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Pharmacokinetics of Amrinone during Cardiac Surgery

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Amrinone is a nonglycosidic noncatecholamine with both vasodilator and positive inotropic effects that may be administered to patients undergoing cardiac surgery. As an initial step toward elucidating the optimal dosage of amrinone for cardiac surgical patients we studied the pharmacokinetics of amrinone during and after cardiac surgery requiring cardiopulmonary bypass. The study population comprised 35 adult patients, each receiving a single dose of amrinone (0.75, 1.5, 2.0, or 2.5 mg/kg) administered into the venous reservoir near the end of cardiopulmonary bypass. Additionally, 15 of the 35 patients also received intravenous infusions of either 5 or 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Arterial blood was sampled over the next 22 h, and plasma concentrations of amrinone were determined by high-performance liquid chromatography. Protein binding of amrinone, assayed by equilibrium dialysis, was 21.6 ± 2.5%. The decay of amrinone concentrations in plasma over time was fit to a biexponential equation by nonlinear least-squares regression. The manufacturer's recommended dose of 0.75 mg/kg followed by an infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was inadequate to maintain the plasma concentration within the therapeutic range based on the pharmacodynamics of amrinone in patients with chronic congestive heart failure. This was due to significant redistribution of amrinone in the body after the loading dose. To maintain a therapeutic plasma concentration of 1.5–2.0 μg/ml, a larger loading dose or a supplemental loading dose as well as a continuous infusion is required. (Key words: Anesthesia: cardiac. Heart, inotropism: amrinone. Pharmacokinetics: amrinone. Surgery, cardiac: cardiopulmonary bypass.)

DURING CARDIAC SURGERY, patients frequently require inotropic and vasodilator therapy support to facilitate separation from cardiopulmonary bypass (CPB). Amrinone (5-amino-3,4′-bipyridine-6(1H)-one lactate) is a unique nonglycosidic, nonsympathomimetic drug that has both vasodilator and positive inotropic effects.[1,2] Amrinone increases myocardial contractility by a mechanism different from those of the catecholamines and digoxin. Amrinone selectively inhibits phosphodiesterase fraction III (also called type IV) to increase cyclic adenosine monophosphate and facilitate intracellular calcium transport, thereby improving myocardial contractility.[3] It is the only specific fraction III phosphodiesterase inhibitor currently available in the United States. In patients with congestive heart failure, intravenous amrinone administration at doses of 0.75–3.0 mg/kg increases cardiac output, decreases ventricular preload and systemic vascular resistance, and decreases myocardial oxygen consumption.[1,2,4] In patients with congestive heart failure, there is a linear correlation between amrinone concentration in plasma and increased cardiac output, with a plasma concentration of 1.7 μg/ml producing a 30% increase in cardiac index.[5]

Unlike catecholamines, amrinone cannot be efficiently titrated to effect simply by changing the infusion rate. The pharmacokinetics of a single intravenous dose of amrinone are best described by a two-compartment open-model of distribution and elimination.[6] Initially there is a sharp decrease in plasma concentration, presumably due to drug distribution to tissues, followed by a much slower elimination phase (biotransformation and excretion). In healthy volunteers, the average distribution clearance is 19.8 $ml \cdot kg^{-1} \cdot min^{-1}$; the metabolic clearance is 4.2 $ml \cdot kg^{-1} \cdot min^{-1}$; the steady-state distribution volume is 1.2 l/kg; and the elimination half-time is 3.6 h.[7]

Safe and effective use of a drug is achieved when dosing is based on knowledge of pharmacokinetics and pharmacodynamics. Amrinone is increasingly being used for inotropic support in patients after cardiac surgery.[8,9] However, available pharmacokinetic data have been obtained only in healthy volunteers.[7] CPB produces marked 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 evaluated the intravenous pharmacokinetics of amrinone during and after CPB in adult cardiac surgical patients.

Materials and Methods

After approval by the Emory University Human Investigations Committee had been obtained, 35 adult patients electively scheduled for cardiac operations requiring CPB consented to this study. The operative procedure, age, body weight, and body surface area of patients enrolled in the study are shown in table 1. Left ventricular function, as assessed by ejection fraction, and New York Heart Association classification of functional impairment, preoperative medications, and creatinine values are shown in table 2. No patient in the study had either clinical or laboratory evidence of hepatic disease.

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TABLE 1. Demographic Data

Age	61.5 ± 13.7 yr
Weight	72.3 ± 15.2 kg
Body surface area	1.87 ± 0.20 m^2
Count of operations	
CABG	14
AVR	8
MVR	5
AVR, CABG	4
MVR, CABG	1
AVR, MVR	2
MVR, ASD	1
Reoperations	8 (included in above count)

Data reported as mean ± standard deviation.
ASD = atrial septal defect; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MVR = mitral valve replacement or repair.

Anesthetic technique was left to the discretion of the attending anesthesiologist. Anesthesia was induced in seven patients with diazepam (0.3–0.5) mg/kg and ketamine (1–2 mg/kg). This was then supplemented with fentanyl (15–81 μg/kg), sufentanil (3.9–7.1 μg/kg), and/or enflurane (< 0.75% inspired concentration). The remaining patients received fentanyl (35–100 μg/kg) or sufentanil (8.4–14 μg/kg) supplemented with diazepam (0.15–0.4 mg/kg), midazolam (0.08–0.12 mg/kg), and/or enflurane (<0.75%). In addition, seven patients received thiopental (11.6–18.1 mg/kg) during CPB for cerebral protection.[10]

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 hetastarch. Hypothermia (23–28° C) and aortic cross-clamping with cold hyperkalemic cardioplegia were used in all patients during CPB with the exception of one patient undergoing mitral valve repair and closure of an atrial septal defect. In this case the repair was done at normothermia without an aortic cross-clamp. The average duration of CPB in all patients was 130 ± 37 min.

After the primary surgical operation and rewarming to a bladder temperature of 36° C but still during CPB, amrinone was administered as a single dose of either 0.75, 1.5, 2.0, or 2.5 mg/kg (n = 5 for each group) into the venous reservoir of the CPB circuit 10–40 min prior to the anticipated time of separation from CPB. Another 15 patients received both an initial bolus dose and a continuous infusion for the duration of the study. The doses used were 0.75 mg/kg plus 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 2.0 mg/kg plus 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 2.0 mg/kg plus 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, with 5 patients in each group. Patients were separated from CPB using catecholamines (epinephrine or norepinephrine), calcium, and vasodilators (nitroglycerin and/or nitroprusside) as needed to maintain satisfactory hemodynamics. This was left to the discretion of the attending anesthesiologist. In all cases the doses or infusion rates of inotropic and/or vasodilator drugs were titrated to achieve a systolic blood pressure > 90 mmHg, a cardiac index > 2.2 $l \cdot min^{-1} \cdot m^{-2}$, and a pulmonary artery occlusion pressure ≤ 18 mm Hg. After separation from CPB, blood remaining in the CPB circuit was transfused into the patient. This was facilitated by Trendelenburg's position and infusion of nitroglycerin.

Amrinone plasma concentrations were assayed in arterial blood samples obtained at 2, 5, 7, 10, 20, 30, 60, 90, 120, 240, 600, 960, and 1,320 min following the initial dose. In a few instances samples were inadvertently not collected, as is evident in figures 1–7. 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 done within 24 h. Amrinone concentrations were determined by high-performance liquid chromatography as described by Kullberg *et al.*[11] A Beckman high-performance liquid chromatography system with a model 114 pump and a 5-μm ultrasphere C_{18}0DS column were used. The coefficient of variation for analysis of known concentrations was 6.65% in the range of 0.125–5 μg/ml. Binding of amrinone to plasma proteins was determined by equilibrium dialysis of plasma[12] from samples drawn prior to induction of anesthesia, immediately after administration of heparin but prior to CPB, during CPB 1 h after its initiation, and 4 h after separation from CPB.

Nonlinear least-squares regression was used to fit two- and three-exponential equations to the data from each patient. Curve stripping was used to determine initial estimates of pharmacokinetic parameters. Nonlinear least-squares regression was performed using the Gauss-Newton algorithm. The data was not weighted. Calculations were implemented using PCNONLIN, Version 3 (Statistical Consultant, Inc., Lexington, KY). A triexponential equation did not enhance the quality of the fit for any patient, as judged by the F-test criterion suggested by

TABLE 2. Preoperative Status

Ejection fraction	0.38 ± 0.07
NYHA classification	
II	5
III	27
IV	3
Preoperative medications	
Nitroglycerin	7
Digoxin	17
Diuretics	13
β-adrenergic blocker	6
Calcium entry blocker	10
Serum creatinine	1.17 ± 0.36 μg/dl

Data reported as mean ± standard deviation.
NYHA = New York Heart Association.

Figure 1a

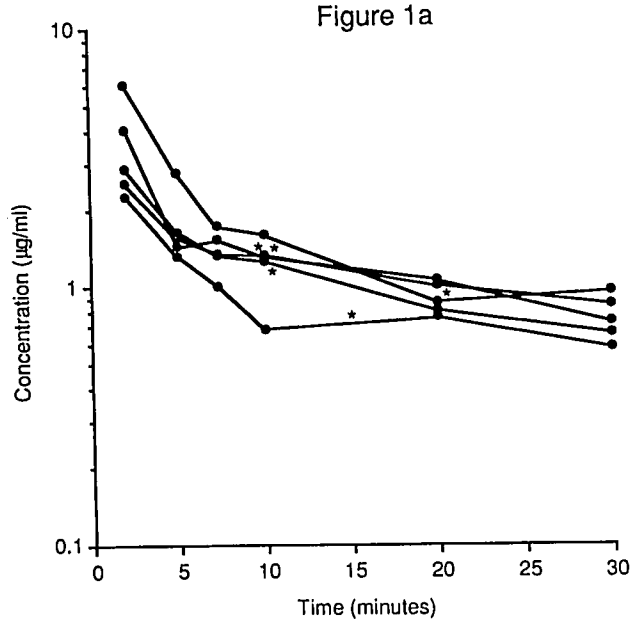


Figure 1b

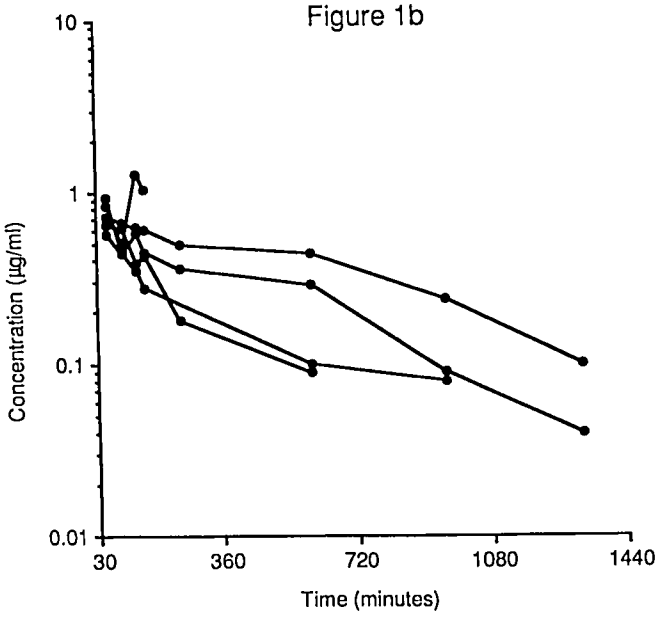


FIG. 1. Plasma concentrations of amrinone as a function of time following a bolus dose of 0.75 mg/kg into the CPB reservoir. *A:* 0–30 min. *B:* 0.5–22 h. Note that the time scales differ in *A* and *B*. *Time of separation from CPB.

Boxenbaum *et al.*[13] Accordingly, a two-compartment model with elimination from the central compartment was used to describe the decline of amrinone plasma concentrations as a function of time after a single dose. Calculated pharmacokinetic parameters included k_{12} (the rate of transfer from the central to the peripheral compartment), k_{21} (the rate of transfer from the peripheral to the central compartment), and k_{10} (the rate of elimination from the central compartment). The macrorate constants and coefficients were determined from the equation

$$C = A\exp(-\alpha \cdot t) + B\exp(-\beta \cdot t)$$

which describes the plasma concentrations for each patient following a single dose (note that these parameters can be evaluated both for patients who received a single dose

Figure 2a

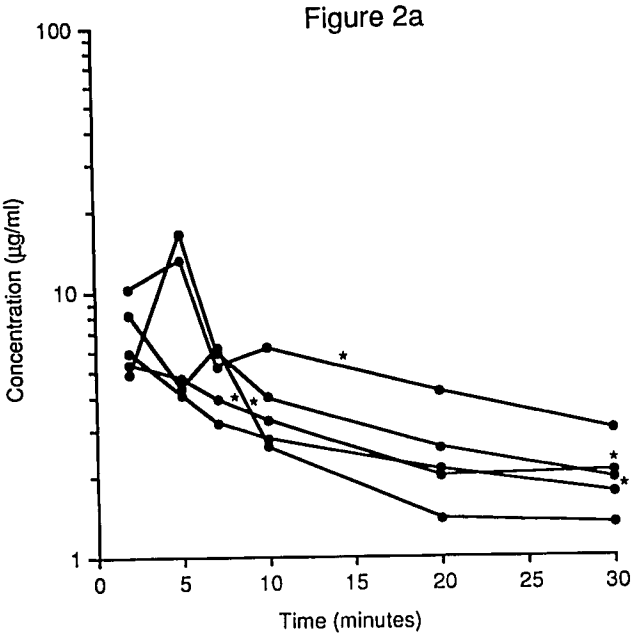


Figure 2b

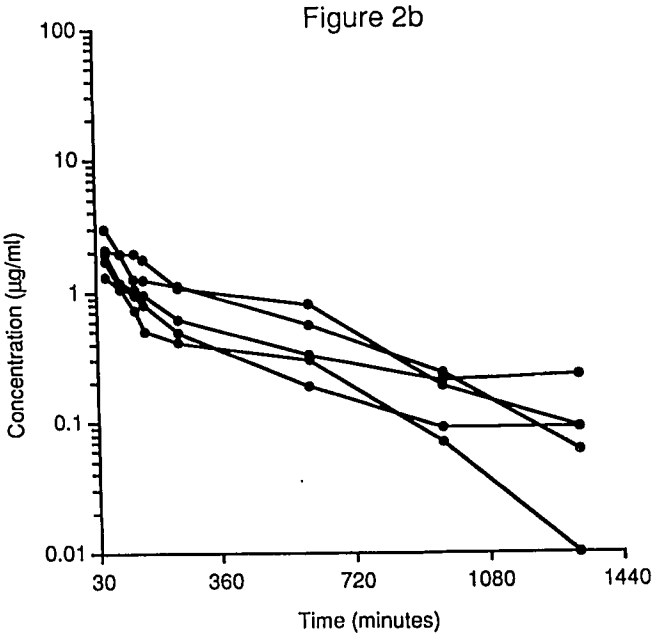


FIG. 2. Plasma concentrations of amrinone as a function of time following a bolus dose of 1.5 mg/kg into the CPB reservoir. *A:* 0–30 min. *B:* 0.5–22 h. Note that the time scales differ in *A* and *B*. *Time of separation from CPB.

Figure 3a

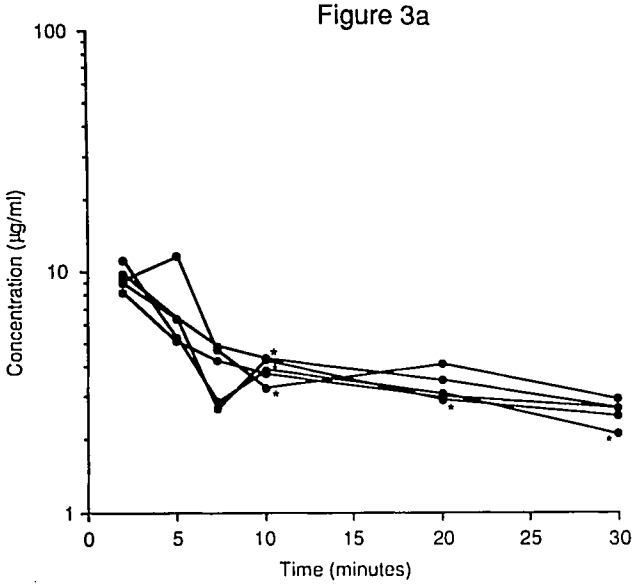


Figure 3b

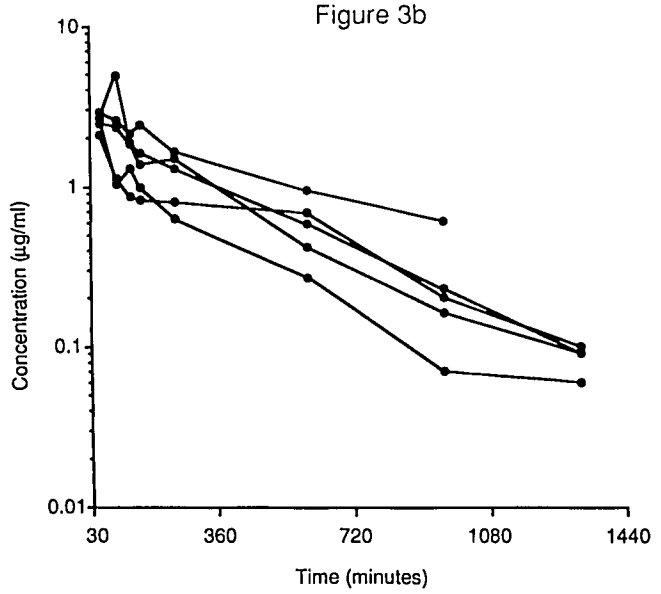


FIG. 3. Plasma concentrations of amrinone as a function of time following a bolus dose of 2.0 mg/kg into the CPB reservoir. *A:* 0–30 min. *B:* 0.5–22 h. Note that concentration and time scales differ in *A* and *B*. *Time of separation from CPB.

and for those who also received an infusion using PCNONLIN). The equation parameters were used to calculate the area under the plasma concentration *versus* time curve ($AUC = A/\alpha + B/\beta$), the volume of the central compartment V_c ([A + B] ÷ dose), distribution clearance Cl_d ($k_{12} \times V_c$), metabolic clearance Cl_m (dose ÷ AUC), the steady-state volume of distribution V_d ($Cl_m \div \beta$), and the elimination half-time ($t_{1/2\beta} = 0.693/\beta$).

Results

All patients were successfully separated from CPB. Other than the single amrinone dose and/or infusion, 5 patients required no other inotropic support; 17 patients received epinephrine infusions; 10 received norepinephrine infusion; 2 received epinephrine and norepinephrine;

Figure 4a

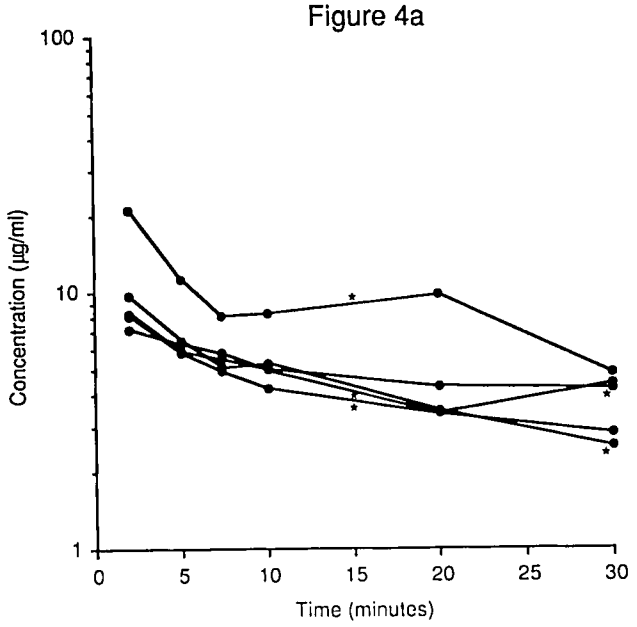


Figure 4b

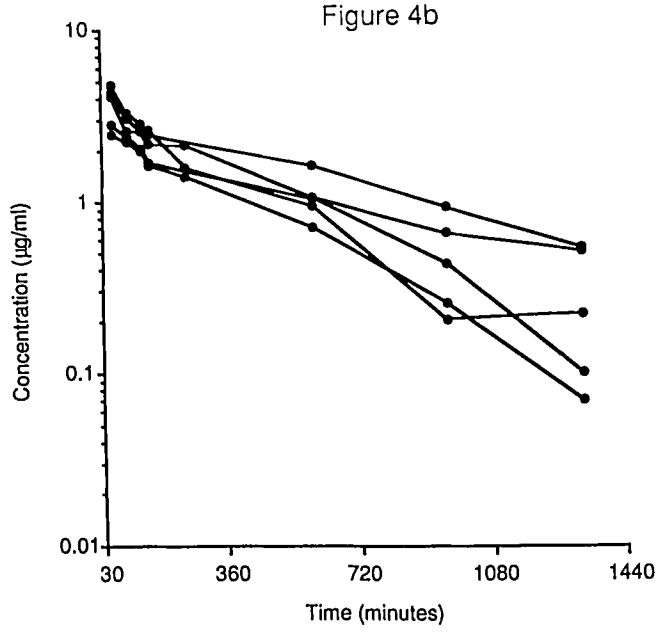


FIG. 4. Plasma concentrations of amrinone as a function of time following a bolus dose of 2.5 mg/kg into the CPB reservoir. *A:* 0–30 min. *B:* 0.5–22 h. Note that the concentration and time scales differ in *A* and *B*. *Time of separation from CPB.

Figure 5a

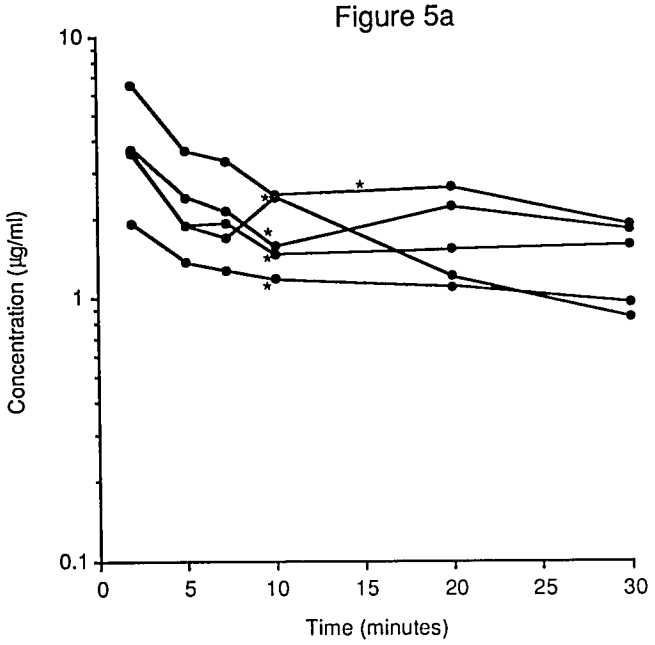


Figure 5b

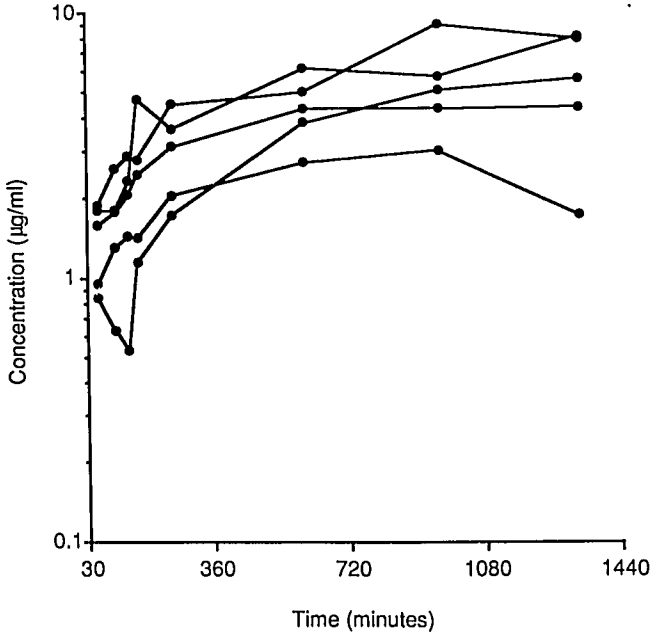


FIG. 5. Plasma concentrations of amrione as a function of time following a CPB bolus of 0.75 mg/kg with concurrent initiation of a continuous infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. *A:* 0–30 min. *B:* 0.5–22 h. Note that the time scales differ in *A* and *B*. *Time of separation from CPB.

and 1 received isoproterenol. One patient had an intraaortic balloon pump that was placed preoperatively.

Amrinone plasma concentrations after a single dose injected into the CPB venous reservoir are illustrated in figures 1–4. After a dose of 0.75 mg/kg (fig. 1), the peak average plasma concentration was approximately 4 μg/ml. However, the concentration declined rapidly and was always less than 2 μg/ml within 10 min. Larger doses resulted in proportionately higher peak concentrations;

Figure 6a

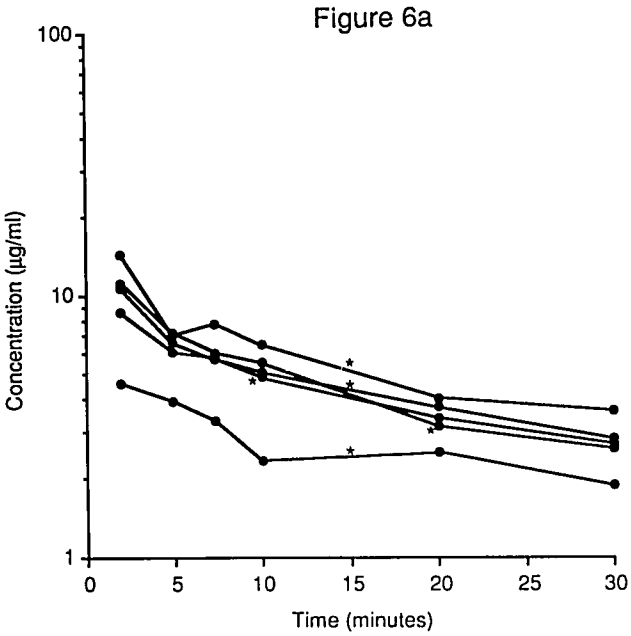


Figure 6b

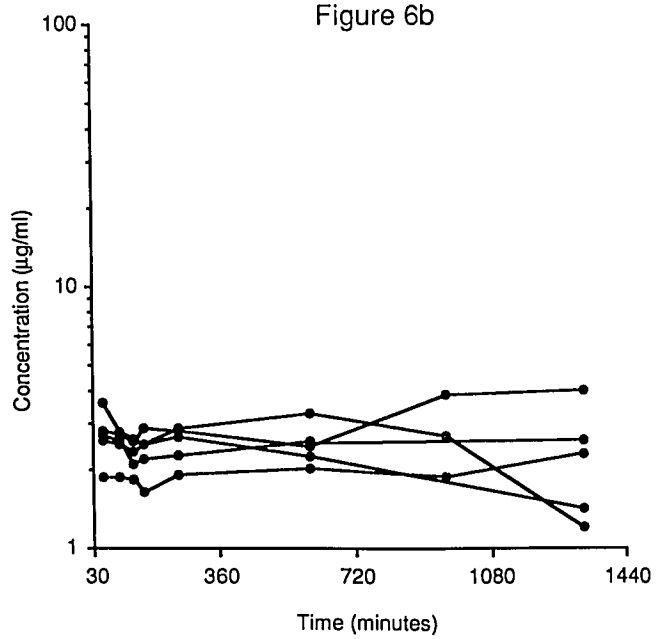
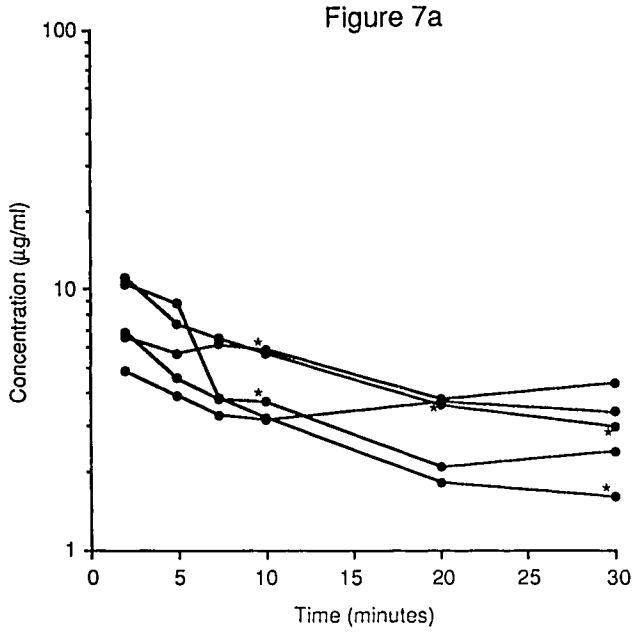


FIG. 6. Plasma concentrations of amrinone as a function of time following a CPB bolus of 2.0 mg/kg with concurrent initiation of a continuous infusion of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. *A:* 0–30 min. *B:* 0.5–22 h. Note that the time scales differ in *A* and *B*. *Time of separation from CPB.



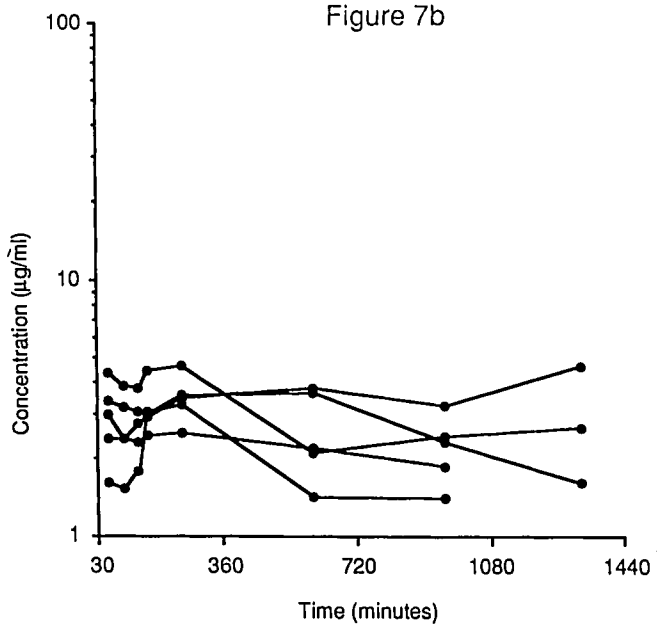


FIG. 7. Plasma concentrations of amrinone as a function of time following a CPB bolus of 2.0 mg/kg with concurrent initiation of a continuous infusion at 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. *A:* 0–30 min. *B:* 0.5–22 h. Note that the time scales differ in *A* and *B*. *Time of separation from CPB.

after 2 mg/kg the average plasma concentrations remained above 2 μg/ml for 90 min (fig. 2).

The plasma concentrations of amrinone when administered as a loading dose in the CPB reservoir immediately followed by a continuous central venous infusion are illustrated in figures 5–7. As expected, the plasma concentrations fell rapidly after the loading dose to a level below that which was ultimately achieved by the constant maintenance infusion. Amrinone concentrations in plasma remained above 2 μg/ml after a loading dose of 2 mg/kg in conjunction with a maintenance infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

The data presented in figures 1–7 were further analyzed by use of a two-compartment model. Pharmacokinetic parameters are presented in tables 3 and 4. By one-way analysis of variance ($P < 0.05$ taken as significant), the pharmacokinetic variables were independent of dose. Results for patients receiving both a bolus and a continuous infusion did not differ from those who were given a single dose. Because the results are essentially independent of dose, average pharmacokinetic parameters were calculated for all patients in this study. These are shown in table 5, with a comparison to previously reported results in healthy volunteers.

Plasma protein binding of amrinone was 21.6 ± 2.5% (mean ± standard deviation) in four patients. Protein binding did not vary significantly between samples drawn prior to induction, after heparinization but prior to CPB, during CPB, or after separation from CPB by one-way analysis of variance.

Discussion

The purpose of this study was to evaluate the pharmacokinetics of amrinone under clinical circumstances in which it is commonly used—that is, at the end of CPB and continuing into the postoperative period. To date, the pharmacokinetics of amrinone have been evaluated only in healthy volunteers.[6,7] CPB would be expected to have significant effects on pharmacokinetics because of alterations in both distribution and elimination secondary to hemodilution, altered regional blood flow, and hypothermia. Because these changes are not immediately reversed after CPB, their impact continues into the postoperative period. Clinically relevant alterations in pharmacokinetics have been reported for many drugs, including fentanyl, sufentanil, digoxin, lidocaine, propranolol, and cephalosporins.[9]

Despite the potential for CPB to alter drug distribution and elimination processes, the pharmacokinetics of amrinone in adults after cardiac surgery did not differ markedly from findings previously reported for healthy volunteers.[6,7] Cardiac surgical patients had a smaller volume of distribution, and metabolic clearance was slightly smaller. However, the differences from values reported for volunteers are unlikely to be of clinical significance. Given the small degree of protein binding of amrinone and the relatively low clearance rate, it is reasonable to surmise that the limiting factor for amrinone elimination

TABLE 3. Pharmacokinetic Parameters for Patients Receiving a Single Bolus Dose

Parameter	Dose (mg/kg)			
	0.75	1.5	2.0	2.5
A (μg/ml)	5.79 (3.61)	8.33 (2.88)	12.94 (5.80)	15.30 (16.95)
B (μg/ml)	0.89 (0.08)	1.65 (0.60)	3.34 (0.54)	4.65 (3.25)
α (min^{-1})	0.342 (0.087)	0.155 (0.095)	0.328 (0.166)	0.262 (0.240)
β (min^{-1})	0.00587 (0.00320)	0.00349 (0.00276)	0.00744 (0.00613)	0.00535 (0.00568)
k12 (min^{-1})	0.257 (0.096)	0.110 (0.079)	0.226 (0.119)	0.100 (0.143)
k21 (min^{-1})	0.0572 (0.0194)	0.030 (0.021)	0.074 (0.034)	0.066 (0.042)
k10 (min^{-1})	0.0036 (0.0162)	0.016 (0.009)	0.035 (0.034)	0.023 (0.029)
V_c (ml/kg)	143 (75)	147 (58)	134 (35)	205 (96)
V_d (ml/kg)	796 (118)	884 (304)	575 (106)	883 (170)
Cl_m ($ml \cdot kg^{-1} \cdot min^{-1}$)	4.8 (3.1)	2.9 (1.6)	3.8 (2.4)	2.3 (0.70)
Cl_d ($ml \cdot kg^{-1} \cdot min^{-1}$)	32.9 (12.4)	15.3 (7.5)	26.8 (6.9)	22.4 (3.1)
t½ β (h)	2.9 (2.4)	4.6 (2.3)	2.9 (2.1)	4.0 (2.3)

Results are presented as means with standard deviations in parentheses. There were five patients in each of the four groups.

is its intrinsic hepatic clearance rather than its delivery to or uptake by the liver.[14] Thus, changes in cardiac output and protein binding would be expected to have small effects on the kinetics of amrinone elimination.

The administration of amrinone prior to separation from CPB is an aspect of this study that is open to criticism. Discontinuation of CPB and return to the patient's own circulation could have significant effects on cardiac output and regional blood flow and alter the pharmacokinetics of the drug. It is also possible that amrinone could bind to components of the CPB system. Although these are concerns, we point out that the study included 15 patients who received an infusion for 22 h after the initial dose. Although the infusion data may provide limited information on the distribution phase, the elimination pharmacokinetic parameters for these patients should to a large extent reflect the influence of the native circulation. The results for these patients did not differ significantly from those for patients who received a single dose prior to separation from CPB. This observation is consistent with the assumption that separation from CPB did not markedly change the elimination pharmacokinetics of amrinone.

We further note that the purpose of this study was to assess amrinone plasma concentrations under conditions that are encountered in clinical practice. The patients enrolled in this study were selected because in our judgment they were likely to require inotropic support for separation from CPB (tables 1 and 2). In this situation it is our clinical practice to administer inotropic drugs prior to separation from CPB to avoid myocardial injury from distention of the heart. Furthermore, amrinone is a potent vasodilator, and we chose to administer the drug on CPB in order to be better prepared to deal with hypotension after the initial bolus dose. In fact, 11 of 35 patients required a norepinephrine infusion to maintain systemic blood pressure.

TABLE 4. Pharmacokinetic Parameters for Patients Receiving an Initial Bolus Dose plus a Continuous Infusion

Parameter	0.75 mg/kg + 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	2.0 mg/kg + 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$	2.0 mg/kg + 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$
A (μg/ml)	4.69 (2.81)	12.71 (.77)	8.59 (4.92)
B (μg/ml)	0.87 (0.35)	3.12 (1.10)	2.64 (1.26)
α (min^{-1})	0.256 (0.098)	0.203 (0.056)	0.167 (0.055)
β (min^{-1})	0.00259 (0.098)	0.00445 (0.00370)	0.00609 (0.00217)
k12 (min^{-1})	0.195 (0.075)	0.144 (0.028)	0.101 (0.048)
k21 (min^{-1})	0.051 (0.033)	0.043 (0.018)	0.046 (0.024)
k10 (min^{-1})	0.013 (0.006)	0.020 (0.014)	0.026 (0.017)
V_c (ml)	170 (83)	128 (23)	195 (59)
V_d (ml)	996 (494)	639 (165)	758 (212)
Cl_m ($mg \cdot kg^{-1} \cdot min^{-1}$)	2.1 (1.2)	2.3 (0.90)	4.4 (1.6)
Cl_d ($mg \cdot kg^{-1} \cdot min^{-1}$)	30.5 (11.8)	18.1 (1.3)	18.1 (7.8)
t½ β (h)	4.0 (1.6)	4.0 (2.1)	2.2 (.99)

Results are presented as means with standard deviations in parenthesis. There were 5 patients in each of the groups.

TABLE 5. Average Pharmacokinetic Parameters for All Patients

Parameter	Current Study	Previously Reported
A (μg/ml)	6.02	4.82
B (μg/ml)	1.40	0.67
α (min^{-1})	0.253	0.149
β (min^{-1})	0.00499	0.00317
k12 (min^{-1})	0.170	0.109
k21 (min^{-1})	0.054	0.021
k10 (min^{-1})	0.023	0.023
V_c (ml/kg)	160	182
V_d (ml/kg)	796	1199
Cl_m ($ml \cdot kg^{-1} \cdot min^{-1}$)	3.2	4.2
Cl_d ($ml \cdot kg^{-1} \cdot min^{-1}$)	21.8	19.8
$t_{1/2}$ β (h)	3.5	3.6

The coefficients A and B are normalized to a dose of 1 mg/kg. Control data previously reported for healthy volunteers was calculated from Park *et al.*[7]

It is not yet possible to draw firm conclusions about the appropriate dose of amrinone in cardiac surgical patients, because we do not know the relationship between plasma concentration and therapeutic effect in this population. Studies of patients with chronic congestive heart failure have demonstrated a linear relationship between plasma concentration and increases in cardiac output, with a plasma concentration of 1.7 μg/ml resulting in an average increase in cardiac output of 30%, which might be considered to be a threshold level of therapeutic effect.[5] If we assume that these findings apply also to patients receiving amrinone for inotropic support after cardiac surgery, the dose scheme recommended by the manufacturer is inadequate. A CPB bolus of 0.75 mg/kg followed by an intravenous infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ administered near the end of CPB resulted in a plasma concentration less than 1.7 μg/ml within 15 min, and the plasma concentrations remained below this level between 20 and 90 min despite the continuous infusion. This conclusion is consistent with a recently reported observation that amrinone 0.75 mg/kg given 10 min prior to separation from CPB had no significant effect on hemodynamic performance.[15] Our results indicate that a CPB bolus dose of 1.5–2.0 mg/kg followed by an intravenous infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ would maintain plasma concentrations above this therapeutic threshold, which has been determined only for patients in chronic congestive heart failure.

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