A Study on the Bioequivalence of Two Ranitidine Preparations

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Zantac and Weichilin 150 mg tablets, both contain ranitidine, were subject to this study for bioequivalence. Twelve healthy male subjects were included. This study was based on a balanced two-way crossover design. Each subject received single oral dose of Zantac tablets and Weichilin tablets in different two treatment periods. Blood sample was collected. Concentrations of ranitidine in plasma sample was determined by an HPLC method. All plasma concentrations were analyzed. AUCs, MRTs and observed Tmax as well as Cmax were then evaluated. Based on ANOVA the parameters resulting from Weichilin tablets are not significantly different from those of Zantac tablets ($P > 0.05$). The 95% confidence limits are all reasonably narrow. The power of analysis for all parameters were all higher than 0.8. According to all evidence obtained Zantac tablets and Weichilin tablets should be considered as bioequivalent.

Key words: Ranitidine, Bioequivalence.

Ranitidine is a new histamine H_2-receptor antagonist. The various pharmacological effects of ranitidine have been mentioned by many research groups[1, 2]. The single dose pharmacokinetics of ranitidine in normal subjects was reported. In summary, following a 300 mg oral dose the peak concentration is approximately 0.836 ± 0.221 μg/ml at 2.5 ± 0.954 hours with a terminal phase half-life of 2.907 ± 0.662 hours [3,4,5]. It is primarily eliminated by renal excretion. The metabolic pathway includes oxidation and degradation. A small proportion of ranitidine is metabolized to the N-oxide, the S-oxide and desmethyl ranitidine[6].

The purpose of this study is to compare the plasma concentrations of ranitidine resulting from Zantac tablets and Weichilin tablets and to access the bioequivalency between the two formulations.

Materials and Methods

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The Drugs

The following drugs were used in the study:

Zantac 150 mg two tablets manufactured by Glaxo Pharm. England. (Lot no. B4058KA);

Weichilin 150 mg two tablets manufactured by Pei Li Pharmaceutical Industrial Co., Ltd. R.O.C. (Lot no. 890103).

Volunteers

Twelve healthy male volunteers aged 20 to 22 years (mean 21.33 years) with a mean body weight of 59.40 kg (range 53 to 68 kg) and a mean body height of 169.25 cm (range 162 to 186 cm) were included in this study. Their backgrounds are listed in Table 1. These volunteers were judged to be in good health based on thorough physical and clinical laboratory examinations. They were free from other drugs within the period from two weeks prior to the study to the end of this study. They were informed about the purpose of the study and the potential hazards of this drug. They have endorsed their written consents based on their own will.

The Drug Administration

This study was based on a single oral dose two-way crossover study. The twelve volunteers were divided randomly into two even groups. They were managed to receive a single oral dose of each drug according to the dosing scheme listed below:

Period I:

Zantac tab.: subjects 1, 4, 5, 8, 11, 12.

Weichilin tab.: subjects 2, 3, 6, 7, 9, 10.

Period II:

Zantac tab.: subjects 2, 3, 6, 7, 9, 10.

Weichilin tab.: subjects 1, 4, 5, 8, 11, 12.

Table 1. Background of the Volunteers in this Study

Subject No.	Code	Age (years)	Body Weight (kg)	Body Height (cm)
1	LMY	21	68	186
2	OCH	20	56	170
3	YCL	21	53	171
4	HTT	22	58	163
5	LCH	20	64	180
6	CCW	22	60	166
7	YPS	21	55	164
8	TSS	22	67	175
9	YCT	22	55	164
10	CCJ	21	54	162
11	HLP	22	68	165
12	LHY	22	55	165
mean		21.33	59.40	169.25
s.d.		0.75	5.54	7.22

The washout period between the two treatment periods was at least one week.

During each treatment period each drug was given after an overnight fasting before the drug administration while all volunteers were held in the hospital overnight with the physician and nurse attended. Each subject was urged to take 200 ml of water along with the drug. A standard food was allowed only four hours from the baseline.

Sampling

Blood samples were collected from the cubital vein approximately 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours after the drug administration. The plasma was separated immediately and stored at $-20^{\circ}C$ till assay.

High Performance Liquid Chromatographic Method, HPLC.

The ranitidine concentrations in the samples were determined by a modified HPLC method[7,8,9]. A HITACHI HPLC with a L-4000 detector and HITACHI chromatocorder were used.

The chromatographic condition

column: Merck RP 18 (5 μ m)

mobile phase: PIC B-6: CH_3CN = 82:18

flow rate: 1.3 ml/min

detector wavelength: 310 nm

The peak area of ranitidine was taken as the basis of quantitation. Standard curves constructed daily were used for analysis.

The inter-day and intra-day precisions were confirmed by the corresponding study and the variations were found to be less than 10%.

The chromatographic condition was checked for specificity. It was found that only one chromatogram appeared when the retention time was shortened or prolonged when the mobile phase was changed.

Statistical and Pharmacokinetics Treatments

The area under the plasma concentration time curve, AUC from time zero to a specified time t, $AUC_{0\to t}$, was calculated by the linear trapezoidal method up to the specified time. The extrapolated area from time t to infinite was calculated by the following formula:

$$AUC_{last} = C_{last} / \beta$$

while C_{last} is the plasma ranitidine concentration of the last sample or last observable concentration and β is obtained from the slope of the terminal phase evaluated by JANA[10,11], a curve stripping computer program. The total AUC or $AUC_{0\to inf}$ was obtained from the sum of the above two AUC,

or $$AUC_{0\to inf} = AUC_{0\to t} + AUC_{last}$$

The terminal phase half-life was calculated by the following equation:

$$T_{1/2} = 0.693/\beta$$

The AUC, observed peak time (T_{max}), observed peak concentration (C_{max}), $T_{1/2}$, and the mean residence time (MRT) for Zantac tablets and Weichilin tablets were compared by the two way ANOVA modified for crossover effects. The breaking point for the singnificance was P=0.05. The 95% confidence interval and the statistical power were also evaluated.

Results and Discussions

Tables 2 and 3 show the summary of plasma ranitidine concentration. Summary of the AUC, T_{max} and C_{max} are listed in Table 4. Fig. 1 show the mean curves of plasma ranitidine concentrations of Zantac tablets and Weichilin tablets following oral adminstration.

Following oral administrations of two Zantac 150 mg tablets the mean C_{max} was 1.515 ± 0.375 μg/ml (CV 24%) with the individual data ranged from 0.805 to 2.161 μg/ml. The mean observed T_{max} was 2.875 ± 1.043 hours (CV 36%) with individual data ranged from 1.5 to 6 hours, the $AUC_{0\to 12}$ ranged from 3.870 to 9.445 μg·hr/ml with

Table 2. Plasma ranitidine concentrations, μ g/ml. following oral adminstration of single 300 mg dose of Zantac tablets

Time (hr) \ Subject	1	2	3	4	5	6	7	8	9	10	11	12	Mean	S.E.
0.5	0.26	0.20	0.25	0.19	0.11	0.15	0.12	0.23	0.32	0.47	0.08	0.41	0.23	0.03
1	0.32	0.43	0.42	0.37	0.20	0.65	0.39	0.47	0.56	0.88	0.41	0.82	0.49	0.05
1.5	0.65	0.35	0.68	0.49	0.43	0.81	0.48	0.62	0.43	0.93	0.49	1.94	0.69	0.12
2	0.99	0.36	1.02	0.68	0.70	1.25	0.55	1.19	1.09	1.06	0.47	1.10	0.87	0.08
2.5	0.76	0.32	1.93	0.81	1.41	2.00	1.00	1.15	1.26	1.70	0.56	0.88	1.15	0.15
3	0.67	0.85	1.52	0.57	1.17	2.16	1.67	1.34	1.33	1.24	1.50	0.95	1.25	0.12
4	0.44	1.27	0.67	0.49	0.66	1.56	0.99	0.78	1.06	0.84	1.24	0.61	0.88	0.09
6	0.36	1.40	0.32	0.30	0.37	0.72	0.49	0.38	0.54	0.40	0.55	0.31	0.51	0.08
8	0.22	0.22	0.12	0.23	0.23	0.45	0.25	0.25	0.32	0.24	0.34	0.19	0.25	0.02
10	0.14	0.12	0.09	0.13	0.15	0.28	0.14	0.15	0.19	0.14	0.17	0.10	0.15	0.01
12	0.09	0.09	0.06	0.11	0.11	0.18	0.08	0.10	0.11	0.09	0.12	0.06	0.10	0.01

Table 3. Plasma ranitidine concentrations, μ g/ml. following oral adminstration of single 300mg dose of Weichilin tablets

Time (hr) \ Subject	1	2	3	4	5	6	7	8	9	10	11	12	Mean	S.E.
0.5	0.10	0.43	0.31	0.06	0.33	0.43	0.32	0.32	0.35	0.52	0.03	0.39	0.30	0.04
1	0.40	0.41	0.29	0.29	0.24	0.60	0.58	0.48	0.64	1.25	0.28	0.63	0.51	0.08
1.5	0.66	0.61	2.39	0.47	0.19	0.64	1.55	0.62	0.75	2.42	0.37	2.02	1.06	0.22
2	1.63	1.20	1.08	0.89	0.30	1.26	1.74	0.92	1.99	1.39	0.41	1.86	1.22	0.15
2.5	1.86	1.25	1.73	0.95	0.54	1.40	1.78	1.26	1.85	1.04	0.53	1.45	1.30	0.13
3	1.37	0.85	0.79	0.84	0.34	0.88	1.31	1.42	1.55	0.88	1.17	1.04	1.03	0.09
4	1.10	0.45	1.59	0.70	0.38	0.57	0.79	0.82	0.99	0.63	1.56	0.67	0.85	0.11
6	0.42	0.30	0.29	0.38	0.24	0.31	0.39	0.47	0.59	0.32	0.51	0.31	0.38	0.03
8	0.28	0.20	0.17	0.32	0.17	0.22	0.17	0.21	0.42	0.21	0.33	0.19	0.24	0.02
10	0.17	0.12	0.10	0.17	0.10	0.14	0.11	0.13	0.27	0.13	0.22	0.11	0.15	0.01
12	0.09	0.09	0.08	0.12	0.08	0.09	0.09	0.07	0.20	0.11	0.14	0.07	0.10	0.01

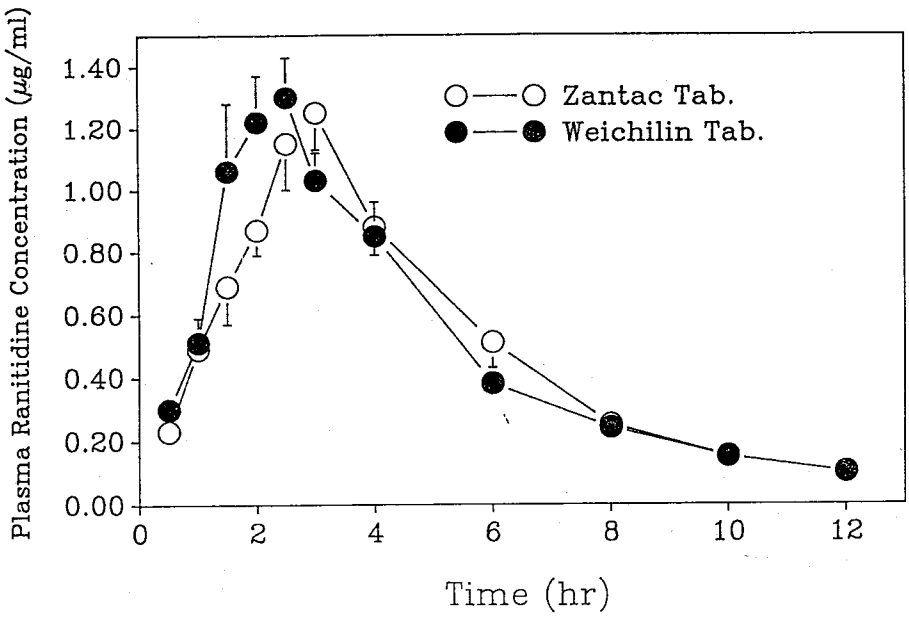

Figure 1. Mean Curves

Table 4. Summary of Pharmacokinetic Parameters

Parameters \ Formulations	Zantac	Weichilin
$AUC_{0\to12}$ ($\mu g \cdot hr/ml$)	5.735 ± 1.372	5.756 ± 1.307
$AUC_{0\to inf}$ ($\mu g \cdot hr/ml$)	6.129 ± 1.413	6.208 ± 1.399
C_{max} ($\mu g/ml$)	1.515 ± 0.375	1.631 ± 0.537
T_{max} (hr)	2.875 ± 1.043	2.375 ± 0.681
$T_{1/2}$ (hr)	2.707 ± 0.441	2.953 ± 0.438
MRT (hr)	5.084 ± 0.644	5.017 ± 0.812
AUMC ($\mu g \cdot hr^2/ml$)	31.008 ± 7.737	30.906 ± 8.702

Each value represents the mean ± S.D. obtained from 12 volunteers.

$AUC_{0\to12}$: Area under the curve from 0–12 hours
$AUC_{0\to inf}$: Area under the curve from 0–infinite hours by extrapolation
C_{max} : Peak concentration
T_{max} : Peak time
$T_{1/2}$: Terminal half-life
MRT : Mean residence time
AUMC : Area under the first moment curve

a mean of 5.735 ± 1.372 μg·hr/ml (CV 24%). The mean $AUC_{0\to inf}$ was 6.129 ± 1.413 μg·hr/ml (CV 23%) with a range of 10.104 to 4.459 μg·hr/ml.

Following oral administration of two Weichilin 150 mg tablets the mean C_{max} was 1.631 ± 0.537 μg/ml (CV 33%) and the individual data ranged from 0.538 to 2.019 μg/ml. The mean observed T_{max} was 2.375 ± 0.681 hours (CV 28%) with individual data ranged from 1.5 to 4 hours. The $AUC_{0\to12}$ ranged from 2.708 to 8.195 μg·hr/ml with a mean of 5.756 ± 1.307 μg·hr/ml (CV 22%). The mean $AUC_{0\to inf}$ was 6.208 ± 1.399 μg·hr/ml (CV 6%) with a range of 3.106 to 9.189 μg·hr/ml.

Table 5 shows the summary of the analysis of variance, ANOVA, on the partial AUC_s or $AUC_{0\to12}$, the total AUC_s, 95% confidence intervals, and statistical powers.

According to the F values obtained from ANOVA, the C_{max}, T_{max}, AUC_s, and MRT for Zantac tablets are not significantly different from those of Weichilin tablets ($P > 0.05$).

The statistical power for the total AUC_s, $AUC_{0\to inf}$, as well as for MRT, T_{max}, C_{max} and β are all higher than 0.8 when 20% differences are to be observed in this study.

According to preliminary studies, ranitidine was found unstable in water and decomposed easily in aqueous solution at room temperature. The urinary ranitidine concentration in some cases in other studies were low and with high inter subject difference[4,5]. Since the purpose of this study is aimed at the comparative ranitidine blood levels which are good enough for the judgement of a bioequivalency, the analysis of urinary ranitidine was not performed.

Table 5. Results of Statistical Treatments

Parameters	F	95% CI	Z beta	1-beta
$AUC_{0\to inf}$	2.983	1.271 – 0.809	1.178	> 0.8
$AUC_{0\to12}$	0.002	1.228 – 0.852	1.109	> 0.8
AUMC	0.001	1.19 – 0.857	0.839	> 0.8
MRT	0.140	1.058 – 0.917	6.081	> 0.8
$T_{1/2}$	2.4	1.26 – 0.97	2.855	> 0.8
C_{max} observed	0.534	1.363 – 0.864	0.684	> 0.8
T_{max} observed	4.138	1.051 – 0.703	1.348	> 0.8

Note:

1. $F = F_{1,10}$ in ANOVA
   The tabulated $F_{1,10}$ at $P = 0.05$ is 4.96
2. The 95% CI is the classical values for the difference of the mean

Based on the data analysis including ANOVA, 95% confidence interval, and the statistical powers for the corresponding parameters evaluated the two formulations, Zantac tablets and Weichilin tablets, should be considered as bioequivalent.

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口服兩種Ranitidine製劑之生體相等性研究

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本研究旨在比較兩種Ranitidine製劑，即Zantac 150 mg錠與Weichilin 150 mg錠於投藥後之血中濃度變化，以評估兩者是否具有生體相等性。共用十二名健康男性志願受試者，按雙向交叉設計，在兩個試驗期每名受試者於單劑量口服Zantac錠或Weichilin錠後均收集其血液樣品，血中Ranitidine濃度採用HPLC法分析，所有血中藥物濃度則按下列項目檢討：AUC_s、MRT_s、C_{max}、T_{max}、$T_{1/2}$和AUMC，以上各參數經用ANOVA統計分析並計算95%Confidence interval及Statistical power，結果顯示上列各參數均無意義差（P〉0.05），各Statistical power均在0.8以上，據此判定Zantac錠和Weichilin錠兩種Ranitidine製劑應具有生體相等性。

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