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A Comparative Bioavailability Study on Two Brands of Cisapride Tablets Using Univariate and Multivariate Statistical Methods

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ABSTRACT

A comparative bioavailability study on the original inventor's (Prepulsid, Janssen) and a generic (Cisapride, Swiss Pharm. Taiwan) cisapride tablets was carried out using a single dose, 2x2 randomized crossover design with 16 normal Chinese males. The pharmacokinetic parameters of cisapride obtained following oral administration of 20 mg dose of Prepulsid and Cisapride tablets were C_{max} (61.97 ± 13.11 and 64.89 ± 14.31 ng/ml, mean ± SD), partial AUC (AUC_t, 402 ± 121.4 and 405.4 ± 117.5 ng·h/ml), total AUC (420.8 ± 123.8 and 421.9 ± 118.0 ng ·h/ml), $T_{1/2}$ (7.8 ± 1.9 and 7.2 ± 1.8 h), T_{max} (1.3 ± 0.5 and 1.2 ± 0.5 h), MRT (8.5 ± 1.7 and 8.1 ± 1.4 h), VRT (102.0 ± 42.6 and 87.4 ± 41.3 h^2) and Cl/F (853.1 ± 238.9 and 850.4 ± 240.7 ml/min), respectively. The bioavailability parameters (C_{max}, AUC_t, AUC, lnC_{max}, lnAUCt and lnAUC) were analyzed by univariate statistical methods of the power of test to detect a 20% difference, 90% confidence interval, FDA's two one-sided tests and 90% joint confidence region. The results show that the two brands of cisapride tablet are bioequivalent based on current bioequivalence criteria. Overall similarity in bioavailability between the two products determined by multivariate statistical method was 94% (C_{max} and AUC) and 92% ($lnC_{max}$and lnAUC); whereas overall similarity was 86% (C_{max}, AUC and MRT) and 76% (lnC_{max}, lnAUC and lnMRT), respectively. The T_{max} obtained in this study was comparable to that reported in Caucasian subjects, but C_{max} and AUC were smaller in Chinese.

Key words: **cisapride, tablets, Chinese, bioavailability, multivariate analysis.**

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INTRODUCTION

Cisapride is a new gastro-intestinal stimulant agent that most likely facilitates the release of acetylcholine at myenteric plexus sites without exerting effects at the secretory gland level[1]. Cisapride is well absorbed after oral administration in man[2] and is used in the treatment of various gastro-intestinal motility disorders[3,4]. In human, cisapride undergoes extensive first-pass metabolism in gut wall and in the liver, primarily by oxidative N-dealkylation and aromatic hydroxylation, and the renal excretion of cisapride is less than 1%[3]. The aim of the present investigations is to determine the comparative bioavailability of cisapride tablets between the original inventor's product (Prepulsid, Janssen) and a generic product manufactured in Taiwan (Cisapride, Swiss Pharm. Taiwan) using univariate and multivariate statistical methods. In spite of the popular use of this drug in Taiwan, available data on the pharmacokinetic behavior of cisapride are based on studies on Caucasian subjects. Current study also aims to reveal the pharmacokinetics of cisapride in normal Chinese males.

MATERIALS AND METHODS

I. *Cisapride Tablets*

Preplusid tablet (Lot No. 115218, 5 mg/tab, Taiwan Janssen) and Cisapride tablet (Lot No. CST-003T, 5 mg/tab, Swiss Pharm. Taiwan) were used as the reference and test products, respectively. The two products showed pharmaceutically equivalent characteristics.

II. *Subjects*

After a review of their personal history, plus medical and laboratory examinations, sixteen normal Chinese males in Taiwan whose age ranged from 21 to 43 years were selected to participate in this study. The study protocol had been reviewed and approved by the Department of Health, Taiwan. The demographic data of subjects are listed in Table 1.

Table 1. Demographic data of subjects

Subject	Age (yrs)	Height (cm)	Weight (kg)
1.	31	178	78.6
2.	24	173	86.0
3.	29	171	64.4
4.	43	174	87.8
5.	28	168.5	60.0
6.	25	174	72.0
7.	23	158	57.0
8.	29	167	59.2
9.	26	173	92.8
10.	34	171	71.2
11.	31	165	63.0
12.	38	171	75.0
13.	29	172	65.6
14.	21	164	56.0
15.	31	175	70.8
16.	36	167.5	64.0
Mean(SD)	29.9(5.8)	170.1(5.0)	70.2(11.3)

III. *Study Design*

A single dose, 2x2 randomized crossover design was used. Sixteen subjects were randomly divided into two groups of eight subjects. Each subject was orally administered 20 mg dose of cisapride tablets (either reference or test product) with a 200 ml drinking water on the morning following a 12 h overnight fast. A two-week washout period was taken between two study periods (reported $T_{1/2}$ = 6-12 h)[4,5]. Blood samples (10 ml) were serially collected via heparin lock immediately prior to the drug administration (time zero) and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 24, 30, 34, and 38 h post-dose. Plasma was promptly separated and immediately stored in a freezer (-20°C) until assayed. Assays of cisapride in plasma were accomplished within two months after the blood had been collected. Woestenborghs *et al.*[6] reported that cisapride in human plasma was stable for at least 9 months when it was stored at -20°C. A preliminary stability study using the spiked plasma samples also revealed that cisapride in the plasma was stable for two months at -20°C.

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IV. *Assays of Cisapride in Plasma*

The clean-up procedure and specific HPLC method reported by Woestenborghs *et al.*[6] were modified to determine the cisapride plasma concentration. Briefly, 1 or 2 ml of plasma was alkalified with 250 µl of 1 N NaOH solution and 100 µl of internal standard solution (20 µg/ml of ticlopidine) was added. After gentle vortex mixing, the solution was extracted using 3 ml of n-hexane/isoamyl alcohol (9/1, v/v). The organic layer was separated and dried at 40°C with N_2 gas. The residue was redissolved in 200 µl of HPLC mobile phase solvent and 50 µl of this solution was injected into HPLC. An HPLC apparatus, Shimadzu LC-6A equipped with SPD-10A detector, CR-4A chromatopac data workstation, SCL-6A system controller and SIL-6A autoinjector was used. The separation was accomplished with a NOVA-PAK™ C_{18} column (3.9x150 mm, 4 µm, Waters) guarded by a Guard-Pak™ C_{18} (8.0x10 mm, Waters). Cisapride and ticlopidine were detected using 270 nm. A mobile phase consisted of 65/35 (v/v) of 50 mM NaH_2PO_4/ Trimethylamine (1000/0.5, pH 4.5) and acetonitrile was run at a flow rate of 1 ml/min and detector attenuation of 0.005 aufs under room temperature.

V. *System Suitability Test*

The system suitability test was performed according to the procedures described in the USP XXIII.

VI. *Bioavailability Relevant Parameters*

Maximum observed plasma concentration (C_{max}) and the time to reach the maximum concentration (T_{max}) were recorded for each individual in each period of study. AUC_t (partial area under the concentration curve, 0-t h) was calculated using the linear trapezoidal method; whereas the remaining area was estimated through dividing the last concentration by the slope of the terminal phase. Mean residence time (MRT) and variance of residence time (VRT) were calculated using the statistical moment method[7]. Apparent oral clearance (Cl/F) was estimated through dividing the dose by total area under the concentration curve (AUC).

VII. *Univariate Statistical Analysis*

Raw and log-transformed data of C_{max} and AUC were analyzed using the methods of univariate statistics, such as the power of test to detect a 20% difference; classical 90% confidence interval of the population mean ratio (test/reference); the FDA's two one-sided tests[8] and the 90% joint confidence region method[9]. The bioequivalence was justified by the current bioequivalence (BE) criteria (90% confidence interval of the population mean ratio, test/reference: 0.8-1.2 for raw scale data and 0.8-1.25 for log-transformed data).

VIII. *Multivariate Statistical Analysis*

The overall similarity in bioavailability (BA) between the test and reference products was estimated using the multivariate approach developed by Hsu *et al.*[10]. Briefly, assuming the BA of a drug product can be defined simultaneously by two variables C_{max} (X_1) and AUC (X_2), or by three variables C_{max} (X_1), AUC (X_2), and MRT (X_3), and under normality assumptions, Hotelling's T^2 can be written as equation 1:[11]

$$n(\bar{x}-\mu)'s^{-1}(\bar{x}-\mu)=\frac{p(n-1)}{(n-p)}F_{(p,n-p,1-\alpha)} \quad (1)$$

where $\bar{x}$ is the sample mean vector, μ is the population mean vector, $(\bar{x}-\mu)^t$ is the transpose of a matrix $(\bar{x}-\mu)$, S^{-1} is the inverse sample variance-covariance matrix, n is the sample size, p is the number of variables, and $F_{(p,n-p,1-\alpha)}$ is the $(1-\alpha)$ quantile of F distribution with degrees of freedom p and n-p.

The border of $(1-\alpha)$ confidence regions for the bivariate and trivariate mean vectors defined by Hotelling's T^2 can be expressed in the form of equations 2 (ellipse) and 3 (ellipsoid), respectively [10]. The fraction of the test confidence ellipse (or ellipsoid) overlapping the reference confidence ellipse (or ellipsoid) representing the degree of overall similarity in BA can be estimated from the equations of confidence regions for the test and

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reference mean vectors using a computer (Details of the procedure were described in Ref. 10).

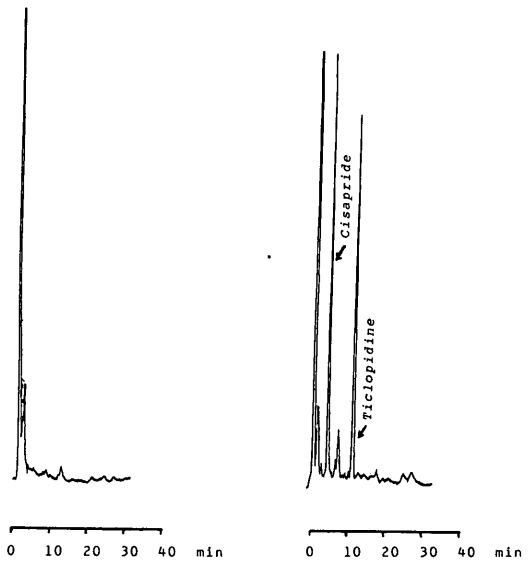
$$A(X_1-\overline{X}_1)^2 + B(X_1-\overline{X}_1)(X_2-\overline{X}_2)+C(X_2-\overline{X}_2)^2 = 1 \quad (2)$$

$$A_1(X_1-\overline{X}_1)^2+A_2(X_2-\overline{X}_2)^2+A_3(X_3-\overline{X}_3)^2+ A_4(X_1-\overline{X}_1)(X_2-\overline{X}_2)+A_5(X_2-\overline{X}_2)(X_3-\overline{X}_3)+ A_6(X_1-\overline{X}_1)(X_3-\overline{X}_3)= A_7 \quad (3)$$

RESULTS AND DISCUSSION

I. *System Suitability Test*

Figure 1 shows the typical HPLC chromatogram of a blank plasma and clinical plasma sample following a clean-up. The relevant parameters are summarized in Table 2.



(a) (b)

Figure 1. Typical chromatogram of blank plasma (a) and clinical plasma sample (b) following clean-up.

Table 2. Summary of system suitability parameters

Parameters	Cisapride	Ticlopidine
Tailing factor	1.0	1.0
Capacity factor	2.4	6.3
Resolution	4.0[a]	3.9[b]

[a]: resolution determined between cisapride and its neighboring peaks.

[b]: resolution between ticlopidine and its neighboring peaks.

II. *Validation of the Assay Method*

The linearity between the response (peak area ratio) and cisapride plasma concentration was established by the Lack-of-Fit test. The linear dynamic range for plasma cisapride concentrations was established for ranges from 1 to 20 ng/ml and from 10 to 200 ng/ml, respectively. The two calibration lines passed through the origin, hence, there was no significant constant bias (e.g., Y=0.0192X for 1 to 20 ng/ml and Y=0.0175X for 10 to 200 ng/ml, Y: peak area ratio, X: cisapride plasma concentration, ng/ml. Each mean regression equation was obtained with 5 concentrations and 6 replicate measurements in each concentration). The recovery data and interday variation are summarized in Table 3. The limit of quantitation (LOQ) was 1 ng/ml.

III. *Cisapride Plasma Concentrations*

Cisapride plasma concentrations following oral administration of Preplusid or Cisapride tablets (20 mg dose) are summarized in Table 4. The mean cisapride plasma concentrations (C) could be fitted to the two-compartment body model using the weighted ($1/C^2$) least-squares method (Program written by Prof. Watanabe, Nagoya City University, Japan) and the mean con-

Table 3. Recovery and interday variation of cisapride assay

Plasma Conc. (ng/ml)	Recovery, %	Interday variation[a]
1	91.8 ± 4.8	9.3
3	106.7 ± 4.3	6.9
5	95.9 ± 7.4	8.6
10	100.0 ± 1.6	5.0
20	93.1 ± 9.0	5.7
50	89.7 ± 3.0	9.9
100	97.0 ± 9.8	9.7
200	97.7 ± 8.9	8.9

Mean ± SD, n=6. [a]: coefficient of variation, %.

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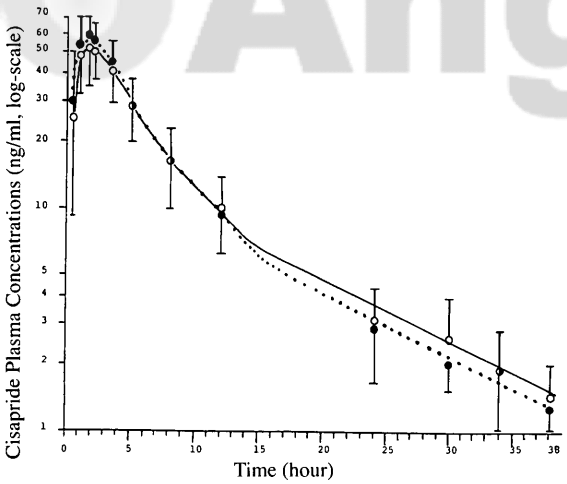

Figure 2. Cisapride plasma concentrations (mean ± SD) and the model fit curves following oral administration of prepulsid (blank circles and solid line) and cisapride (solid circles and dotted line).

Table 4. Summary of cisapride plasma concentration following oral administration of 20 mg (mean ± SD, ng/ml)

Time (h)	Prepulsid (n)	Cisapride (n)
0.5	25.50 ± 17.15 (16)	29.77 ± 21.21 (16)
1.0	48.73 ± 16.74 (16)	51.62 ± 18.25 (16)
1.5	52.22 ± 12.29 (16)	56.99 ± 17.14 (16)
2.0	49.85 ± 13.62 (16)	53.29 ± 14.08 (16)
3.0	40.75 ± 12.60 (16)	43.07 ± 11.92 (16)
5.0	28.87 ± 9.65 (16)	28.88 ± 9.18 (16)
8.0	16.84 ± 6.08 (16)	16.94 ± 6.18 (16)
12.0	9.77 ± 4.18 (16)	8.65 ± 3.18 (16)
24.0	3.16 ± 1.85 (16)	2.89 ± 1.49 (16)
30.0	2.65 ± 1.36 (10)	2.13 ± 0.64 (9)
34.0	1.88 ± 0.86 (9)	1.89 ± 0.87 (4)
38.0	1.44 ± 0.44 (3)	1.20 ± 0.16 (3)

n: number of observations.

Table 5. Individual bioavailability relevant pharmacokinetic parameters of cisapride

	C_{max}		AUC		T_{max}		$T_{1/2}$		MRT		Cl/F		VRT		AUC_t	
Subj	R	T	R	T	R	T	R	T	R	T	R	T	R	T	R	T
1	56.31	64.14	383.8	416.2	1.5	1.5	6.1	5.9	7.3	7.7	868.5	800.9	67.3	61.9	362.4	394.8
2	54.01	71.18	403.2	441.6	1.5	1.5	10.4	8.9	10.7	8.9	826.7	754.8	175.9	118.0	368.0	417.2
3	60.17	70.86	420.5	503.6	0.5	0.5	9.3	8.4	8.2	8.1	792.7	661.9	112.4	103.6	404.8	480.0
4	71.57	71.39	503.5	416.9	2.0	1.0	7.4	5.1	8.3	6.2	662.0	799.6	87.2	41.1	488.9	405.2
5	54.55	55.98	294.9	341.7	1.0	1.0	5.2	5.0	6.6	6.5	1130.3	975.5	48.0	43.6	284.8	331.2
6	48.63	55.83	399.1	456.2	1.5	1.5	8.8	7.1	10.3	9.7	835.2	730.7	135.5	94.6	378.8	435.2
7	54.11	64.76	520.5	495.4	2.0	1.5	8.0	7.2	11.3	8.7	640.4	672.9	128.9	89.1	494.4	481.6
8	79.08	82.54	395.9	303.1	1.0	1.0	8.2	9.4	6.8	6.9	842.0	1099.7	81.4	99.3	382.0	283.4
9	67.46	56.10	382.3	332.1	1.0	1.0	11.4	12.2	10.4	11.3	871.9	1003.7	182.8	215.7	362.4	311.7
10	71.25	79.44	565.9	629.5	2.0	2.0	9.9	6.6	9.3	8.9	589.0	529.5	121.5	87.1	547.6	618.2
11	83.11	69.82	415.7	469.0	1.0	1.0	9.8	7.5	8.2	8.0	801.9	710.7	129.7	89.8	379.1	449.5
12	82.21	96.75	753.7	661.8	1.5	1.5	7.0	6.5	10.7	9.4	442.3	503.7	115.7	99.5	731.8	647.7
13	38.20	40.13	234.2	264.9	1.0	1.5	5.0	5.8	6.3	7.4	1423.3	1258.3	42.4	60.1	227.3	252.1
14	47.45	44.22	288.2	252.4	1.0	0.5	6.5	6.9	6.4	6.2	1156.6	1320.7	62.1	58.0	275.0	242.1
15	56.70	56.23	330.1	442.5	1.0	2.0	6.5	7.5	7.3	8.1	1009.8	753.3	70.8	83.7	311.9	425.2
16	66.72	58.93	440.6	323.5	1.0	0.5	5.9	5.3	8.6	7.3	756.5	1030.4	69.9	52.6	432.1	311.0
Mean	61.97	64.89	420.8	421.9	1.3	1.2	7.8	7.2	8.5	8.1	853.1	850.4	102.0	87.4	402.0	405.4
SD	13.11	14.31	123.8	118.0	0.5	0.5	1.9	1.8	1.7	1.4	238.9	240.7	42.6	41.3	121.4	117.5

R: Prepulsid; T: Cisapride; C_{max}: ng/ml; AUC: total AUC, ng h/ml;
T_{max} and $T_{1/2}$: h; MRT: h; Cl/F: ml/min; VRT: h^2; AUC_t: partial AUC, ng·h/ml.

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Table 6. Summary of the statistical bioequivalence assessment by univariate methods

Parameters	C_{max}	lnC_{max}	AUC	lnAUC	AUC_t	$lnAUC_t$
Power of Test	1.0	1.0	0.98	0.98	0.97	0.98
90% Confidence	0.99	0.99	0.93	0.93	0.93	0.93
interval	1.10	1.10	1.08	1.09	1.09	1.10
90% Joint	1.03	1.02	0.98	0.98	0.98	0.98
confidence region	1.07	1.07	1.03	1.04	1.04	1.04
FDA's two one-sided tests	BE	BE	BE	BE	BE	BE

AUC: total AUC, AUC_t: partial AUC for 0-t h, BE: bioequivalent.

Table 7. Summary of the statistical bioequivalence assessment by multivariate method (raw scale data)

Equation form of the 90% confidence ellipse constructed with C_{max} and AUC:
$A(C_{max}\text{-}a)^2 + B(C_{max}\text{-}a)(AUC\text{-}b)+C(AUC\text{-}b)^2=1$

	Reference product	Test product
A	1.85×10^{-3}	1.88×10^{-3}
a	61.97	64.89
B	-2.55×10^{-4}	-3.32×10^{-4}
b	420.75	421.9
C	2.07×10^{-5}	2.77×10^{-5}

The fraction of test confidence ellipse overlapping reference confidence ellipse is 0.94.

Equation form of the 90% confidence ellipsoid constructed with C_{max}, AUC and MRT: $A_1(C_{max}\text{-}a)^2+A_2(AUC\text{-}b)^2+A_3(MRT\text{-}c)^2+A_4(C_{max}\text{-}a)(AUC\text{-}b)+A_5(AUC\text{-}b)(MRT\text{-}c)+A_6(C_{max}\text{-}a)(MRT\text{-}c)=A_7$

	Reference product	Test product
A_1	1.0	1.0
a	61.97	64.89
A_2	0.0188	0.0177
b	420.76	421.9
A_3	59.63	63.46
c	8.54	8.08
A_4	-0.191	-0.194
A_5	-1.48	-0.965
A_6	5.75	3.404
A_7	707.64	768.43

The fraction of test confidence ellipsoid overlapping reference confidence ellipsoid is 0.86.

centration profiles can be described by the following equations

$C = 65.8\ e^{-0.244t} + 11.8\ e^{-0.0544t} - 140.6\ e^{-2.31t}$ (Prepulsid) and

$C = 77.6\ e^{-0.267t} + 11.2\ e^{-0.0565t} - 135.4\ e^{-2.03t}$ (Cisapride), respectively. Figure 2 illustrates the observed cisapride plasma concentrations and the model fit curves.

IV. *Relative Bioavailability of Cisapride Tablets*

Table 5 shows the individual pharmacokinetic parameters of cisapride. The intersubject variability in pharmacokinetic parameters was considerably large, probably due to the different rates of first-pass metabolism and elimination.

V. *Statistical Assessment of Bioequivalence*

The results of statistical assessment are summarized in Tables 6 (univariate methods), 7 and 8 (multivariate method). The results of univariate analysis suggest that the bioequivalence between the two products can be justified based on current criteria of bioequivalence. The confidence interval method does not account for the correlation between the bioavailability parameters of the test and reference products. The correlation coefficients between the parameters of reference and test products in this study were C_{max} (0.80), lnC_{max} (0.82), AUC_t (0.81), $lnAUC_t$ (0.78), AUC (0.82) and lnAUC (0.80), respectively. These correlations are statistically significant ($p < 0.05$). Therefore, the 90% joint confidence region method can be applied[9,13]. The confidence region is always narrower than the confidence interval

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Table 8. Summary of the statistical bioequivalence assessment by multivariate method (log-transformed data)

Equation form of the 90% confidence ellipse constructed with $\ln C_{max}$ and lnAUC: $A(\ln C_{max}-a)^2+B(\ln C_{max}-a)(\ln AUC-b)+C(\ln AUC-b)^2=1$

	Reference product	Test product
A	7.74	7.73
a	4.11	4.15
B	-8.46	-8.99
b	6.0	6.01
C	4.63	4.93

The fraction of test confidence ellipse overlapping reference confidence ellipse is 0.92.

Equation form of the 90% confidence ellipsoid constructed with $\ln C_{max}$, lnAUC and lnMRT: $A_1(\ln C_{max}-a)^2+A_2(\ln AUC-b)^2+A_3(\ln MRT-c)^2+A_4(\ln C_{max}-a)(\ln AUC-b)+A_5(\ln AUC-b)(\ln MRT-c)+A_6(\ln C_{max}-a)(\ln MRT-c)=A_7$

	Reference product	Test product
A_1	1.0	1.0
a	4.11	4.15
A_2	0.39	0.30
b	6.0	6.0
A_3	0.42	0.42
c	2.13	2.08
A_4	- 0.55	-0.49
A_5	- 0.62	-0.36
A_6	0.34	0.18
A_7	0.054	0.07

The fraction of test confidence ellipsoid overlapping reference confidence ellipsoid is 0.76.

when high correlation between the parameters of reference and test products exists[14]. The 20% rule is adopted as the bioequivalence decision-making criteria in the current univariate method (90% confidence interval). This means that at least 80% similarity in bioavailability between reference and test products is required for C_{max} and AUC respectively with 90% assurance. In fact MRT is a useful estimate of the rate of drug absorption. Since these BA relevant parameters are mutually correlated, the required degree of overall similarity between the reference and test products is unknown when the univariate method is used. If these parameters were mutually independent, then the accepted degree of overall similarity in BA to conclude bioequivalence would be no less than $(80\%)^2$ or 64% for simultaneous assessment of C_{max} and AUC; and would be no less than $(80\%)^3$ or 51.2% for simultaneous assessment of C_{max}, AUC and MRT with 90% assurance. The 64% or 51.2% similarity in BA may not be acceptable in justifying bioequivalence. Theoretically, the BE of two drug products may be determined by simultaneous similarity in C_{max}, AUC and MRT. Univariate statistical methods do not provide the information about the degree of overall similarity in BA between the two drug products. While the analysis of variance can be used as a screening tool to test the existence of sequence and/or period effects in the crossover study, the multivariate approach may serve as supporting evidence to confirm the bioequivalence. The degrees of overall similarity in bioavailability between the two products are 94% (C_{max} and AUC) and 92% ($\ln C_{max}$ and lnAUC), and 86% (C_{max}, AUC and MRT) and 76% ($\ln C_{max}$, lnAUC and lnMRT), respectively with 90% assurance. These values may provide very useful information to determine whether it is reasonable to accept or not to accept the bioequivalence.

VI. *Pharmacokinetic Difference of Cisapride Between Caucasian and Chinese Subjects*

Hedner *et al.*[12] reported that following oral administration of 15 mg cisapride tablets (Janssen Lot No. 87K27/127) in 12 Caucasian subjects (79.0±8.4 kg), the pharmacokinetic parameters were T_{max} (1.5±0.4 h), C_{max} (74.3±18.4 ng/ml), $T_{1/2}$ (9.8±3.0 h) and AUC (855±258 ngh/ml), respectively. It is intriguing to note that the terminal phase half-life $T_{1/2}$, C_{max}, and AUC following oral administration of 20 mg dose in Chinese were all significantly smaller than those of in Caucasians with 15 mg dose ($p < 0.05$); whereas

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the difference in T_{max} was insignificant. The results imply that the rate of absorption may not be different, but the elimination rate of cisapride in Chinese may be much faster than that in Caucasians (by comparison of $T_{1/2}$). Since larger dose and smaller apparent distribution volume (proportional to the body weight) in Chinese resulted in smaller C_{max} and AUC values, the first-pass metabolism of cisapride in gut wall and in the liver may be much faster in Chinese. However, it is noted that the pharmacokinetic data could change when different assay methods were used. Hence, it is difficult to justify the observed pharmacokinetic difference at present time. Further studies will be required to elucidate the details.

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以單變項和多變項統計解析法檢定二種廠牌的Cisapride錠劑之生體可用率

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摘 要

本文報告原開發廠Janssen公司之Prepulsid和瑞士藥廠之學名藥品cisapride錠劑口服後之相對性生體可用率。以單劑量(20mg)交叉試驗方式使用16名健康男性進行試驗。其血漿藥物動力學參數值(prepulsid和cisapride)分別爲：

C_{max} (61.97 ± 13.11 and 64.89 ± 14.31 ng/ml, mean ± SD), partial AUC (AUC_t, 402 ± 121.4 and 405.4 ± 117.5 ng·h/ml), total AUC (420.8 ± 123.8 and 421.9 ± 118.0 ng·h/ml), $T_{1/2}$ (7.8 ± 1.9 and 7.2 ± 1.8 h), T_{max} (1.3 ± 0.5 and 1.2 ± 0.5 h), MRT (8.5 ± 1.7 and 8.1 ± 1.4 h), VRT (102.0 ± 42.6 and 87.4 ± 41.3 h^2) and Cl/F (853.1 ± 238.9 and 850.4 ± 240.7 ml/min)

單變項統計解析之結果，皆符合現行生體相等性規定，故二種廠牌之cisapride錠劑具生體相等性。

多變項統計解析得知，若同時評估C_{max}及AUC，二產品之生體可用率類同度爲94%，同時評估$\ln C_{max}$及lnAUC，類同度爲92%。若同時評估C_{max}，AUC和MRT，則類同度爲86%，若同時評估$\ln C_{max}$，lnAUC和lnMRT，則類同度爲76%。華人和白種人服藥後之T_{max}無差異，但華人之C_{max}及AUC比白種人低。

關鍵詞：cisapride，藥物動力學，生體相等性，多變項統計解析。