Pharmacokinetics and dynamics of famotidine in patients with renal failure

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Famotidine, a new histamine H₂-receptor antagonist was administered intravenously (20 mg) to 22 patients with end stage renal disease during a dialysis free interval (n = 6) and during different blood purification processes including haemodialysis (HD; n = 4), intermittent haemofiltration (HF; n = 4), continuous haemofiltration (CHF; n = 4) and continuous ambulatory peritoneal dialysis (CAPD; n = 4). The plasma, the dialysate/ filtrate and the urine concentrations of famotidine were analysed by h.p.l.c.

In addition, intra-gastric pH was measured by a long-term-pH probe in seven patients with renal failure and in six patients with normal renal function (control group) following 20 mg famotidine.

A 7 to 10 fold prolongation of famotidine’s elimination half-life (27.2 ± 8.5 h; mean ± s.d.) was observed in patients with renal failure as compared with the half-life (2.6-3.6 h) in subjects with normal renal function.

Total body clearance (CL) and volume of distribution (V) were found to be 33.5 ± 10.1 ml min⁻¹ and 1.3 ± 0.71 kg⁻¹, respectively in patients with end-stage renal failure.

Blood purification processes have shown considerable variation in clearing famotidine from the body: 16.4 ± 8.9 and 6.0 ± 2.9% of the administered dose in HD with polysulphone and cuprophan membranes respectively, 7.7 ± 5.2% in HF with a polyacrylonitrile membrane (each for 5 h), 4.5 ± 1.1% in CAPD and 16.2 ± 4.9% in CHF with a polysulphone membrane within 24 h.

In patients with renal failure a reduction in the normal dose of famotidine is strongly recommended but there is no need to supplement the dose after any of the blood purification processes studied.

The pharmacodynamic investigation showed a twofold prolongation in the duration of acid suppression in patients with renal failure as compared with patients with normal renal function.

Keywords famotidine renal failure pharmacokinetics pharmacodynamics blood purification

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Introduction

Many investigations have documented that the increased incidence of peptic ulcer and gastrointestinal bleeding in patients with renal insufficiency is partly due to the hypersecretion of gastrin and hydrochloric acid (Goldstein et al., 1967; Ritz et al., 1971; Venkateswaran et al., 1972; Shepherd et al., 1973; Milito et al., 1983, 1985).

Histamine H2-receptor antagonists are most commonly used for the treatment of peptic ulcers. Famotidine, a relatively new drug, is approximately six times more potent than ranitidine and 30 times more potent than cimetidine (on a molar basis) in suppressing acid secretion. Following i.v. administration in normal subjects about 72% of a dose is excreted unchanged with a renal clearance of about 222 to 304 ml min⁻¹, exceeding the glomerular filtration rate (Takabatake et al., 1985; Kroemer & Klotz, 1987). This suggests that tubular secretion plays a predominant role in the renal elimination of famotidine. The plasma half-life and steady state volume of distribution in normal subjects have been reported to be 2.6 to 3.6 h and 1.13 to 1.14 l kg⁻¹, respectively. The half-life is prolonged in patients with kidney failure and total body clearance (CL) depends on renal function (Takabatake et al., 1985; Kroemer & Klotz, 1987).

In view of the low molecular weight (337.4 Dalton) and low plasma protein binding of famotidine (about 15%, Kroemer & Klotz, 1987) it is possible that a great part of the dose could be removed by extracorporeal methods of blood purification. The trials of Takabatake et al. (1983) and Halstenson et al. (1986) revealed that the half-life in renal patients undergoing dialysis was about four times (six times in case of dialysis-free patients) longer than in subjects with normal kidney function. One may anticipate that such a reduced elimination may lead to accumulation of the drug in the body and may produce adverse effects. Therefore, it seems important and clinically relevant to investigate in renal insufficiency the pharmacokinetics and dynamics of this drug which is essentially eliminated by the renal route and to see whether its disposition is affected by different blood purification processes.

Methods

Patients and protocol

Twenty-six patients (17 males and 9 females) in the age range of 24–73 (average 50) years with acute renal failure or with end stage renal disease (ESRD) were included in the study after obtaining their informed consent. The study was in accordance with the declaration of Helsinki (1964) as revised in Tokyo (1975). Depending on the degree of renal failure and the blood purification process, the patients were divided into five groups (Table 1). In addition, six patients (four males and two females) with normal renal function served as a control group in the pharmacodynamic study.

All patients received 20 mg famotidine by intravenous bolus. The pharmacokinetics were studied in two groups of patients. Groups 1 and 2 consisted of patients during a dialysis free interval and while undergoing CHF respectively. The details of the different blood purification processes are given in Table 2. CHF was performed for a total period of 9 to 38 h. In groups 1 and 2, venous blood samples were collected from the patients at 0.25, 0.5, 1, 2, 3, 6, 12, 24 and 48 h following drug administration. CAPD for 24 h was performed in patients of group 3. All subjects were considered to be stable CAPD patients who had been without evidence of peritonitis for a minimum of 2 months. Each subject underwent four daily exchanges with a volume of 2.0 l each. Famotidine was administered at the beginning of the dialysis. Blood specimens were taken after 4, 8, 12 and 24 h of starting the process, additional samples being taken from each effluent bag. Samples were obtained from the urine collected over periods of 0–12, 12–24, 24–48 and 48–72 h. In patients of groups 4 and 5 HD (with two different dialyzers in a cross over design) and HF were performed respectively and famotidine was administered 4 h before starting the process. Blood samples were taken from the arterial blood line at the beginning and end of HD and at the beginning, during and after stopping HF. Filtrate/dialysate samples were collected at different stages of every process. Since the measurement of drugs is made difficult because some hundred litres of dialysate have to be collected, a dialysate divider was used which split off the flowing dialysate stream in a ratio 1:10. The smaller part was collected during dialysis whereas the larger part was discarded (Schäfer et al., 1986).

Famotidine assay

All samples were stored at −20°C until analysed. Famotidine in plasma, dialysates/filtrates and urine (suitably diluted in 0.067 m phosphate buffer of pH 7.4) was measured by the h.p.l.c. method of Kroemer & Klotz, (1987) with some modifications. The modifications were as follows.
## Table 1 Clinical characteristics of the patients studied

<table>
<thead>
<tr>
<th>Patient (sex)</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Hct (%)</th>
<th>Albumin (g l(^{-1}))</th>
<th>CL(creat) (ml min(^{-1}))</th>
<th>Dialysed since (months)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HG(m)</td>
<td>60</td>
<td>76</td>
<td>26</td>
<td>48</td>
<td>3</td>
<td>3</td>
<td>3 Goodpasture-syndrome</td>
</tr>
<tr>
<td>MB(f)</td>
<td>63</td>
<td>61</td>
<td>25</td>
<td>51</td>
<td>3</td>
<td>8</td>
<td>Chronic glomerulonephritis</td>
</tr>
<tr>
<td>US(f)</td>
<td>24</td>
<td>52</td>
<td>30</td>
<td>79</td>
<td>0</td>
<td>69</td>
<td>Chronic pyelonephritis</td>
</tr>
<tr>
<td>RL(f)</td>
<td>52</td>
<td>66</td>
<td>22</td>
<td>50</td>
<td>5</td>
<td>63</td>
<td>Analgesic nephropathy</td>
</tr>
<tr>
<td>KP(m)</td>
<td>62</td>
<td>64</td>
<td>29</td>
<td>51</td>
<td>0</td>
<td>38</td>
<td>Polycystic renal disease</td>
</tr>
<tr>
<td>MU(f)</td>
<td>61</td>
<td>43</td>
<td>31</td>
<td>70</td>
<td>0</td>
<td>102</td>
<td>Polycystic renal disease</td>
</tr>
</tbody>
</table>

1. **Kinetic study (during dialysis free interval):**

   - HG(m): Goodpasture-syndrome
   - MB(f): Chronic glomerulonephritis
   - US(f): Chronic pyelonephritis
   - RL(f): Analgesic nephropathy
   - KP(m): Polycystic renal disease
   - MU(f): Polycystic renal disease

2. **Kinetic and excretion study (during CHF):**

   - GR(m): Acute renal failure

3. **Excretion study (during CAPD):**

   - KE(m): Chronic glomerulonephritis
   - HT(m): Diabetic nephropathy

4. **Excretion study (during HD):**

   - HB(m): Chronic glomerulonephritis
   - RG(m): Diabetic nephropathy
   - WL(m): Chronic glomerulonephritis
   - MH(m): Mesangio proliferative glomerulonephritis

5. **Excretion study (during HF):**

   - GR(f): Acute renal failure
   - MD(f): Polycystic renal disease
   - HS(f): Analgesic nephropathy
   - KW(f): Chronic pyelonephritis

## Table 2 Methods of blood purification

<table>
<thead>
<tr>
<th></th>
<th>CHF</th>
<th>CAPD</th>
<th>HD</th>
<th>HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (h)</td>
<td>24.3 (mean)</td>
<td>24</td>
<td>5</td>
<td>4.2 (mean)</td>
</tr>
<tr>
<td></td>
<td>20 l filtrate</td>
<td></td>
<td>50</td>
<td>109</td>
</tr>
<tr>
<td>QB (ml min(^{-1}))</td>
<td>50</td>
<td>10-15</td>
<td>6</td>
<td>500</td>
</tr>
<tr>
<td>QD;QF (ml min(^{-1}))</td>
<td>50</td>
<td>10-15</td>
<td>6</td>
<td>500</td>
</tr>
<tr>
<td>Membrane (area in m(^2))</td>
<td>polysulphone (1.35)</td>
<td>peritoneum (a) cuprophan(^\circ) (1.3)</td>
<td>polycrylonitrile (1.4)</td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td>Ultraflux AV600</td>
<td>(b) Hemoflow F60</td>
<td>(a) BL 613/H</td>
<td>PAN 200</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Fresenius AG</td>
<td>(b) Belco</td>
<td>Asahi Medical</td>
<td>Tokyo, Japan</td>
</tr>
<tr>
<td></td>
<td>Oberursel, FRG</td>
<td>Mirandola, Italy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Q\(_B\) = blood flow maintained by pump
Q\(_D\) = dialysate flow
Q\(_F\) = filtrate flow
Metiamide, instead of cimetidine was used as the internal standard (1.0 μg ml⁻¹). The eluate from the silica gel column (Baker system) was dried under N₂ at 40°C and the residue was dissolved in NaHCO₃ (50 mM). Subsequently it was extracted with ethylacetate (4 ml). The separated organic phase was evaporated under N₂ at 40°C. The residue was dissolved in ethylacetate (100 μl) and 80 μl were injected into the h.p.l.c. system. The lower limit of sensitivity of the method was 10 to 25 ng ml⁻¹ in plasma and dialysate/urine, respectively. The coefficients of variation of the assays were 5.5 and 8.2%, respectively.

Calculation of kinetic parameters

The primary pharmacokinetic parameters (C₁, C₂, λ₁, λ₂) in subjects of groups 1 and 2 were computed after fitting the plasma concentration-time data by a two-compartment open model using a non linear least squares regression program (Peck & Barrett, 1979). The distribution and terminal half-lives were calculated from the equations 0.693/λ₁ and 0.693/λ₂, respectively.

The total body clearance and volume of distribution were calculated from the equations CL = Dose/AUC and V = (k₁₂ + k₂₁) V₁/k₂₁. The area under plasma concentration-time curve (AUC) was calculated by the trapezoidal rule to the last measured plasma concentration (Cₙₐₙ) and then extrapolated to infinity by the term Cₙₐₙ/λ₂. The terms k₁₂, k₂₁ and V₁ were calculated using the primary parameters (Wagner, 1975). The plasma half-life in CAPD, HD and HF subjects was calculated from the log-linear slope by least squares regression.

Pharmacodynamics

The gastric acid suppression induced by famotidine was studied in seven patients with renal failure and in six patients with normal renal function by a long-term pH probe. The intragastric pH was monitored by a long-term-pH meter (Digitrapper MK II, Synectics Medical) which measures H⁺ activity for more than 24 h. An antimony electrode was inserted trans-nasally into the gastric corpus and remained there for 24 to 48 h. The patients were asked to record their activities during pH-measurement so that these factors could be taken into account at the time of data interpretation.

Statistical analysis

Student’s t-test was applied to compare the means of % dose removed between the two short term methods (HD vs HF) and between the two long term methods (CAPD vs CHF) and to compare the means of pharmacokinetic parameters between groups 1 and 2. In all these tests significance levels P of < 0.05 were used.

Results

Figure 1 shows the plasma concentrations of famotidine in the renal patients during dialysis-free intervals. The plasma concentrations in patients undergoing CHF, declined with a significantly (P < 0.05) shorter terminal half-life. The distribution half-life in dialysis-free patients was nearly the same as in patients treated by CHF. The plasma clearance in patients undergoing

![Figure 1](image-url)  
**Figure 1**  Plasma concentrations of famotidine after a single i.v. bolus (20 mg) in six patients with ESRD, during a dialysis-free interval.
CHF was significantly ($P < 0.05$) higher than in untreated patients. No marked difference in the volume of distribution was observed between the two groups (see Table 3).

The mean ± s.d. values for apparent half-life, amount and percentage of dose removed during CAPD, HD and HF are given in Table 4. There was residual kidney function in all the patients undergoing CAPD (see Table 1) and the amount of drug excreted in the 24 h urine was significantly ($P < 0.05$) higher than the amount removed extracorporeally. In addition, the amount cleared by CAPD was significantly ($P < 0.05$) lower than the amount removed by CHF over a period of 24 h (see Table 4). In patients undergoing HD, the dialyzer with polysulphone membrane was able to remove significantly ($P < 0.05$) larger amounts of drug than that using the cuprophan membrane. The amount of famotidine that could be removed within 5 h (extrapolated) in HF was nearly the same as that in HD with cuprophan. With respect to the pharmacodynamic activity of famotidine, it was observed that a gastric pH of 4 was reached after 94 ± 34 min in the patients with renal failure and after 39 ± 8 min in the subjects with normal renal function ($P < 0.002$). The pH remained above this level in the two groups for 19 ± 1 h ($n = 3$) and 9 ± 3 h, respectively (see Figure 2). In 4 of 7 renal subjects the pH remained above 4 for more than 24 h.

**Discussion**

The study of Takabatake et al. (1985) on the disposition of famotidine in patients with renal failure revealed that with decreasing creatinine clearance the half-life of famotidine was significantly prolonged. This is supported by our finding in patients with a creatinine clearance less than 5 ml min$^{-1}$. From the kinetic study we observed that the half-life in some patients was longer than 24 h, which is relatively higher than the reported value of 13.7 h (Takabatake et al., 1985) for patients with similar creatinine clearance. We also noticed a significant reduction in the half-life and an increase in the clearance of famotidine in patients undergoing CHF compared with patients in dialysis free interval. The fact that only about 16% of the dose (72% in subjects with normal renal function) could be removed in 24 h by CHF explains why the $t_{1/2}$ and clearance are not close to the values reported in patients with normal renal function.

A comparison of different blood purification processes revealed that among the two long-term processes CHF was more efficient than CAPD in clearing famotidine. On the other hand amongst the short-term processes HD with the high flux membrane polysulphone was superior to HD with standard cuprophan. The lower removal of famotidine by HF is explained by the fact that in this case a filtration rate of only 85 ml min$^{-1}$ could be achieved (see Table 2). Factors, such as the creatinine clearance of the dialyzer or haemofilter, the selectivity of the membrane towards the size of the molecule and blood flow rate, are probably responsible for the differences observed. The relatively low blood flow rate (50 ml min$^{-1}$) and the low creatinine clearance (10 ml min$^{-1}$) are probably responsible for a five-fold increase in $t_{1/2}$ in patients undergoing CHF as compared with subjects with normal renal function. The volume of distribution in dialysis free patients and patients undergoing CHF did not differ significantly from that in subjects with normal kidney function. These findings are in agreement with those of Takabatake et al. (1986). Similar results have been reported for the clearance of other H$_2$-receptor antagonists including cimetidine and ranitidine, which are also primarily eliminated by the kidney (77 and 70% of the dose respectively). In renal failure the half-life is prolonged 2 to 3 fold for cimetidine (Jones et al., 1979) and 4 to 5 fold for ranitidine (Garg et al., 1983). Based on the extent of extra-

**Table 3** Pharmacokinetic parameters (mean ± s.d.) of famotidine in patients with renal failure during a dialysis free interval ($n = 6$) and during CHF ($n = 4$)

<table>
<thead>
<tr>
<th>Study in</th>
<th>Distribution</th>
<th>Terminal</th>
<th>Clearance</th>
<th>Volume of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis</td>
<td>$t_{1/2}$ (h)</td>
<td>$t_{1/2}$ (h)</td>
<td>(ml min$^{-1}$)</td>
<td>distribution</td>
</tr>
<tr>
<td>free interval</td>
<td>0.37 ± 0.13</td>
<td>27.2 ± 8.5</td>
<td>33.5 ± 10.1</td>
<td>1.30 ± 0.70</td>
</tr>
<tr>
<td>CHF patients</td>
<td>0.50 ± 0.34</td>
<td>13.7 ± 5.6</td>
<td>60.1 ± 15.5</td>
<td>1.24 ± 0.84</td>
</tr>
</tbody>
</table>
Table 4  Apparent half-life ($t_{1/2}$), amount ($Ae$) and % of dose excreted (% $Ae$) in dialysate/filtrate or in urine (mean ± s.d.) in patients during intermittent treatment (HD, $n = 4$ and HF, $n = 4$) or continuous treatment (CAPD, $n = 4$ and CHF, $n = 4$) dialysis/filtration processes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Membrane</th>
<th>$t_{1/2}$ (h)</th>
<th>$Ae$ (mg)</th>
<th>$Ae$ (removed) % of dose</th>
<th>% $Ae$ (in urine) in 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intermittent treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5 h)</td>
<td>Polysulphone</td>
<td>7.5 ± 3.5</td>
<td>3.3 ± 1.8</td>
<td>16.4 ± 8.9</td>
<td>-</td>
</tr>
<tr>
<td>HD</td>
<td>Cuprophan</td>
<td>11.4 ± 9.7</td>
<td>1.2 ± 0.6</td>
<td>6.0 ± 2.9</td>
<td>-</td>
</tr>
<tr>
<td>HF</td>
<td>Polyacrylonitrile</td>
<td>10.4 ± 5.7</td>
<td>1.3 ± 0.7</td>
<td>7.7 ± 5.2 (extrapolated to 5 h)</td>
<td></td>
</tr>
<tr>
<td><strong>Continuous treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(24 h)</td>
<td>Peritoneum</td>
<td>15.5 ± 4.0</td>
<td>0.9 ± 0.2</td>
<td>4.5 ± 1.1</td>
<td>13.3 ± 8.8</td>
</tr>
<tr>
<td>CHF</td>
<td>Polysulphone</td>
<td>13.7 ± 5.6</td>
<td>3.0 ± 1.1</td>
<td>16.2 ± 4.9</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 2  24 h pH-profile in two typical patients following an i.v. bolus of 20 mg famotidine. (a) patient with renal failure and (b) subject with normal renal function; —— following famotidine administration; ——— control pH measurement without drug.

corporeal clearance cimetidine has been categorised as a slightly dialysable (5 to 20%) drug (Knoben & Anderson, 1983). A recent report on the peritoneal clearance of ranitidine revealed that only 1.3 and 0.9% of the administered dose was removed by CAPD over a period of 20 h following intravenous and oral routes, respectively (Sica et al., 1987).

The observed prolongation in the duration of action of famotidine in patients with ESRD as compared with subjects with normal renal function, could be attributed to decreased elimination.

Mann et al. (1984), Brodde & Daul (1984) and Daul et al. (1984) reported that an altered sensitivity of adrenergic receptors and a reduced c-AMP activity are observed in patients with ESRD. Such disease induced modifications in the c-AMP messenger system might be one explanation for the observed delay in the onset of action in these patients. However, in the present study it could be also due to a raised acid pool in renal patients (Ventkateswaran et al., 1972; Shepherd et al., 1973; Milito et al., 1985).

In conclusion, in view of the low extracorporeal clearance famotidine may be regarded as a slightly dialysable and filterable drug. In patients with severe renal failure a reduction of the normal dose to one third is recommended and patients undergoing dialysis/filtration do not require a dosage supplementation after the treatment.
References


(Received 17 November 1987, accepted 10 May 1988)