Oral and Intravenous Pharmacokinetics of Milrinone in Human Volunteers

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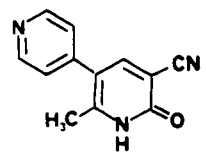
Received May 19, 1983, from the *Department of Drug Metabolism and Disposition, Sterling-Winthrop Research Institute, Rensselaer, NY 12144.* Accepted for publication November 29, 1983.

Abstract □ Thirty-nine healthy men received milrinone either orally or intravenously in two separate double-blind, placebo-controlled studies. The mean bioavailability, based on the area under the plasma concentration *versus* time curves, was 0.92. The plasma data for those subjects in the intravenous study were described by an open two-compartment model with a mean (±*SD*) apparent first-order terminal elimination rate constant (β) of 0.86 (± 0.23) h^{-1}, which corresponds to a half-life of 0.8 h. In the intravenous study, the renal clearance and total body clearance were 21.1 and 25.9 L/h, respectively. The corresponding values in the oral study were 23.8 and 29.7 L/h. Between 79.9 and 84.5% of the total doses were recovered in the urine samples taken at 0–24 h.

Keyphrases □ Milrinone—blood plasma levels, human volunteers, oral and intravenous administration, bioavailability □ Pharmacokinetics—milrinone, an open two-compartment body model □ Cardiotonic agents—milrinone, pharmacokinetics, bioavailability

Milrinone[1] (1,6-dihydro-2-methyl-6-oxo[3,4′-bipyridine]-5-carbonitrile; I), is an experimental cardiotonic agent that is chemically related to amrinone (1). Both compounds, which are neither glycosides nor catechols, have demonstrated positive inotropic effects in animal models (2). In dogs, an intravenous bolus injection of milrinone (0.01–1.0 mg/kg) caused an increase in cardiac contractile force within 1 min, with a duration of action of up to 2 h. The effects could be maintained by intravenous infusion (0.3–10 μg/kg/min) for several hours. Oral activity (0.1–1.0 mg/kg) in dogs was also demonstrated, with an onset of activity within 30 min and a duration of more than 6 h (3).



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Milrinone has been given to patients with severe chronic heart failure (4, 5). Intravenous bolus administration (25–150 μg/kg) resulted in significant increases in the cardiac index. Hemodynamic improvements were maintained with intravenous infusion (0.25–1.0 μg/kg/min) over periods of 24–48 h (5). Thus far, preliminary data disclosed that after intravenous treatment, the oral administration of milrinone (10–20 mg/d divided into three or four doses) maintained the improvement in cardiac function without reported adverse effects (4).

The analytical method for analysis of milrinone in human plasma and urine and the pharmacokinetic parameters following intravenous administration in dogs have been described previously (6). In this report, the results of our investigations into the pharmacokinetics of milrinone in humans following intravenous medication are described, and plasma levels following oral and intravenous administration are compared.

[1] Sterling Drug, Inc., New York, N.Y.

EXPERIMENTAL SECTION

Human Subjects—As part of the safety and pharmacokinetic evaluation of milrinone, 21 normal male volunteers between the ages of 19 and 40 years (mean, 28.5 years) and 18 normal male volunteers between the ages of 18 and 41 years (mean, 28.9 years) were selected to receive milrinone in an intravenous study and an oral study, respectively. Prior to acceptance in a study, each volunteer was examined to ensure that there were no clinical findings indicative of renal, hepatic, or cardiac dysfunction. Appropriate institutional review and approval were obtained prior to initiation of the study, and each volunteer gave informed consent. Subjects were admitted to the clinic the evening before initiation of the study, and all subjects remained in the clinic at least 24 h after receiving medication or placebo.

Study Design—The intravenous and oral studies consisted of six or seven groups of three volunteers each. In the intravenous study, subjects received single injections of 10, 30, 45, 60, 75, 100, or 125 μg of milrinone/kg. Three subjects received each of the seven doses. In the oral study, volunteers received single doses of 1.0, 2.5, 5.0, 7.5, 10.0, or 12.5 mg of either milrinone or placebo; three subjects received each of the six doses. Blood samples (10 mL) were collected in evacuated tubes containing oxalate anticoagulant before medication and at ~2, 5, 10, 15, 30, and 45 min and 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, and 24.0 h after medication. The blood was centrifuged; plasma was separated and frozen until it was analyzed.

In both studies, urine was collected and measured for total volume, and an aliquot was removed for analysis. Collection times included the following intervals: premedication and 0–4, 4–8, 8–12, and 12–24 h after medication.

Assay Procedure—The analysis of plasma and urine for milrinone concentration followed that described previously (6). The method required extraction of milrinone from plasma or urine with ethyl acetate and back-extraction into acid; the samples were then neutralized and subjected to reverse-phase HPLC. Plasma and urine standards, which were freshly prepared in normal human plasma and urine, were extracted and analyzed with each set of samples from the study subjects. The concentrations of milrinone in plasma were determined by comparison with the regression line of the peak height ratios (drug–internal standard) *versus* milrinone concentration in the standards; the mean (±*SE*) correlation coefficients were 0.9967 (±0.0012) for plasma (n = 19) and 0.9997 (±0.0002) for urine (n = 9). The minimum quantifiable level of milrinone was estimated as that concentration at which the lower 80% confidence limit just encompassed zero (7) and was ~1.9 ng/mL for plasma samples and 19.6 ng/mL for urine samples. The HPLC system used consisted of an automatic injector[2], a pump[3], a precolumn[4], a column[5], and a UV detector[6] which monitored the column effluent at 340 nm. The detector was interfaced with a data processing system[7] for data collection and processing.

Pharmacokinetic Calculations—The data obtained from the analysis of the human plasma samples from the intravenous study were described by an open two-compartment model by a nonlinear regression (NLIN) procedure (8). The concentrations were weighted as the square of their reciprocals. An attempt was made to describe the plasma concentration data obtained from the oral study by either an open one- or two-compartment model with first-order absorption.

The plasma concentration data were also analyzed with respect to the following regression-independent parameters: the maximum observed plasma concentration (C_{max}, oral study only); the time at which C_{max} was observed (t_{max}, oral study only); and the area under the plasma concentration *versus* time curve (AUC_0^∞), which was calculated by using the trapezoidal rule plus

[2] Model 710B WISP; Waters Associates Milford, Mass.
[3] Either model M-45; Waters Associates or mini-pump; Milton-Roy, Riviera Beach, Fla.
[4] Corasil C-18 (37–50 μm); Waters Associates.
[5] Partisil 10/25 ODS-3; Whatman, Clifton, N.J.
[6] Model 440; Waters Associates.
[7] Model 3356 LAS; Hewlett-Packard, Santa Clara, Calif.

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Table I—Pharmacokinetic Parameters in Volunteers after Intravenous Administration of Milrinone

		Regression-Dependent Parameters						Regression-Independent Parameters					
Subject	Dose, μg/kg	α, h^{-1}	β, h^{-1}	A, ng/mL	B, ng/mL	Vd_{ss}, L[a]	Vd_{ss}, L/kg	AUC_0^∞, ng·mL^{-1}·h	AUC_0^∞/ Dose	Vd_{ss}, L/kg[b]	Renal Clearance, L/h	CL_B, L/h	Dose Recovered from Urine, %
1	10	11.5	0.995	79.5	18.1	24.3	0.299	29.6	2.96	0.252	19.6	27.4	71.6
2	10	17.9	1.40	69.7	28.2	21.8	0.253	24.3	2.43	0.170	—[c]	35.4	2.3[c]
3	10	8.85	0.884	38.8	16.0	24.9	0.413	23.5	2.35	0.268	21.3	25.5	83.3
Mean ± *SD*				62.7 ± 21.2	20.8 ± 6.52			25.8 ± 3.3					
4	30	12.0	1.09	244	46.2	26.7	0.311	64.2	2.14	0.222	27.2	40.2	67.8
5	30	10.4	1.04	175	47.8	21.2	0.346	64.7	2.16	0.241	20.3	28.3	71.6
6	30	10.1	0.885	203	54.1	24.9	0.321	87.6	2.92	0.250	21.9	26.4	83.1
Mean ± *SD*				207 ± 34.7	49.4 ± 4.18			72.2 ± 13.4					
7	45	9.62	0.897	336	54.7	26.7	0.349	103	2.29	0.282	25.6	33.2	77.2
8	45	7.95	0.919	491	105	15.6	0.192	182	4.04	0.165	17.6	20.0	87.6
9	45	9.05	0.973	246	59.9	23.5	0.378	93.7	2.08	0.304	24.2	29.8	81.4
Mean ± *SD*				358 ± 124	73.2 ± 27.7			126 ± 48.5					
10	60	10.4	0.910	552	98.0	18.9	0.285	182	3.03	0.197	18.5	21.8	84.8
11	60	10.2	0.939	531	112	19.2	0.269	179	2.98	0.232	20.0	23.8	84.3
12	60	10.2	1.04	628	119	19.3	0.222	182	3.03	0.197	24.0	28.4	84.5
Mean ± *SD*				570 ± 51.0	110 ± 10.7			181 ± 1.7					
13	75	3.36	0.612	297	70.4	22.1	0.383	213	2.84	0.282	18.3	20.0	91.6
14	75	11.2	0.956	792	134	16.8	0.257	223	2.97	0.209	19.9	21.9	90.8
15	75	8.77	0.856	685	140	17.7	0.257	249	3.32	0.213	22.8	20.7	110
Mean ± *SD*				591 ± 260	115 ± 38.6			228 ± 18.6					
16	100	2.80	0.355	442	31.7	34.2	0.499	282	2.82	0.294	18.7	24.1	77.6
17	100	6.45	0.708	600	112	29.8	0.375	272	2.72	0.318	23.6	29.1	81.5
18	100	3.03	0.579	401	88.9	25.3	0.374	306	3.06	0.302	18.5	21.9	84.6
Mean ± *SD*				481 ± 105	77.5 ± 41.3			287 ± 17.5					
19	125	9.14	0.886	923	282	22.1	0.263	436	3.49	0.213	21.7	24.0	89.0
20	125	3.18	0.469	485	50.3	30.3	0.509	286	2.29	0.394	—[c]	25.8	28.5[c]
21	125	2.80	0.707	510	242	17.5	0.248	554	4.43	0.217	16.3	15.8	103
Mean ± *SD*				639 ± 246	191 ± 124			425 ± 134					
Overall mean		8.52	0.862			23.0	0.324		2.87	0.249	21.1	25.9	84.5
± *SD*		3.80	0.230			4.85	0.084		0.61	0.055	2.92	5.69	10.1

[a] $Vd_{ss} = [\text{Dose}(A/\alpha^2 + B/\beta^2)]/(A/\alpha + B/\beta)^2$. [b] $Vd_{ss} = [\text{Dose}(\text{AUMC}_0^\infty)]/(\text{AUC}_0^\infty)^2$. [c] Incomplete urine collection.

Table II—Pharmacokinetic Parameters in Volunteers after Oral Administration of Milrinone

Subject	Dose, mg	Dose, μg/kg	k_e, h^{-1}	AUC_0^∞, ng mL^{-1} h	AUC_0^∞/ Dose	C_{max}, ng/mL	t_{max}, h	Renal Clearance, L/h	CL_B, L/h	Percent Dose Recovered from Urine
22	1.0	12.8	0.72	28.0	2.19	16.7	1.00	11.8[a]	35.7	33.0[a]
23	1.0	13.3	0.78	44.7	3.36	25.4	1.00	17.9	22.4	80.0
24	1.0	13.0	1.20	42.6	3.28	40.9	0.53	8.49[a]	23.5	36.0[a]
Mean ± *SD*				38.4		27.7				
				9.1		12.3				
25	2.5	28.8	1.00	76.4	2.65	50.5	1.50	23.4	32.7	71.6
26	2.5	31.3	0.50	67.3	2.15	32.0	0.48	24.7	37.1	66.4
27	2.5	31.2	0.93	74.5	2.39	41.4	1.00	26.7	33.5	79.6
Mean ± *SD*				72.7		41.3				
				4.8		9.25				
28	5.0	66.9	1.12	121	1.81	105	1.03	36.8	41.3	88.8
29	5.0	74.4	0.62	217	2.92	101	0.50	19.6	23.1	85.2
30	5.0	75.9	1.10	196	2.59	141	1.50	21.3	25.5	83.6
Mean ± *SD*				178		116				
				50.5		22.0				
31	7.5	94.9	0.60	358	3.77	148	1.50	15.4	21.0	79.2
32	7.5	104.5	0.66	286	2.74	125	1.53	19.0	26.2	83.2
33	7.5	90.3	0.67	296	3.27	1184	1.00	2.06[a]	25.3	15.6[a]
Mean ± *SD*				313		152				
				39.0		29.7				
34	10.0	137.6	0.60	392	2.85	231	0.50	20.3	25.5	73.3
35	10.0	148.8	0.74	392	2.64	130	3.00	21.2	25.5	72.7
36	10.0	149.7	0.56	275	1.83	114	1.53	5.68[a]	36.3	8.1[a]
Mean ± *SD*				353		158				
				67.6		63.4				
37	12.5	160.1	0.60	494	3.09	245	1.00	9.09[a]	25.3	35.8[a]
38	12.5	179.3	0.92	382	2.13	334	1.03	35.0	32.7	107
39	12.5	184.6	0.51	297	1.61	123	0.62	28.5	42.1	67.8
Mean ± *SD*				391		234				
				98.8		106				
Overall mean ± *SD*			0.77		2.63		1.13	23.8[b]	29.7	79.9[b]
			0.22		0.60		0.60	6.4[b]	6.7	10.7[b]

[a] Incomplete urine collection. [b] Excluding incomplete collection data.

terminal plasma concentration divided by the terminal elimination rate constant (to correct to infinite time). Total body clearance was determined by dividing the dose by the AUC_0^∞. Other pharmacokinetic parameters were estimated by classical techniques (9).

The data obtained from urine were used to calculate the renal clearance of milrinone by dividing the amount of unchanged milrinone excreted in the urine over a given period by the AUC for that period. The relative bioavailability was determined by dividing the mean normalized AUC_0^∞ for the oral dose by the mean normalized AUC_0^∞ for the intravenous dose.

RESULTS AND DISCUSSION

The concentrations of milrinone in the plasma samples from each volunteer were determined. After intravenous medication, the plasma concentrations declined biexponentially with time, suggesting that a two-compartment model would be appropriate. Pharmacokinetic parameters for each subject in the intravenous study were estimated after computer fitting the data obtained from plasma by an iterative nonlinear least-squares regression technique (8) (Table I).

The mean apparent first-order terminal elimination half-life for milrinone following intravenous medication was ~50 min. The mean apparent volume of distribution at steady state Vd_{ss} was 23.0 L or, dividing by body weight, 0.32 L/kg. The mean value for α (8.52 h^{-1}) corresponded to a distributive-phase half-life of <5 min. The mean regression-independent total body clearance (dose/AUC_0^∞) was 25.9 L/h, whereas the mean regression-independent renal clearance (total intact drug in urine/AUC_0^∞) was 21.1 L/h, which exceeds the glomerular filtration rate and suggests an active excretion mechanism. The values obtained by the trapezoidal rule for the regression-independent AUC_0^∞ were consistently higher than the corresponding regression-dependent AUC_0^∞ ($A/\alpha + B/\beta$). Since the Vd_{ss} values are inversely related to the square of the AUC_0^∞, the regression-independent Vd_{ss} values are consistently lower than the corresponding regression-dependent values. Although there is almost a threefold difference between the highest (subject 4) and lowest (subject 21) clearances, the observed concentration data from the intravenous study were adequately described by the model for both of these subjects; a comparison of the observed and predicted concentrations is shown in Fig. 1. The agreement between the observed values and those predicted by the open two-compartment body model is apparent. The amount of intact milrinone present in the urine over the 24-h period following drug administration was similar in both studies: 84.5% of the dose following intravenous administration and 79.9% of the dose following oral administration. The dosage ratio, oral-intravenous, suggests that the fraction of the oral dose that is bioavailable is ~0.95 (see below).

The plasma concentration data obtained in the oral study were not adequately described by either the open one- or two-compartment model with first-order absorption, although several weighting schemes were tried. Regression-independent parameters were determined for the oral study (Table II). The mean time of maximum plasma concentration was 1.13 h after medication. The renal clearance (23.8 ± 6.4 L/h) was comparable to that found in the intravenous study, as was the total body clearance (29.7 ± 6.7 L/h). The terminal elimination half-life was ~55 min.

Although the same subjects were not used in a crossover manner in the intravenous and oral investigations, an estimate of the absolute bioavailability was obtained by comparing the data from the two independent studies. The mean absolute bioavailability or oral-parenteral ratio, defined as the ratio of the AUC_0^∞/dose for the tablet to the regression-independent AUC_0^∞/dose for the intravenous solution, was 0.92, which is consistent with the urinary excretion data. Analysis of variance indicated that the AUC_0^∞/dose values for medication administered either by the intravenous or oral routes were not significantly different ($p = 0.21$). Furthermore, a statistical analysis of AUC_0^∞/dose against administered dose showed that the AUC_0^∞/dose was not dose dependent ($p = 0.94$).

The mean terminal elimination half-life of milrinone obtained in these human volunteers varied substantially from the value of 3.6-h obtained in dogs at intravenous doses of 5 mg/kg (6). This difference is surprising in light of the relatively good correlation in the amrinone studies between the mean terminal elimination half-life in dogs receiving doses of 5 mg/kg iv (2.37 h) (10) and human volunteers receiving doses of 75 mg iv (3.6 h) (1). Following

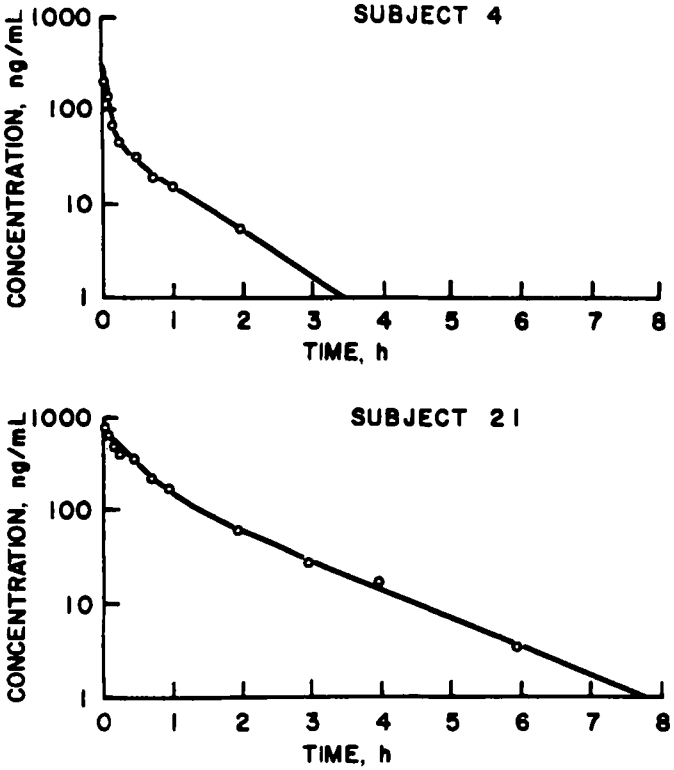

Figure 1—*Plasma concentration of milrinone in human volunteers after intravenous administration. Data points are plasma concentrations observed in two subjects with widely divergent clearance rates and concentrations predicted by the open two-compartment model (solid line).*

oral administration of 75 mg to volunteers, the mean terminal elimination half-life of amrinone was 4.33 h (1).

The mean half-life of amrinone in patients with congestive heart failure was 8.3 h (11), which is more than twice that seen in volunteers with normal cardiac function. We anticipate a similar increase in the terminal elimination half-life of milrinone in patients with congestive heart failure. The decrease in renal and hepatic blood flow in patients with severe cardiac impairment may be responsible for this increase in the duration of the drug in plasma. We are currently studying the pharmacokinetics of milrinone in patients with congestive heart failure as part of clinical efficacy trials. Attempts will be made to correlate the effects of dose on the terminal elimination half-life of milrinone.

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Crystallinity and Dissolution Rate of Tolbutamide Solid Dispersions Prepared by the Melt Method

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Abstract □ The influence of cooling rate of solid dispersions prepared by the melt method was studied by X-ray diffraction and scanning electron microscopy. Tolbutamide was the model drug investigated, and the carriers included urea and polyethylene glycol 6000. Slow-cooled urea dispersions of tolbutamide demonstrated a complete lack of crystallinity suggesting the formation of an amorphous material. The rapidly cooled dispersion showed peaks for urea and an absence of drug in the X-ray pattern, suggesting that a true molecular dispersion was formed. The X-ray patterns of rapid- and slow-cooled dispersions of tolbutamide and polyethylene glycol 6000 demonstrated that a physical mixture of drug and carrier resulted from both methods of dispersion preparation.

Keyphrases □ Solid dispersions—melt method of preparation, cooling rates and physicochemical properties □ Tolbutamide—solid dispersions with urea and polyethylene glycol 6000 □ X-ray diffraction—tolbutamide, solid dispersions, carriers □ Scanning electron microscopy—solid dispersions □ Dissolution rates—tolbutamide, solid dispersions

The rate-determining step in the absorption process for drugs of low solubility is generally the dissolution rate of such drugs in the GI fluids rather than the rapidity of their diffusion across the gut wall. The formation of solid dispersions of the drug with a water-soluble carrier is one of several techniques that can be used to improve the dissolution properties of poorly soluble or hydrophobic drugs. In 1961, Sekiguchi and Obi (1) became the first researchers to propose the use of solid dis-

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