(10)

International Journal of Clinical Pharmacology and Therapeutics, Vol. 36, No.54 – 1998 (270–274)

Comparative bioavailability of two tablet formulations of ranitidine hydrochloride in healthy volunteers

S.A. BAWAZIR[1], M. WAFIK GOUDA[1], Y.M. EL-SAYED[1], K.I. AL-KHAMIS[1], M.J. AL-YAMANI[1], E.M. NIAZY[2] and K.A. AL-RASHOOD[1]

[1]*College of Pharmacy, King Saud University, Riyadh, and*
[2]*Tabuk Pharmaceutical Manufacturing Company, Tabuk, Saudi Arabia*

Abstract. This investigation was carried out to evaluate the bioavailability of a new tablet formulation of ranitidine HCl (300 mg), Ranid, relative to the reference product, Zantac, (300 mg) tablets. The bioavailability was carried out on 24 healthy male volunteers who received a single dose (300 mg) of the test (T) and the reference (R) products in the fasting state, in a randomized balanced 2-way crossover design. After dosing, serial blood samples were collected for a period of 16 hours. Plasma harvested from blood was analyzed for ranitidine by a sensitive and validated high-performance liquid chromatographic assay. The maximum plasma concentration (C_{max}), area under the plasma concentration time curve up to the last measurable concentration (AUC_{0-t}), and to infinity ($AUC_{0-\infty}$) and the absorption rate ($C_{max}/AUC_{0-\infty}$) were analyzed statistically under the assumption of a multiplicative model. The time to maximum concentration (T_{max}) was analyzed assuming an additive model. The parametric confidence intervals (90%) of the mean values of the pharmacokinetic characteristics (AUC_{0-t}, $AUC_{0-\infty}$, C_{max} and $C_{max}/AUC_{0-\infty}$) for T/R ratio were in each case well within the bioequivalence acceptable range of 80 – 125%. The test formulation was found bioequivalent to the reference formulation by the Schuirmann's two one-sided t-tests and by Wilcoxon Mann Whitney two one-sided tests procedure. Therefore, the 2 formulations were considered to be bioequivalent.

Key words: ranitidine – comparative bioavailability – ranid – zantac – healthy volunteers

Introduction

Ranitidine is a histamine H_2 receptor antagonist, which inhibits competitively and reversibly the interaction of histamine with H_2 receptors. It reduces gastric acid secretion elicited by histamine and gastrin and stimulated by betazole and food. Ranitidine also inhibits basal and nocturnal acid secretion [Brogden et al. 1982, Grant et al. 1989, Woodings and Richards 1980]. Ranitidine HCl is indicated in active and maintenance therapies of duodenal ulcer. It is also used in treatment of active, benign gastric ulcer, pathological hypersecretory conditions, and gastroesophageal reflux disease. Serum concentrations of 36 – 94 ng/ml of ranitidine have been shown to inhibit 50% of stimulated gastric acid secretion. The recommended oral dosage of ranitidine HCl tablets for active duodenal ulcer is 150 mg twice a day, or 300 mg at bedtime [Physician's Desk Reference 1994].

Received January 7, 1998.

Correspondence to Prof. Dr. K.A. Al-Rashood, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia.

The drug has an absolute bioavailability of 50 – 60% following oral administration of 150 mg tablets [Grag and Eshelman 1983, Vanhecken et al. 1982]. A linear relationship has been found between the dose and the area under the plasma concentration time curve following the administration of oral doses of 100, 150, 250, and 400 mg of ranitidine tablets [Grag et al. 1985]. A secondary peak in plasma concentration time curve has been reported for ranitidine following oral administration of 100 and 150 mg tablets in fasting studies [Grag et al. 1983, Shim and Hong, 1989, Vanhecken et al. 1982]. The mean values reported for the peaks were 1.5 hours for the first peak and 3.9 hours for the second [Shim and Hong 1989]. The reported elimination half-life of ranitidine is 2.5 – 3.0 hours. Approximately 30% of ranitidine is excreted unchanged in urine within 24 hours following the administration of an oral dose [Physician's Desk Reference 1994].

The objective of this study was to compare the rate and extent of absorption of ranitidine from a new commercial tablet formulation (Ranid) relative to the reference formulation (Zantac). Bioequivalence of the 2 products was assessed based on the plasma concentration data ob-

tained following their administration to 24 healthy male volunteers in a balanced 2-way crossover design.

Subjects, materials and methods

Subjects

Twenty-four healthy male adult volunteers participated in the study. Their mean age (± SD) was 36.6 ± 7.28 years with a range of 19 – 49 years, body weight of 79.8 ± 7.68 kg with a range of 60 – 90 kg and height of 171.6 ± 5.16 cm with a range of 161 – 185 cm. On the basis of medical history, clinical examination, and laboratory investigation (hematology, blood biochemistry, and urine analysis), no subject had a history or evidence of hepatic, renal, gastrointestinal, or hematologic deviations or any acute or chronic diseases or drug allergy. The volunteers were asked to abstain from taking any drug including OTC for at least 2 weeks prior to and during the study. Informed consent was obtained from the subjects after explaining the nature and purpose of the study. The study protocol was approved by King Khalid University Hospital, College of Medicine Research Center (CMRC), King Saud University, Riyadh, Saudi Arabia.

Study products

Test product (T): Ranid – ranitidine HCl 300 mg tablets, batch No: PD-05, expiration date: 12/1997, Tabuk Pharmaceutical Manufacturing Co., Tabuk, Saudi Arabia.

Reference product (R): Zantac – ranitidine HCl 300 mg tablets, batch No: W1164LL, expiration date: 9/1997, Glaxo Laboratory, England.

Study design and blood samples

The administration of the 2 products to the subjects was carried out by means of a 2-way crossover design with a 1-week washout period. Subjects were randomly divided into 2 equal groups and assigned to 1 of the 2 sequences of administration. Each subject received a single dose of 300 mg tablet of either brand with 240 ml of water after overnight fast for at least 10 hours. Subjects were allowed to eat a standard breakfast at 4 h, lunch at 8 h, and dinner at 12 h after drug administration. Beverages and food containing caffeine were not permitted over the entire course of the study. Volunteers were ambulatory during the study, but strenuous activity was prohibited.

Multiple blood samples (7 ml) were collected in evacuated glass tubes (heparinized vacutainers, Beckton and Dickinson, Rutherford, NJ, USA) through an indwelling cannula placed in the forearm veins before and at 0.33, 0.50, 0.67, 1.0, 1.33, 1.50, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 14.0, and 16.0 hours post dosing. The plasma was then separated after centrifugation and stored frozen at –20° C pending analysis.

Analysis of plasma samples

The concentrations of ranitidine in plasma were measured by a specific and validated HPLC method using UV detection at 330 nm. The assay is performed after single extraction of ranitidine and procainamide (internal standard) from alkalinized plasma into methylene chloride. The drug and the internal standard were eluted from a μ-Bondapak C18 column at ambient temperature with a mobile phase consisting of acetonitrile: 0.1 M potassium dihydrogen phosphate (8 : 92% v/v) adjusted with phosphoric acid to an apparent pH 5.1 at a flow rate of 2.0 ml/min. Standard curves for the analyte in plasma were generated daily and were linear ($r > 0.997$) in the range of 20.0 – 2,000 ng/ml over the entire period of the study. The limit of quantitation for ranitidine in plasma is 20.0 ng/ml. Intraday coefficients of variation (CV) ranged from 3.22% – 6.27% (n = 11) and interday CVs ranged from 3.76% – 9.24% (n = 12) at 5 different concentrations (40, 175, 400, 800, and 1,750 ng/ml). The relative recoveries ranged from 89.97% – 112.10% (n = 12) at the 5 different concentrations. The test samples from the dosed volunteers were always analyzed along with standard and quality control samples. All specimens used to study precision and bias were interspersed with clinical specimens during analysis.

Pharmacokinetic analysis

The pharmacokinetic characteristics for ranitidine were determined from the plasma concentration time data. The maximum plasma concentration (C_{max}) and time to reach maximum plasma concentration (T_{max}) were obtained directly from the plasma concentration time data and used as measures of rate of absorption. The area under the plasma concentration time curve up to the last time (t) showing a measurable concentration (C_t) of the analyte (AUC_{0-t}) was determined by using the linear trapezoidal rule. The apparent elimination rate constant (K_{el}) was calculated by the technique of least-square regression from the data of the last 4 – 6 points of each plasma concentration time curve. The $AUC_{0-\infty}$ values (express the magnitude of absorption) were determined by adding the quotient $\hat{C}_t$ and the appropriate K_{el} to the corresponding AUC_{0-t}, that is:

$$AUC_{0-\infty} = AUC_{0-t} + \hat{C}_t/K_{el}$$

where $\hat{C}_t$ is the estimated last plasma concentration. The sampling period covered more than 96% of total AUCs for both brands T and R. The apparent elimination half-life

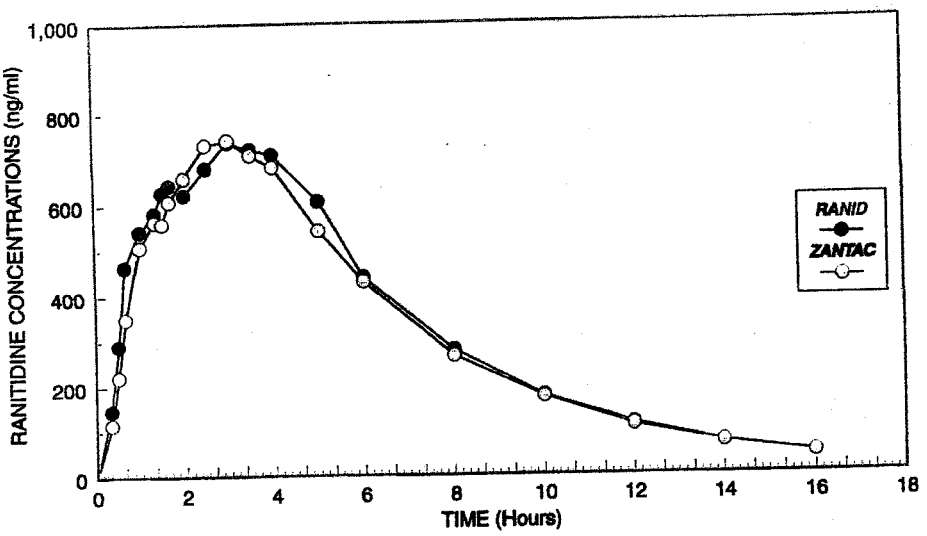

Fig. 1 Mean plasma concentration time profiles of ranitidine following oral administration of the 2 brands to 24 healthy male volunteers

($t_{1/2}$) for ranitidine in plasma was calculated by using the following equation:

$t_{1/2} = (\ln 2)/K_{el}$.

The rate of absorption was also evaluated by means of the ratio $C_{max}/AUC_{0-\infty}$.

Statistical analysis

The 2-way analysis of variance (ANOVA) for cross-over design was used to assess the effect of formulations, periods, sequences, and subjects within sequence on logarithmically transformed data of AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, $C_{max}/AUC_{0-\infty}$, K_{el}, and $t_{1/2}$ parameters. The ANOVA for T_{max} was carried out on the untransformed data. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. Parametric 90% confidence intervals based on the ANOVA of the mean T/R ratios of AUC parameters $C_{max}/AUC_{0-\infty}$ and C_{max} were computed under the assumption of a multiplicative model. Parametric 90% confidence intervals for the characteristic T_{max} was performed under the assumption of additive model and the equivalence range was expressed in absolute differences of the mean T – R. Nonparametric confidence interval was also performed [Hauschke et al. 1990]. In addition, bioequivalence between the 2 formulations was also assessed by Schuirmann's two one-sided t-tests [Schuirmann 1987] and by means of nonparametric Mann Whitney Wilcoxon tests procedures [Hauschke et al. 1990]. Plots of residuals versus predicted and univariate analyses were performed for the AUCs and C_{max} to screen for extreme outliers and departure from normality. For all analyses effects were considered statistically significant if the probability associated with F was < 0.05. All analyses of the data were performed with the statistical software package SAS using the GLM procedure (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA).

Results and discussion

Ranitidine was well tolerated by the subjects. Unexpected incidents that could have influenced the outcome of the study did not occur. All volunteers who started the study continued to the end and were discharged in good health.

Both of the formulations of ranitidine were readily absorbed from the gastrointestinal tract of the volunteers. Ranitidine was measurable at the first sampling time (0.33 h) in all volunteers following the administration of the T and R formulations. The mean plasma concentration time curves for the 2 brands are demonstrated in Figure 1. It can be seen that the mean plasma concentration time profiles from brands T and R are almost superimposable. Nineteen ANOVAs were performed to compare ranitidine plasma concentrations at each sampling time. Ranitidine plasma concentrations were statistically higher following administration of Ranid relative to Zantac at 0.5 and 0.67 hours. There was no statistical difference between the 2 formulations at the 17 remaining time points. The parameters used to measure bioavailability were AUC_{0-t} and $AUC_{0-\infty}$ for the extent of absorption and T_{max}, C_{max}, and $C_{max}/AUC_{0-\infty}$ for the absorption rate and they were calculated in a model-independent manner. Table 1 shows the geometric mean values and the range for the above parameters (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, and $C_{max}/AUC_{0-\infty}$) along with K_{el} and $t_{1/2}$. The pharmacokinetic characteristic T_{max} is presented as mean (± SD). The relative bioavailability of the generic formulation was found to be 107.9%, 107.7%, and 106.2% based on AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, respectively.

Table 1 Mean pharmacokinetic characteristics for ranitidine after administration of the 2 formulations to 24 subjects.

Parameter	Test formulation	Reference formulation
AUC_{0-t} (ng×h/ml)		
Geometric mean	5046.2	4866.8
Range	3770.3 – 6754.1	3670.2 – 6453.6
$AUC_{0-\infty}$ (ng×h/ml)		
Geometric mean	5,238.5	5,062.9
Range	3906.9 – 7024.1	3808.5 – 6730.5
C_{max} (ng/ml)		
Geometric mean	944.0	951.5
Range	695.3 – 1281.6	697.4 – 1298.2
T_{max} (h)		
Mean	3.17	2.78
± SD	1.16	1.02
K_{el} (h^{-1})		
Geometric mean	0.225	0.222
Range	0.205 – 0.248	0.204 – 0.242
$t_{1/2}$ (h)		
Geometric mean	3.08	3.12
Range	2.80 – 3.38	2.87 – 3.40
$C_{max}/AUC_{0-\infty}$ (h^{-1})		
Geometric mean	0.179	0.188
Range	0.143 – 0.223	0.145 – 0.244

Geometric mean = exp (mean(Ln)), range = exp (mean(Ln) ± SD (Ln)), the pharmacokinetic characteristics AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, K_{el}, $t_{1/2}$, and $C_{max}/AUC_{0-\infty}$ were determined based on a multiplicative model, T_{max} was analyzed assuming additive model

Table 2 Parametric and nonparametric 90% confidence intervals for the mean pharmacokinetic characteristics of ranitidine formulations

Model multiplicative	T/R point estimate	Confidence limits	Level of confidence
Parametric analysis*			
$AUC_{0->t}$	103.7	95.5 – 112.5	90
$AUC0->\infty$	103.5	95.4 – 112.2	90
C_{max}	99.2	89.1 – 110.4	90
K_{el}	101.5	99.8 – 103.2	90
$t_{1/2}$	98.5	96.9 – 100.2	90
$C_{max}/AUC_{0->\infty}$	95.0	88.1 - 102.4	90
Nonparametric analysis**			
$AUC_{0->t}$	106.7	92.8 – 119.6	91.13
$AUC_{0->\infty}$	105.4	93.4 – 118.9	91.13
C_{max}	101.8	89.2 – 117.0	91.13
K_{el}	101.9	99.2 – 101.9	91.13
$t_{1/2}$	98.0	95.8 – 100.8	91.13
$C_{max}/AUC_{0->\infty}$	95.4	85.3 – 107.4	91.13
Model additive	**T – R (hours) point estimate**	**Confidence limits**	**Level of confidence**
Parametric analysis*			
T_{max}	–0.39	0.01 – 0.75	90
Nonparametric analysis**			
T_{max}	0.25	0.0 – 0.75	91.13

* = two one-sided t-tests, ** = two one-sided Wilcoxon tests

Table 3 Two one-sided t-tests and power values for $AUC_{0-\infty}$, C_{max}, and $C_{max}/AUC_{0-\infty}$ using multiplicative model

Parameter	Tl	Tu	t 0.95,22	Power*
$AUC_{0-\infty}$	4.1751	3.0685	1.7171	0.9650
C_{max}	2.6505	2.8459	1.7171	0.8431
$C_{max}/AUC_{0-\infty}$	3.0045	4.8118	1.7171	0.9803

Tl = lower limit of the calculated test statistics, Tu = upper limit of the calculated test statistics, * = power of Schuirmann's two 1-sided t tests using log-transformed data

Analysis (by ANOVA) of the bioavailability data showed that there were no significant differences between formulations on any of the pharmacokinetic characteristics (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, and $C_{max}/AUC_{0-\infty}$). Neither was there any period and sequence effect on these parameters. However, there were significant intersubject variations in these parameters except that on C_{max} and T_{max}. This was expected in view of wide intersubject variations in these parameters probably due to differences in drug clearance. The intraindividual variations in the AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, and $C_{max}/AUC_{0-\infty}$ estimated from the coefficients of variation as determined by ANOVA were 20.33%, 20.31%, 25.19%, 32.37%, and 20.97%, respectively.

Table 2 shows the parametric 90% confidence intervals of the mean values of the pharmacokinetic characteristics (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, K_{el}, $t_{1/2}$, and $C_{max}/AUC_{0-\infty}$) as well as the point estimates for T/R ratio assuming multiplicative model. Nonparametric confidence interval was also included. The confidence limits for the mean AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, K_{el}, $t_{1/2}$, and $C_{max}/AUC_{0-\infty}$ indicate that these values are entirely within the bioequivalence acceptable range of 80 – 125%. With regard to the characteristic T_{max}, untransformed data were used and the bioequivalence range was expressed in absolute difference instead of proportions (Table 2). It can be seen from Table 2 that the parametric point estimate of the difference (T – R) is –0.39 h and thus within the stipulated bioequivalence range of ± 0.56 h (± 20% of the mean of the reference formulation). The 90% confidence interval ranges from 0.01 – 0.75 h, hence, equivalence with respect to the rate of absorption can be concluded. Further, the test formulation was found bioequivalent to the reference formulation by the Schuirmann's two one-sided t-tests and by Wilcoxon Mann Whitney two one-sided tests procedure. Table 3 shows that the results of the two one-sided t-tests and power values of the two one-sided t-tests for the pharmacokinetic characteristics $AUC_{0-\infty}$, C_{max}, and C_{max}/AUC_{0-}

$_{\infty}$ assuming multiplicative model. It can be seen from Table 3 that both the upper and lower limits of the calculated test statistics are greater than the t value, therefore, the 2 formulations are concluded to be bioequivalent.

In conclusion, based on the pharmacokinetic and statistical results of this study, we can assume interchangeability of both preparations in clinical practice.

REFERENCES

Brogden RN, Carmin AA, Heel RC 1982 Ranitidine. A review of its pharmacology and therapeutic use in peptic ulcer disease and other allied diseases. Drugs *24:* 267-303

Grag DC, Weidler DJ, Eshelman FN 1983 Ranitidine bioavailability and kinetics in normal male subjects. Clin Pharmacol Ther *33:* 445-452

Grag DC, Eshelman FN 1985 Pharmacokinetics of ranitidine following oral administration with ascending doses and with multiple-fixed doses. J Clin Pharmacol *25:* 434-443

Grant SM, Langtry HD, Brogden RN 1989 Ranitidine: uptake review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in peptic ulcer disease and other allied diseases. Drugs *37:* 801-870

Hauschke D, Steinijans VW, Diletti E 1990 A distribution-free procedure for the statistical analysis of bioequivalence studies. Int J Clin Pharmacol Ther Toxicol *28:* 72-78

Physician's Desk Reference 1994 48th edn, Medical Economic Company, Montvale, pp 1019-1021

Schuirmann DJ 1987 A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokin Biopharm *15:* 657-680

Shim CK, Hong JS 1989 Inter- and intrasubject variations of ranitidine pharmacokinetics after oral administration to normal male subjects. J Pharm Sci *78:* 990-994

Vanhecken AM, Tjandramage TB, Mullie A, Verbesselt R, Deschepper PJ 1982 Ranitidine: Single dose pharmacokinetics and absolute bioavailability in man. Br J Clin Pharmacol *14:* 195-200

Woodings EP, Richards DA 1980 Ranitidne – a new H_2 receptor antagonist. Gut *21:* 187-191