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SINGLE-DOSE PHARMACOKINETICS AND BIOAVAILABILITY OF FAMOTIDINE IN MAN. RESULTS OF MULTICENTER COLLABORATIVE STUDIES

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ABSTRACT

Pharmacokinetics and bioavailability of famotidine, a new H_2-receptor antagonist, were investigated in healthy subjects in five clinical studies. Linear pharmacokinetics were observed following either intravenous or oral administration. Plasma clearance averaged 463 ml min^{-1}. Renal clearance averaged 310 ml min^{-1}, which exceeded the glomerular filtration rate. Renal excretion was the major route of elimination. Urinary recovery of unchanged drug following intravenous administration was about 67 per cent. Famotidine plasma half-life was approximately 2·6 h. Oral absorption was incomplete. The bioavailability averaged 43 per cent of the dose.

KEY WORDS Famotidine Pharmacokinetics Bioavailability Protein binding

INTRODUCTION

Famotidine (3-[[[2-[(aminoiminomethyl)amino]-4-thiazolyl]methyl]-thio]-N-(amino-sulfonyl)-propanimidamide) is a new histamine H_2-receptor antagonist for treatment of duodenal and gastric ulcers, prophylactic therapy of duodenal ulcer, Zollinger–Ellison syndrome, and other hyper-secretory states.[1–4] It is more potent than cimetidine and ranitidine in inhibiting the acid secretory response during histamine stimulation in dogs.[5] The ED_{50} for reduction in total acid output evoked by histamine for famotidine (0·03 mg kg^{-1}) was less than that of ranitidine (0·42 mg kg^{-1}), and cimetidine (2·86 mg kg^{-1}). In man, 5 mg of famotidine and 300 mg cimetidine were equipotent but famotidine was longer-acting.[4] Similarly, famotidine 40 mg h.s. was equipotent to ranitidine 150 mg b.i.d.[1] Famotidine differs structurally from the two earlier compounds in that it is a guanylthiazole derivative

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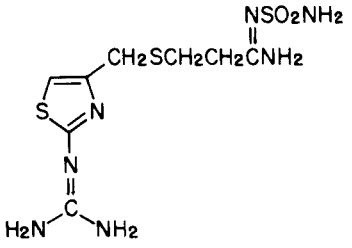

Figure 1. Structure of Famotidine

(Figure 1). This communication reports pharmacokinetics and the bioavailability characteristics of the drug in healthy subjects based on results from single dose clinical studies.

MATERIALS AND METHODS

*Rising dose study**

This was a double-blind, single dose, placebo-controlled study to determine the safety, tolerability, and dose-proportionality of orally administered famotidine. Fifteen male healthy volunteers (subjects 1–15) were studied in five separate treatment periods after an overnight fast. On the morning of the study day, each subject received either a single oral capsule dose of famotidine in increasing strengths (5, 10, 20, or 40 mg) or a placebo randomly interspersed as one treatment. Four hours following the drug administration, normal diet was resumed. There was a 7-day interval between treatments. Blood samples were collected in heparinized tubes at 0, 0·5, 1·25, 2, 3, 4, 6, 8, 12, and 24 hours. Urine was collected at the following intervals: −1 to 0, 0–2, 2–4, 4–6, 6–8, 8–12, 12–24, 24–36, and 36–48 hours. Specimens were kept frozen until the time of analysis.

Radiolabel study†

This was an open-labelled, single-dose study conducted in four healthy male volunteers (subjects 16–19). Radiolabelled famotidine (20 mg containing 20 μCi in 100 ml of purified water) was administered in the morning of the study day after having fasted since the preceding night. Heparinized blood was collected at 0, 20, and 40 min and 1, 1·5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h. Plasma was immediately separated from precipitated formed elements. Both the plasma and the formed elements were kept frozen until the time of analysis. Fractional urines were collected at zero-hour, 0–3, 3–6, 6–12, 12–24,

*Clinical phase completed at Medical and Technical Research Associates, Needham, MA.
†Study conducted at Thomas Jefferson University Hospital, Philadelphia, PA.

24–36, 36–48, 48–72, 72–96, and 96–120 h after drug administration. All faeces up to 96 h after drug administration were collected in separate containers. The entire urine and faecal collection was labelled and kept frozen until the time of analysis.

Secretion inhibition study‡

This was a double-blind, four-way crossover, placebo-controlled, single-dose study in eight male subjects (subjects 20–27) without active disease but with basal gastric acid secretion of ≥ 5 mEq h^{-1}. The purpose of the study was to investigate the inhibitory effect of intravenous and oral famotidine on overnight basal gastric secretion. In the evening of the study day, the assigned medication was administered 2–3 h after a standard dinner meal. Treatments were separated by a minimum washout of 72 h. The four treatments were: (A) famotidine 10 mg i.v. bolus; (B) famotidine 20 mg i.v. bolus; (C) famotidine tablet 20 mg p.o.; and (D) placebo. Heparinized blood samples were obtained at 0, 15, 30, 60, and 90 min and 2, 3, 4, 6, 8, 10, and 12 h after treatment administration. Plasma was immediately separated and kept frozen until the time of analysis.

Bioavailability study§

This was an open, single-dose, four-way crossover study in 16 healthy volunteers of either sex (subjects 28–43) with random assignment of treatment sequences. It was designed to define the disposition kinetics of famotidine after intravenous administration and its absolute bioavailability after oral administration. The four treatments were: (A) famotidine capsule 20 mg; (B) famotidine tablet 20 mg; (C) famotidine tablet 40 mg; and (D) famotidine 20 mg i.v. bolus. Heparinized blood samples were collected at 0, 1, 1·5, 2, 2·5, 3, 4, 6, 8, 10, 12, 24, and 36 h following each treatment. Additional samples were collected at 30 min following treatments A, B, and C, and at 5, 10, and 20 min following treatment D. Plasma was immediately separated and kept frozen until the time of analysis.

Urine was collected at the following intervals: −1 to 0 (control), 0–2, 2–4, 4–6, 6–8, 8–12, 12–24, 24–36, 36–48, and 48–72 h. Specimens were kept frozen until the time of analysis.

Oral bioequivalence study‖

This was an open, two-way crossover study in 16 healthy male voulnteers (subjects 44–59) to compare the relative bioavailability of famotidine 40 mg tablet and an equal dose of oral suspension. The plasma sampling scheme was identical to that of treatment A in the bioavailability study. The urine

‡Study conducted at Clinical Research Center, Inc., New Orleans, LA.
§Study conducted at Drug Study Unit, University of California, San Francisco, CA.
‖Clinical phase completed at Biodecision Laboratories, Pittsburgh, PA.

sampling scheme was identical to that of the rising dose study. Specimens were kept frozen until the time of analysis.

Famotidine assay

A previously published reverse-phase HPLC method[6] was used for the determination of famotidine levels in plasma and urine. The method is specific for unchanged famotidine. Briefly, famotidine in biological fluids was adsorbed onto silica gel, eluted with solvent (acetonitrile for plasma, and 50 per cent N,N-dimethyl formamide in water for urine) after washing with water. For urine, the eluent was chromatographed on a C-8 reverse-phase column. For plasma, the acetonitrile was evaporated to dryness, and the drug was reconstituted in 0·17N acetic acid and chromatographed. The mobile phase consisted of a 9 to 1 mixture of 0·85 per cent phosphoric acid and acetonitrile. The methods were quantitative, reproducible, and linear for plasma (5 to 70 ng ml^{-1}) and urine (0·5 to 30 μg ml^{-1}). All assays were performed at Merck Sharp and Dohme Research Laboratories.

Protein binding study

The binding of famotidine to plasma protein was examined in two experiments using equilibrium dialysis: *in vitro* binding to pooled human plasma spiked with ^{14}C-famotidine, and in plasma from five subjects (subjects 60–64) who received 40 mg famotidine orally. In the first experiment, assay of famotidine was by liquid scintillation counting. In the second experiment, the above HPLC method was used for famotidine quantitation.

Pharmacokinetic analysis

Model-independent methods were used in the analysis of the data. The area under the plasma concentration curve [AUC] was obtained by the spline method, or the trapezoidal rule was used if stable interpolations were not produced by the former.[7] Renal clearance over the time interval $[t_1, t_2]$ was obtained from the following:

$$\text{Renal clearance} = \frac{[U]_{t_1 \to t_2}}{[AUC]_{t_1 \to t_2}}$$

where [U] is the amount of unchanged famotidine excreted in the urine over the indicated time interval, and [AUC] is the corresponding area under the famotidine plasma concentration curve over the same interval. Plasma clearance following the intravenous administration was obtained from the following:

$$\text{Plasma clearance} = \frac{[\text{Dose}]\,[\text{Renal clearance}]}{[\text{Total urinary recovery}]}$$

Total 0-to-∞ [AUC] was calculated[8] from the following:

$$[AUC]_{0\to\infty} = [AUC]_{t_1\to t_2} \frac{[\text{Total urinary recovery}]}{[U]_{t_1\to t_2}}$$

The plasma half-life was computed from the following:

$$t_{1/2} = \frac{0{\cdot}693}{\beta}$$

where β is the terminal log linear decay slope. In the rising dose study, β was obtained by regression analysis of the deficit-plot of the urinary recovery data. In the remaining studies, it was obtained from the terminal plasma concentration data.

The relative bioavailability was calculated as previously described,[8] assuming constant non-renal clearance between treatments.

Statistical analysis

Pharmacokinetic parameters, plasma concentrations, and urinary recovery results are given as mean ± S.D. Confidence intervals of relative bioavailabilities were calculated using one-sample *t*-distribution methods applied either to the absolute bioavailabilities, or to the log-transformed relative bioavailabilities.

RESULTS

Rising dose study

Figure 2 displays mean plasma concentration–time profiles of famotidine. Table 1 summarizes the mean pharmacokinetic parameters. Large inter-subject variation was noted. Peak plasma concentrations following the oral administration occurred between 1 and 3 h, and are essentially dose-proportional. Plasma half-life was moderately short, averaged 2·6 h. Urinary recovery of famotidine totalled 20–28 per cent of the dose. Renal clearance ranged between a mean of 227 to 294 ml min^{-1}, which is in excess of the normal glomerular filtration rate. Relative to the 40 mg dose, the bioavailability[8] of the 5 mg, the 10 mg, and the 20 mg averaged 1·21, 1·51, and 1·17, respectively.

Famotidine had no significant drug-related effects on the clinical and laboratory safety parameters measured, which included haemoglobin, haematocrit, complete blood count, serum electrolytes, BUN, creatinine, total bilirubin, SGOT, SGPT, alkaline phosphatase, LDH, uric acid, total protein, A/G ratio, fasting blood sugar, urine specific activity, pH, protein, sugar RBC's, casts and epithelials, and a 12-lead ECG.

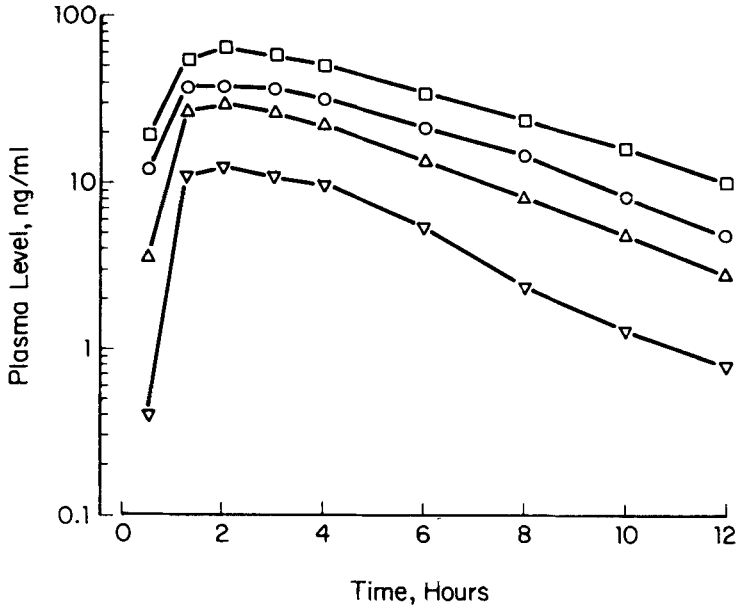

Figure 2. Mean plasma level profiles of famotidine following single oral dose administration to 15 young healthy subjects in the rising dose study. Key: □ 40 mg; ○ 20 mg; △ 10 mg; ▽ 5 mg

Table 1. Famotidine pharmacokinetic parameters (mean ± S.D.) following single-dose administration to 15 healthy subjects in the rising dose study

Parameter	Dose 5 mg	10 mg	20 mg	40 mg
Peak plasma level, ng ml^{-1}	14·0 ± 5·7	32·7 ± 11·0	43·4 ± 17·7	75·5 ± 28·6
Time to peak, h	2·3 ± 1·1	1·9 ± 0·7	2·3 ± 0·9	1·9 ± 0·8
Total [AUC], ng-h ml^{-1}	68·9 ± 42·6	183·3 ± 86·3	281·2 ± 125·3	482·3 ± 181·2
Terminal half-life, h	—*	2·5 ± 1·0	2·6 ± 0·8	2·6 ± 0·9
Renal clearance,† ml min^{-1}	395 ± 218 (294)	277 ± 141 (227)	311 ± 112 (276)	310 ± 160 (264)
Urinary recovery, % of dose	27·4 ± 13·6	27·7 ± 8·5	23·7 ± 6·7	19·5 ± 5·3
Relative bioavailability‡	1·21 (0·94, 1·57)	1·51 (1·15, 1·99)	1·17 (1·00, 1·37)	–

* Data extremely variable, not amenable to determination.
† Value in parenthesis indicates harmonic mean.
‡ Geometric mean, relative to the 40 mg dose; values in parentheses indicated 95 per cent confidence interval.

Table 2. Urinary and faecal excretion (% dose) of radioactivity in four subjects following oral administration of 20 mg famotidine containing 20 μCi in the raiolabel study

	Subject				
	16	17	18	19	Mean ± S.D.
0–96 h fecal recovery	47·24	27·91	48·29	78·90	50·6 ± 21·1
0·120 h* Urinary recovery	29·24 (24·69)	56·45 (29·84)	42·70 (27·77)	23·63 (17·03)	38·0 ± 14·7 (24·8 ± 5·6)
Total recovery (urine + faeces)	75·48	84·36	90·99	102·53	88·3 ± 11·4

* Value in parentheses indicate 0–24 h urinary recovery of unchanged drug.

Radiolabel study

Table 2 lists the urinary and faecal excretion of radioactivity following the oral administration of radiolabelled famotidine in four healthy subjects. Plasma radioactivity levels are similar to the unchanged famotidine over the first 8 h. An average of 38·0 ± 14·7 per cent of the radioactivity dose was recovered in the urine. Faeces accounted for 50·6 ± 21·1 per cent of the dose. Unchanged famotidine in urine was analysed and found to account for 24·8 ± 5·6 per cent of the ingested dose. Thus, approximately 53–88 per cent of the urinary radioactivity could be attributed to the unchanged famotidine, indicating the presence of metabolite(s) in the urine.

Secretion inhibition study

Table 3 summarizes the pharmacokinetic parameters observed in the study.

Table 3. Famotidine pharmacokinetic parameters (mean ± S.D.) observed in eight subjects in the secretion–inhibition study

	Dose		
	10 mg i.v.	20 mg i.v.	20 mg p.o.
Plasma clearance, ml min^{-1}	489 ± 157	450 ±120	–
Half-life, h	2·4 ± 1·0	2·8 ± 0·3	3·8 ± 1·4
[AUC] ratio	–	2·24* (1·58, 2·91)	0·48† (0·34, 0·62)

* Arithmetic mean, relative to the 10 mg i.v. dose; values in parenthesis indicate 95 per cent confidence interval.

† Arithmetic mean, relative to the 20 mg i.v. dose; values in parenthesis indicate 95 per cent confidence interval.

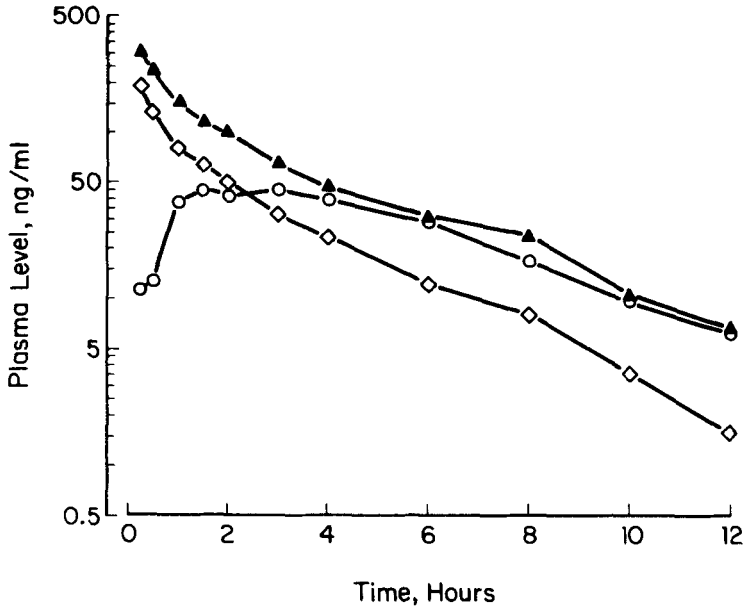

Figure 3. Mean plasma levels of famotidine following 20 mg tablet (○), 20 mg i.v. (▲), and 10 mg i.v. (◇) to eight subjects in the secretion inhibition study

Results are consistent with those observed in the rising dose study, i.e., short half-life and dose-proportionality of the plasma concentrations. These data further indicate high plasma clearance for famotidine. The [AUC] ratio between the oral dose and the intravenous dose indicate incomplete absorption of the drug. Mean plasma levels are shown in Figure 3.

Bioavailability study

Table 4 summarizes the pharmacokinetic parameters. Following oral administration, peak plasma levels occur at approximately 2·2–2·4 h. There was a dose-related increase in peak plasma levels. Renal clearance ranged from 217 ml min^{-1} to 346 ml min^{-1}. Relative to the intravenous dose, the bioavailability of the orally administered famotidine averaged 0·42 ± 0·14, 0·45 ± 0·12, and 0·49 ± 0·17 for the 40 mg tablets, 20 mg tablets, and 20 mg capsules, respectively.

Following the intravenous administration, mean urinary recovery of unchanged famotidine accounted for almost 67 per cent of the dose, while following oral administration, the recovery averaged 27–32 per cent. The observed mean half-life of 2·8 ± 1·0 h and the large plasma and renal clearance are comparable to those found in the rising dose and secretion-inhibition study.

Table 4. Famotidine pharmacokinetic parameters (mean ± S.D.) observed in 16 subjects in the bioavailability study

	Dose			
	20 mg i.v.	20 mg capsule	20 mg tablet	40 mg tablet
Plasma clearance, ml min^{-1}	463 ± 160	–	–	–
Renal clearance, ml min^{-1}	310 ± 120	247 ± 82	217 ± 60	346 ± 153
Non-renal clearance,* ml min^{-1}	152 ± 78	–	–	–
Half-life, h	2·8 ± 1·0	3·0 ± 0·5	3·5 ± 0·9	3·3 ± 0·8
Urinary recovery, % of dose	66·8 ± 14·9	31·8 ± 12·7	27·6 ± 9·1	31·2 ± 17·6
Peak plasma level, ng ml^{-1}	–	78·7 ± 37·2	78·9 ± 29·8	109·3 ± 41·6
Time to peak plasma level, h	–	2·2 ± 0·9	2·4 ± 1·4	2·3 ± 1·4
Bioavailability†	–	0·49 (0·40, 0·58)	0·45 (0·38, 0·51)	0·42 (0·34, 0·50)

* Difference between plasma clearance and renal clearance.
† Dose adjusted arithmetic mean, relative to the 20 mg i.v. dose; values in parenthesis indicate 95 per cent confidence interval.

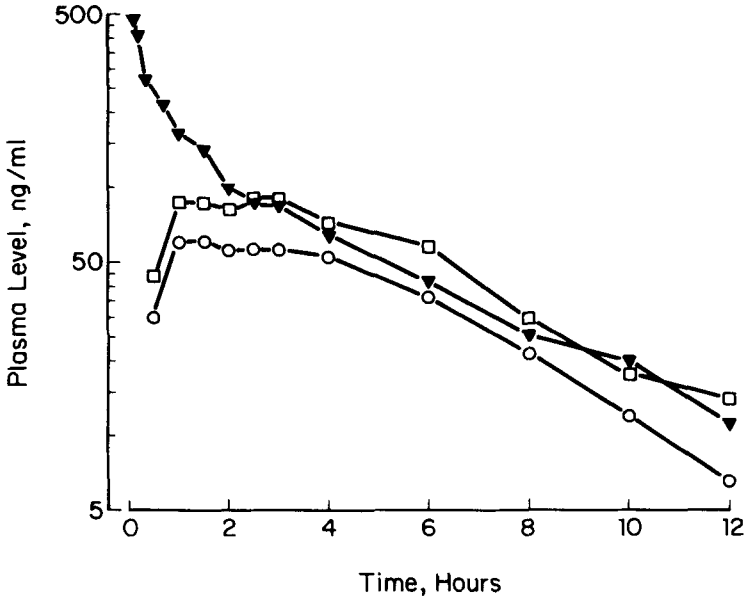

Figure 4. Mean plasma levels of famotidine following administration of 20 mg i.v. (▼), 40 mg tablet (□), and 20 mg tablet (○) to 16 healthy young subjects in the bioavailability study

Table 5. Summary of the oral bioequivalence study, evaluating the relative bioavailability of famotidine tablet and an oral suspension in 16 healthy subjects (mean ± S.D.)

	Dose	
	40 mg Tablet	40 mg Oral suspension
Peak plasma level, ng/ml	88·9 ± 39·7	97·3 ± 58·3
Time to plasma peak level, h	2·0 ± 0·9	2·3 ± 0·8
Half-life, h	3·3 ± 0·8	3·0 ± 0·7
Urinary recovery, % of dose	23·9 ± 8·0	25·4 ± 14·4
Renal clearance, ml min^{-1}	320 ± 115	383 ± 216
Bioavailability*	1·08 (0·89, 1·30)	–

* Geometric mean relative to the oral suspension; values in parenthesis indicate 95 per cent confidence interval.

Oral bioequivalence study

Shown in Table 5 are the pharmacokinetic data obtained. These results indicate that the two dosage forms are bioequivalent.

Protein binding

Famotidine is not extensively bound to plasma protein. The binding is not concentration-dependent over the range of 43–500 ng ml^{-1} (Table 6).

Table 6. Plasma protein binding of famotidine

	Concentration, ng ml^{-1}	Bound fraction, %
Pooled plasma	50	15·0
	100	12·3
	200	16·2
	500	18·3
	Mean ± S.D.	15·5 ± 2·5
Individual plasma		
Subject 60	42·6	17·0
Subject 61	53·3	10·7
Subject 62	54·0	19·0
Subject 63	126·8	9·6
Subject 64	155·0	28·3
	Mean ± S.D.	16·9 ± 7·5

DISCUSSION

The above studies indicate that famotidine follows linear pharmacokinetics in the dose range studied. Urinary excretion is the major route of famotidine elimination. After intravenous administration in healthy young subjects, approximately 67 per cent of the dose is recovered in the urine. The extent of metabolism could not be quantitatively estimated based on the available data from the radiolabel study. However, it has been reported that in animal and human metabolism studies, the only metabolite identified in urine has been the S-oxide of famotidine which accounts for approximately 5–20 per cent of each collection.[9]

Famotidine has a moderately short plasma half-life of approximately 2·6 h, which is slightly greater than that of ranitidine[10–15] and cimetidine.[16–18] Famotidine is also similar to ranitidine[10–13] and cimetidine[16,17,19] in that its renal clearance exceeds the glomerular filtration, suggesting the presence of net tubular secretion. However, there is no indication that the renal clearance is concentration-dependent at the observed levels. Following oral administration, peak plasma concentrations occur at 2·2 h, with mean peak concentrations of 71 ng ml^{-1} for the 20 mg tablet and 132 ng ml^{-1} for the 40 mg tablet. The absorption of famotidine is incomplete, with a bioavailability of 43 per cent. The observation that the tablet and the oral suspension show comparable bioavailability suggest that the incomplete absorption may not be formulation-related. It has been reported that other H_2-receptor antagonists are also incompletely absorbed.[11,12,16,20–22] Because of the short half-life, famotidine plasma levels are not expected to accumulate following repeated administration at the recommended once-daily dosing regimen.

The above results are in agreement with those obtained from earlier animal and pilot human studies with respect to plasma concentration data and plasma half-life.[23–25] However, it is not known if the higher urinary recoveries reported in those earlier studies are related to the improved specificity of the assay methodology for the present studies.

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