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Dose Regimen Adjustment for Milrinone in Congestive Heart Failure Patients with Moderate and Severe Renal Failure

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Abstract

This study was designed to test a proposed dose modification for intravenous milrinone in congestive heart failure patients (CHF, NYHA I–II) with either moderate or severe renal impairment.

All the patients were administered an intravenous loading dose of drug at 50 $\mu g\,kg^{-1}$ over 10 min. This was followed by an 18 h maintenance infusion of milrinone at 0·45 or 0·35 $\mu g\,kg^{-1}\,min^{-1}$ for the moderate (chromium-EDTA clearance of 31–75 $mL\,min^{-1}$, n = 10) and severe renally impaired subjects (chromium-EDTA of clearance 10–30 $mL\,min^{-1}$, n = 11), respectively. Plasma and urine samples were collected for up to 34 h and analysed for parent drug by validated HPLC methods. The mean (± s.d.) steady-state plasma concentrations of milrinone were within the therapeutic range (100–300 $ng\,mL^{-1}$) for both groups, with values of 239 ± 71 $ng\,mL^{-1}$ and 269 ± 32 $ng\,mL^{-1}$ for the moderate and severe patients, respectively. No statistical differences were observed between the steady-state values for the two groups. With the exception of two patients per group, individual steady-state levels were also within the therapeutic range. Those outside the nominal range showed steady-state levels, ranging between 308 and 353 $ng\,mL^{-1}$, that were not associated with any serious adverse events. As predicted for this highly renally cleared drug, there were differences ($P < 0·001$) in the total plasma clearance (CL_p), renal clearance (CL_r), and plasma terminal half-life ($t_{\frac{1}{2}}$) of drug, with values in the severe group being 44% lower, 75% lower, and about 134% longer respectively, when compared with the moderate group. High (correlation coefficient > 0·8) and significant correlations ($P < 0·001$) were observed between CL_p and CL_r and the degree of renal impairment (chromium-EDTA clearance). The apparent volume of distribution was approximately 40% higher ($P < 0·01$) in the severe group compared with that for the moderate group (moderates were 0·443 ± 0·155 $L\,kg^{-1}$). This volume difference suggests a decrease in the plasma protein-binding of milrinone because of the renal disease. The fraction of drug excreted in the urine was 0·705 ± 0·100 for the moderate group and 0·320 ± 0·089 for the severe group ($P < 0·001$).

These results may suggest an increase in non-renal clearance of the compound, representing a partial compensation mechanism for the reduced renal function. In conclusion, this study has confirmed that the current dose reductions recommended for the use of intravenous milrinone in CHF patients with impaired renal function will yield plasma concentrations of the drug within the therapeutic range.

Milrinone is a nonadrenergic, nonglycosidic agent that selectively inhibits peak III phosphodiesterase (Evans 1989). As a result the compound has been shown to have a positive inotropic effect upon cardiac muscle, with a direct vasodilator effect as a consequence of its action on vascular smooth muscle. The compound can, therefore, increase the force of cardiac contraction while simultaneously reducing peripheral vascular resistance (Evans 1989), unlike other agents with positive inotropic activity, such as dobutamine (Colucci et al 1986).

Milrinone is currently marketed for the short-term intravenous treatment of congestive heart failure (CHF). In patients with normal renal function, the compound is administered as an intravenous infusion between 0·375 and 0·75 $\mu g\,kg^{-1}\,min^{-1}$. To rapidly achieve therapeutic plasma concentrations (100–300 $ng\,mL^{-1}$) for a compound with a half-life of about 2 h, the maintenance infusion is normally preceded by a loading dose of 50 $\mu g\,kg^{-1}$ given over approximately 10 min.

Milrinone shows dose-independent pharmacokinetics and is largely renally excreted by both glomerular filtration and active secretion; the renal clearance has been reported to be very similar to total body clearance in normal volunteers (Stroshane et al 1984b). As a result, the pharmacokinetics of milrinone are profoundly influenced by renal failure, resulting in decreased clearance and a prolonged plasma half-life. In patients with severe renal failure, the half-life of the drug has been reported to increase to approximately three times that observed in individuals with normal renal function (Larsson et al 1986). It is, therefore, recommended that the dose of milrinone be reduced in patients with a significant degree of renal impairment.

The object of this study was to assess the current recommendations for the short-term use of milrinone in CHF patients, with moderate or severe renal impairment. Previous studies have been limited to either the intravenous treatment of volunteers with renal impairment (data on file

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at Sanofi Winthrop), or the treatment of volunteers and CHF patients with renal disease using the oral form (Larsson et al 1986). To fully evaluate the recommended dose regimens, the pharmacokinetics of the compound were determined in detail for both groups of subjects.

Materials and Methods

Materials

Milrinone and the internal standards for the plasma and urine assays were obtained from Sterling Winthrop Pharmaceuticals Research Division, Rensselaer, NY, USA. All other chemicals were of reagent grade or better and used as received. Milrinone clinical supplies were provided as an aqueous solution of the lactate salt in 20-mL ampoules ($1\,mg\,mL^{-1}$).

Study design

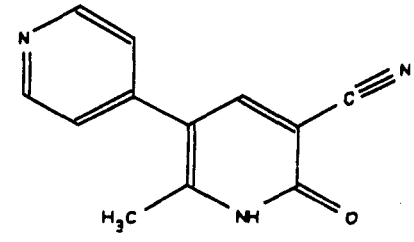
This was an open, single-centre study carried out in patients with CHF (NYHA classes I–II, n = 21) and moderate or severe renal impairment as described below. Various concomitant medications were being used by the patients who were considered stable and not in need of acute milrinone therapy: 8 severe and 9 moderate cases received single or multiple antihypertensive therapy; 3 of each group were receiving diuretic therapy; 6 of each group were receiving ACE inhibitors; 7 severe and 4 moderate cases were receiving β-blockers; one severe case was receiving an α-blocker; 3 severe and 4 moderate cases were receiving a calcium-antagonist. The subjects in this study were patient volunteers who gave their informed consent. Approval for the study was obtained both from the Ethics Committee, Faculty of Medicine, University of Lund, and the Swedish Board of Health. The demographic details of the patient population are given in Table 1.

The patients were divided into two groups based on their renal function. Those with a chromium-EDTA clearance of $31–75\,mL\,min^{-1}$ (n = 10) were classified as having moderate renal impairment and those with a clearance of $10–30\,mL\,min^{-1}$ (n = 11), with severe renal impairment. An intravenous loading dose of milrinone ($50\,\mu g\,kg^{-1}$ over 10 min) was administered not less than 1 h after a light breakfast, followed by an 18-h maintenance infusion of 0·45 or $0·35\,\mu g\,kg^{-1}\,min^{-1}$ for the moderate and severe groups, respectively. Plasma and urine samples were taken at various times up to 34 h after the start of the loading dose. The blood samples were taken from a site remote from that used for the infusion. Patients were hospitalized during the study and received standardized meals throughout the study period.

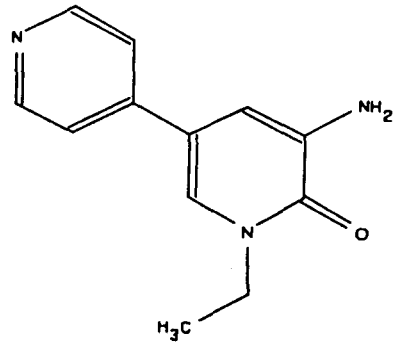
Table 1. Demographic details.

Parameter	Renal impairment	
	Moderate (n = 10)	Severe* (n = 11)
Height (m)	1·77 ± 0·07	1·80 ± 0·11
Weight (kg)	82 ± 12	77 ± 13
Age (yrs)	53 ± 12	45 ± 13
Sex	9 m/1 f	9 m/2 f
Caucasian	10	11
NYHA I	7	7
NYHA II	3	4
Chromium-EDTA clearance ($mL\,min^{-1}$)	50·6 ± 13·9	16·8 ± 3·6

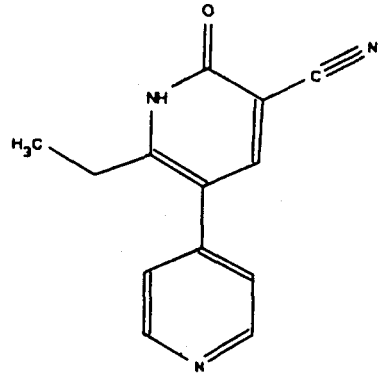
Data are given as mean ± s.d. when appropriate. * Data included for patient who showed an adverse event.



Milrinone



WIN 41417



WIN 47306

FIG. 1. Chemical structures of milrinone and internal standards.

Analysis of milrinone in plasma and urine

Plasma (1 mL) was mixed with internal standard (WIN 41417, Fig. 1) and saturated ammonium sulphate solution (0·50 mL) before centrifugation for 10 min at 3000 rev min^{-1}. The supernatant was added to 0·1 M sodium dihydrogen phosphate solution (0·5 mL, pH 4) and the mixture loaded onto a C_{18} AASP cassette, which was preconditioned with methanol, water, and 0·1 M sodium dihydrogen phosphate solution (pH 4). The cassette was then washed with water (1 mL) and inserted onto the AASP injection system (Varian, Runcorn, UK). The chromatography system comprised a Partisil ODS-3, 10 μ (25 cm × 4·6 mm i.d.) HPLC column (Jones Chromatography, Hengoed, UK), which was maintained at 40°C. The eluent was 0·1 M sodium phosphate : acetonitrile (4 : 1), which was delivered at a flow rate of 2·5 mL min^{-1}. Detection was by UV absorption at 340 nm. The AASP cartridge was eluted with mobile phase after a pre-rinse of 375 μL water.

Urine (1 mL) was mixed with internal standard (WIN 47306, Fig. 1) and 0·5 M sodium phosphate buffer (0·5 mL) before a 10-min extraction with ethyl acetate (8 mL). After centrifugation (5 min, 2000 rev min^{-1}), the compounds of interest were back-extracted from the ethyl acetate into a small volume of 0·1 M hydrochloric acid (0·4 mL). The acid was separated by centrifugation (5 min at 2000 rev min^{-1}) and any residual ethyl acetate removed under a stream of nitrogen (60°C, 20 min). Sodium phosphate buffer (0·5 M, 0·05 mL) was then added and an aliquot (0·10 mL) of the neutralized solution injected onto the HPLC system (WISP, Waters, UK). The chromatography system comprised a Merck Lichrocart guard column (RP-8e) protecting a Partisil ODS-3, 10 μ (25 cm × 4·6 mm i.d.) HPLC column (Jones Chromatography, Hengoed, UK), which was maintained at 35°C. The eluent was 0·1 M sodium phosphate buffer : acetonitrile : tetrahydrofuran (250 : 65 : 7), which was delivered at a flow rate of 1·5 mL min^{-1}. Detection was by UV absorption at 340 nm.

A weighted linear least-squares regression analysis of peak height ratio (milrinone/internal standard) vs the concentration of calibration standards was used to determine the concentration of unknowns. Validation work carried out as part of the study indicated a minimum quantifiable level of 5 ng mL^{-1} for the plasma assay and 100 ng mL^{-1} for the urine assay, with an accuracy and precision of ± 15%.

Pharmacokinetic analysis

The steady-state concentration of milrinone (C_{ss}) was determined from the individual plasma concentration–time profiles by inspection. From this, the total plasma clearance (CL_p) was determined using standard model-independent techniques (Rowland & Tozer 1980). The terminal plasma half-life ($t_{\frac{1}{2}}$) was calculated from the terminal rate constant (k_e), which was estimated by regression analysis. Using this value, the apparent volume of distribution (Vd_β) was calculated as shown in equation 1:

$$Vd_\beta = \frac{CL_p}{k_e} \quad (1)$$

The fraction of intact drug excreted in the urine (f_e) was determined according to equation 2:

$$f_e = \frac{E}{\text{Infusion rate}} \quad (2)$$

where the excretion rate at plateau (E) was determined from the mean value estimated during steady-state. The renal clearance (CL_r) was derived from E and C_{ss} using standard model-independent methods (Rowland & Tozer 1980).

Statistical analysis

Differences between the two groups were analysed using a Student's unpaired *t*-test. A modified *t*-statistic was computed using Satterthwaite's approximation when the variances for the two groups were statistically different at the 5% level (F-test for the equality of the variances). The association between pairs of variables was analysed using Pearson's correlation coefficient. Ordinary least squares was used for the regression analysis (Sokal & Rohlff 1981).

Results

After administration of the loading dose to patients with moderate renal impairment, milrinone plasma concentrations rapidly attained a steady-state level of 239 ± 71 ng mL^{-1} (mean ± s.d., n = 10). Two patients showed individual steady-state levels slightly above the therapeutic range, most likely reflecting their low renal function within the group (chromium-EDTA clearance < 40 mL min^{-1}). The total plasma clearance of milrinone was 0·122 ± 0·035 L h^{-1} kg^{-1}, with a volume of distribution of 0·443 ± 0·155 L kg^{-1}. As expected, the terminal half-life was relatively short at 2·73 ± 1·25 h. The fraction of milrinone excreted in urine was high (0·705 ± 0·100) giving a renal clearance of 0·088 ± 0·034 L h^{-1} kg^{-1} (Table 2, Fig. 2).

The plasma levels of milrinone in patients with severe renal impairment reached a mean steady-state of 269 ± 32 ng mL^{-1} (n = 10); this was not significantly different from that of the moderate group. Two patients showed values slightly above the nominal therapeutic range for milrinone but the chromium-EDTA clearances for these individuals were close to the lower range of the severe

Table 2. Pharmacokinetic parameters for milrinone after intravenous administration to patients with moderate or severe renal impairment.

Parameter	Renal impairment	
	Moderate (n = 10)	Severe (n = 10)
C_{ss} (ng mL^{-1})[a]	239 ± 71	269 ± 32
$t_{\frac{1}{2}}$ (h)	2·73 ± 1·25	6·40 ± 1·27**
CL_p (L h^{-1} kg^{-1})	0·122 ± 0·035	0·068 ± 0·009**
CL_r (L h^{-1} kg^{-1})	0·088 ± 0·034	0·022 ± 0·008**
Vd_β (L kg^{-1})	0·443 ± 0·155	0·620 ± 0·113*
f_e	0·705 ± 0·100	0·320 ± 0·089**

Data are given as mean ± s.d. One patient in the severe group was not included because of an adverse event. [a] Two patients in each group had plasma concentrations of milrinone slightly above the therapeutic range: 328 and 353 ng mL^{-1} for the moderate group and 308 and 311 ng mL^{-1} for the severe group. * $P < 0·01$, ** $P < 0·001$ compared with the values for the moderate group.

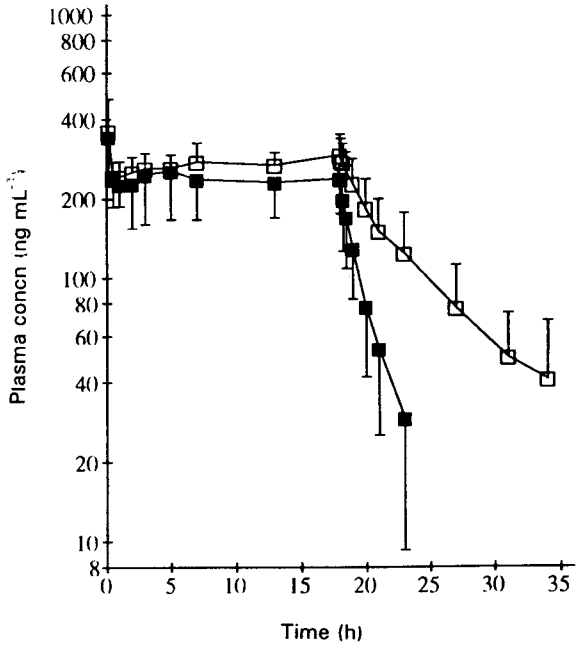


FIG. 2. Plasma concentration–time profiles for milrinone (± s.d.) after intravenous administration to CHF patients with moderate (■) or severe (□) renal impairment.

classification (<12 mL min^{-1}). The total plasma clearance in patients with severe renal impairment was 0·068 ± 0·009 L h^{-1} kg^{-1}, which was approximately half (44%) ($P < 0·001$) that observed for the moderate group. Correspondingly, the terminal half-life (6·40 ± 1·27 h) was about

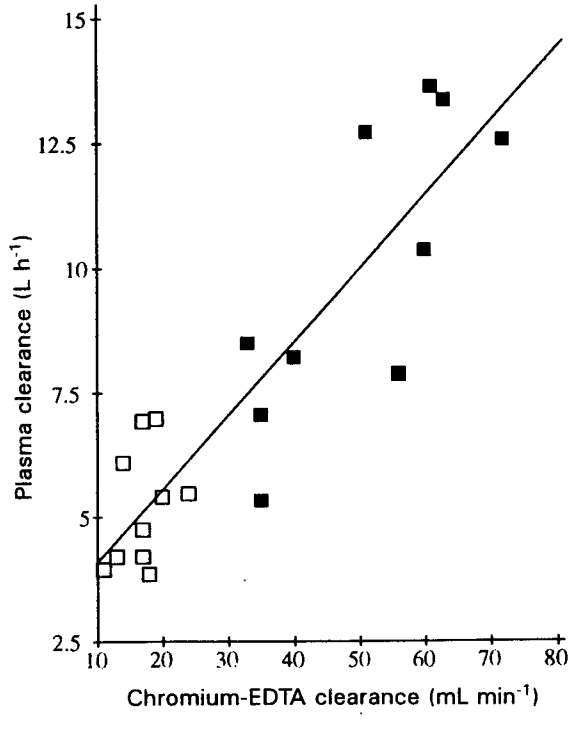


FIG. 3. Linear regression analysis of renal function (chromium-EDTA clearance) and total plasma clearance of milrinone. ■, Moderate; □, severe renal impairment. Regression equation y = 0·147x + 2·616.

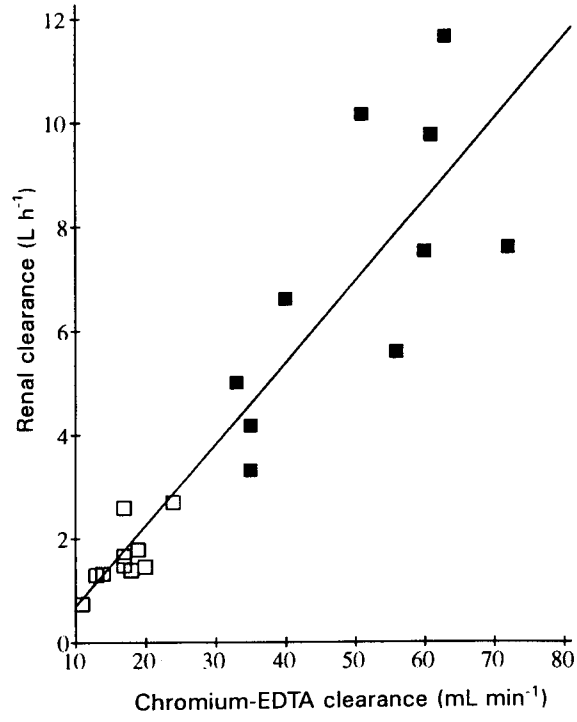


FIG. 4. Linear regression analysis of renal function (chromium-EDTA clearance) and renal clearance of milrinone. ■, Moderate; □, severe renal impairment. Regression equation y = 0·157x − 0·879.

twice ($P < 0·001$) that observed in the moderate group. The volume of distribution for milrinone in the severe group was 0·620 ± 0·113 L kg^{-1}, which was about 40% greater ($P < 0·01$) than that observed in the moderate group. The renal clearance of milrinone in the severe group (0·022 ± 0·008 L h^{-1} kg^{-1}) was approximately one-quarter ($P < 0·001$) of the value observed for the moderate group, and the fraction excreted in the urine (0·320 ± 0·089) was less than one-half ($P < 0·001$) (Table 2, Fig. 2).

High and significant correlations were observed between the degree of renal impairment and total plasma clearance, CL_p (r = 0·891, $P < 0·001$), and the renal clearance, CL_r (r = 0·912, $P < 0·001$) (Figs 3, 4).

In the severe group, one subject (male) experienced hypotension at approximately 5 h by which time his blood pressure had fallen to 60/40 mmHg. This was still present after a further hour at which point the maintenance infusion was stopped. The pharmacokinetic data generated for this subject have, therefore, not been included in the statistical analysis. At 5 h post-dose the plasma concentrations of milrinone were about 280 ng mL^{-1}, well within the therapeutic range (100–300 ng mL^{-1}). The patient made a complete recovery and was later characterized as being sensitive to vasodilatory agents. The only other reported adverse events were minor, consisting of nausea and headache.

Discussion

The mean steady-state plasma concentrations for milrinone were 239 and 269 ng mL^{-1} for the moderate and severe groups, respectively. These values were within the therapeutic range for milrinone (100–300 ng mL^{-1}) and showed no

statistically significant differences between groups. The individual values for two patients in each group were slightly above the therapeutic range, however, these individuals showed chromium-EDTA clearances relatively near to the limits of the renal impairment classifications. A correlation was not observed between these patients and any adverse events.

The pharmacokinetics of milrinone following intravenous administration to volunteers and CHF patients have been characterized using a biexponential model (Stroshane et al 1984a, b). The current data in renally impaired patients were generally consistent with such a mathematical function. In healthy volunteers, milrinone is cleared predominantly by the renal route, with over 80% of the compound being recovered in urine (Stroshane et al 1984b). The high correlation between the degree of renal impairment and parameters such as renal clearance, and total plasma clearance were consistent with this observation.

In healthy volunteers, about 12% of the milrinone dose was reported to be excreted in urine as the glucuronide (Stroshane et al 1984b). The lower urine excretion of unchanged drug observed for the severe group may, therefore, partially reflect an increased non-renal clearance of the compound. Such changes are not uncommon when the primary route of clearance has been blocked. Increases in hepatic metabolism of the normally highly renal-cleared diuretic, frusemide, have been observed in renally impaired patients (Cutler & Blair 1979).

Changes in the plasma protein-binding of a variety of both acidic and basic compounds have been reported in renal failure (Gambertoglio 1985). Milrinone is a highly plasma protein-bound drug (95–98%; data on file at Sanofi Winthrop), in which changes in binding would be expected to alter the pharmacokinetics. It is likely that the apparent difference in the distribution of milrinone between the two groups reflects a decrease in the plasma protein-binding of drug in the severely renally impaired patients. A patient with decreased plasma-protein binding should have approximately the same level of unbound drug as a normal subject, provided that the tissue binding has not altered. The total plasma concentration, however, should be less, since the unbound drug is now in equilibrium with a smaller concentration of plasma-bound material. As the volume term is calculated using total drug levels in the plasma, this results in a higher apparent volume of distribution. Similar effects were reported by Odar-Cederlof & Borga (1974) for diphenylhydantoin when administered to normal volunteers and uraemic patients.

In conclusion, this study has confirmed that the current dose reductions recommended for the use of intravenous milrinone in CHF patients with impaired renal function will yield plasma concentrations of the drug within the therapeutic range.

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