COMPARATIVE BIOAVAILABILITY OF TWO DIFFERENT TABLETS OF FAMOTIDINE IN TWENTY FOUR HEALTHY VOLUNTEERS

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ABSTRACT

Objective: A comparative bioavailability study was established on two 40 mg tablets of famotidine (test product: Famodin 40 mg İlsan İlaçları A.Ş., Turkey; reference product: Pepdine 40mg, Merck, Sharp & Dohme, France) after the application of a single oral dose to twenty four healthy volunteers.

Methods: A two-way crossover randomized study applied to 12 female and 12 male subjects with a one-week wash-out period between two formulations. Blood samples were collected prior to (time zero) and at 14 time points within 24 hrs after dosing. Plasma concentrations of famotidine were determined via high performance liquid chromatographic method in France by CEPHAC Bioanalytical Research Center.

Results: Absorption and disposition of famotidine after a single oral administration of 40 mg are comparable between the two formulations. C_{max} values were determined as 174 ± 59 ng/ml and 151 ± 49 ng/ml (90% confidence intervals 1.00-1.32), and $AUC_{0-\infty}$ values were 947 ± 273 $ng.ml^{-1}.h$ and 868 ± 265 $ng.ml^{-1}.h$ (90% confidence intervals 0.99-1.21) for the test and the reference formulations, respectively.

Conclusion: The study has shown that the two formulations are bioequivalent with respect to the rate and extent of absorption of famotidine after a single oral administration of 40 mg famotidine in healthy volunteers.

Key Words: Famotidine, Bioavailability, Bioequivalence.

INTRODUCTION

Famotidine is a highly selective histamine H_2-receptor antagonist which is widely used for the treatment of duodenal ulcers, benign gastric ulcer and Zollinger-Ellison syndrome (1). It is more potent than cimetidine and ranitidine in inhibiting the acid secretion from the parietal cells of gastric mucosa. After oral administration of 40 mg famotidine peak plasma concentrations of 75.5 to 109 µg/L are reported to be attained approximately within 1 to 3.5 hours. The oral bioavailability is about 43 % because of the incomplete absorption of famotidine (2,3). Food does not appear to affect the bioavailability. Because of the short elimination half-life (2.5 to 3.5 h after oral or intravenous administration in young healthy subjects), famotidine does not accumulate following repeated administration. The apparent volume of distribution of famotidine following intravenous application is approximately 1.2 L/kg (4). Famotidine is not extensively bound to plasma proteins in humans. After 40 mg famotidine given orally to healthy men, the fraction of famotidine bound to plasma proteins was determined as 16 % (2). Binding was not concentration-dependent over the range of 0.05 to 0.5 mg/L. Famotidine is mainly excreted into urine. The only metobolite identified in the urine is an S-oxide metabolite which has been reported in animal and human metabolism studies, but the biological activity of this metabolite, if any, is unknown. Urinary recovery of unchanged famotidine accounts for 65 to 80% of an intravenous dose (5-7). The renal clearance of famotidine in healthy volunteers following intravenous administration is 2.5 to 5 ml/min/kg (4,8).

The present study was planned to investigate the comparative bioavailability (bioequivalance) of a generic preparation (Famodin®, İlsan İlaçları A.Ş.) and a patented brand (Pepdine®, Merck, Sharp & Dohme) each containing 40 mg of famotidine.

MATERIAL AND METHOD

Subjects: Twenty four healthy volunteers (12 females and 12 males) aged between 19-26 years, weighing between 47-80 kg (Table I) gave their written informed consent to participate in the study which was approved by the Ethics Committee of Marmara University, School of Medicine. The study was conducted according to the principles of the Declaration of Helsinki and its ammendments. Subjects were assessed by a medical history, physical examination, biochemical investigations for kidney and liver functions and hematological examinations; the values and findings were within normal limits. The subjects were hospitalized on the treatment days. They did not take other medication 4 weeks prior to and during the study, except two subjects who took one tablet of 500 mg paracetamol for the relief of headache. None of the subjects consumed alcohol starting 36 h, and caffeine containing beverages 12 h before dosing until the end of blood sampling at each study period. Smoking was not forbidden since the major route of elimination of famotidine was renal (9). The subjects received two different preparations on two separate occasions, with a wash-out period of one week. The randomization was done according to a Latin Square randomized numbers table. After an overnight fast, each subject took one tablet of 40 mg famotidine with 150 ml of water. The subjects ate a standard breakfast one hour after the drug application. They were given lunch and dinner 4 h and 8 h after dosing, respectively. Blood samples were collected by venipuncture from the forearm to heparinized tubes about 5 ml at 0;0.5;1;1.5;2;2.5;3;3.5;4;6;8;10;12;15 and 24 h after the drug administration. The plasma was separated by centrifugation at about +4 °C for 10 minutes at 1100 G within 0.5 h after sampling, and stored at -20°C until shipment to the analytical facilities.

Analysis: Study samples were transferred to CEPHAC facilities (Paris, France) in a container filled with enough dry ice to ensure that samples were kept deep-frozen during the shipment, via an international door-to-door courier company (World Courier) in two parties one week apart. Duplicate samples of an individual were sent separately. The analytical facilities guaranteed the validation of the analytical method, accuracy and precision of the analysis of study samples with an inter- and intra-assay coefficients of variations data of the calibration curve (5 to 500 ng/ml CV 12%) and at least four quality control samples (CV 20%) in each batch of study samples. The HPLC system used for the analysis of the study samples consisted of a pump (LC-9A, Shimadzu), an automatic injector (WISP 710, Waters Ass.), a column oven (Lisa Heater I&T), a UV detector (SPD-10A, Shimadzu), and a column (Kromasil C18, 5µm, 100A, 250x4.6 mm, Touzart & Matignon).

Statistics: The peak plasma concentration (C_{max}) and the time taken to reach peak plasma concentration (t_{max}) were calculated from the actual observed data of each volunteer. The area under the plasma famotidine concentration - time curve (AUC_{0-t}) was calculated by trapezoidal rule and ($AUC_{t-\infty}$) was derived by dividing the last observed famotidine concentration by elimination rate constant. Analysis of C_{max} and AUC were carried out by analysis of variance using PROC ANOVA on the logarithmically transformed data. The analysis of t_{max} were done with non-parametric Wilcoxon signed rank test by using PROC UNIVARIATE.

RESULTS

All subjects completed the study and no adverse effects were observed. The study was carried out according to the protocol except for one deviation. Drug administration and blood sampling at all time points were performed with a 30 min delay for Subject No. E5 at the second study period. Two different formulations of famotidine were found bioequivalent with acceptable confidence intervals of the differences in C_{max}, t_{max} and $AUC_{0-\infty}$. Mean plasma concentration versus time profiles of Famodin (İlsan-İltaş A.Ş.) and Pepdine (Merck, Sharp and Dohme) in the twenty four study subjects after a single oral dose of 40 mg are shown in Fig 1.

Table II presents the bioavailability parameters following the administration of each formulation. The mean (±SD) maximum plasma concentrations are 174 ± 59 ng/ml (males:171±45 ng/ml, females: 178±73 ng/ml) for the test formulation and 151±49 ng/ml (males: 133±40 ng/ml, females: 169+53 ng/ml) for the reference formulation following single oral administration of 40 mg famotidine. Maximal plasma concentrations were observed between 1 h to 4 h for the test and between 0.5 h to 3.5 h for the reference formulation, and mean (±SD) AUC is 947±273 $ng.ml^{-1}.h$ (males: 862±175 $ng.ml^{-1}.h$, females: 1032±330 $ng.ml^{-1}.h$) and 868±265 $ng.ml^{-1}.h$ (males: 751±194 $ng.ml^{-1}.h$, females: 985±82 $ng.ml^{-1}.h$) for the test and reference formulations, respectively. Elimination half-life ($t_{1/2}$) was found about 3 h for each product (3.27±1.82 for the test formulation and 2.99±0.53 for the reference formulation). The mean C_{max} and the mean AUC values after administration of

the test formulation are slightly (13 and 8%, respectively) higher than the reference formulation, however, the differences were within the acceptable range of confidence intervals. The individual relative bioavailability ranges from 0.57 to 1.92 with a mean relative bioavailability (±SD) of 1.14+0.31.

DISCUSSION

In the present study, the area under the plasma famotidine concentration - time curves (AUC) was similar following a single dose of both products. The coefficients of variation for AUC were comparable between the two formulations (about 30%), and the time to reach maximal plasma concentrations (t_{max}) also did not show a remarkable difference. The 90% confidence interval for AUC (0.91 to 1.21) is included within the bioequivalence range (0.80 - 1.25) (10,11). Mean C_{max} value obtained with the test formulation is slightly higher than that of the reference product, but the difference was not statistically significant. The 90% confidence interval for C_{max} (1.00 to 1.32) was within the extended bioequivalence range (0.70-1.43). The final version of the European Committee for Proprietary Medicine Products (CPMP) guidance states that for the C_{max}-ratio a wider acceptance range may be necessary than for the AUC-ratio, because single concentrations, in particular extreme concentrations like C_{max}, generally have a larger variation than integrated characteristics like AUC (10,11).

In conclusion, the study has shown that after administration of a single oral dose of 40 mg, the two famotidine formulations are bioequivalent with respect to the rate and extent of the absorption of famotidine.

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Table I. Age, body weight, height and administered treatment of the subjects.

Subject No	Age (yr)	Weight (kg)	Height (cm)	Period 1	Period 2
K1	20	56	158	A	B
K2	23	55	158	B	A
K3	24	64	173	A	B
K4	23	59	158	B	A
K5	22	55	162	B	A
K6	22	47	160	B	A
K7	20	62	173	B	A
K8	25	62	169	A	B
K9	25	60	163	B	A
K10	20	54	165	A	B
K11	19	58	164	A	B
K12	20	58	165	A	B
E1	21	65	169	A	B
E2	25	79	185	B	A
E3	23	65	182	B	A
E4	23	70	170	A	B
E5	25	67	182	A	B
E6	26	64	175	B	A
E7	24	65	170	B	A
E8	21	65	170	A	B
E9	25	80	180	B	A
E10	24	73	170	A	B
E11	22	80	178	B	A
E12	21	62	176	A	B
Median	23	63	170		
Minimum	19	47	158		
Maximum	26	80	185		

K: females; **E:** males; **A:** one tablet of 40 mg Famodin® (test formulation);
B: one tablet of 40 mg Pepdine® (reference formulation).

Table II. The mean (S.D.) pharmacokinetic parameters of famotidine following administration of a single oral dose of 40 mg of two different formulations to 24 healthy volunteers.

Famotidine	C_{max} (ng/ml)	t_{max} (h)	AUC_{0-t} (ng.ml-1.h)	$AUC_{0-\infty}$ (ng.ml-1.h)	$t_{1/2}$ (h)
A (test)					
Mean	174	2.29	904	947	3.27
SD	59	0.92	262	273	1.82
B (reference)					
Mean	151	2.00	834	868	2.99
SD	49	0.93	261	265	0.53
Statistics	NS(1)	NS(2)	NS(1)	NS(1)	NS(2)
90 % confidence intervals	1.00-1.32	-	0.99-1.21	0.99-1.21	

(1): Analysis of variance on log-transformed data
(2): Wilcoxon signed rank test

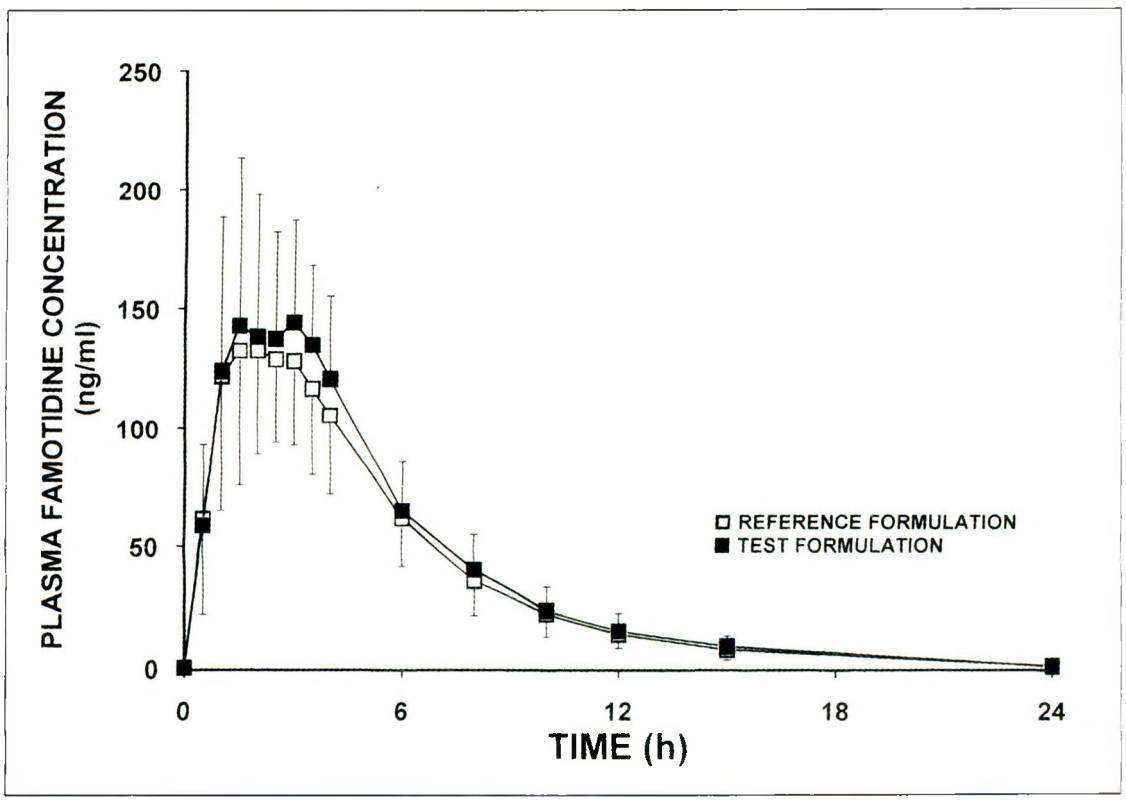

Fig. 1.: Plasma famotidine concentration - time curves after administration of a single oral dose of 40 mg to 24 healthy volunteers (12 females and 12 males). The data are expressed as mean±SD.

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