

Saturable Urinary Excretion Kinetics of Famotidine in the Dog

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Abstract

An important elimination route of the histamine H₂ antagonist famotidine is active tubular secretion via the renal organic cation transport system. To characterize the excretion kinetics of famotidine in-vivo, the relationship between plasma concentration and urinary excretion rate was investigated in the beagle dog over a wide concentration range. The maximum transport capacity and the apparent Michaelis–Menten constant of tubular secretion were estimated.

Concentration-dependent renal clearance was determined either after intravenous infusion of high doses of famotidine for a short time or during continuous infusion. From individual experiments only indications of saturation were observed; these could not be quantified. A tubular titration curve, in which the active tubular famotidine secretion was plotted against the plasma concentration, was constructed from the data from all the experiments. Active tubular secretion was calculated for each experiment separately by subtracting the famotidine filtration rate from the total excretion rate. A tubular transport maximum of $2400 \pm 220 \mu\text{g min}^{-1}$ and an apparent Michaelis–Menten constant for tubular secretion of $26 \pm 4 \mu\text{g mL}^{-1}$ ($76 \pm 12 \mu\text{M}$) were estimated from the curve.

To the best of our knowledge, this is the first time that saturation of famotidine renal clearance has been fully quantified in-vivo. Considering the low therapeutic plasma concentrations of famotidine ($< 0.1 \mu\text{g mL}^{-1}$), these results suggest that clinically the drug has a low interactive potential.

Famotidine, a relatively new histamine H₂ antagonist, is commonly used for the treatment of peptic ulcers. Famotidine is approximately eight times more potent than ranitidine and thirty times more potent than cimetidine at inhibiting gastric acid secretion. The therapeutic dosing regimen of 40 mg day^{-1} , resulting in a plasma concentration of $10\text{--}100 \text{ ng mL}^{-1}$, is much lower than that of either cimetidine or ranitidine. After intravenous administration in man, $10\text{--}28\%$ of the drug is weakly bound to plasma proteins and approximately 70% is excreted unchanged in the urine. The renal clearance of approximately 250 mL min^{-1} clearly exceeds the glomerular filtration rate, and famotidine is, therefore, considered to be excreted by active tubular secretion (Echizen & Ishizaki 1991). Because famotidine is a weak base, it is secreted by the tubular organic cation transport system and its inhibitory potency against cationic drug transport has been determined in various in-vitro studies. Although famotidine seems to be a potent inhibitor of renal organic cation transport, comparable with cimetidine, whereas both nizatidine and ranitidine are less potent (Bendayan et al 1990; Boom et al 1992; Boom & Russel 1993; Somogyi et al 1994; David et al 1995), there seems to be a discrepancy between data obtained in cellular and subcellular preparations and those obtained by studies at the organ level. In the isolated perfused rat kidney, cimetidine and ranitidine were equipotent in inhibiting triamterene clearance, whereas famotidine was less potent (Muirhead & Somogyi 1991). In in-vivo studies in rats, it was shown that cimetidine inhibited the tubular secretion of famotidine, but that famotidine could not reduce the renal clearance of cimetidine (Lin et al 1988).

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To characterize the excretion kinetics of famotidine in-vivo, the relationship between plasma concentration and active renal clearance was investigated in the beagle dog. The purpose of this study was to estimate the maximum transport capacity and the apparent Michaelis–Menten constant of tubular secretion. To the best of our knowledge, this is the first study in which these kinetic parameters have been determined for famotidine.

Materials and Methods

Materials

Famotidine was generously donated by MSD Research Laboratories (Rahway, USA) and famotidine powder for injection (Pepcidin) was obtained from MSD (Haarlem, The Netherlands). Braunule-T cannulas were obtained from Braun (Melsungen, Germany), the double-walled urinary catheter from Talas (Ommen, The Netherlands), and Visking 8 dialysis tubing from Instrumentenhandel Z. H. (The Hague, The Netherlands). Sodium pentobarbital was from Apharma (Arnhem, The Netherlands), heparin from Organon (Oss, The Netherlands), and atropine sulphate and mannitol were from OPG (Utrecht, The Netherlands). Hydrochloric acid (32%, analytical reagent) was from Baker (Deventer, The Netherlands) and 1-heptanesulphonic acid from Janssen Chimica (Geel, Belgium). All other chemicals were of reagent grade and obtained from either Sigma (St Louis, MO) or Merck (Darmstadt, Germany). Vac Elut manifold and Bond Elut C₁₈ columns (1 mL capacity) were from Analytichem (Habor City, CA).

Dogs

Male beagle dogs, 2–3 years old, were obtained from the Central Animals Laboratory of the University of Nijmegen.

The dogs were housed individually with free access to tap water. They were fed once daily with a commercially available diet.

Clearance experiment

The clearance experiments were performed as described in detail elsewhere (Russel et al 1987). Briefly, male beagle dogs, 13 to 16 kg, were anaesthetized by intravenous administration of sodium pentobarbital (30 mg kg^{-1}) with atropine sulphate (0.5% , 1 mL) as premedication. Both cephalic veins were cannulated (Braunule T, length 50 mm , $1.0 \text{ mm o.d.} \times 1.5 \text{ mm i.d.}$) for blood sampling and drug administration. A constant infusion of 5% mannitol and 0.5% inulin (2 mL min^{-1}) was administered to obtain a sufficiently high urine flow and for determination of the glomerular filtration rate. During the experiment, body temperature and heart rate were monitored continuously. Famotidine (Pepcidin) was administered intravenously either for a short time or as a continuous infusion. Blood samples (7 mL) were taken at regular intervals into heparinized tubes and plasma was separated by centrifugation for 6 min at 2000 g . Urine was collected quantitatively by use of a double-walled urinary catheter by rinsing the bladder at the end of each collection interval with $10 \text{ mL } 0.9\% \text{ NaCl}$ (saline). Plasma and urine samples were stored at -20°C until analysis. The dogs were left to recover for at least three weeks before being used again.

Analytical methods

Famotidine was analysed by high-performance liquid chromatography (HPLC). The Spectra Physics Analytical (Eindhoven, The Netherlands) system used consisted of a P2000 binary gradient pump, an AS3000 autosampler with built-in column heater, a model UV1000 variable-wavelength detector set at 228 nm and an SP4400 integrator. Separation was performed on a $125 \times 4 \text{ mm i.d.}$ stainless-steel column and a $4 \times 4 \text{ mm i.d.}$ guard column packed with $5 \mu\text{m}$ LiChrospher 60 RP-select B (Merck, Germany). The mobile phase was $10:90$, v/v, acetonitrile– 0.02 M , pH 3.0 phosphate buffer containing 1.0 g L^{-1} heptanesulphonic acid. The flow rate was 1 mL min^{-1} , the column temperature 40°C and the autosampler temperature 4°C .

Famotidine and procaine (internal standard) were separated from plasma with bonded silica solid-phase extraction columns (Bond Elut C_{18} , 1 mL capacity). The plasma samples were pre-treated by adding 1.0 mL of 0.01 M sodium carbonate solution containing $5 \mu\text{g}$ internal standard (procaine) to 1.0 mL of plasma. After vortex-mixing, the sample was loaded on to extraction columns previously conditioned with methanol ($3 \times 1 \text{ mL}$) then 0.01 M sodium bicarbonate solution ($3 \times 1 \text{ mL}$). The pre-treated plasma samples were passed through the column, which was subsequently washed with 0.01 M sodium bicarbonate solution (5 mL). Famotidine and procaine were eluted from the column with $40:60$, v/v, methanol– 0.01 M , pH 5.0 citric acid (1 mL) and $20 \mu\text{L}$ was injected on to the column. Under these conditions the retention times of famotidine and internal standard were 6.5 and 13 min , respectively.

Urine samples were pre-treated by adding sodium carbonate solution (0.01 M ; $900 \mu\text{L}$) containing internal standard (procaine; $5 \mu\text{g}$) to urine ($100 \mu\text{L}$). The urine samples were extracted in the same way as the plasma samples except that

the column was washed with 10 mL of 0.01 M sodium bicarbonate solution rather than 5 mL .

The concentration of famotidine in plasma and urine was determined by comparing the peak area ratio of famotidine/internal standard (procaine) with a calibration curve. Linear calibration curves were always obtained ($r^2 > 0.99$). The inter-day coefficient of variation (mean of five experiments) varied between 2.9 and 5.7% for plasma (concentration range 0.5 – $10.0 \mu\text{g mL}^{-1}$) and between 2.9 and 7.1% for urine (concentration range 5 – $100 \mu\text{g mL}^{-1}$). The recovery of famotidine from plasma was 89% , that from urine 82% . Accuracy ranged from 96.1 to 105.6% .

The limit of quantification and limit of detection were not formally assessed because the concentrations used in the experiments could easily be detected. The detection limit of famotidine was well below $0.05 \mu\text{g mL}^{-1}$ for plasma and $0.5 \mu\text{g mL}^{-1}$ for urine.

Binding of famotidine to plasma protein was determined by ultrafiltration with Visking dialysis tubing (Russel et al 1987). The ultrafiltrates ($200 \mu\text{L}$) were treated and analysed in the same way as urine samples.

Inulin in urine and plasma samples was assayed according to the method of Heyrovski (1956) for calculation of glomerular filtration rate.

Pharmacokinetic analysis

Plasma and urine data were analysed separately according to a two-compartment model with the non-linear regression program Nonlin (Metzler et al 1974). Basic pharmacokinetic parameters (clearance and distribution volume) were calculated model-independently by applying statistical moments theory, using standard equations (Gibaldi & Perrier 1982). Half-lives ($t_{1/2}$) of the drug in plasma and urine were determined from the terminal phase. The area under the plasma concentration–time curve (AUC) and the area under the renal excretion rate–time curve (AUR) were determined by integration after extrapolation of the terminal phase of the curve to infinity. The overall renal clearance (CL_R) was estimated by the total excretion method, by dividing the total amount excreted into the urine in infinite time, which equals the AUR, by the AUC.

Because passive re-absorption was considered to be negligible, the part of renal famotidine clearance attributable to active tubular secretion (R_{TS}) can be calculated by subtracting the filtration rate (R_{GF}) from the total excretion rate (R_{R}) for each experiment: $R_{\text{TS}} = R_{\text{R}} - R_{\text{GF}}$.

$R_{\text{GF}} = \text{GFR} \times f_u \times C_p$, where GFR is the glomerular filtration rate determined from the inulin clearance, f_u is the fraction unbound in plasma and C_p is the total plasma concentration. A linear plot of R_{TS} against C_p , the so-called tubular titration curve, was analysed with Nonlin according to the Michaelis–Menten equation:

$$R_{\text{TS}} = (T_M \times C_p) / (K_T + C_p) \quad (1)$$

where T_M is the maximum transport capacity ($\mu\text{g min}^{-1}$) and K_T the Michaelis–Menten constant of the tubular secretion mechanism ($\mu\text{g mL}^{-1}$).

Average values are expressed as means \pm s.d. Statistical significance was determined by analysis of variance then post tests (two-samples *t*-test with Bonferoni correction). A value of $P < 0.05$ was considered significant.

Table 1. Pharmacokinetic and experimental parameters characterizing the renal handling of famotidine after intravenous infusion in the dog.

	Short-term infusion			Continuous infusion	
	Dog 1	Dog 2	Dog 3	Dog 1	Dog 2
Weight of dog (kg)	15.1	14.3	15.6	14.8	14.0
Dose (mg)	46	67	80	1270	254
Infusion rate (mg min ⁻¹)	6	6	8	—*	—†
Glomerular filtration rate‡(mL min ⁻¹)	66 ± 8	26 ± 4	43 ± 7	74 ± 13	41 ± 3
Urine flow§ (mL min ⁻¹)	0.68 ± 0.13	0.68 ± 0.06	0.65 ± 0.12	0.76 ± 0.25	0.88 ± 0.40
Urine pH§	7.57 ± 0.20	7.80 ± 0.09	7.76 ± 0.26	7.51 ± 0.12	7.67 ± 0.12
Fraction of dose excreted into urine in infinite time (% dose)	63	47	74	69	52
Half-life of terminal phase of drug in plasma (min)	126	73	93	62	53
Total plasma clearance (mL min ⁻¹)	120	120	148	127	142
Renal clearance (mL min ⁻¹)	74	56	101	76	65
Distribution volume at steady-state (L)	14.5	8.6	12.7	7.7	8.6

Data are expressed as means ± s.d. *Subsequent 85-min infusions of 2.25, 4.50 and 6.75 mg min⁻¹ famotidine, each preceded by 5 min of 8 mg min⁻¹ famotidine. †Subsequent 115-min infusions of 0.02 and 2 mg min⁻¹ famotidine, preceded by 5 min of 0.5 and 4 mg min⁻¹, respectively. ‡Average of steady-state inulin clearance (n = 7). §Average of all urine samples (n = 25).

Results

Increasing doses of famotidine were administered with the objective of achieving saturation of tubular secretion. A summary of the results from all the experiments is given in Table 1. No clear indications of saturation of the renal clearance were observed. The doses of famotidine administered were not identical for all dogs. For saturation of active tubular secretion we intended to administer very high famotidine doses but the size of the dose was limited by cardiovascular side-effects caused by the peak famotidine plasma concentrations after short-term infusion. A maximum heart rate of 200 beats min⁻¹ was used as an indication of the highest dose that could be administered safely to a dog by short-term infusion.

Renal clearance of famotidine was also studied in experiments with continuous famotidine infusion at increasing dosing rates. The infusion schedule and the derived pharmacokinetic parameters are given in Table 1. When the infusion rate was increased from 2.25 mg min⁻¹ to 4.5 mg min⁻¹ (dog 1), the mean plasma concentration increased from 10.9 ± 1.5 to 28.4 ± 4.0 µg mL⁻¹ and the renal clearance decreased from 97 ± 14 to 84 ± 5 mL min⁻¹. A further increase of the infusion rate to 6.75 mg min⁻¹ (mean plasma concentration 46.2 ± 2.8 µg mL⁻¹) only resulted in a minor decrease in renal clearance to 81 ± 5 mL min⁻¹. In another experiment (dog 2), the infusion rate was increased from 0.02 mg min⁻¹ to 2.0 mg min⁻¹, which resulted in an increase of mean plasma concentration from 0.17 ± 0.03 to 8.7 ± 1.7 µg mL⁻¹ and a significant reduction of renal clearance from 117 ± 33 to 87 ± 18 mL min⁻¹. The plots of plasma concentration and renal excretion against time for this experiment are shown in Fig. 1. These data suggest saturable renal clearance of famotidine in the dog. The unbound famotidine fraction in plasma was determined to be 0.72 ± 0.16 (n=28) and was concentration-independent over a plasma concentration range from 0.5 to 50 µg mL⁻¹.

No evidence of passive re-absorption of famotidine was observed. Non-ionic back diffusion seems unlikely under the experimental circumstances, because of the relatively high urine flow (mannitol-induced) and high urinary pH (7.30–8.00)

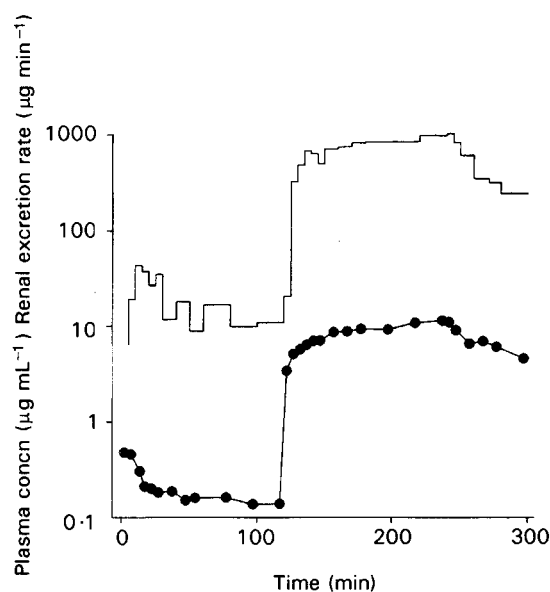


FIG. 1. Renal excretion rate (—) and plasma concentration (●) as a function of time during continuous infusion of famotidine in beagle dogs. Infusion was started at t = 0 min with 5 min of 0.5 mg min⁻¹ then 115 min of 0.02 mg min⁻¹. At t = 120 min, high dose infusion was started with 5 min of 4.0 mg min⁻¹ then 115 min of 2.0 mg min⁻¹.

as compared with the dissociation constant of famotidine (pK_a = 6.7; Echizen & Ishizaki 1991). Saturability of renal famotidine clearance can be seen clearly from a tubular titration plot in which the data from all experiments are depicted (Fig. 2). In this figure, the active tubular famotidine secretion (R_{TS}) is plotted against plasma concentration. Active tubular secretion was calculated for each experiment separately by subtracting the filtration rate (R_{GF}) from the total excretion rate (R_R). From this curve it is obvious that the active renal excretion of famotidine becomes saturated. A tubular transport maximum of 2400 ± 220 µg min⁻¹ and an apparent Michaelis-Menten constant of tubular secretion of 26 ± 4 µg mL⁻¹ (76 ± 12 µM) were calculated.

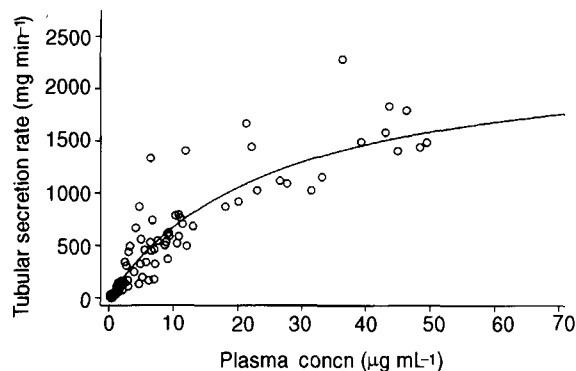


FIG. 2. Tubular titration curve of famotidine in beagle dogs in which the active tubular secretion rate is plotted against the plasma concentration. The line in the figure represents the result of data analysis according to the Michaelis-Menten equation.

Discussion

We demonstrated that the renal clearance of famotidine in the dog becomes saturated at high, supratherapeutic, plasma concentrations. Saturability was characterized by a maximum transport capacity of $2400 \pm 220 \mu\text{g min}^{-1}$ and a Michaelis-Menten constant for tubular secretion of $26 \pm 4 \mu\text{g mL}^{-1}$. To the best of our knowledge this is the first study in which saturation of famotidine renal clearance has been fully quantified in-vivo.

Famotidine is known as a substrate for the renal organic cation transporter. The understanding of the mechanisms involved in the renal tubular secretion of organic cations has been enlarged by mechanistic studies in cellular and sub-cellular experimental models. The first step in proximal tubular secretion of organic cations involves entrance into the tubular cell across the basolateral membrane by facilitated diffusion or by active-carrier-mediated transport (Schäli et al 1983; Tarloff & Brand 1986). Transport is assisted by the negative cell interior. The organic cation then leaves the cell across the brush-border membrane by active carrier-mediated transport against the electrochemical gradient (Pritchard & Miller 1993).

In-vitro, famotidine is a potent inhibitor of transport of other cationic drugs. The inhibitory constants for transport at the brush-border membrane reported in the literature range from 1.5 to 3.0 μM for inhibition of tetraethylammonium uptake in isolated rat proximal tubular cells and membrane vesicles (Boom et al 1992; Somogyi et al 1994), inhibition of cimetidine uptake in rat proximal tubular cells (Boom & Russel 1993) and N^1 -methylnicotinamide uptake in canine membrane vesicles (Bendayan et al 1990). A much higher value of $0.20 \pm 0.06 \text{ mM}$ was observed for inhibition of N -methyl-4-phenylpyridinium transport in rat proximal tubules determined with the stop-flow microperfusion method (David et al 1995). The inhibitory potency of famotidine against basolateral organic cation transport is considerably lower and ranges from 0.1 to 1.0 mM for inhibition of N^1 -methylnicotinamide transport in rat proximal tubules determined with stop-flow microperfusion (David et al 1995) and inhibition of tetraethylammonium and cimetidine uptake in isolated rat proximal tubular cells (Boom et al 1992; Boom & Russel 1993). Our observed apparent K_T value of 76 μM must be interpreted as an

overall parameter accounting for transport across both the basolateral and brush-border membranes.

Although famotidine is a potent cationic drug inhibitor in-vitro, renal interactions of famotidine in-vivo have not yet been reported. Klotz et al (1985) and Abraham et al (1987) showed that famotidine in therapeutic doses did not inhibit the renal elimination of procainamide, N -acetylprocainamide and creatinine, probably because of the low famotidine plasma concentrations ($< 0.3 \mu\text{g mL}^{-1}$) used in these studies. In the rat, famotidine in a steady-state concentration of $50\text{--}94 \mu\text{g mL}^{-1}$ did not reduce the renal clearance of cimetidine ($1.2\text{--}3.8 \mu\text{g mL}^{-1}$), whereas cimetidine at a steady-state concentration of $112\text{--}250 \mu\text{g mL}^{-1}$ reduced the renal clearance of famotidine ($0.11\text{--}0.5 \mu\text{g mL}^{-1}$) by 70% (Lin et al 1988). These apparently contradictory results can be explained by comparing plasma concentrations and affinities for the organic cation transport system. In the experiment with cimetidine as inhibitor, the ratio of inhibitor drug to inhibited drug was much higher than in the experiment with famotidine as inhibitor. A high apparent Michaelis-Menten constant for tubular secretion of $0.8 \mu\text{M}$ was, moreover, reported for cimetidine in the isolated perfused rat kidney (Boom et al 1994). The tubular transport maximum of famotidine in the rat was $180 \mu\text{g min}^{-1} \text{ kg}^{-1}$ (Lin et al 1987), which is in agreement with our value of $2400 \mu\text{g min}^{-1}$, which corresponds to $162 \mu\text{g min}^{-1} \text{ kg}^{-1}$.

In summary, it is clear from the results in this paper that therapeutic plasma concentrations of famotidine, which in general are below $0.1 \mu\text{g mL}^{-1}$, are not high enough to saturate tubular secretion or to compete with the renal transport of other cationic drugs whose therapeutic concentrations are usually much higher, even though the affinity of famotidine for the organic cation transporter is relatively high. Clinically important renal interactions with the use of famotidine are therefore not to be expected.

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