Disposition of milrinone in patients after cardiac surgery


SUMMARY
We have evaluated the disposition of milrinone in seven patients with low cardiac output after elective cardiac surgery involving cardiopulmonary bypass. Patients received a loading dose of milrinone 50 μg kg⁻¹ given over 10 min followed immediately by an infusion of 0.5 μg kg⁻¹ min⁻¹, continued for a minimum of 5 h. Plasma concentrations of milrinone were measured at designated intervals during the infusion and for 6 h after its termination, by high pressure liquid chromatography. Concentrations greater than 100 ng ml⁻¹ were produced in all patients within 2 min of starting the loading dose and were maintained for the duration of the infusion. Volume of distribution, clearance and terminal half-life were similar to those found in patients with chronic cardiac failure. (Br. J. Anaesth. 1994; 72: 426-429)

KEY WORDS

Milrinone, a bipyridine derivative, is a non-catecholamine, non-glycoside agent with positive inotropic and vasodilator properties. It is indicated clinically for use in the short-term treatment of severe chronic cardiac failure (CCF) and acute circulatory failure, including low-output states, after cardiac surgery [1]. After cardiac surgery a loading dose of milrinone 50 μg kg⁻¹ given over a period of 10 min, followed by a continuous maintenance infusion of 0.375-0.75 μg kg⁻¹ min⁻¹, has been shown to be effective in these patients. The beneficial haemodynamic effects are an increase in cardiac output, with reductions in mean pulmonary wedge pressure and systemic vascular resistance [1-4]. Although the pharmacokinetics of milrinone have been studied in human volunteers [5] and patients with CCF [6,7], they have not been described previously in patients after cardiac surgery, where changes in fluid volumes and plasma protein concentration might be expected to have an effect on the disposition of the drug.

The aims of this study were to measure the plasma concentrations of milrinone in patients with low cardiac output after cardiac surgery involving cardiopulmonary bypass (CPB), using a dose regimen shown previously to be effective clinically and to compare the derived pharmacokinetic variables in these patients with those reported in other study populations.

PATIENTS AND METHODS
After obtaining Ethics Committee approval, written informed consent was obtained from patients undergoing cardiac surgery who were considered possible candidates for postoperative inotropic support on the basis of impaired left ventricular kinetic function, as shown by angiographic assessment before operation. No patient had biochemical evidence of hepatic or renal impairment. Anaesthesia was conducted according to the preferred practice of the individual anaesthetist, with the proviso that no long-acting vasodilators or inotropic agents were allowed in the 12 h before administration of milrinone. Patients received premedication comprising an opioid drug, usually morphine, and an anti-sialogogue, usually hyoscine, 1 h before anaesthesia. Anaesthesia consisted of high-dose fentanyl analgesia, midazolam or propofol sedation and a neuromuscular blocking agent. The patients' lungs were ventilated with a Siemens Servo ventilator (C or D) before and after CPB using at least 50% oxygen in air. The pump prime for CPB consisted of 2000 ml of crystalloid with 20% mannitol 200 ml. Myocardial protection was provided with cold crystalloid cardioplegia (St Thomas' solution) or haemodiluted blood cardioplegia. Patients were cooled to 28-30°C during aortic cross-clamping. Postoperative analgesia was maintained with i.v. doses of morphine or papaveretum.

Seven adult patients (three male) who needed inotropic support (cardiac index ≤ 2.0 litre min⁻¹ m⁻² with a pulmonary capillary wedge pressure ≥ 10 mm Hg) after cardiac surgery (two myocardial revascularization and five valve replacement operations) were enrolled in the study. Patient data are presented in table I. An i.v. loading dose of milrinone 50 μg kg⁻¹ was given over 10 min followed immediately by an i.v. infusion of 0.5 μg kg⁻¹ min⁻¹ for a minimum of 5 h. During the infusion...
of milrinone, no other drug with inotropic, vasodilator or vasoconstrictor activity was allowed and, in particular, no patient received dopamine. Patients remained sedated and their lungs were ventilated for the duration of the infusion of milrinone.

After removal of the deadspace from the arterial cannula, arterial blood samples (10 ml) were obtained in lithium heparin bottles at 2-min intervals during the loading dose (10 min), at 15, 30, 45, 60, 90, 120 min and hourly thereafter during the infusion. The arterial cannula was flushed thoroughly between samples. After stopping the infusion, samples were obtained at 15, 30, 60, 120, 180, 240, 300 and 360 min. All the samples were centrifuged at 3000 rpm for 5 min, the plasma separated and stored at \(-20^\circ\text{C}\). Sterling Winthrop Research Centre (Alnwick, Northumberland, U.K.) analysed the plasma samples for parent drug using a validated solid phase extraction high pressure liquid chromatography (HPLC) technique with a minimum concentration of 5 ng ml\(^{-1}\). The precision and accuracy of the assay were determined to be within \(\pm 15\%\).

The plasma concentration-time data for each patient were plotted on semi-logarithmic paper. Based on the known half-life of 0.8 h in healthy volunteers [5], steady state conditions would be produced after approximately 3.2 h (four half-lives). To ensure steady state conditions had been attained in our study, milrinone was infused for at least 5 h and longer if indicated clinically. The milrinone plasma concentration immediately before termination of the infusion was used as the “plasma concentration at steady state” in the calculations. Clearance (\(Cl\)) was derived from the equation

\[
Cl = \frac{\text{Infusion rate}}{\text{Plasma concentration at steady state}}
\]

After stopping the milrinone infusion, the post-infusion decrease to less than a plasma concentration of 100 ng ml\(^{-1}\) was examined. Regression analysis was used to determine the elimination rate constant (\(k\)) using the Lotus 123W program on an IBM-compatible computer. The initial elimination half life (\(T_1/2\)) was then calculated from the equation

\[
T_1/2 = \frac{0.693}{k}
\]

Volume of distribution (\(Vd\)) was derived from the formula

\[
Vd = \frac{Cl}{k}
\]

RESULTS

Seven patients were recruited (table I) and plasma samples analysed. However, in one patient because of a technical error, the milrinone infusion was given
at a sub-therapeutic dose. The remaining six sets of data were analysed.

Plasma concentrations of milrinone exceeded 100 ng ml\(^{-1}\) within 2 min of starting the loading dose (fig. 1) and were maintained above this concentration for the duration of the infusion (fig. 2). The post-infusion decrease in the concentration of milrinone for each patient is shown in figure 3. The derived kinetic variables for milrinone are shown in table II.

**DISCUSSION**

Table I shows that all our patients weighed less than 70 kg and as such this represents a group of relatively small adults. This would not be expected to influence the results to any great extent, however. The majority of patients in our study presented with valvular lesions and this group might be expected to have a degree of heart failure, but none of our patients had uncontrolled congestive cardiac failure. The addition of crystalloid and blood is based usually on blood haemoglobin, haemocrit and arterial and venous pressure measurements rather than volume measurements. Because of these fluid fluxes, patients often have a residual excess fluid load after cardiac surgery, a situation similar to that in patients who have CCF. Previous studies have shown that patients with CCF given milrinone have a similar V\(\text{d}\) to healthy volunteers but reduced Cl and prolonged \(T_1\) [5-7]. Our derived kinetic variables indicate that patients with low cardiac output after cardiac surgery have a similar disposition of milrinone as patients with CCF (table III).

In conclusion, we have shown that in patients with low cardiac output after cardiac surgery, i.e. milrinone given as a loading dose of 50 \(\mu\)g kg\(^{-1}\) followed by an infusion of 0.5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) achieves effective

**TABLE II. Individual derived kinetic variables for milrinone.**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Infusion rate (ng min(^{-1}))</th>
<th>Concentration (ng ml(^{-1}))</th>
<th>(Cl) (ml min(^{-1}))</th>
<th>(Conc_{ss}) (litre kg(^{-1}) h(^{-1}))</th>
<th>(Vd) (litre kg(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30000.00</td>
<td>298.71</td>
<td>100.43</td>
<td>0.10</td>
<td>1.70</td>
</tr>
<tr>
<td>2</td>
<td>27250.00</td>
<td>179.63</td>
<td>151.70</td>
<td>0.17</td>
<td>1.75</td>
</tr>
<tr>
<td>3</td>
<td>27000.00</td>
<td>228.43</td>
<td>118.20</td>
<td>0.13</td>
<td>1.55</td>
</tr>
<tr>
<td>4</td>
<td>32000.00</td>
<td>166.43</td>
<td>195.28</td>
<td>0.18</td>
<td>1.96</td>
</tr>
<tr>
<td>5</td>
<td>32500.00</td>
<td>388.26</td>
<td>83.71</td>
<td>0.08</td>
<td>1.71</td>
</tr>
<tr>
<td>6</td>
<td>23000.00</td>
<td>307.76</td>
<td>74.73</td>
<td>0.10</td>
<td>1.45</td>
</tr>
<tr>
<td>7</td>
<td>No post-infusion data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td>0.13</td>
<td>1.69</td>
</tr>
</tbody>
</table>

**TABLE III. Comparison of the results of the present study with previous studies of disposition variables for milrinone.**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. patients</th>
<th>Condition</th>
<th>Study type</th>
<th>(Cl) (litre kg(^{-1}) h(^{-1}))</th>
<th>(Vd) (litre kg(^{-1}))</th>
<th>(T_1) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benotti [6]</td>
<td>13</td>
<td>CCF</td>
<td>Bolus 12.5-75 (\mu)g kg(^{-1})</td>
<td>0.15</td>
<td>0.35</td>
<td>1.70</td>
</tr>
<tr>
<td>Edelson [7]</td>
<td>26</td>
<td>CCF</td>
<td>Bolus 12.5-125 (\mu)g kg(^{-1})</td>
<td>0.11</td>
<td>0.38</td>
<td>2.3</td>
</tr>
<tr>
<td>Stroshane [5]</td>
<td>39</td>
<td>Volunteers</td>
<td>Infusion 0.2-0.7 (\mu)g kg(^{-1}) min(^{-1})</td>
<td>0.14</td>
<td>0.47</td>
<td>2.6</td>
</tr>
<tr>
<td>Present study</td>
<td>6</td>
<td>Cardiac patients</td>
<td>Bolus 10-125 (\mu)g kg(^{-1})</td>
<td>0.36</td>
<td>0.32</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ infusion 0.5 (\mu)g kg(^{-1}) min(^{-1})</td>
<td>0.13</td>
<td>0.31</td>
<td>1.69</td>
</tr>
</tbody>
</table>
plasma concentrations within 2 min which are sustained for the duration of the infusion. The disposition variables $C_l$, $V_d$ and $T_1/2$ are similar to those found in patients with CCF.

ACKNOWLEDGEMENTS
The authors thank Sanofi Winthrop Limited for the supply of milrinone and Sterling Winthrop Research Centre for carrying out the drug assays.

REFERENCES