REPORTS

The Pharmacokinetics of Amrinone at Three Dose Levels in the Rabbit

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Abstract: Amrinone is a positive inotropic and vasodilatory compound being used to improve cardiocirculatory function in chronic cardiac failure. The linearity of the pharmacokinetics of amrinone was examined in New Zealand white rabbits given i.v. bolus doses of 1.5, 3.0, and 7.5 mg/kg amrinone. Blood samples were obtained serially for a period of 6 hours following amrinone administration. Serum concentration-time data were analyzed by nonlinear least squares regression, as well as non-compartmental techniques. There were no differences as a function of dose in the systemic clearance, elimination half-life, mean residence time, or average concentration of amrinone. The pharmacokinetics of amrinone appear to be linear in rabbits. The rabbit may be useful as an animal model to study various aspects of amrinone pharmacokinetics.

Amrinone is a bipyridine derivative recently approved for the intravenous treatment of cardiac failure. Although the precise mechanism of action of amrinone is not entirely clear, the dose-related hemodynamic improvements following amrinone administration have been reported to result from both positive inotropic as well as vasodilatory effects (1).

The pharmacokinetics of amrinone have been studied in normal volunteers and in patients suffering from refractory chronic cardiac failure (2–4). Little information exists to date on the linearity of amrinone pharmacokinetics over a wide range of doses in either of these populations. Since amrinone improves cardiocirculatory function in a dose-related manner, alterations in regional and renal perfusion could result in dose-related alterations in its distribution and clearance. The purpose of this study was to examine the linearity of the pharmacokinetics of amrinone administered over a wide dosage range using the rabbit as an animal model.

Materials and Methods

The study was initiated as a balanced, three-way, repeated measures design in 7 rabbits with a one-week wash-out period between treatment sequences. Owing to difficulties in auricular artery catheterization during the second and third dosing sequences, many of the rabbits did not receive all doses. To compensate for these missing dose sequences, additional rabbits were employed to ensure that 7 rabbits were examined at each dose level.

The pharmacokinetics of amrinone were evaluated in 10 male, non-anesthetized New Zealand white rabbits. Amrinone was administered over one minute through a marginal ear vein as either a 1.5, 3.0 or 7.5 mg/kg i. v. bolus in a lactic acid vehicle of pH 4. Serial blood samples (2 ml) were obtained for measuring amrinone concentrations from the auricular artery of the opposite ear for a period of 6 hours following amrinone administration. Blood samples were replaced with an equal volume of normal saline after each sampling. The blood samples were immediately centrifuged and the plasma was separated and stored at −20° C until analysis. The serum concentrations of amrinone were determined by the high performance liquid chromatographic method of Kullberg et al. (5).

Serum concentration-time data were fitted to a two-compartment, open model using nonlinear least squares regression for the purpose of obtaining an unbiased estimate for the initial amrinone plasma concentration (C^o), as well as the terminal elimination rate constant (λ_2). These pharmacokinetic parameters were then used in the LAGRAN computer program to provide estimates for the systemic clearance (CL), volume of distribution at steady state (v_{ss}), and mean residence time (MRT) (6).

The distributional and elimination half-lives ($t_{1/2}$) were computed as the ratios of 0.693 and the exponential coefficients (λ_1 or λ_2) derived from the curve fitting procedures described above. The average concentration of amrinone ($\overline{C}_p$) following each dose was obtained as the ratio of the area under the serum concentration-time curve for amrinone and the MRT.

Differences in the pharmacokinetic parameters of amrinone following the different i.v. doses were assessed by an analysis of variance taking into consideration the incomplete study design through the assignment of missing values to the treatment sequences that were lacking for each rabbit. A statistical level of $p < 0.05$ was considered significant. All results were expressed as the mean (± SD).

Results and Discussion

The mean amrinone serum concentration-time profiles after the 1.5, 3.0 and

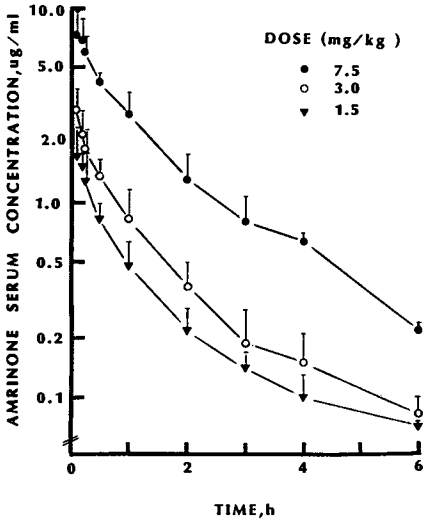

Fig. 1 Mean (± SD) serum concentration versus time profiles for amrinone following 1.5 (▼), 3.0 (○) and 7.5 (●) mg/kg i.v. bolus doses.

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7.5 mg/kg intravenous doses are presented in Figure 1. The time course of amrinone serum concentrations were characterized by mean (± SD) distributional half-lives of 0.33 (0.11), 0.28 (0.12) and 0.25 (0.15) h for the 1.5, 3.0 and 7.5 mg/kg doses, respectively. Corresponding mean elimination, half-lives for these doses were 1.4 (0.63), 1.4 (0.65) and 1.4 (0.42) h respectively. The mean (± SD) CL, V_{ss}, MRT and $\frac{\overline{C}_p}{\text{Dose}}$ of amrinone are presented as a function of dose in Table I. No changes in any of the pharmacokinetic parameters were evident with changes in dose.

Table I. Selected Pharmacokinetic Parameters of Amrinone as a Function of Dose

	Dose		
	1.5 mg/kg	3.0 mg/kg	7.5 mg/kg
CL (ml/min/kg)	0.91 (0.19)	1.01 (0.20)	0.84 (0.16)
V_{ss} (l/kg)	1.33 (0.49)	1.69 (0.57)	1.35 (0.35)
MRT (h)	1.57 (0.46)	1.67(0.49)	1.62 (0.35
$\frac{\overline{C}_p \text{ (mg/l)}}{\text{Dose (mg)}}$	0.28 (0.13)	0.25 (0.08)	0.28 (0.07)

No alterations in the pharmacokinetics of amrinone occur following i.v. administration of the drug over a wide dosage range in rabbits. Studies performed in normal volunteers have demonstrated that renal elimination of unmetabolized amrinone is a primary route of elimination (7, 8). Assuming the total systemic clearance of amrinone in the present study (~ 0.90 ml/min/kg) approximates amrinone renal clearance (which is likely an over estimation), the magnitude of this clearance value corrected for the modest (~ 40 %) serum binding of the drug (obtained in humans) (9) yields a free renal clearance of 1.5 ml/min/kg. This value is considerably less than the range of inulin clearance values (5.0–8.4 ml/min/kg) encountered in the rabbit (10). This suggests that glomerular filtration and tubular reabsorption are the primary modes of renal handling of amrinone, a finding consistent with that observed in humans (8).

Amrinone rapidly improves cardiac performance by decreasing pre-load and after-load while improving cardiac contractility (1). Changes in cardiac index (CI) following the administration of amrinone correlate with the serum concentration of amrinone (4), with peak increases averaging approximately 50 % (11). Since amrinone significantly increases CI and renal blood flow (12), one might have envisioned a change in amrinone clearance and/or distribution with improvements in cardiac function, a finding which could not be demonstrated in the present study.

Edelson et al. (13) have recently examined the dose proportionality of amrinone elimination half-life following three different oral doses in healthy subjects and found no dose dependence in their half-life estimates, a finding consistent with the results of this study. The use of oral doses in their study, however, precluded direct examination of the effects of amrinone dose on its clearance and volume of distribution as was done in our animal study.

The lack of an effect of amrinone on its own pharmacokinetics in an animal model with normal cardiocirculatory function may not be reflective of the effects which might be seen in the failing heart. Much more dramatic improvements in cardiac index and pulmonary capillary wedge pressures have been observed in patients with chronic cardiac failure versus normal volunteers (7). Further studies are warranted to examine the effects of amrinone on its pharmacokinetics in an appropriate cardiac failure model.

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