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Pharmacokinetics and bioavailability of famotidine in 10 Chinese healthy volunteers[1]

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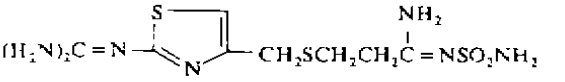
ABSTRACT The pharmacokinetics and bioavailability of famotidine were investigated by HPLC method in 10 Chinese healthy volunteers. Data obtained from HPLC were analysed automatically using a MCPKP program on microcomputer. Linear pharmacokinetics were observed following either iv or po administration. After 20 mg iv, plasma levels declined biexponentially with an initial $T_{\frac{1}{2}}$ of 0.3 ± 0.2 h and terminal $T_{\frac{1}{2}}$ of 3.5 ± 0.8 h. The plasma elimination $T_{\frac{1}{2}}$ following po administration were 3.4 ± 0.7 h and 3.5 ± 0.5 h for capsules and tablets respectively. Oral absorption was incomplete. The absolute bioavailabilities were 38 ± 10% for capsules and 43 ± 11% for tablets. Renal excretion was the major route of elimination. About 72% of the dose were recovered as unchanged famotidine in urine. Mean renal and plasma clearance were 416 and 541 ml · min^{-1} respectively.

KEY WORDS famotidine; pharmacokinetics; biological availability; capsules; tablets; histamine H_2 receptor blockaders

Famotidine (Fam), *N*-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]-propanimidamide, is a new histamine H_2 receptor antagonist, which differs structurally from earlier cimetidine and ranitidine in having a thiazole rather than an imidazole or furan nuclei (Fig 1). It is used for treatment of peptic ulcers and other acid hypersecretory diseases[1,2]. Fam is approximately 20–50 times more potent at inhibiting gastric acid secretion than cimetidine and 8 times more potent than ranitidine[1]. The purpose of this paper is to report the pharmacokinetics and bioavailability of Fam in 10 healthy Chinese volunteers following iv and po administrations.



Famotidine (Fam)

MATERIALS AND METHODS

Drugs and instrument Fam injection in 2 ml ampoules (lot No 891127) and Fam tablets (lot No 891123) were supplied by Shanghai Sine Pharmaceutical Factory and Fam capsules (lot No 891115) by Shanghai Yan-an Pharmaceutical Factory. All preparations contained 20 mg Fam each. The HPLC instruments consisted of Hitachi 655 HPLC system equipped with a model 655A-12 pump, 655A-22 wavelength adjustable uv detector, 655-71B data processor and Rheodyne 7125 sample injector. The analytical column (150 mm × 5 mm) was packed with the YWG-C_{18}, particle size 10 μm.

Subjects Ten healthy Chinese volunteers (8 M, 2 F) aged 30 ± SD 5 yr and weighed 62 ± SD 3 kg were selected. They all had normal heart, liver, kidney and gut with no history of smoking.

Study design The single dose, self-controlled method was taken in studying the pharmacokinetics and bioavailability of Fam. Each subject received three separate treatments: (a) iv bolus of 20 mg Fam; (b) po capsules of 40 mg Fam; (c) po tablets of 40 mg Fam. The washout period was at least 7 d. Other drugs and alcoholic drinks were prohibited within 2 wk prior to and during the

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study. In the morning of study day, each subject received an assigned dose of Fam by iv or po at random after an overnight fast. After 2 h, a uniform diet was supplied. Physical labor was refrained during that day.

Plasma and urine sampling Blood samples were collected into heparinized tubes at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 h after po Fam and 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h after iv Fam. Plasma was immediately obtained by centrifuging. Urine was collected during 0–12 h and 12–24 h and the volumes were recorded. Specimens were kept at −20℃ until analysis.

Drug analysis Fam in plasma and urine was assayed by the chromatographic method[3] except that HPLC was done on a C–18 column with acetonitrile : water : phosphoric acid : diethylamine − 1 : 9 : 0.2 : 0.25 (vol : vol, pH = 3.5) as mobile phase for assay of Fam in plasma. For determination of Fam in urine, 1–2 μl of urine was injected into HPLC system after the pH of mobile phase was adjusted to 5.0 with diethyl amine. The regression was linear within 5–100 ng · ml^{-1} for plasma and 1–30 μg · ml^{-1} for urine. The recoveries were 91.18 ± 6.32% for plasma and 93.56 ± 5.54% for urine with CV < 10%.

Pharmacokinetic analysis The data of plasma concentrations were analysed with a MCPKP program[4] on IBM–pc computer. Compartments model of Fam disposition were fitted automatically and then pharmacokinetic parameters were calculated. The absolute bioavailability (F) was calculated from $F = (AUC_{po} \times D_{iv} / AUC_{iv} \times D_{po}) \times 100\%$. Where D_{iv} = iv dose and D_{po} = po dose. Renal clearance (Cl_r) was computed from $Cl_r = U_{t_1-t_2} / AUC_{t_1-t_2}$. Where U was the amount of unchanged Fam excreted in urine over the indicated time interval, and AUC was the corresponding area under the Fam plasma concentrations curve over the same interval. Non–renal clearance (Cl_{nr}) was $Cl_p - Cl_r$.

RESULTS

The mean plasma level–time curves of Fam following iv 20 mg and po 40 mg capsules or tablets were shown in Fig 2. A two–compartment open model was used to describe the Fam disposition in body after iv administration. The $T_{\frac{1}{2}\alpha}$ and $T_{\frac{1}{2}\beta}$ were found to be 0.3 ± 0.2 and 3.5 ± 0.8 h respectively. V_D = 162 ± 44 L and AUC = 643 ± 146 h · ng · ml^{-1}. Tab 1 listed the other pharmacokinetic parameters following iv injection. The plasma level–time curve after po capsules or tablets comformed to single compartment open model with a first order absorption. Following po capsules, the peak plasma level (C_p) occurring at 2.5 ± 1.0 h was 60.4 ± 11.8 ng · ml^{-1}, and $T_{\frac{1}{2}k}$ was 3.4 ± 0.7 h. For po tablets the C_p value taking place at 2.0 ± 0.5 h was 77.1 ± 18.6 ng · ml^{-1}, which was a bit higher than that of po capsules. The $T_{\frac{1}{2}k}$ following po tablets, 3.5 ± 0.5 h, was similar to that of po capsules. There was no significant difference between the pharmacokinetic parameters of tablets and capsules. The pharmacokinetic parameters were shown in Tab 1.

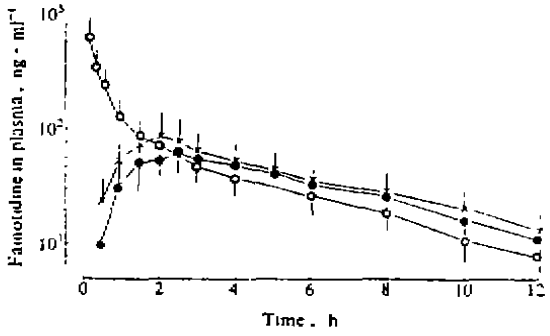

Fig 1. Plasma levels of Fam after 20 mg iv (○), 40 mg capsules (●) or tablets (×) in 10 healthy volunteers. $\bar{x}$ ± SD.

Tab 1. Pharmacokinetic parameters of Fam after 20 mg iv, 40 mg capsule and 40 mg tablet in 10 healthy volunteers. $\bar{x}\pm$ SD. * $P>0.05$ *vs* capsules.

Parameters	iv	Capsules	Tablets
α, h^{-1}	2.96 ± 1.96	–	–
β or K, h^{-1}	0.20 ± 0.04	0.21 ± 0.04	0.22 ± 0.03*
$T_{\frac{1}{2}\alpha}$, h	0.30 ± 0.2	–	–
$T_{\frac{1}{2}\beta}$ or $T_{\frac{1}{2}k}$, h	3.5 ± 0.8	3.4 ± 0.7	3.5 ± 0.5*
K_{12}, h^{-1}	1.57 ± 1.45	–	–
K_{21}, h^{-1}	0.64 ± 0.30	–	–
K_{el}, h^{-1}	0.97 ± 0.34	–	–
V_c, L	38 ± 18	–	–
V_D, L	162 ± 44	–	–
K_a, h^{-1}	–	1.61 ± 1.63	1.66 ± 0.66*
$T_{\frac{1}{2}ka}$, h	–	0.9 ± 0.7	0.5 ± 0.4*
T_p, h	–	2.5 ± 1.0	2.0 ± 0.5*
C_p, mg · ml^{-1}	–	60.4 ± 11.8	77.1 ± 18.6*
Cl_p, ml · min^{-1}	541 ± 116	–	–
Cl_r, ml · min^{-1}	399 ± 112	406 ± 80	442 ± 110*
AUC, h · ng · ml^{-1}	643 ± 146	470 ± 94	544 ± 110*
Lag time, h	–	0.42 ± 0.04	0.35 ± 0.22*

The AUC, bioavailability parameters following po, were 470 ± 94 and 544 ± 110 h · ng · ml^{-1} for capsules and tablets respectively. Relative to that of 20 mg iv of Fam, the absolute bioavailability of 40 mg capsule and 40 mg tablet were 38 ± 10% and 43 ± 11% respectively.

Tab 2 summarized the data of Fam excreted from urine at 12 and 24 h after medication. Approximately 72 ± 12% of the dose were recovered in urine as unchanged Fam 24 h after 20 mg iv. About 67% of unchanged Fam were recovered from urine for the first 12 h and accounted for 5% of unchanged Fam for the next 12 h. It suggests that Fam was largely eliminated within 12 h and almost entirely at 24 h. After po the recovered amounts during the same time were 28 ± 7% for capsules and 35 ± 9% for tablets. The Cl_r were found to be 399 ± 112 (iv), 406 ± 80 (capsule) and 442 ± 110 (tablet) ml · min^{-1}.

Tab 2. Urinary excretion of Fam after 20 mg iv, 40 mg capsule or tablet to 10 healthy volunteers. $\bar{x}\pm$ SD. * $P>0.05$ *vs* capsule.

Urinary recovery	iv	Capsules	Tablets
0–12 h			
mg	13.4 ± 2.2	9.7 ± 2.9	12.2 ± 3.6*
%	67 ± 11	24 ± 7	30 ± 9*
12 – 24 h			
mg	1.0 ± 0.5	1.4 ± 1.0	1.9 ± 1.2*
%	5 ± 2	4 ± 3	5 ± 3*
0 – 24 h			
mg	14.4 ± 2.3	11.2 ± 2.6	14.0 ± 3.6*
%	72 ± 12	28 ± 7	35 ± 9*

DISCUSSION

The results of present study showed that pharmacokinetic properties of Fam were similar to those of cimetidine and ranitidine with a linear kinetics. The mean $T_{\frac{1}{2}}$ of three kinds of formulas conformed well with each other, so that there was no significant difference ($P>0.05$) between them. The pharmacokinetic parameters of Fam obtained from our study were in good agreement with those of earlier publications[5,6]. The major route of Fam elimination was urinary excretion. Because of the shorter $T_{\frac{1}{2}}$ and quick renal excretion, the accumulation of Fam in body was not expected when repeated administrations at recommended dosing regimen. However, the plasma elimination and renal excretion of Fam were decreased in the elderly and patients with impaired renal function[7], which would result in prolongation of $T_{\frac{1}{2}}$. Therefore, a dose adjustment would be appropriate for patients with renal insufficiency to avoid excessive accumulation and potential undesirable effects. Following po administration there was a lag time of 0.4 ± 0.0 and 0.4 ± 0.2 h for capsules and tablets at

absorbable phase,which suggested that there were disaggregation and dissolution process in gastrointestinal tract both for capsules and tablets of Fam. The absolute bioavailability of Fam was relative low. The results in our crossover study were in agreement with those of reported[5,6].

Because Cl_{nr} (125 ml · min^{-1}) contributed about one fourth of total plasma Cl (541 ml · min^{-1}), the hepatic extraction was low and a high first-pass effect was very unlikely. The Cl_r of Fam averaged 416 ml · min^{-1} and exceeded the mean Cl_{cr} of 102 ml · min^{-1} in subjects. This indicated that besides glomerular filtration, the net tubular secretion was an important elimination mode for Fam. It accounted to about 58% of plasma Cl. Thus, those drugs affecting tubular secretion may influence the Fam renal excretion.

According to the gastric acid inhibition study in healthy voluteers by Miwa *et al*[2], the IC_{50} (concentration producing 50% acid inhibition) was 0.013 mg · L^{-1}. Similar conclusions were also reported by Ryan *et al*[8]. From this paper such effective plasma levels could persist for about 12 h or more, which fitted the need well with clinical therapy. It also indicated that the dosing regimens of 40 mg · d^{-1} were suitable for Chinese populations. The relationship, however, between plasma concentration and clinical response was still not clear.

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法莫替丁在十个中国健康志愿者体内的药物动力学和生物利用度

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提要　应用 HPLC 法研究了国产法莫替丁(Fam)在10例正常人体内的药动学和生物利用度。iv 给药后，体内呈二室开放模型，$T_{\frac{1}{2}\beta}$ = 3.5 ± 0.8 h；po给药均呈一室开放模型，$T_{\frac{1}{2}k}$ 分别为3.4 ± 0.7和3.5 ± 0.5 h. 肾脏为 Fam 的主要消除途径，大约剂量的 72%以原型从尿中排泄。口服吸收不完全，胶囊和片剂的绝对生物利用度分别为 38 ± 10%和 43 ± 11%.

关键词　法莫替丁；药物动力学；生物利用度；胶囊；片剂；组织胺 H_2 受体阻滞剂