

Compartmental analysis of ranitidine doubled peak plasma profile after oral administration to healthy volunteers

Virna Josiane Aurelio Schuck¹, Teresa Dalla Costa¹, Sérgio G.S. de Barros², Carlos Gruber², Elfrides Eva Schermann Schapoval^{1*}

¹Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul, ²Hospital de Clínicas de Porto Alegre, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul

The aim of this study was to describe the double peak plasma pharmacokinetic profile of ranitidine after oral administration to healthy volunteers using non-compartmental and compartmental analysis. A single 300 mg dose of ranitidine was given to ten healthy volunteers (5 male and 5 female). Blood samples were drawn at different times and analyzed by HPLC. Plasma profiles were evaluated by non-compartmental and compartmental approaches. The non-compartmental parameters determined were k ($0.0054 \pm 0.0010 \text{ min}^{-1}$), $t_{1/2}$ ($2.2 \pm 0.4 \text{ h}$), Vd_{ss}/F ($265.3 \pm 70.6 \text{ L}$), Cl/F ($84.8 \pm 24.3 \text{ L/h}$) and AUC ($225916 \pm 54099 \text{ ng} \cdot \text{min/mL}$). The compartmental analysis was carried out using a two compartments body model, with first order absorption from two different sites. The parameters determined were k_{21} ($0.0149 \pm 0.0133 \text{ min}^{-1}$), k_{a1} ($0.0117 \pm 0.0073 \text{ min}^{-1}$), k_{a2} ($0.1496 \pm 0.1699 \text{ min}^{-1}$), Vc ($128 \pm 75.2 \text{ L}$), a ($0.0299 \pm 0.0319 \text{ min}^{-1}$), b ($0.0074 \pm 0.0014 \text{ min}^{-1}$) and time for the beginning of the absorption from the second site ($126.7 \pm 58.1 \text{ min}$). The model used in the compartmental analysis was adequate to describe the double peak of ranitidine plasma profile and to determine the pharmacokinetic parameters.

Uniterms:

- Ranitidine
- Pharmacokinetics
- Compartmental analysis
- Double peak plasma profile

*Correspondence:

E. E. S. Schapoval
Universidade Federal do Rio Grande do Sul
Faculdade de Farmácia
Av. Ipiranga, 2752 - Bairro Santana
90610-000 - Porto Alegre - RS
E-mail: elf@farmacia.ufrgs.br

INTRODUCTION

Ranitidine is histamine H_2 receptor antagonist used in the treatment of gastric disease related to acid gastric hypersecretion (Grant *et al.*, 1989).

Ranitidine pharmacokinetics has been evaluated in many studies after intravenous and oral administration (Van Hecken *et al.*, 1982; Richards, 1983; Roberts, 1984; Grant *et al.*, 1989; Shim, Hong, 1989; Santos *et al.*, 1996). The plasma concentration-time profile of ranitidine after intravenous administration shows a biexponential behavior that is characteristic of a two compartment open model.

It has been shown in the literature that ranitidine presents double peak profile after oral administration. These pharmacokinetics profiles have been evaluated according to a non-compartmental analysis for bioavailability and bioequivalence determination (Hilgenstock *et al.*, 1987). Several mechanisms have been postulated to explain the double peak phenomenon such as enterohepatic recirculation, delayed gastric emptying, drug storage and subsequent release from a post-absorptive depot, variable absorption rates along the gastrointestinal tract, and discontinuous absorption (Suttle *et al.*, 1992; Suttle, Brouwer, 1994; Reynolds *et al.*, 1998). In this way, ranitidine

compartmental analysis requires the use of a modified absorption equation that properly describes the double peak observed. A compartmental analysis after oral administration of this drug is not reported in the literature. Pharmacokinetic compartmental analysis is important to allow forecasting drug concentrations in the peripheral compartment for pharmacokinetic-pharmacodynamic modeling (PK-PD modeling) when the biophase is in a different compartment than the blood (Stanski, 1991; Shargel, Yu, 1999).

Considering the status of ranitidine pharmacokinetics evaluation, the aim of this study was to describe ranitidine pharmacokinetics after oral administration to healthy volunteers using non-compartmental and compartmental analysis. The compartmental analysis was conducted aiming to find an appropriate pharmacokinetic model to describe the individual double peak plasma profiles observed for the drug.

METHODS

Subjects

Ten healthy volunteers (5 male and 5 female) with an average age of 24.5 ± 2.7 years and an average body weight of 65.0 ± 11.0 kg were included in the study. They were selected based on their medical history, as well as physical and clinical examination. Informed written consent was obtained from all volunteers. The protocol was reviewed and approved by the Ethics Committee of the University Hospital (Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brazil).

Study design

The subjects were instructed to avoid drug and alcohol intake for a week before the study. In the day of the experiment each volunteer received a single tablet of 300 mg of ranitidine (Glaxo Wellcome, Brazil) with 200 mL of water at 9 am, after 8 hour fasting. Standard meals were given after 4 hour of drug administration. Blood samples were collected into heparinized tubes before and at 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 240, 360, 480 and 600 minutes after drug administration. Samples were harvest into heparinized tubes, plasma was separated by centrifugation and frozen to -20 °C until analyzed.

Analytcs

Ranitidine plasma concentration was determined by a validated HPLC method (Koch *et al.*, 1997). Briefly, plasma (1 mL) was desproteinated with 4% perchloric acid and centrifuged at 3000 rpm for 5 min. The supernatant (500 μ L) was neutralized with 500 μ L of 1 M sodium carbonate. This mixture (100 μ L) was injected into the system which consisted of a guard column Perisorb 30-40 μ m 4 x 10 mm, an analytical column Beta Basic RP8 5 μ m 250 x 4.6 mm, a pump Shimadzu LC-10AD, an ultraviolet detector Shimadzu SPD-10^A and an integrator Shimadzu C-R6A. The flow rate was set to 1 mL/min and the mobile phase consisted of 0.05 M phosphate buffer (pH 4.0): acetonitrile (94:8 v/v).

The assay was validated according to the International Conference of Harmonization (ICH) (Swartz, Krull, 1998). The method showed to be linear over the range of 25 to 1400 ng/mL with correlation coefficients better than 0.9991. The LOQ was 25 ng/mL. The intra-day precision was higher than 94% while the inter-day precision was higher than 88%. The accuracy was bigger than 95%. Since the acceptance criteria for precision and accuracy is variation inferior to 15% for both parameters (Shah *et al.*, 1992), the method was considered adequate for the measurement of ranitidine in plasma.

Pharmacokinetic analysis

Individual plasma concentration-time profiles were analyzed according to non-compartmental and compartmental analysis. The independent model parameters determined were the elimination rate constant (k), the half-life ($t_{1/2}$), the relative total clearance (Cl/F), the relative volume of distribution at steady state (Vd_{ss}/F), the area under the concentration time curve (AUC), area under the first moment curve (AUMC), and the mean residence time (MRT) (Gibaldi, Perrier, 1982). The plasma concentration peak (Cp_{max}) and the time to reach this peak (T_{max}) were obtained directly from the plots.

The compartmental analysis was carried out according to a two-compartments open model with two first order absorption rate constants from two different sites in the gastrointestinal tract. The schematic representation of the model is showed in Figure 1.

The equation that describes the drug concentration in the central compartment of this model is shown below (Wagner, 1993):

$$Cp = \left\{ \left[\frac{ka_1 \cdot f \cdot F \cdot D}{Vc} \right] \times \left[\left(\frac{(k_{21} - \alpha)e^{-\alpha \cdot t}}{(ka_1 - \alpha)(\beta - \alpha)} \right) + \left(\frac{(k_{21} - \beta)e^{-\beta \cdot t}}{(ka_1 - \beta)(\alpha - \beta)} \right) + \left(\frac{(k_{21} - ka_1)e^{-ka_1 \cdot t}}{(\alpha - ka_1)(\beta - ka_1)} \right) \right] \right\} + \left\{ \left[\frac{ka_2 \cdot (1 - f) \cdot F \cdot D}{Vc} \right] \times \left[\left(\frac{(k_{21} - \alpha)e^{-\alpha \cdot (t - t_x)}}{(ka_2 - \alpha)(\beta - \alpha)} \right) + \left(\frac{(k_{21} - \beta)e^{-\beta \cdot (t - t_x)}}{(ka_2 - \beta)(\alpha - \beta)} \right) + \left(\frac{(k_{21} - ka_2)e^{-ka_2 \cdot (t - t_x)}}{(\alpha - ka_2)(\beta - ka_2)} \right) \right] \right\}$$

Equation 1

where C_p is the drug plasma concentration, D is the dose administered, F is the drug bioavailability, f is the fraction of the drug absorbed at each site, k_{a1} is the first absorption rate constant, k_{a2} is the second absorption rate constant, t_x

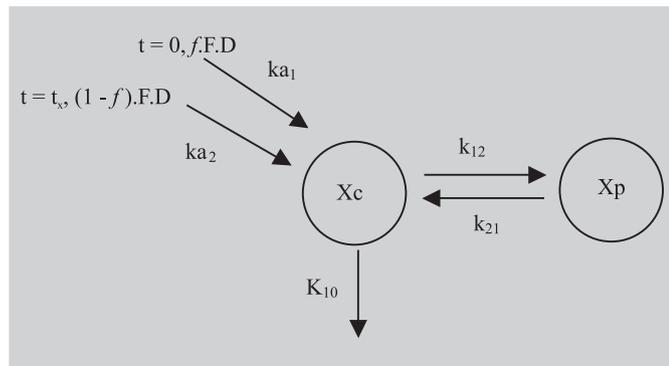


FIGURE 1 - Scheme of the two compartments open model with two parallel sites of absorption used in the compartmental analysis. X_c and X_p = amount of drug in the central and peripheral compartments, respectively; D = dose; F = drug bioavailability, f = fraction of the drug absorbed at each absorption site; k_{a1} = absorption rate constant at the first absorption site, k_{a2} = absorption rate constant at the second absorption site, t_x = time for the second fraction of the drug to begin to be absorbed; k_{12} = distribution rate constant from the central to the peripheral compartment; k_{21} = redistribution rate constant from the peripheral to the central compartment; k_{10} = elimination rate constant from the central compartment. Adapted from Wagner, 1993.

is the time for the second fraction of the drug to begin to be absorbed, k_{21} is the redistribution rate constant from the peripheral to the central compartment, a and b are the hybrid constants for distribution and elimination phases, respectively, V_c is the volume of distribution of the central compartment, and t is the time.

The individual plasma profiles from the volunteers were fitted to this model using the computer program SCIENTIST® v. 2.0 (MicroMath, Salt Lake City). The data points were not weighted for the analysis. The goodness of fit was evaluated using the model selection criteria (MSC) provided by the program. MSC is a modified Aikake information criterion that allows comparisons of variations data sets fitted to a selected model. Increased MSC values indicate more appropriate fits (SCIENTIST, 1995).

RESULTS

The average plasma concentration-time curves are shown in Figure 2. The first average plasma concentration peak ($C_{p_{max1}}$) was 765.4 ± 369.2 ng/mL and it was observed at 75 ± 27 min (T_{max1}). The second average peak ($C_{p_{max2}}$) was 898.6 ± 348.6 ng/mL and it was observed at 172 ± 58 min (T_{max2}). The plasma double peak was observed in all volunteers but two, whose plasma profiles showed a plateau in the time interval corresponding to the second peak. Representative profiles of two volunteers who presented doubled peak in plasma are presented in Figure 3. The individual and averaged $C_{p_{max}}$ and T_{max} are

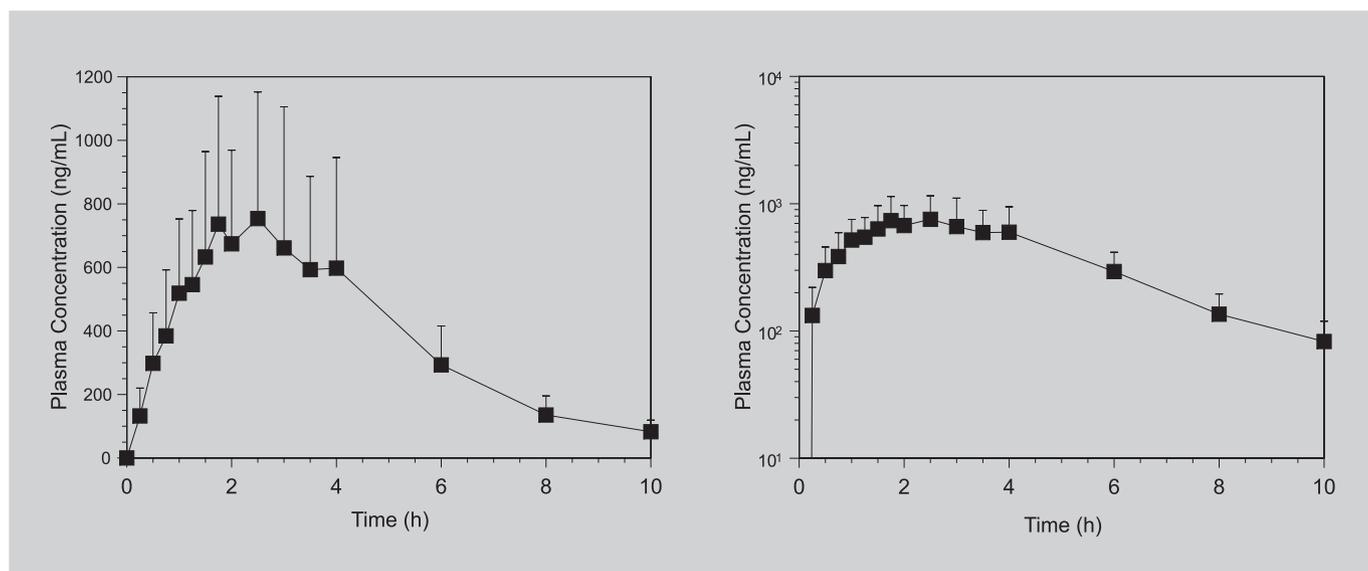


FIGURE 2 - Mean ranitidine plasma concentration *versus* time (left panel) and log mean plasma concentration *versus* time (right panel) profiles obtained after the administration of a single 300 mg oral dose of ranitidine to 10 healthy volunteers. Error bars indicate SD.

presented in Table I. The individual and average pharmacokinetic parameters determined by non-compartmental analysis are summarized in Table II.

The plasma concentration-time curve of each volunteer was fitted to the two-compartments open model described by Equation 1. The mean fit is shown in Figure 4. The individual and average pharmacokinetic parameters obtained from the fittings are depicted in Table III.

DISCUSSION

All parameters obtained in the non-compartmental analysis were similar to those shown in literature (Richards, 1983; Roberts, 1984; Desmond *et al.*, 1990;

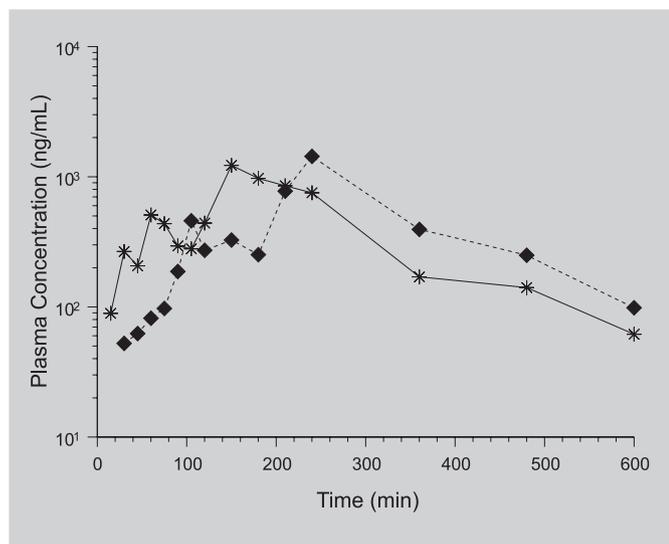


FIGURE 3 - Ranitidine plasma concentration *versus* time profiles obtained after the administration of a single 300 mg oral dose of ranitidine to subject 5 (◆) and subject 8 (*).

Santos *et al.*, 1996). Since in our study the bioavailability of ranitidine was not determined, the clearance and the volume of distribution calculated are relative. Assuming a bioavailability of 50%, reported for ranitidine after oral administration (Roberts, 1984), the mean CI obtained would be 706.5 ± 202.7 mL/min which is in good agreement with range of 600 to 700 mL/min reported in the literature (Van Hechen *et al.*, 1982; Roberts, 1984). The same is valid for the volume of distribution (Vd_{ss}) obtained which would be 132.7 ± 35.3 L, in a similar range of values reported by other authors (1.2 to 1.9 L/kg) (Van Hechen *et al.*, 1982; Richards, 1983).

The double peak observed in the plasma profiles of the volunteers after ranitidine oral administration is well described in the literature, although some author did not observed it in their studies (Lebert *et al.*, 1981; Hilgenstock *et al.*, 1987). The diverse plasma peak patterns observed by different authors have been related to the blood sampling intervals, to the inter-subject variation among the subjects employed in the studies and to the analytic methods used to measure ranitidine in plasma. Some authors related the second peak occurrence to the food intake (Shim, Hong, 1989). However, in our study, the food intake was allowed only four hours (240 min) after drug dosing and the second peak occurred between 105 and 240 min.

Both Cp_{max} and both T_{max} observed in this study showed a big variability among the volunteers which can be explained using the discontinuous absorption model suggested by Suttle and co-workers (1992). In this model, the gastrointestinal tract is divided into compartments connected according to a catenary system and the drug absorption occurs only in the first and in the last compartment. According to simulations done by these

TABLE I - Peak and time to peak values obtained from the plasma concentration-time curve of each volunteer after administration of an oral dose of 300 mg of ranitidine

Subject	Cp_{max1} (ng/mL)	T_{max1} (min)	Cp_{max2} (ng/mL)	T_{max2} (min)
1	1111.5	90	567.7	236
2	439.1	45	1143.2	105
3	657.0	60	—	—
4	898.8	60	435.8	150
5	458.8	105	1433.5	240
6	1220.0	105	—	—
7	494.6	90	782.3	150
8	508.2	60	1221.6	150
9	445.6	30	953.3	105
10	1419.9	105	642.1	240
Average \pm SD	765.4 \pm 369.2	75 \pm 27	898.6 \pm 348.6	172 \pm 58

TABLE II - Independent model parameters calculated from the plasma concentration-time curve of each volunteer after administration of an oral dose of 300 mg of ranitidine

Subject	K (min ⁻¹)	t _{1/2} (h)	AUC _{0-∞} (ng.h/mL)	Cl/F* (L/h)	Vd _{ss} /F* (L)	AUMC _{0-∞} (ng.h ² /mL)	MRT (h)
1	0.0057	2.0	4673	64.2	188.0	203233	4.4
2	0.0040	2.9	4547	66.0	278.1	217595	4.8
3	0.0060	1.9	2668	112.5	314.1	104816	3.9
4	0.0065	1.8	2187	137.2	350.6	65318	2.9
5	0.0058	2.0	4473	67.1	193.5	231981	5.2
6	0.0047	2.5	3306	90.8	322.6	151232	4.6
7	0.0056	2.1	3698	81.1	240.9	170667	4.6
8	0.0042	2.7	4017	74.7	294.4	171170	4.3
9	0.0047	2.5	3250	92.3	328.8	118414	3.6
10	0.0073	1.6	4834	62.1	142.1	185364	3.8
Mean ± SD	0.0054 ± 0.0010	2.2 ± 0.4	3765 ± 855	84.8 ± 24.3	265.3 ± 70.6	161979 ± 52732	4.2 ± 0.6

* F = absolute bioavailability

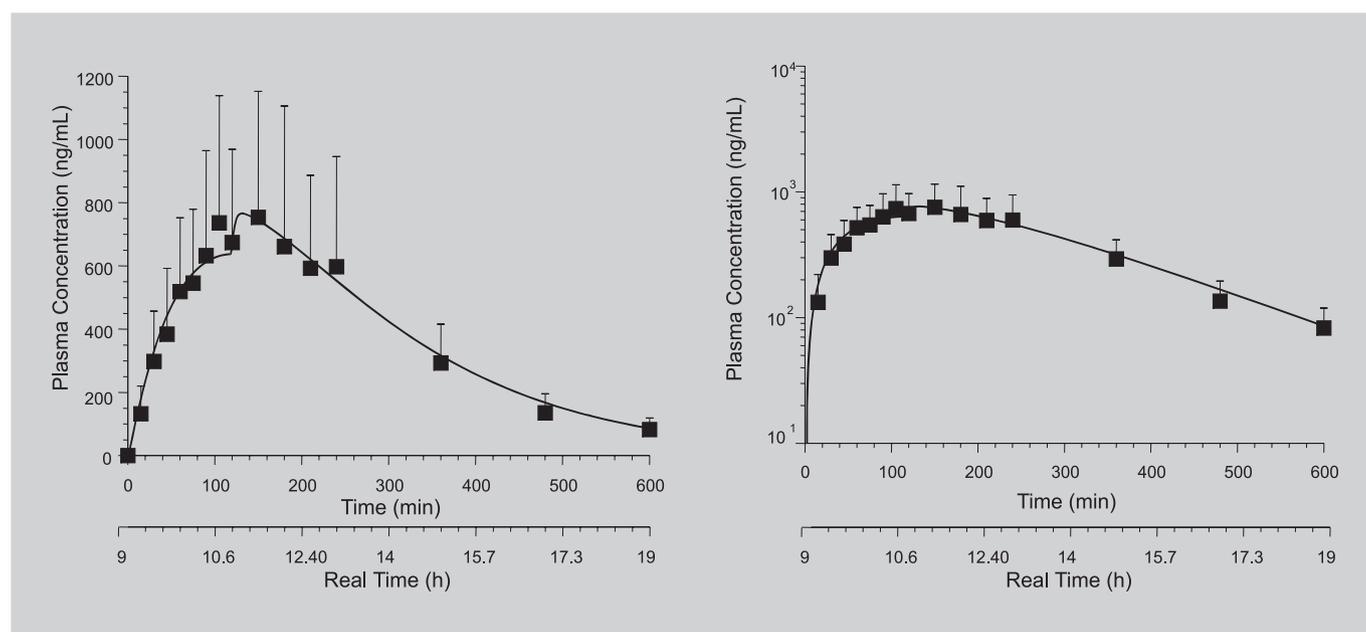


FIGURE 4 - Mean ranitidine plasma concentration *versus* time profile (left panel) and log mean plasma concentration *versus* time profile (right panel) after the administration of a single 300 mg dose to 10 healthy volunteers fitted to a two compartments open model with two sites of absorption (Eq. 1). Error bars indicate SD.

authors using the discontinuous absorption model, the intensity and variability of $C_{p,max}$ and T_{max} observed could be attributed to the following factors: the dose administered, the drug transfer rate from the stomach to the first site of absorption, the number of gut compartments, the distance between the two absorption sites, the drug transfer rate among the compartments, and the absorption rate in each site of absorption.

The compartmental analysis was carried out using

the individual plasma profiles. Although some studies indicate that ranitidine behaves in the body as a two compartments open model after intravenous administration, the plasma concentration-time curves obtained in this study after oral drug administration decline linearly as a single order process. After oral administration, the mono or biphasic declining of the drug plasma concentration-time profile will depend upon the rate of drug absorption, the number of samples taken within the collection period and

TABLE III - Pharmacokinetic parameters obtained from the analysis of the individual plasma concentration profiles using the two compartments model equation with two sites of absorption (Eq.1)*

Subject	k_{a_1} (min ⁻¹)	k_{a_2} (min ⁻¹)	α (min ⁻¹)	β (min ⁻¹)	k_{21} (min ⁻¹)	f	Vc/F (L)	t_x (min)
1	0.0100	0.0046	0.0072	0.0075	0.0031	0.574	66.0	206
2	0.0082	0.3520	0.0646	0.0062	0.0370	0.656	105.2	90
3	0.0152	0.0053	0.0081	0.0080	0.0047	0.632	136.5	196
4	0.0232	0.0284	0.0246	0.0089	0.0149	0.806	166.9	120
5	0.0024	0.1912	0.0108	0.0085	0.0074	0.538	85.1	208
6	0.0035	0.2959	0.1021	0.0096	0.0391	0.623	56.8	89
7	0.0213	0.0271	0.0053	0.0052	0.0062	0.630	301.4	88
8	0.0137	0.4766	0.0073	0.0071	0.0063	0.461	169.4	143
9	0.0151	0.0456	0.0442	0.0061	0.0212	0.539	142.3	54
10	0.0041	0.0694	0.0254	0.0071	0.0093	0.782	50.4	73
Mean ± SD	0.0117 ± 0.0073	0.1496 ± 0.1699	0.0299 ± 0.0319	0.0074 ± 0.0014	0.0149 ± 0.0133	0.62 ± 0.11	128.0 ± 75.2	127 ± 58

* See text for legend

the relative magnitude of the micro-constants of the model (k_{21} , k_a , k_{10}). If the drug distribution occurs faster than the absorption, the distribution phase will not be observed in the plasma concentration profile because the system will not provide enough time for the drug to distribute after absorption (Liang, Derendorf, 1998; Shargel, Yu, 1999).

The choice of the adequate compartmental model to analyze ranitidine profiles in this study was based on the best fit to the double peak obtained for the model tested. Although the concentration profiles show a log-linear declining, the one compartment open model with two sites of absorption did not fit well the double peak observed even though the resulting MSC was 1.32 ± 0.57 . The best fit was obtained using the equation that describes the two compartments open model with two sites of absorption, as shown in Figure 4. The mean MSC value obtained was 1.94 ± 0.67 which was considered adequate for this analysis.

As stated before, according to the discontinuous absorption theory, in the two compartments model with two sites of absorption, the gastrointestinal tract is divided into different compartments but the absorption will occur only in the first and in the last sites (Suttle *et al.*, 1992) (Figure 1). After the administration, the drug reaches the first site of absorption and a fraction of the dose (f) is absorbed. After absorption, this fraction of the drug reaches the central compartment (X_c) and distributes to the peripheral compartment (X_p) with a distribution rate constant k_{12} . The drug redistributes to the central compartment with a rate constant k_{21} , from where it will be eliminated. After the first absorption, the fraction not

absorbed in the first site passes through the gut and reaches the second site of absorption. In this site, the fraction of the drug remained in the bowel ($1-f$) will be absorbed and will be distributed in the body as the first fraction.

Some evidences in the literature also corroborate the choice for the discontinuous absorption model to describe the data obtained in this study. According to Suttle and Brouwer (1994) the gastric emptying or enterohepatic recirculation cannot contribute to the occurrence of a second peak in the ranitidine plasma profile because the amount of drug secreted in the bile in humans is too small, less than 3%, to promote a significant peak. Furthermore, the concentration time profiles observed when the drug is administered directly in the stomach did not show two peaks, indicating that the gastric emptying alone is not enough to promote a secondary peak (Williams *et al.*, 1992).

Although there are no reports in the literature on the compartmental analysis of ranitidine after oral administration which could be used to compare the pharmacokinetic parameters determined in this study, a comparison between the compartmental and non-compartmental results can be carried out. As expected, the volume of distribution of the central compartment (V_c/F) determined by the compartmental approach is smaller than the $V_{d_{ss}}/F$ calculated. The elimination rate constant (k) determined in the non-compartmental analysis (0.0054 ± 0.0010 min⁻¹) is similar to β -rate constant (0.0074 ± 0.0014 min⁻¹), showing that the compartmental approach appropriately described the elimination phase of the drug

from the body. Finally, the time to begin the drug absorption from the second absorption site (127 ± 58 min), according to the model theory, is smaller than the time observed for the drug to reach the second plasma peak (172 ± 58 min). These observations corroborate the adequacy of the compartmental model used to describe the data obtained.

CONCLUSIONS

The parameters calculated in the non-compartment analysis were similar to those reported in the literature indicating that the data obtained from the volunteers in this study are consistent with the previous reports. Eighth out of ten plasma concentration profiles of ranitidine after oral administration showed a double peak. This phenomenon was described appropriately using the two compartmental open model with two sites of absorption which considers that the absorption occurs in two different places in the gut as described by the discontinuous absorption theory. In conclusion, the double peak observed in the ranitidine plasma concentration could be explained mainly by the discontinuous absorption theory.

ACKNOWLEDGEMENTS

We thank the Fundação de Amparo à Pesquisa do Rio Grande do Sul (FAPERGS, Brazil) and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil) for the financial support. Virna Josiane Aurelio Schuck thanks the CNPq for the scholarship.

RESUMO

Análise compartimental do perfil de duplo pico plasmático da ranitidina após administração oral a voluntários sadios

O objetivo deste trabalho foi o duplo pico observado no perfil farmacocinético plasmático da ranitidina após administração oral a voluntários sadios através de análise compartimental. Uma dose simples de 300 mg de ranitidina foi administrada a dez voluntários sadios (5 homens e 5 mulheres). Amostras de sangue foram coletadas em diferentes tempos e analisadas por HPLC. Os perfis plasmáticos foram avaliados pela abordagem compartimental e não-compartimental. Os parâmetros não compartimentais determinados foram k ($0,0054 \pm 0,001 \text{ min}^{-1}$), $t_{1/2}$ ($2,2 \pm 0,4 \text{ h}$), Vd/F ($265,3 \pm 70,6 \text{ L}$), Cl/F ($84,8 \pm 24,3 \text{ L/h}$) e AUC

($225916 \pm 54099 \text{ ng} \cdot \text{min/mL}$). A análise compartimental foi conduzida utilizando-se o modelo de dois compartimentos corporais com constantes de absorção de primeira ordem a partir de dois sítios de absorção diferentes. Os parâmetros determinados foram k_{21} ($0,0149 \pm 0,0133 \text{ min}^{-1}$), k_{a1} ($0,0117 \pm 0,0073 \text{ min}^{-1}$), k_{a2} ($0,1496 \pm 0,1699 \text{ min}^{-1}$), Vc ($128 \pm 75,2 \text{ L}$), a ($0,0299 \pm 0,0319 \text{ min}^{-1}$), b ($0,0074 \pm 0,0014 \text{ min}^{-1}$) e o tempo para o início da absorção no segundo sítio ($126,7 \pm 58,1 \text{ min}$). O modelo usado na análise compartimental foi adequado para descrever o duplo pico no perfil plasmático da ranitidina e para determinar os parâmetros farmacocinéticos.

UNITERMOS: Ranitidina. Farmacocinética. Análise compartimental. Duplo pico plasmático.

REFERENCES

- DESMOND, P. V., HARMAN, P. J., GANNOULIS, M., KAMM, M., MASHFORD, M. L. The effect of an antacid and food on the absorption of cimetidine and ranitidine. *J. Pharm. Pharmacol.*, v. 42, p. 352-354, 1990.
- GIBALDI, M., PERRIER, D. *Pharmacokinetics*. 2.ed. New York: Marcel Dekker, 1982. 494 p.
- GRANT, S. M., LANGTRY, H. D., BRODGEN, R. N. Ranitidine: An update review of its pharmacokinetics and pharmacodynamics properties and therapeutics use in peptic ulcer disease and other allied disease. *Drugs*, v. 37, p. 801-870, 1989.
- HILGENSTOCK, C., SCHMIEDEL, G., BÜHRENS, K. G. Study of the bioequivalence of two ranitidine formulations. *Arzn. Forsch.*, v. 37, n. 8, p. 974-976, 1987.
- KOCH, K. M., LIU, M., DAVIS, I. M., SHAW, S., YIN, Y. Pharmacokinetics and pharmacodynamics of ranitidine in renal impairment. *Eur. J. Clin. Pharmacol.*, v. 52, p. 229-234, 1997.
- LEBERT, P. A., MCLEOD, S. M., MAHON, W. A., SOLDIN, S. J., VANDENBERGHE, H. M. Ranitidine kinetics and dynamics: I. Oral dose study. *Clin. Pharmacol. Ther.*, v. 30, n. 4, p. 539-544, 1981.
- LIANG, E., DERENDORF, H. Pitfalls in pharmacokinetic multicompartment analysis. *J. Pharmacok. Biopharm.*, v. 26, n. 2, p. 247-260, 1998.

- REYNOLDS, K. S., SONG, M. H., HEIZER, W. D., BURNS, C. B., SICA, D. A., BROUWER, K. L. R. Effect of pancreatic-biliary secretions and GI transit time on the absorption and pharmacokinetics profile of ranitidine in humans. *Pharm. Res.*, v. 15, n. 8, p. 1281-1285, 1998.
- RICHARDS, D. A. Comparative Pharmacodynamics and pharmacokinetics of cimetidine and ranitidine. *J. Clin. Gastroenterol.*, v.5, suppl. 1, p. 81-90, 1983.
- ROBERTS, C. J. C. Clinical pharmacokinetics of ranitidine. *Clin. Pharmacok.*, v. 9, p. 211-221, 1984.
- SANTOS, F. A., CARCAS, A. J., GUERRA, P., GOVANTES, C., MONTUEGA, C., GOMEZ, E., FERNANDEZ, A., FRIAS, J. Evaluation of sex differences in the pharmacokinetics of ranitidine in humans. *J. Clin. Pharmacol.*, v. 36, p. 748-751, 1996.
- SCIENTIST User Handbook; Version 2.0. Salt Lake City: MicroMath Scientific Software, UT84121, 1995.
- SHAH, V. P., MIDHA, K. K., DIGHE, S., MCGILVERAY, I. J., SKELLY, J. P., YACOBI, A., LAYLOFF, T., VISWANATHAN, C. T., COOK, C. E., MCDOWALL, R. D., PITTMANN, K. A., SPECTOR, S. Analytical methods validation: bioavailability, bioequivalence and pharmacokinetics studies. *J. Pharm. Sci.*, v. 78, n. 12, p. 990-993, 1992.
- SHARGEL, L., YU, A. B. C. *Applied biopharmaceutics and pharmacokinetics*. 4.ed. Connecticut: Appleton & Lange, 1999. 768 p.
- SHIM, C. K., HONG, J. S. Inter and intra-subject variations of ranitidine pharmacokinetics after oral administration to normal male subjects. *J. Pharm. Sci.*, v. 78, n. 12, p. 990-993, 1989.
- STANSKI, D. R. Pharmacokinetics and pharmacodynamics for the clinicians. *Can. J. Anest.*, v. 38, n. 4, p. R48-R53, 1991.
- SUTTLE, A. B., POLLACK, G. M., BROUWER, K. L. R. Use of Pharmacokinetics Model incorporating discontinuous gastrointestinal absorption to examine the occurrence of double peaks in oral concentration time profile. *Pharm. Res.*, v. 9, n. 3, p. 350-355, 1992.
- SUTTLE, A. B., BROUWER, K. L. R. Bile flow but not enterohepatic recirculation influences the pharmacokinetics of ranitidine in the rat. *Drug. Met. Dis.*, v. 22, n. 2, p. 224-232, 1994.
- SWARTZ, M. E., KRULL, I. S. Validação de métodos cromatográficos. *Pharm. Technol.*, v. 2, n. 3, p. 12-20, 1998.
- VAN HECKEN, A. M., TJANDRAMAGA, T. B., MULLIE, A., VERBESSELT, R. D. E., SCHEPPER, P. J. Ranitidine: single dose pharmacokinetics and absolute bioavailability in man. *Br. J. Clin. Pharmacol. Ther.*, v. 14, p. 195-200, 1982.
- WAGNER, J. G. *Pharmacokinetics for the pharmaceutical scientist*. Lancaster: Technomic, 1993. 316 p.
- WILLIAMS, M. F., DUKES, G. E., HEIZER, W., HAN, Y. H., HERMANN, D. J., LAMPKIN, T., KAK, L. J. Influence of gastrointestinal site of drug delivery on the absorption characteristics of ranitidine. *Pharm. Res.*, v. 9, n. 9, p. 1190-1194, 1992.

Recebido para publicação em 20 de novembro de 2000.