A Pharmacokinetic and Pharmacodynamic Evaluation of Milrinone in Adults Undergoing Cardiac Surgery

John F. Butterworth IV, MD*, Roberta L. Hines, MD†, Roger L. Royster, MD*, and Robert L. James, MStat*

Departments of Anesthesia, *The Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina, and †Yale University School of Medicine, New Haven, Connecticut

Milrinone can reverse acute postischemic myocardial dysfunction after cardiopulmonary bypass, although neither the appropriate bolus dose nor its pharmacokinetics has been established for cardiac surgical patients. Consenting patients undergoing cardiac surgery received milrinone (25, 50, or 75 μg/kg) in an open-label, dose-escalating study if their cardiac index was <3 L · min⁻¹ · m⁻² after separation from bypass. Heart rate, mean arterial blood pressure, pulmonary capillary wedge pressure, and cardiac index were determined before and after the administration of milrinone. Timed blood samples were obtained for measurement of milrinone plasma concentrations and pharmacokinetic analysis. Twenty-nine of 60 consenting patients had cardiac indices <3 L · min⁻¹ · m⁻² after separation from bypass, received milrinone, and completed the protocol. All three bolus doses of milrinone significantly increased cardiac index. The 50- and 75-μg/kg doses produced significantly larger increases in cardiac index than the 25-μg/kg dose; however, the 75-μg/kg dose did not produce a significantly larger increase in cardiac index than did the 50-μg/kg dose. Two of 10 patients receiving milrinone 25 μg/kg, but no patient receiving either 50 or 75 μg/kg, required early epinephrine rescue when the cardiac index failed to increase by >15%. The 75-μg/kg dose was associated with a case of ventricular tachycardia. The three-compartment model better described milrinone drug disposition than the two-compartment model by both visual inspection and Schwartz-Bayesian criterion. There was only limited evidence of dose-dependence, so data from all three doses are reported together (and normalized to the 50-μg/kg dose). Data from one patient was discarded (samples mislabeled). Using mixed-effects nonlinear regression (for n = 28), the following volumes were determined for the three compartments: V₁ = 11.1 L, V₂ = 16.9 L, and V₃ = 363 L. Similarly, the following clearances were estimated for the three compartments: Cl₁ = 0.067 L/min, Cl₂ = 1.05 L/min, and Cl₃ = 0.31 L/min. The 50-μg/kg loading dose appeared more potent than the 25 μg/kg dose, and, as potent, but with possibly fewer side-effects than the 75-μg/kg dose. The short context-sensitive half-times of 6.7 or 10.2 min after 1- or 10-min bolus infusions underscore the need for prompt institution of a maintenance infusion when milrinone concentrations must be maintained. Simulations based on our best drug disposition using this study's variables predict a context-sensitive half-time of 4.9 h for plasma milrinone concentrations after a 50-μg/kg bolus 1-min infusion with an immediate 24-h maintenance infusion of 0.5 μg · min⁻¹ · kg⁻¹. (Anesth Analg 1995;81:783-92)

Myocardial function is often depressed after cardiopulmonary bypass and aortic cross-clamping, even in patients with apparently normal preoperative indices of left-ventricular function (1,2). The preferred treatment for mild to moderate degrees of left-ventricular dysfunction after cardiac surgery remains controversial. There appears to be no clear consensus concerning either the choice of inotropic or vasodilator drugs or when mechanical support (i.e., intraaortic balloon counterpulsation) should be added to or precede vasoactive drug support.

Milrinone, an inhibitor of the low-Kₗ cyclic adenosine monophosphate-specific, cyclic guanosine monophosphate-inhibited phosphodiesterase enzyme, was released for use in the United States during autumn 1992. Although intravenous milrinone has been evaluated in many studies of patients with chronic congestive heart failure, the available studies do not provide a complete evaluation of the drug's actions in surgical patients (3-5). Specifically, whether the loading (bolus) dose should be increased in cardiac surgical patients (as has proved to be necessary for amrinone, a closely related drug) remains unclear.
although this is a distinct possibility, since patients after cardiopulmonary bypass typically exhibit a form of heart failure with a different pathophysiology from that underlying chronic forms of heart failure (6). In the present study, we administered milrinone to patients with normal and mildly reduced cardiac index after cardiopulmonary bypass, to determine the drug’s pharmacokinetic characteristics and its dose-response and concentration-response hemodynamic relationships.

Methods

After our study was reviewed and approved by the Institutional Review Boards of the Bowman Gray School of Medicine/North Carolina Baptist Hospital and the Yale-New Haven Medical Center, patients undergoing elective aortocoronary bypass or valvular surgery with normal preoperative left-ventricular function (defined as left-ventricular ejection fraction \( \geq 40\% \) during radiocontrast ventriculography) were asked to participate. All participants gave their written, informed consent. Patients were excluded preoperatively if they had suffered a myocardial infarction within 7 days or had abnormal renal function (defined as a blood creatinine concentration \( > 2 \text{ mg/dL} \)). Theoretical contraindications to the study also included age \( < 18 \text{ yr} \), thrombocytopenia (platelet count \( < 100,000 \text{ cells/dL} \)), and the possibility of pregnancy; however, no patients were excluded based on these criteria. During surgery, patients were excluded from the study if they required inotropic drugs (including “renal-dose” dopamine) or intraaortic balloon counterpulsation prior to or during separation from cardiopulmonary bypass. Conversely, patients with cardiac index \( \geq 3 \text{ L/min} \cdot \text{m}^{-2} \) after separation from cardiopulmonary bypass were excluded. We choose this variable, at a normal value, to ensure a relatively high study completion rate among enrolled subjects. We also wished to exclude patients who clearly did not require inotropic support (under the usual practice guidelines of the two institutions).

We recognize that the choice of any cardiac index value is, inevitably, arbitrary and that some of the patients we studied would not, under ordinary circumstances, receive inotropic drug support. Finally, after separation from cardiopulmonary bypass, patients with severe arrhythmias which required drug therapy and/or cardioversion were excluded.

Patients were sedated with intramuscular (IM) morphine (up to 0.1 mg/kg) and either oral lorazepam (up to 50 \( \mu \text{g/kg} \)) or IM scopolamine (up to 6 \( \mu \text{g/kg} \)) prior to their arrival in the surgical suite. Intravenous (IV) and radial artery catheters were inserted percutaneously with local anesthesia. A balloon-tipped thermodilution pulmonary artery catheter was inserted either with local anesthesia and the patient awake, or after induction of general anesthesia. Patients were anesthetized with IV fentanyl (50–75 \( \mu \text{g/kg} \)) or sufentanil (10–70 \( \mu \text{g/kg} \)), and midazolam (0.1–0.3 \( \mu \text{g/kg} \)). Paralysis was maintained with pancuronium (up to 0.2 \( \mu \text{g/kg} \)), in some cases combined with metocurine (up to 0.4 \( \mu \text{g/kg} \)). Potent inhalational anesthetics (enflurane or isoflurane), if used, were discontinued upon rewarming. The cardiopulmonary bypass circuits were primed with blood-free solutions. Blood cardioplegia was delivered antegrade at 20- to 30-min intervals at both institutions.

During rewarming, phenylephrine was continuously infused (10–100 \( \mu \text{g/min} \)) to increase systolic arterial pressure \( > 90 \text{ mm Hg} \) despite bypass pump flow \( \geq 2.5 \text{ L/min} \cdot \text{m}^{-2} \). Those patients who required phenylephrine immediately prior to their separation from bypass were maintained on that same dose of phenylephrine during the initial (\( \sim 10 \text{ min} \)) phase of our study. Upon successful separation from bypass, patients were transfused from the reservoir of the pump-oxygenator until the pulmonary artery diastolic pressure exceeded 10 mm Hg to maintain an adequate perfusion pressure. Most patients required transfusion to a higher pulmonary artery diastolic pressure (typically 12–15 mm Hg) during weaning. The observed “optimal” filling pressure was maintained for each patient by infusing volume from the pump reservoir during the study to avoid hypotension and to follow usual clinical practices. Duplicate baseline measurements of cardiac output were performed starting within 2 min after separation from bypass. Cardiac index was then calculated. If the first two determinations differed by more than 20%, a third measurement was obtained. For purposes of statistical analysis, the mean value of these two or three measurements was used as the baseline value. The following additional hemodynamic values were recorded at all measurement times: heart rate, systemic and pulmonary arterial blood pressures, pulmonary artery occlusion pressure, and central venous pressure.

This was an open-label, dose-escalating study. The three milrinone doses studied were 25, 50, and 75 \( \mu \text{g/kg} \); 10 patients, five at each site, were to receive each dose. Each patient was given a single bolus dose of milrinone IV over 60 s (using a stopwatch) by hand. Since doses and responses had not been evaluated previously in surgical patients, the safety of each dose was to be established before the next higher dose could be initiated. In each patient, milrinone was judged efficacious if it increased cardiac index \( > 3 \text{ L/min} \cdot \text{m}^{-2} \) or by at least 15% (compared with baseline measurements). Epinephrine (30–90 ng \( \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)) was to be used as rescue therapy, if necessary, for cardiac index \( < 2 \text{ L/min} \cdot \text{m}^{-2} \) despite milrinone.

For each patient, the study contained two parts. In the first part, the efficacy (as defined above) of the
Milrinone initial dose was evaluated. Hemodynamic measurements were obtained 2.5, 5, 7.5, 10, 20, 30, 45, and 60 min after administration of the milrinone bolus dose. During the first 10 min after milrinone was given, surgical manipulation of the heart was limited and no nonessential drugs with major hemodynamic side effects were administered. For the second part of the study, blood samples (3–5 mL of heparin-anticoagulated blood aspirated from the radial artery catheter) were collected 1, 2.5, 5, 7.5, 10, 20, 30, 45, 60, 120, 240, and 360 min after administration of the milrinone and centrifuged to isolate the plasma. (Milrinone doses were infused between time 0 and 1 min.) Although we initially planned to use all the data points in our pharmacokinetic calculations, it became apparent that the 1-min measurement did not permit adequate mixing, so it was not used. Plasma samples were frozen at -70°C for batch determination of milrinone concentration by high-performance liquid chromatography (Harris Laboratories, Lincoln, NE). A pilot study demonstrated that milrinone samples in plasma would yield consistent measurements, despite repeated freezing and thawing over several months.

We used a modification of the method of Stroshane et al. (7) to measure milrinone in plasma. Milrinone determinations were accomplished with reference to a standard curve which included 5, 10, 20, 40, 60, 80, 100, 150, 200, 250, 350, and 500 ng/mL standards. The coefficient of variation of the points on the standard curve ranged from 1.3% to 5.3%. The percent relative error in the measurement of these standards ranged from -3.01% to +2.75%. The percent coefficient of variation of the slopes of the standard curves was 4.2%. Linear correlation coefficients of these standard curves all exceeded 0.999 with a percent coefficient of variation of 0.03%. The milrinone plasma concentrations were used for pharmacokinetic analysis.

All numerical analyses were performed using either the SAS (SAS Institute, Cary, NC) or NONMEM (NONMEM Project Group, University of California, San Francisco, CA) microcomputer programs. We used SAS to perform statistical analysis of the pharmacodynamic data, and to test for dose-dependency of population pharmacokinetic variability using a Kruskal-Wallis nonparametric test. We used NONMEM to calculate the actual pharmacokinetic variables which we report herein and to compare the suitability of two- and three-compartment models. All treatment variables were declared statistically significant at the 5% α level using two-tailed tests. When appropriate, Holm’s sequentially rejective Bonferroni test was used to account for multiple comparisons. Continuous variables (e.g., heart rate or cardiac index) were compared among dose groups (using SAS) using analysis of variance, with effects for dose group, test site (Winston Salem or New Haven), and dose by site interaction. Instances where the dose by site interaction was significant were noted because overall conclusions were not valid in the presence of the interaction. Continuous variables were evaluated within the three dose groups using an analysis of variance model. Post-hoc testing consisted of a series of t-tests (adjusted for multiple comparisons using Holm’s method). Comparisons of categorical data were accomplished using Cochran-Mantel-Haenszel tests (controlling for test site).

Plots of the milrinone blood concentration versus time from each patient were visually examined to determine whether drug elimination curves were similarly shaped in all patients. Data were fit to both two- and three-compartment models using extended least-squares nonlinear regression with a mixed-effects population model. The NONMEM program, with the NMVCL Fortran subroutine was used for this statistical analysis (Steven L. Shafer, Stanford University School of Medicine, Palo Alto, CA). These models were fit to volumes of distribution and clearances. The traditional A, B, Γ, α, β, γ variables of the bi- and triexponential disposition functions were then calculated from the model-estimated volumes and clearances. Drug elimination half-lives can be calculated directly from α, β, and γ. The NMVCL subroutine was adjusted for the 60-sec infusion of milrinone. The individual patient data sets and larger data sets pooled by both dose group and overall were fit to the multicompartment models.

Extended least-squares nonlinear regression uses the following maximum likelihood objective function.

$$\text{Objective function} = \sum \frac{(C_i - \hat{C}_i)^2}{\text{var}_i} + \ln(\text{var}_i)$$

where $C_i$ = observed milrinone concentration at time $i$, $\hat{C}_i$ = predicted (from model milrinone concentration at time $i$, and $\text{var}_i$ = expected variance at time $i$. The expected variance at time $i$ was modeled as: $\text{var}_i = \sigma^2 C_i^2$.

The proportionality coefficient, $\alpha'$, is set so that the sum of the weighted residuals equals the number of observations. For any specified model, the set of variable estimates that minimizes the objective function is considered the best fit. Model fits were graphed over the assay data to confirm that the fits were reasonable.

Both a two-stage analysis and NONMEM’s mixed effects model were used to estimate population variables. The two-stage method (8) entails fitting each patient’s data separately using extended least-squares nonlinear regression and then combining the individual variable estimates by using the geometric mean and its 95% confidence limits. With the NONMEM mixed effects approach, interpatient variability of the volumes of distribution and clearances was assumed.
to be lognormal in distribution and modeled by NMVCL as follows:

\[ P_i = P_e \eta_i \]

where \( P_i \) = variable estimate of individual patient \( i \), \( P_e \) = population variable estimate, \( \eta_i \) = random variable normally distributed with mean 0 that accounts for interpatient variability associated with patient.

We used the Schwartz-Bayesian criterion (SBC) to determine whether the two- or three-compartment model better described the data. Using the value of the objective function obtained from NONMEM, the SBC for each model can be calculated as follows:

\[ \text{SBC} = \log(L) - \frac{p}{2} \log n \]

where \( \log(\cdot) \) = natural log, \( L \) = maximum likelihood, \( \text{obj} \) = objective function, \( n \) = total data points, and \( p \) = number of variables estimated in the model. The model with the largest SBC is considered best (9).

Using the pharmacokinetic population variables for a "typical" patient, simulations were performed to determine the context-sensitive half-times after a 1-min and a 10-min bolus infusion of 50 \( \mu \)g/kg milrinone, and a 1-min bolus infusion of 50 \( \mu \)g/kg followed by a 24-h maintenance infusion of 0.5 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \). Context-sensitive elimination times for 80% and 90% drug elimination from the serum were also calculated. The triexponential disposition function used in this simulation was adjusted for infusion rates as described by Wagner (10).

**Results**

Of the 60 patients consenting to participate in the study, 26 had cardiac indices >3 L \( \cdot \) min\(^{-1} \cdot \) m\(^{-2} \) and were excluded. One patient could not be separated from bypass without immediate institution of inotropic drug support and was excluded. One patient could not be studied due to our inability to increase pulmonary artery diastolic pressure to >10 mm Hg. The 30 remaining patients (29 of whom underwent coronary artery surgery and one who underwent isolated mitral valve replacement after originally being posted for combined coronary artery and vascular surgery), received one of the three loading doses of milrinone. One patient receiving the 75-\( \mu \)g/kg dose developed ventricular tachycardia within 2 min of receiving milrinone, required cardioversion and resumption of cardiopulmonary bypass, and was dropped from the study. Thus, data are reported for only nine patients in the 75-\( \mu \)g/kg dose group. Two additional patients, one each in the 25 and 75-\( \mu \)g/kg groups, demonstrated frequent premature ventricular beats within the first 10 min after receiving milrinone, as a consequence of which they received a lidocaine bolus and maintenance infusion, but remained in the study.

Preoperative medical history and demographic data for the patients are given in Table 1. There were no significant differences among the three groups in any of these factors.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dose Dose Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 ( \mu )g/kg</td>
</tr>
<tr>
<td>Total in group (n)</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>71</td>
</tr>
<tr>
<td>Range</td>
<td>54-86</td>
</tr>
<tr>
<td>Female (n)</td>
<td>3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>75</td>
</tr>
<tr>
<td>Range</td>
<td>54-110</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>60</td>
</tr>
<tr>
<td>Range</td>
<td>40-86</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
</tr>
<tr>
<td>Class II (n)</td>
<td>1</td>
</tr>
<tr>
<td>Class III (n)</td>
<td>6</td>
</tr>
<tr>
<td>Class IV (n)</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>4</td>
</tr>
<tr>
<td>Preoperative medications</td>
<td></td>
</tr>
<tr>
<td>Nitrates (n)</td>
<td>7</td>
</tr>
<tr>
<td>( \beta )-Adrenergic receptor blockers (n)</td>
<td>7 4 4</td>
</tr>
<tr>
<td>Ca channel blockers (n)</td>
<td>4 7 7</td>
</tr>
<tr>
<td>Digoxin (n)</td>
<td>1</td>
</tr>
<tr>
<td>Diuretics (n)</td>
<td>2</td>
</tr>
<tr>
<td>Insulin (n)</td>
<td>1</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.0 1.2 1.1</td>
</tr>
<tr>
<td>Median</td>
<td>1.0</td>
</tr>
<tr>
<td>Range</td>
<td>0.8-1.9</td>
</tr>
<tr>
<td>Distal bypass grafts (n)</td>
<td>3 3 3</td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
</tr>
<tr>
<td>Range</td>
<td>0'- 4</td>
</tr>
</tbody>
</table>

1 LVEF = left ventricular ejection fraction measured by radiocontrast ventriculography; NYHA = New York Heart Association.

Data are presented as incidences, or as medians and ranges, as appropriate. \( P < 0.05 \) was considered significant. There were no significant differences among the three groups in any of these factors.

This patient underwent isolated mitral valve replacement.

---

Table 1. Characteristics of Patients in Milrinone Dose Groups

---
and hypertension, were receiving similar preoperative medications, and underwent operations of similar complexity. Baseline renal function (as assessed by serum creatinine) was also similar in the three groups.

After administration of milrinone, there were no significant changes in heart rate relative to baseline; moreover, there were no differences among the three groups in heart rate at any measurement time (Figure 1). Milrinone significantly increased cardiac index at all three doses (Figure 2). In the 25-µg/kg dose group, cardiac index significantly increased relative to baseline by the 5-min measurement and remained significantly increased until the 30-min measurement. In the 50-µg/kg dose group, cardiac index was significantly increased relative to baseline at all measurements until 45 min after the milrinone loading dose. In the 75-µg/kg dose group, cardiac index remained significantly increased only during the first 20 min of observation. There were significant differences between the dose groups at 2.5 and 7.5 min (cardiac index was significantly less in the 25-µg/kg group than in the 50- or 75-µg/kg group at 2.5 min, and was significantly less than in the 50-µg/kg group at 7.5 min). There were no significant differences between the 50- and 75-µg/kg doses at any time point. One patient in the 25-µg/kg group required infusion of epinephrine within the first 10 min after receiving milrinone to achieve a satisfactory cardiac index (and thus did not satisfy our efficacy criteria); no patient who received either of the higher two doses required epinephrine rescue within the first 10 min (P = not significant [NS]). Six additional patients required epinephrine infusion after the first 10 min of the study (4, 1, and 1 in the 25-, 50-, and 75-µg/kg dose groups, respectively) (P = NS).

Despite administration of phenylephrine, blood from the pump-oxygenator, and IV fluid, mean arterial pressure decreased significantly (P = 0.04, comparing baseline measurements to those obtained at 2.5 min) only after administration of the 75-µg/kg milrinone dose (Figure 3); however, this group also had the highest baseline blood pressure. During the first 10 min after receiving milrinone, 5 of 10 patients in the 25-µg/kg dose group received phenylephrine (median dose 1.16, range 0.32-2.22 µg · kg⁻¹ · min⁻¹); 5 of 10 patients in the 50-µg/kg dose group received phenylephrine (median dose 1.16, range 0.56-1.40 µg · kg⁻¹ · min⁻¹); and five of nine patients in the 75-µg/kg dose group received phenylephrine (median dose 1.00, range 0.60-2.17 µg · kg⁻¹ · min⁻¹). The median total volumes (in milliliters) of blood and IV fluid transfused during the first 10 min after the milrinone loading doses were: 420 (range, 380-470), 650 (range 470-820), and 900 (range 410-1070), respectively, for the 25, 50, and 75 µg/kg doses (P = NS). There were no other significant changes in mean arterial pressure relative to baseline at any time in any of the three groups. Likewise, there were no significant differences between the three dose groups at any time.

There were no significant changes in pulmonary capillary wedge pressure relative to baseline in any of the three groups. This is likely the result of our attempt to maintain a constant pulmonary artery diastolic pressure during the study by infusion of blood...
Figure 3. Effects of three milrinone loading doses on mean arterial pressure recorded after separation from cardiopulmonary bypass. B1 and B2 denote the two baseline measurements which were recorded immediately before administration of the milrinone loading doses. Mean arterial pressure was decreased significantly only by the 75-μg/kg dose (P = 0.04 at the 2.5 min measurements), relative to baseline values; however, there were no significant differences among the three loading doses in mean arterial pressure measured at any time during the study.

from the pump oxygenator as needed. The three groups differed significantly only at the 20 min measurement, where the 25-μg/kg dose group was significantly higher than the other two dose groups.

Concentrations of milrinone in plasma after the three loading doses (normalized and plotted as if all patients had received 50 μg/kg) are displayed in Figure 4. Maximum milrinone concentrations differed significantly among the three groups. Mean maximal values were 460, 610, and 1170 ng/mL for the 25-, 50-, and 75-μg/kg dose groups, respectively. Pairwise comparisons demonstrated that the maximal concentrations achieved in the 75-μg/kg dose group were significantly greater than in the two smaller dose groups. The maximum milrinone blood concentration was recorded at the 1-min determination in nearly every patient; there were no differences among the dose groups with respect to the time delay until the maximum concentration was reached. Neither the cardiac index nor the percent increase in cardiac index measured at 5 min were correlated with the concentration of milrinone in blood at that time. Table 2 lists the frequency with which milrinone achieved clinical efficacy. Milrinone achieved clinical efficacy (cardiac index increased by 15% or exceeded 3 L·min⁻¹·m⁻²) in more than half of the patients at all milrinone blood concentration ranges at the 10-min assessment. Thus we were unable to define either the EC₅₀ or concentration thresholds for milrinone efficacy. We observed >50% efficacy at concentrations less than 100 ng/mL, which is commonly regarded as the concentration threshold above which milrinone shows efficacy in patients with chronic congestive heart failure (11,12).

Figure 4. Plasma concentrations of milrinone as a function of time after bolus intravenous administration of 25, 50, or 75 μg/kg shortly after separation from cardiopulmonary bypass. Data from all patients have been normalized to the 50-μg/kg dose. Fits of the overall data to both a two- and three-compartment model are shown on the figure.

Only the measurements taken 2.5 min or later after administration of milrinone were used for the pharmacokinetic calculations, due to our concern that the 1-min measurements may not have permitted sufficient time for drug mixing within the central compartment. Figure 4 of the assay data supports this decision. It clearly shows a much wider variance in concentrations at the 1-min measurements compared to the times that follow. Data from one patient were not used due to what appeared to be mislabeling of samples.

The estimated pharmacokinetic variables for the individual patients are listed in Table 3. They were found to not be significantly influenced by dose (P > 0.05; see Figure 5). Thus, the population variable estimates were determined using the data from all patients, from all dose groups. These variable estimates for both, the two- and three-compartment models, and calculated using both, the NONMEM and the two-stage methods, are given in Table 4. The three-compartment model was found to be better than the two-compartment model based upon the SBC. Also, using the three-compartment model, the population estimates appeared to better fit the data when fit using NONMEM rather than using the two-stage method. The graphs of Figures 4 and 5 support both the choice of the three-compartment model, and the use of NONMEM, in estimating the population variables.

Pharmacokinetic simulation, using the NONMEM population variable estimates of the three-compartment model, was used to determine context-sensitive elimination times for 50%, 80%, and 90% serum drug elimination. A 1-min milrinone bolus infusion gave context-sensitive elimination times of 6.7, 41, and 107 min for 50%, 80%, and 90% drug elimination (elimination calculated using the concentration measured at the completion of the
Table 2. Efficacy of Milrinone at 10 min as Defined by $\geq 15\%$ Increase in Cardiac Index (CI) from the Baseline Values or by Increase in CI to $\geq 3 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$

<table>
<thead>
<tr>
<th>Milrinone Concentration</th>
<th>% Increase in CI</th>
<th>CI $\geq 3 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Efficacy (%)</td>
<td>No Efficacy (%)</td>
<td></td>
</tr>
<tr>
<td>25 $\mu$g/kg</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>50 $\mu$g/kg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>75 $\mu$g/kg</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

*Patient received epinephrine 60 $\mu$g $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$.

Table 3. Pharmacokinetic Variables of Patients Receiving 25, 50, or 75 $\mu$g/kg Milrinone Bolus Dose

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>$V_1$ (L) $V_2$ (L) $V_3$ (L)</th>
<th>$C_{l1}$ (L/min)</th>
<th>$C_{l2}$ (L/min)</th>
<th>$C_{l3}$ (L/min)</th>
<th>$A$</th>
<th>$B$</th>
<th>$\Gamma$</th>
<th>$\alpha$ (min$^{-1}$)</th>
<th>$\beta$ (min$^{-1}$)</th>
<th>$\gamma$ (min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 $\mu$g/kg</td>
<td>1.950</td>
<td>0.094</td>
<td>0.0061</td>
<td>0.041</td>
<td>0.041</td>
<td>0.032</td>
<td>0.00006</td>
<td>0.115</td>
<td>1.756</td>
<td>0.0182</td>
</tr>
<tr>
<td>50 $\mu$g/kg</td>
<td>1.192</td>
<td>0.120</td>
<td>0.0090</td>
<td>0.032</td>
<td>0.032</td>
<td>0.036</td>
<td>0.0020</td>
<td>0.041</td>
<td>0.732</td>
<td>0.00001</td>
</tr>
<tr>
<td>75 $\mu$g/kg</td>
<td>0.605</td>
<td>0.063</td>
<td>0.0082</td>
<td>0.0047</td>
<td>0.0047</td>
<td>0.037</td>
<td>0.00001</td>
<td>0.039</td>
<td>0.323</td>
<td>0.000001</td>
</tr>
</tbody>
</table>

$V_1$ = volume of central compartment; $V_2$ = volume of second compartment; $V_3$ = volume of third compartment; $C_{l1}$ = clearance of central compartment; $C_{l2}$ = clearance of second compartment; $C_{l3}$ = clearance of third compartment; $A$, $B$, $\alpha$, $\beta$, $\gamma$ = variables of bi- and triexponential disposition function. $A$, $B$, $\Gamma$ are given as fractional coefficients. Thus, to convert for any given dose, multiply all three coefficients by (absolute dose/$V_1$). For example, if a patient with $V_1 = 11.1$ L is given a bolus of 2045 $\mu$g, then the fractional coefficients $A = 0.07$, $B = 0.28$, and $\Gamma = 0.20$ become the dose-specific coefficients $A = 1.29$, $B = 0.31$, and $\Gamma = 0.00002$. $V_1$ is the volume of distribution at steady state.

infusion), respectively. Likewise, a 10-min bolus infusion gave context-sensitive elimination times of 10, 76, and 149 min for 50%, 80%, and 90% drug elimination. Finally, simulation of a typical clinical milrinone administration (1-min bolus infusion of 50 $\mu$g/kg followed by a 24-h 0.5-$\mu$g $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$ maintenance infusion) exhibited context-sensitive elimination times (upon termination of the milrinone infusion) of 4.9, 108, and 188 h for 50%, 80%, and 90% drug elimination, respectively.
Thus, we recommend that 50 pg/kg be used as the or 75 pg/kg required early infusion of epinephrine to 25 pg/kg milrinone required infusion of epinephrine. The 75-pg/kg dose produced no greater increase in than the 25-pg/kg dose; no patient receiving either 50 The 50- and 75+g/kg doses were more efficacious data is also given. The terminal chase of the 25-un/kg dose grout was influenped by a foreshortened sampling inteyvarin eight pa-

patients (milrinone concentrations were detectable in only 2 of 10 patients after 120 min).

Discussion

Our data confirm that milrinone increases cardiac index in patients recently separated from cardiopulmonary bypass. We found a dose-dependent response. The 50- and 75-µg/kg doses were more efficacious than the 25-µg/kg dose; no patient receiving either 50 or 75 µg/kg required early infusion of epinephrine to achieve stability, whereas multiple patients receiving 25 µg/kg milrinone required infusion of epinephrine. The 75-µg/kg dose produced no greater increase in cardiac index than the 50-µg/kg dose; on the other hand, the 75-µg/kg dose was associated with a single (perhaps random) case of ventricular tachycardia. Thus, we recommend that 50 µg/kg be used as the initial milrinone bolus dose in coronary surgical pa-

tients after cardiopulmonary bypass.

Bolus administration of milrinone rapidly increased milrinone plasma concentrations. At the 5-min mea-

surement, most patients had achieved their maximal increase in cardiac index; however, neither the absolute cardiac index nor the percent increase in cardiac index (comparing the 5-min measurement to baseline) was related to the measured milrinone concentration in blood. Our data suggest that the threshold concentra-

tion for clinical efficacy in cardiac surgical patients may be less than the concentration (100 ng/mL) pre-

viously reported as the threshold for efficacy in pa-

tients with chronic congestive heart failure (12).

Elimination half-lives often fail to adequately de-

scribe the rate of drug disposition of multicompart-

ment models at clinically relevant drug concentrations (or after completion of clinically relevant dosing schemes). Hughes et al. (13) coined the term “context-sensitive half-time” as a measure of the time needed for the concentration of the central (serum) compart-

ment to decrease in drug concentration by half after one or more infusions of the drug. Young and Shafer (14), Shafer and Verve1 (15), and Shafer and Stanski (16) further demonstrated the usefulness of “context-
sensitive” drug disposition and expanded the measures to include times to concentration reductions greater than 50%. Our milrinone three-compartment disposition model gave context-sensitive elimination times that agreed well with the milrinone serum concen-

trations of our assay data. The terminal half-life of milrinone (ln2/γ) derived from our data of 4780 min only begins to accurately reflect milrinone elimination after eight half-lives (at 4.8 days) when milrinone concentrations are probably well below clinically relevant concentrations. The context-sensitive elimination times reported in this study for milrinone should be of much greater use to the clinician than the terminal elimination half-life derived from γ.

We fit our milrinone blood concentration data to a three-compartment, triexponential model. In common with Bailey et al. (17), we found that some individual patients were better fit to a two-compartment model than a three-compartment model. Neverthe-

less, the three-compartment model fit the overall data better (using the mixed effect, nonlinear least-squares regression).

We recognize that because our study was not blinded or controlled, some bias is inevitable. A control group might have been particularly helpful in evaluating the potential significance of the single case of ventricular tachycardia we encountered. Some cli-

nicians might also argue that our criteria for milrinone administration were not as strict as might be used in normal clinical decision-making. Our purpose was to determine the dose- and concentration-response rela-
tionship to milrinone in surgical patients with mild to moderate depression of cardiac function. We chose to study patients who could be separated from bypass without inotropic drug support so we could assess directly the response to milrinone (using cardiac index) relative to a true baseline measurement. Of course, if clinical practice with milrinone resembles that with amrinone, some practitioners will choose to administer milrinone to patients prior to, rather than after, separation from cardiopulmonary bypass as was done in this study (18,19). Some clinicians may worry that our conclusions regarding the appropriate dose of milrinone might be incorrect, since we studied pa-

tients who were not in desperate need of inotropic drug support. However, our previous work with am-

rinone (similar in structure and activity to milrinone) has shown that the doses identified as efficacious in “healthier” cardiac surgical patients will also be appropriate in “sicker” ones (6,18,20,21).

Our conclusion that a three-compartment model was preferable to a two-compartment model could
have been influenced by our sampling and measurement techniques. Indeed, as Table 4 demonstrates, there was limited difference between the two- and three-compartment models. The two models only diverged after 120 when fewer data points were involved. The error estimates (ie, 95% confidence interval) of the population variables should be viewed cautiously. Sheiner and Beal (22) demonstrated, using simulation that both the two-stage and NONMEM methods of population variable estimation produce unacceptable variable error estimates. No 95% confidence intervals were estimated for the \( C_l \) population estimate of two-compartment model or the \( V_3 \) population estimate of the three-compartment model due to failure of NONMEM to converge on the interindividual variability of these two estimates. Finally, extrapolations of milrinone concentrations to many hours and days beyond the 3-h time frame of our study should be viewed as model-dependent predictions only. It is possible that other unaccounted for factors (fourth-compartment, metabolic changes, etc.) begin to influence milrinone concentration after prolonged times and exposure to the drug.

In summary, we have demonstrated that a 50-\( \mu \)g/kg bolus dose of milrinone is effective after cardio pulmonary bypass. This dose achieves adequate hemodynamic efficacy with minimal side effects as compared with 25- and 75-\( \mu \)g/kg doses. Only one patient demonstrated severe arrhythmia after milrinone and that patient received a dose of 75 \( \mu \)g/kg. This rare occurrence of arrhythmia compares favorably with our experience with amrinone, which we also found to be rarely arrhythmogenic, compared with other positive inotropes (18,20,21,23). Milrinone's short context-sensitive half-time after a 1- to 10 min bolus infusion, in surgical as in medical patients, indicates the need for prompt institution of a maintenance infusion (11,17).

For their assistance in the conduct of this study, we thank the clinical coordinators, Judy Bennett, RN, and Heidi Lippmann, RN; the clinical monitor, Janet Becket, RN; and Jaime Coelho, MD, formerly Senior Associate Medical Director, Sanofi-Winthrop Pharmaceuticals, New York, NY.

References

10. Wagner JG. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. J Pharmacokin Biopharm 1976;4:443–67.


