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Pharmacokinetics of Intravenous Milrinone in Patients Undergoing Cardiac Surgery

James M. Bailey, M.D., Ph.D., Jerrold H. Levy, M.D.,† Mutsuhito Kikura, M.D.,‡ Fania Szlam, M.S.,§ Carl C. Hug, Jr., M.D, Ph.D.‖*

Background: **Milrinone is a phosphodiesterase inhibitor with positive inotropic and vasodilator effects that are useful in the treatment of ventricular dysfunction after cardiac surgery. However, the pharmacokinetics of the drug have been investigated only in healthy volunteers and in patients with chronic congestive heart failure. This study investigates the pharmacokinetics of milrinone in adult cardiac surgical patients after cardiopulmonary bypass.**

Methods: **Milrinone was administered to 25 patients just before or immediately after separation from cardiopulmonary bypass. Arterial blood was sampled over the next 16 h and milrinone plasma concentrations were determined by high-performance liquid chromatography. Data were analyzed by extended nonlinear least-squares regression. The relation between milrinone plasma concentration and hemodynamic effect was examined in an additional 11 patients who had cardiac indices less than 2.5 $l \cdot min^{-1} \cdot m^{-2}$ immediately after separation from cardiopulmonary bypass. Milrinone was administered and plasma concentrations were related to changes in cardiac index during the next 10 min.**

Results: **A milrinone dose of 50 $\mu g/kg$ in conjunction with an infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ consistently maintained plasma concentrations in excess of 100 ng/ml. A triexponential equation describing the plasma concentration as a function of time was used to describe the data. Central-compartment volume was 102 ml/kg, volume of distribution was 1,698 ml/kg, and elimination clearance was 1.88 $ml \cdot kg^{-1} \cdot min^{-1}$. Pharmacokinetic parameters were independent of dose. The relation between plasma concentration and percentage increase in cardiac index could be described by a sigmoidal curve with the plasma concentration associated with a 50% increase in cardiac index equal to 167 ng/ml.**

Conclusions: **A milrinone dose of 50 $\mu g/kg$ with an infusion at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ maintains plasma concentrations at or above the threshold of therapeutic effects. (Key words: Anesthesia: cardiac. Heart, inotropy: milrinone. Pharmacokinetics: milrinone. Surgery, cardiac: cardiopulmonary bypass.)**

MILRINONE is both an inotropic agent and vasodilator that has minimal effects on heart rate and myocardial oxygen consumption. It acts beyond the β-adrenergic receptors to increase cyclic adenosine monophosphate by inhibiting the enzyme phosphodiesterase III, possibly enhancing the effects of catecholamines that increase the production of cyclic adenosine monophosphate through β-receptor stimulation.[1–4] The currently available phosphodiesterase inhibitors, amrinone and milrinone, are widely used in cardiac surgical patients after cardiopulmonary bypass (CPB). Effective and safe use of these drugs would be enhanced by definition of their pharmacokinetics and pharmacodynamics in the clinical settings in which they are used. Determination of pharmacokinetic characteristics is the first step to development of administration schemes (*e.g.*, loading dose and continuous infusion) able to produce stable plasma (and cardiac) concentrations to evaluate pharmacodynamics and to sustain desirable drug effect.

Milrinone has only recently been introduced for clinical use in the United States. Pharmacokinetic data have been obtained in healthy volunteers and in patients with chronic congestive heart failure.[5–8] Extracorporeal circulation results in significant physiologic changes, including hypothermia, hemodilution, exclusion of the lungs from the circulation, and changes in plasma proteins, all of which can have major effects on the pharmacokinetics of drugs administered in the perioperative period.[9] For this reason we have evaluated the pharmacokinetics of intravenous milrinone in adult patients undergoing cardiac surgery requiring CPB.

Materials and Methods

The protocol was approved by the Emory University Human Investigations Committee. Informed consent

* Assistant Professor of Anesthesiology and Pediatrics.

† Associate Professor of Anesthesiology.

‡ Research Fellow.

§ Research Associate.

‖ Professor of Anesthesiology and Pharmacology.

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Address reprint requests to Dr. Bailey: Department of Anesthesiology, Emory University Hospital, 1364 Clifton Road Northeast, Atlanta, Georgia 30322-1104.

was obtained from adult patients scheduled for elective cardiac surgery. Demographic data are presented in table 1. No patient in the study had historical, clinical, or laboratory evidence of hepatic or renal disease.

Anesthetic technique was left to the discretion of the attending anesthesiologist, but in all cases it included opioids (fentanyl 40–90 μg/kg or sufentanil 5–9 μg/kg) supplemented with small doses of midazolam (<0.15 mg/kg) or enflurane. CPB was conducted using a Cobe CML membrane oxygenator. The circuit was primed with 1,500 ml balanced salt solution, 150 ml 15% mannitol, and 500 ml hydroxyethyl starch. Hypothermia (23–28°C) and aortic cross-clamping with cold hyperkalemic cardioplegia were used in all patients.

After the primary surgical operation and rewarming to normothermia but before separation from CPB, milrinone was administered as a single dose of 25, 50, or 75 μg/kg into the venous reservoir of the extracorporeal circuit. There were five patients in each dose group. A fourth group of five patients received a single dose of 50 μg/kg and simultaneously a continuous infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which was continued for the duration of the study. In these patients the time between administration of the initial dose and separation from CPB was 15 ± 8 min (mean ± SD). A fifth group of five patients received a single 50-μg/kg dose of milrinone immediately after separation from CPB. Hemodynamic therapy included catecholamines and/or nitroglycerin as needed to maintain stable hemodynamics during and after the conclusion of CPB. This was left to the discretion of the attending anesthesiologist. In all cases, the doses or infusion rates of vasoactive drugs were titrated to achieve a systolic blood pressure less than 90 mmHg, a cardiac index less than 2.5 $l \cdot min^{-1} \cdot m^{-2}$ and a pulmonary artery occlusion pressure ≤ 18 mmHg. Blood remaining in the extracorporeal circuit was transfused into the patient at the end of CPB.

Milrinone plasma concentrations were assayed in arterial blood samples obtained at 2, 5, 7, 10, 20, 30, 60, 90, 120, 180, 240, 600, and 960 min after the initial dose with the exception that the 2-minute sample was omitted and a 3-min sample substituted in the five patients who received milrinone immediately after separation from CPB. Heparinized 10-ml samples of blood were drawn from an indwelling arterial catheter into plastic syringes and stored at 4°C. Plasma was separated by centrifugation and stored at −20°C if the analysis could not be completed within 24 h. Milrinone concentrations were determined by high-performance liquid chromatography as described by Edelson *et al.*[10] A Beckman high-performance liquid chromatography system with a model 114 pump and a 5-μm ultrasphere C_{18}ODS column were used. The coefficient of variation for analysis of known concentrations was 6.8% in the range of 5–500 ng/ml. At a concentration less than 5 ng/ml the coefficient of variation increased nearly exponentially and data less than this level were omitted from analysis.

Table 1. Demographic Data

Pharmacokinetics	
Age (yr)	61.3 ± 10.3
Weight (kg)	86.8 ± 18.4
Height (cm)	175.4 ± 9.3
Gender (female/male)	6/19
No. of operations	
CABG	19
AVR	6
Pharmacodynamics	
Age (yr)	62.6 ± 10.4
Weight (kg)	79.9 ± 16.9
Height (cm)	174.2 ± 11.9
Gender (female/male)	2/9
No. of operations	
CABG	8
AVR	1
MVR	2

Data are reported as mean ± SD.

CABG = coronary artery bypass grafting; AVR = aortic valve replacement; MVR = mitral valve replacement.

Extended nonlinear least-squares regression was used to fit two- or three-compartment models to the data from each patient.[11] The variance function needed for extended least-squares analysis was assumed to be proportional to the predicted milrinone concentration.[2] Calculations were implemented using MK-MODEL (available from Dr. Nicholas Holford, Department of Pharmacology and Clinical Pharmacology, University of Aukland, Aukland, New Zealand). The optimal model was evaluated as described by Schwartz.[12] Pharmacokinetic parameters for the different dose groups, for both two- and three-compartment models, were compared by analysis of variance with $P < 0.05$ considered significant. Because there was no difference in parameters among doses, average pharmacokinetic parameters were derived by pooling the data and simultaneously fitting the observations for all 25 patients to a single three-compartment model.[13–16]

Calculated pharmacokinetic parameters included the compartment volumes, elimination clearance, distri-

butional clearances from the central to the second and third compartment volumes (second and third clearances, respectively), and the macro- constants and coefficients of the equation describing the milrinone concentration after a single dose (predicted concentration = A exp $(-\alpha t)$ + B exp$(-\beta t)$) + C exp $(-\delta t)$), where t is the time in minutes.

The relation between milrinone plasma concentration and cardiac index was analyzed in an additional 11 patients having a cardiac index less than 2.5 $l \cdot min^{-1} \cdot m^{-2}$ after separation from CPB. Separation from CPB was facilitated by administration of norepinephrine as needed if systolic blood pressure was ≤90 mmHg despite volume infusion to achieve the preoperative pulmonary artery occlusion pressure. After measurement of hemodynamic variables (systolic blood pressure, pulmonary artery occlusion pressure, and cardiac index) immediately after separation from CPB, milrinone, 50 μg/kg, was administered. Filling pressure (pulmonary artery occlusion pressure) was maintained constant by transfusion from the CPB reservoir, as needed, and norepinephrine infusion rates were not altered. Cardiac index was measured at 3, 5, and 10 min after the milrinone dose and blood samples were taken at these times for assay of milrinone plasma concentration. Data were analyzed by nonlinear least-squares regression fitting the equation

$$\% \text{ increase in cardiac index} = 100 \times (C^{\gamma}/C^{\gamma} + C50^{\gamma})$$

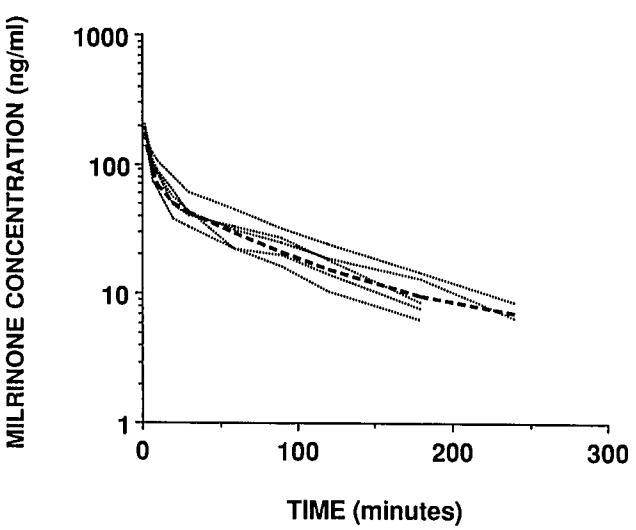

Fig. 1. The plasma concentrations of milrinone as a function of time after single doses of 25 μg/kg given before separation from cardiopulmonary bypass (dotted lines). Dashed line = concentration predicted by the parameters listed in table 2.

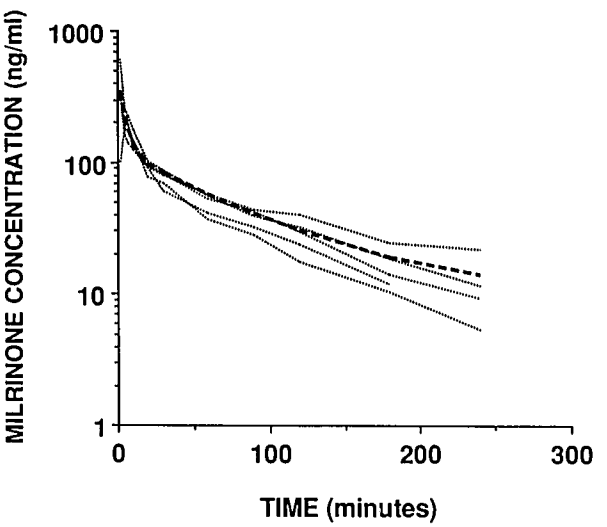

Fig. 2. The plasma concentrations of milrinone as a function of time after single doses of 50 μg/kg given before separation from cardiopulmonary bypass (dotted lines). Dashed line = concentration predicted by the parameters listed in table 2.

to the data. In this equation C = the milrinone plasma concentration; γ = a parameter describing the steepness of the curve; and C50 = the milrinone plasma concentration associated with a 50% increase in cardiac index.

Results

All patients were successfully separated from CPB. Of the 25 patients in the pharmacokinetic study, 12 patients required no inotropic support other than milrinone; 2 patients received an infusion of epinephrine; and 11 patients received norepinephrine. In the pharmacodynamic study of 11 patients, 9 received norepinephrine. The duration of CPB was 123 ± 42 min, and the average ischemic time was 55 ± 27 min (mean ± SD)

Milrinone plasma concentrations in the five dose groups are illustrated in figures 1–5. The average peak milrinone concentration was in excess of 150 ng/ml in each dose group, and the peak concentration was proportional to size of the bolus dose. There was no discernible differences in plasma concentrations between the patients who received single doses of 50 μg/kg before or after separation from CPB. In the absence of a continuous infusion, the plasma concentration decreased rapidly to less than 100 ng/ml within 30 min in 19 of the 20 patients receiving a single dose. In contrast, the average plasma concentration remained

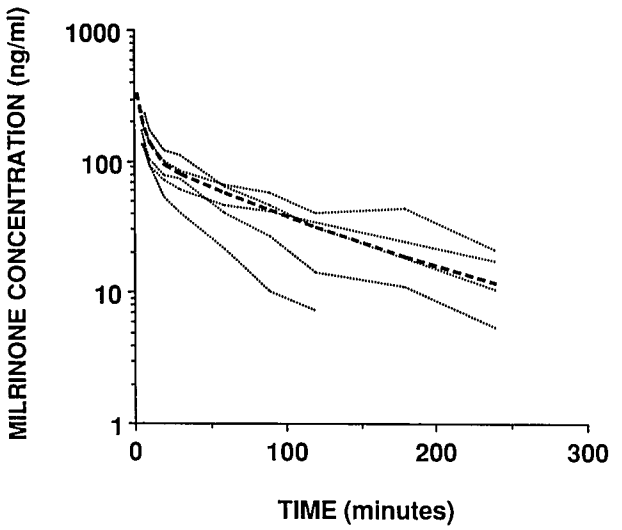

Fig. 3. The plasma concentrations of milrinone as a function of time after single doses of 50 μg/kg given immediately after separation from cardiopulmonary bypass (dotted lines). Dashed line = concentration predicted by the parameters listed in table 2.

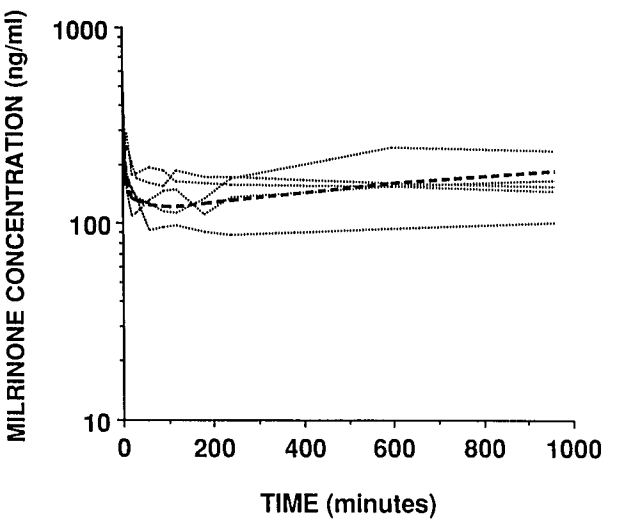

Fig. 5. The plasma concentrations of milrinone as a function of time after single doses of 50 μg/kg given before separation from cardiopulmonary bypass with concomitant institution of infusions at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (dotted lines). Dashed line = concentration predicted by the parameters listed in table 2.

greater than 100 ng/ml when patients receiving a bolus dose of 50 μg/kg also received a continuous infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

A three-compartment model provided a better description of the data than a two-compartment model in 13 of the 25 patients, using the Schwartz criterion.[12] The three-compartment model was preferable by this criterion when data from all patients was pooled. Pharmacokinetic parameters were independent of dose regimen by one-way analysis of variance of the results derived for individual patients. Average pharmacokinetic parameters were derived by fitting a single model to the data from all 25 patients and are presented in table 2. The concentrations predicted for each dose using these parameters are shown in figures 1–5 as dashed lines.

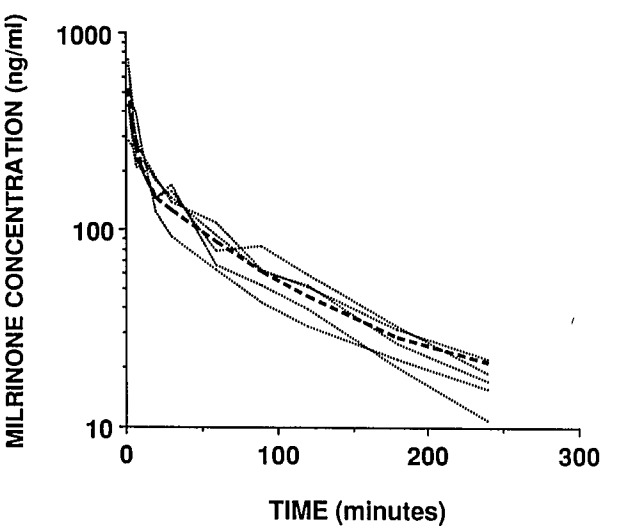

Fig. 4. The plasma concentrations of milrinone as a function of time after single doses of 75 μg/kg given before separation from cardiopulmonary bypass (dotted lines). Dashed line = concentration predicted by the parameters cited in table 2.

Table 2. Average Pharmacokinetic Parameters for All Patients

V_1	V_2	V_3	Cl_1	Cl_2	Cl_3
102	198	1398	1.88	14.40	2.91
A	B	C	α	β	δ
365.7	110.8	13.2	.2478	.0150	.0008

Parameters were calculated by pooling data from all patients. Parameters include compartment volumes (V_1, V_2, V_3), elimination and intercompartment distribution clearances (Cl_1, Cl_2, Cl_3), and the macro-rate constants and coefficients of the equations describing the concentration CP that would result from a bolus dose of 50 μg/kg $Cp = A \exp(-\alpha \cdot t) + \beta \exp(-\beta \cdot t) + C \exp(-\Delta \cdot t)$. Units are as follows: A, B, C = ng/ml; α, β, δ = min; V_1, V_2, V_3 = ml/kg; Cl_1, Cl_2, Cl_3 = $ml \cdot kg^{-1} \cdot min^{-1}$.

Pharmacodynamic results are presented in figure 6. In patients having an initial cardiac index less than 2.5 $l \cdot min^{-1} \cdot m^{-2}$ the relation between percentage increase in cardiac index and milrinone plasma concentration could be described by the equation.

% increase in cardiac index

$$= 100 \times (C^{1.16}/C^{1.16} + (167)^{1.16})$$

The 95% confidence limits of y (= 1.16) were 0.13–2.19 and of C50 (=167) were 100–235.

Discussion

Phosphodiesterase inhibitors produce positive inotropic effects and vasodilation, increasing cardiac output while decreasing preload and afterload. Several studies have demonstrated the utility of these drugs in the treatment of congestive heart failure and perioperative ventricular dysfunction.[17–20]

Effective use of the phosphodiesterase inhibitors requires an understanding of their pharmacokinetic properties. The pharmacokinetics of milrinone, recently approved for clinical use in the United States, has been studied in healthy volunteers and in patients with chronic heart failure but has not been investigated in cardiac surgical patients.[6–8] Extracorporeal circulation could be expected to have significant effects on pharmacokinetics because of alterations in regional blood flow, hemodilution with changes in fluid balance, and hypothermia. These changes are not always immediately reversed after CPB, and their impact can continue into the postoperative period. Because of this potential for perturbation of pharmacokinetics, the current study evaluated the pharmacokinetics of milrinone under clinical circumstances in which it is typically used, that is, at the end of CPB.

Previous pharmacokinetic studies of milrinone, conducted with healthy volunteers and patients with chronic congestive heart failure, reported their results using a two-compartment model without apparent consideration of a three-compartment description. We found that the data from this study were best described by a three-compartment model. We calculated "average" pharmacokinetic parameters by pooling data from all patients and finding the single model that best fit the pooled data. The more conventional (two-stage) approach for calculating average pharmacokinetic parameters is to calculate the mean of the individual parameters derived for each patient. The pooled data approach has the disadvantage of not distinguishing between interpatient and intrapatient variabilities.[21] However, there are also disadvantages to the two-stage approach, discussed in detail by Dyck *et al.*[14] and Kataria *et al.*[16] These include the assumption of a normal distribution of the parameters and a process of calculating the mean that does not account for variation in the uncertainty of individual parameter estimates. Several groups of investigators have shown that the pooled-data technique can produce robust parameter estimates superior to two-stage estimates on the basis of the utility of the parameters for determining the drug dose to achieve a desired target plasma concentration.[13–16] Furthermore, in the current study, use of the two-stage approach was complicated because the same model (two- *vs.* three-compartment) was not optimal for all patients. If we had used a two-stage calculation we would have either had to report *two* sets of pharmacokinetic parameters (for two- and three-compartment models) or to use the three-compartment model and either include parameters from patients for whom this model clearly did not fit the data optimally or to simply disregard the data from these patients. Given the documented utility of the pooled data technique, we selected this method of analysis. We pooled data from patients receiving different doses of milrinone. Thus, our analysis is predicated on the assumption of linear kinetics. We could find no difference in pharmacokinetic parameters among dose groups by analysis of

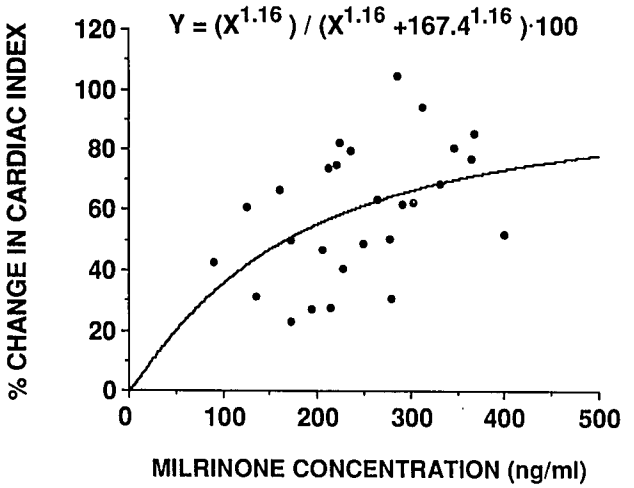

Fig. 6. The percentage change in cardiac index as a function of milrinone plasma concentration. These patients had an initial cardiac index less than 2.5 $l \cdot min^{-1} \cdot m^{-2}$ after separation from cardiopulmonary bypass and then received milrinone 50 μg/kg. Nonlinear least-squares regression analysis.

variance, but with only five patients in each group the power to detect differences is quite limited.

An alternative method for analyzing population pharmacokinetics, NONMEM, independently accounts for interpatient and intrapatient variability.[21,22] The "naive" pooled data approach used in this study does not characterize data variance as well as NONMEM, but structural model parameter estimates appear to be robust. The pooled data average parameters clearly were able to predict the observed milrinone plasma concentrations (figs. 1–5). This study was balanced (*i.e.*, had similar sampling regimens for all patients) and did not use observational data. These characteristics are essential for the use of pooled data analysis.[16,22]

Most of the patients in this study received their loading dose of milrinone before separation from extracorporeal circulation. Discontinuation of CPB could alter the pharmacokinetics of a drug *via* changes in cardiac output and regional blood flow. We also cannot exclude the possibility that milrinone could bind to components of the extracorporeal circuit. However, in five patients the drug was administered after separation from CPB, and another group of five patients received an infusion for the duration of the study. The pharmacokinetics for these patients did not differ significantly from those in patients who received a single dose before separation CPB. These observations are consistent with the assumption that CPB does not substantially alter the pharmacokinetics of milrinone.

Given the availability in the United States of two phosphodiesterase inhibitors, amrinone and milrinone, the relative pharmacokinetic merits of the two drugs should be considered. Of significance is the rate at which plasma levels decrease after administration of the drug is discontinued. To make this comparison we have used a previously published study of amrinone and the results of the current study to calculate context-sensitive half-times.[23,24] We simulated the decrease in plasma milrinone and amrinone concentrations after continuous infusions of various durations. It was assumed that the infusions maintained constant target concentrations of amrinone and milrinone of 2.0 μg/ml and 120 ng/ml respectively.[25,26] Context-sensitive half-times for infusions of 30, 45, 60, 120, 180, 300, 400, and 600 min were calculated.[24] The context-sensitive half-times for amrinone were 86, 105, 114, 118, 119, 120, 120, and 120 min respectively. The context-sensitive half-times for milrinone were 36, 43, 45, 49, 61, 78, 120, and 138 min, respectively. These simulations suggest that milrinone is more rapidly removed from plasma than amrinone if the drugs are administered for less than 400 min. Milrinone may be more slowly cleared from plasma than amrinone for longer periods of drug administration. Interpretation of these calculations must be tempered, however, by the understanding that they use "average" pharmacokinetic parameters and ignore interpatient variability. Also, in any particular clinical situation the time necessary for plasma concentrations to decrease by a factor other than one half may be more relevant.

To make recommendations about the optimal dose of milrinone it is necessary to know the relation between therapeutic effect and plasma concentration in the patient population under consideration. Studies of patients with chronic congestive heart failure have found significant increases in cardiac index at plasma concentrations as low as 100 ng/ml.[25] However, it is not immediately clear that this can be extrapolated to patients with ventricular dysfunction after cardiac surgery. We report a limited analysis of the relation between cardiac index (percentage increase) and milrinone plasma concentration. The administration of milrinone consistently resulted in increased cardiac index in a group of patients who had cardiac indices less than 2.5 $l \cdot min^{-1} \cdot min^{-2}$ immediately after separation from CPB. Because we had no true controls, we cannot rule out the possibility that the cardiac index would have improved without milrinone administration. However, there is a significant relation between plasma concentration and hemodynamic effect. We analyzed our data by assuming a sigmoidal relation between milrinone plasma concentration and percentage increase in cardiac index. Earlier studies of patients with chronic congestive heart failure have assumed a linear relation.[25] To provide a comparison with this earlier result, we note that linear regression analysis of the data points in figure 6 leads to a correlation coefficient of 0.47, which is statistically significant ($P < 0.05$), and a correlation equation of $y = 0.126x + 28.3$. However, a sigmoidal relation is more plausible on the basis of pharmacologic principles. The 95% confidence limits for C50 (the milrinone concentration associated with a 50% increase in cardiac index) were 100–235. This observation is in near agreement with the earlier studies of patients with chronic congestive heart failure. Using this therapeutic threshold we see from the data of figure 5 that a dose regimen consisting of 50 μg/kg bolus with an infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is typically therapeutic and larger doses may result in a more pronounced therapeutic effect. This conclusion should be

viewed as approximate. Our pharmacodynamic results were derived from a small number of patients over a limited period of time. Furthermore, we arbitrarily selected a cardiac index less than 2.5 $l \cdot min^{-1} \cdot m^{-2}$ as our threshold for analysis. We cannot rule out the possibility that the relation between milrinone plasma concentration and therapeutic effect would be different if our treatment threshold were lower. Finally, we note that the patients in our pharmacokinetic analysis were not restricted to those in a low–cardiac-output state. Thus, one must be cautious about the relevance of these parameters for patients with severe ventricular dysfunction because the kinetics of the drug could be altered by profoundly low cardiac output or by other drugs used to treat low cardiac output.

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