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Pharmacokinetic Properties of Tranilast in Chinese People

MIN-JI CHARNG[1], PHILIP YU-AN DING[1], MEI-HUA CHUANG[2], CHIN-YI LO[3], PEI-SHAN CHIANG[3] AND LI-HENG PAO[4]*

[1.] Division of Cardiology, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, R.O.C.

[2.] Buddhist Dalin Tzu Chi General Hospital, Taipei, R.O.C.

[3.] Lotus Pharmaceutical Co.,LTD, Taipei, R.O.C.

[4.] School of Pharmacy, National Defense Medical Center, P.O. Box 90048-508, NeiHu,Taipei, R.O.C.

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ABSTRACT

The pharmacokinetics and relative bioavailability of two different formulated tranilast capsules were determined after single dosing in twelve healthy Chinese subjects in a two-way crossover study. Blood samples were obtained from predose until 24 h postdose. Plasma concentration of tranilast was determined by an HPLC method. Since no differences in pharmacokinetic parameters were found between the two distinctive tranilast products (Tranpro® and Rizaben®), the data were pooled together to characterize the pharmacokinetic property of tranilast. Mean peak plasma concentrations after dosing and the time at which it occurred (T_{max}) were 42.2 ± 5.92 μg/mL and 2.79 ± 1.14 h, respectively. The elimination half-life and total body plasma clearance were 7.58 ± 1.44 h and 8.12 ± 1.31 mL/h/kg, respectively. The respective areas under the concentration-time curve from time 0 to infinity for Tranpro® and Rizaben® were 431 ± 97 and 412 ± 60 μg·h/mL. The results also indicated that the two tranilast products can be considered as bioequivalent.

Key words: tranilast, pharmacokinetics, bioequivalence, Chinese.

INTRODUCTION

Tranilast (N-(3,4-dimethoxycinnamoyl) anthranilic acid), an anti-allergic drug, has been widely used in Japan in the treatment of bronchial asthma, allergic rhinitis and atopic dermatitis. Its action mechanism lies in the inhibition of the release of chemical mediators from mast cells and basophils[1,2]. Recent studies have shown that tranilast can prevent or reduce the formation of keloids and hypertrophic scars by inhibition of production of cytokines and oxygen-free radicals from activated macrophages and neutrophils[3-5]. The effect of tranilast on the inhibition of migration and proliferation of vascular smooth muscle has also provided the use of tranilast on human restenosis[2,6-8]. Despite the increasing interest in tranilast's clinical applications, information on clinical pharmacokinetic properties of tranilast was limited[9-12].

The purpose of the present study was to determine the pharmacokinetic properties of tranilast in healthy Chinese subjects, and estimate the relative bioavailability of two different formulated tranilast capsules (Tranpro® and Rizaben®).

MATERIALS AND METHODS

I. *Study Products*

Tranpro® capsule (100 mg/capsule, manufactured by Lotus Pharmaceutical Co. Ltd., Lot No. 131D) and Rizaben® capsule (100 mg/capsule, manufactured by KISSEI Co. Ltd., Lot No. KN001KX) were obtained from the manufactures. All solvents used were of HPLC grade, while other chemicals and reagents were of analytical grade. Tranilast standard was purchased from USP Reference, Rockville, MD. USA, and flufenamic acid (internal standard) was purchased from SIGMA Co. Ltd., MO, USA.

II. *Study Subjects*

The study was carried out at the Veterans General Hospital, Taipei, Taiwan, R.O.C.. Twelve healthy male subjects were recruited for the study after full clinical examination. The mean age was 21.83 ± 1.64 years (range: 20 - 25) and the mean body weight was 59.33 ± 4.79 kg (range: 50-65). The subjects were in good physical condition as approved by the physician based on their medical history, physical examinations, and routine laboratory tests (hematology, blood biochemistry, and urinalysis). The subjects were instructed to abstain from any drug for 2 weeks prior to and throughout the study. Written informed consent was obtained from each subject prior to entry into the study. The study protocol was approved by the Institutional Review Board (IRB) of the Veterans General Hospital, Taipei, Taiwan, R.O.C..

III. *Study Design*

Twelve healthy male subjects were enrolled in a randomized two-way crossover study with a one week washout

* Author for correspondence. Tel:886-2-87924867; Fax: 886-2-87924859; E-mail: paolh@ndmctsgh.edu.tw

between the treatments. After an overnight fasting, each subject received a single dose of two 100 mg tranilast capsules with 200 mL of water. Food and drinks were not allowed until 4 h after capsules administration. A standard meal was given at 4 and 8 h after the dose. Subjects were ambulatory during the study but prohibited from strenuous activity at study site. Ten mL of blood samples were drawn into evacuated heparinized glass tubes through an indwelling cannula before (0 h) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12 and 24 h after dosing. Blood samples were centrifuged immediately at 3000 rpm to separated plasma, which was then stored at -70˚C pending analysis.

IV. *Analytical Methods*

The plasma samples were analyzed by a sensitive and accurate high performance liquid chromatographic (HPLC) method, which was modified from a method described in the literature[9]. To 0.2 mL of plasma sample, 750 µL (7.14 ng/mL in 75% acetonitrile) flufenamic acid solution was added as an internal standard. After vortexing and centrifuged, the upper layer was transferred to another clean tube and diluted with 250 µL water with 2% acetic acid. After vortexing, the 25 µL was then injected onto the HPLC. Analysis of plasma samples was performance by HPLC with a UV-detector (model L-7400, Hitachi, Japan) wavelength at 333 nm. Chromatographic separations were obtained using a Cosmosil 5C18-MS column (4.6 × 250 mm, 5 µm particle size). The column was maintained at 40˚C. Tranilast and flufenamic acid were eluted isocratically with a mobile phase consisting of CH_3OH / CH_3COOH /H_2O (75:0.5:24.5, v/v/v). Quantitation was achieved by measurement of the peak height ratio of the drug to the internal standard. Calibration curves were determined after spiking blank plasma with tranilast standard at nine different concentrations, followed by extraction and HPLC analysis. The calibration curve for tranilast was linear over the range from 0.1to 60 µg/mL (r2 = 0.994). The within- and between-day precision and accuracy were all within 8%. The limit of quantitation for tranilast was 0.1 µg/mL in plasma. Tranilast is stable in plasma after three cycles of freeze and thaw. The stability of the assay was surveyed by quality control samples.

V. *Pharmacokinetic Analysis*

Pharmacokinetic parameters of tranilast were calculated by standard non-compartmental method[13]. The maximum plasma concentration (C_{max}) and the time to peak (T_{max}) were determined by visual inspection of plasma concentration-time profiles. The area under the plasma concentration-time curve (AUC) was determined by the trapezoidal rule. AUC_{0-t} was calculated from zero time to the last measurable concentration C_t, and $AUC_{0-\infty}$ was calculated by extrapolation of AUC_{0-t} to time infinity by adding C_t/k_e to AUC_{0-t}. The slope of the log linear portion of the terminal phase was evaluated by least square linear regression. It is assumed to be the elimination rate constant ke though direct evidence is no available. Tranilast total clearance was calculated as Cl/F = Dose/AUC. The volume of distribution was calculated as Vd/F = Dose/(AUC*k_e). The relative bioavailability (BA) of tranilast was calculated as [$AUC_{Tranpo}/AUC_{Rizaben}$]*100.

VI. *Statistical Analysis*

All results are expressed as mean ± S.D.. All pharmacokinetic parameters were analyzed by analysis of variance using SAS® (version 8.1), through GLM procedure. Statistical significance was assumed for $p<0.05$. The ANOVA model included sequence, subject nested within sequence, period, and treatment. Bioequivalence was determined using the two one-sided test approach with an alpha of 0.05 for each tail, and 90% confidence intervals. The 90% confidence intervals were obtained from the antilogs of the lower and upper bounds of the 90% confidence intervals for the difference in the means of the Log-transformed data (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$). The products were considered bioequivalent if the confidence interval was contained within the limits, 0.8 to 1.25.

RESULTS AND DISCUSSION

This study was performed to determine the pharmacokinetics of tranilast after oral administration to healthy Chinese male subjects. Tranilast showed no adverse events and was well-tolerated for this study. No significant variation in blood pressure or heart rate as observed at any time after the administration of either of the tranilast formulations when compared with basal value.

The mean plasma concentration-time profiles of tranilast in twelve Chinese healthy male volunteers after oral administration of 200 mg capsule are shown in Figure 1. The non-compartmental pharmacokinetic parameters of tranilast obtained for both tranilast capsules formulations are shown in Table 1. Since no pharmacokinetic differences were found between the two tranilast products (Tranpro® versus Rizaben®), the mean values of the pharmacokinetic parameters of these two products were also listed in Table 1. The

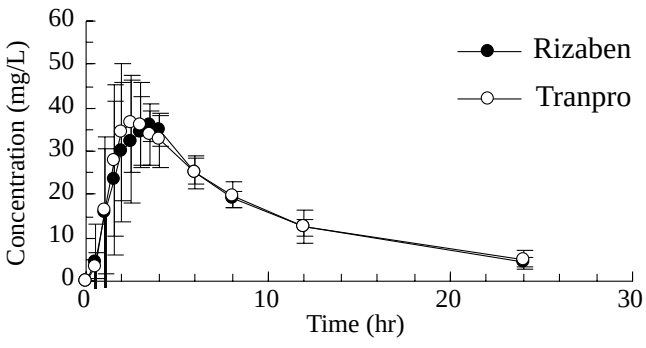

Figure 1. Mean (± SD) plasma tranilast concentration following 200 mg Rizabin® capsule (•) or Tranpro® capsule (◦) to healthy volunteers.

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Table 1. Non-compartmental pharmacokinetic parameters following a 200 mg dose of tranilast in healthy volunteers. n=12 (mean ± SD)

Parameter	Pharmacokinetic parameters (Rizaben®) (n=12)	(Tranpro®) (n=12)	Over all (n=24)	Statistical analysis ANOVA GLM (*p*-value)	90%CI
C_{max} (μg/mL)	42.0 ± 4.7	42.3 ± 7.2	42.2 ± 5.92	3.741 (0.600)	93.5-106%
T_{max} (h)	2.83 ± 0.98	2.75 ± 1.32	2.79 ± 1.14	—	—
$t_{1/2}$ (h)	7.53 ± 1.43	7.71 ± 1.61	7.58 ± 1.44	—	—
AUC_{0-24} (μg·h/mL)	363 ± 44	373 ± 59	368 ± 51	5.908 (0.315)	97.3-107%
$AUC_{0-\infty}$ (μg·h/mL)	412 ± 60	431 ± 97	422 ± 80	6.043 (0.388)	97.6-110%
AUC_{0-24} / $AUC_{0-\infty}$	0.88 ± 0.04	0.87 ± 0.05	0.88 ± 0.05	—	—
Cl / F (mL/h/kg)	8.35 ± 1.32	8.12 ± 1.35	8.12 ± 1.31	—	—
Vd / F (mL/kg)	89.03 ± 11.46	87.75 ± 7.51	88.39± 9.50	—	—

absorption by the gastrointestinal tract of tranilast following the capsule administration took place gradually with Cmax of 42.3 ± 7.2 μg/mL obtained at 2.75 ± 1.32 h for Tranpro® and Cmax of 42.0 ± 4.7 μg/mL obtained at 2.83 ± 0.98 h for Rizaben®. The terminal half-life and total plasma clearance were 7.71± 1.61 h and 8.12 ± 1.35 mL/h/kg for Tranpro® and 7.53 ± 1.43 h and 8.35 ± 1.32 mL/h/kg for Rizaben®, respectively. The areas under the concentration-time curve from 0 to infinity ($AUC_{0-\infty}$) following Tranpro® and Rizaben® administration were 431 ± 97 and 412 ± 60 μg·h/mL, respectively. The relatively bioavailability of Tranpro® versus Rizaben® was 104.6 ± 23.6 %.

No significant difference was observed in any of the pharmacokinetic parameters analyzed between the two tranilast capsule formulations. The statistical analysis for bioequivalence assessment is also listed in Tablet 1. The 90% confidence intervals for $AUC_{0-\infty}$ and Cmax lay within the bioequivalence range of 80-125%. The 90% confidence intervals for the natural log-transformed data were calculated based on the FDA guidelines. No difference in either the extent or the rate of absorption was observed. These data indicate that tranilast are equally available *in vivo* from the two capsules formulations.

This study provided the pharmacokinetic characteristics of tranilast following oral administration in Chinese healthy subjects. Contrary to the increasing interest in tranilast's clinical applications, only limited and incomplete pharmacokinetic information can be found in the literature[9-12]. The individual C_{max} of 48.0 and 34.4 μg/mL and terminal half-life of 3.8 and 4.1 h had been reported after oral administration of 200 mg of tranilast in two Japanese healthy subjects[9]. The same dose of tranilast capsule had been given orally to ten healthy Chinese volunteers[10]. However, only the mean plasma concentration-time curve was present in the paper. The Tmax occurred at around 3 h with C_{max} around 40 μg/mL, which could only be read from the concentration-time graph. Takehana *et al.*[11] stated in their paper that the C_{max} was 31.7 μg/mL at 4.7 h, with AUC of 369.2 μg·h/mL and the terminal half-life of 8.4 h after tranilast (200 mg single dose) was administered orally to Japanese patients with angina (through the personal communication with Hideo Tami). A C_{max} of 37.7 ± 50.9 μg/mL and $t_{1/2}$ of 4.54 ± 1.53 h after single dose of 200 mg tranilast was administered to Japanese patients with asthma have been reported in Japanese language[12].

The C_{max} of tranilast in this study was similar to that reported in healthy subjects[9,10] as well as in Japanese patients with asthma[12], while it seemed to be higher in comparison to that measured in the patient with angina[11]. Interestingly, the terminal $t_{1/2}$ of tranilast in this study was similar in patients with angina[11], while longer $t_{1/2}$ was observed as compared to other reports[9,12]. The differences in $t_{1/2}$ may be resulted from insufficient sampling collection in their studies[9,12]. Based on these limited comparisons, the ethnic differences between Chinese and Japanese and the effect of diseases on the pharmacokinetics of tranilast may need further investigations.

CONCLUSION

The results of this study indicate that the two test products exhibited equal availability *in vivo*, and data of clinical pharmacokinetics of oral tranilast in healthy Chinese subjects are presented. The study thus provides the basic pharmacokinetic characteristic of tranilast for future clinical applications.

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Tranilast在華人的藥物動力學

常敏之[1]　丁予安[1]　莊美華[2]　羅芹懿[3]　江佩珊[3]　鮑力恒[4*]

[1.] 台北榮民總醫院　台北市石牌路二段201號
[2.] 財團法人佛教綜合醫院大林分院　嘉義縣大林鎮民生路2號
[3.] 美時化學股份有限公司　台北市復興南路一段200號11樓
[4.] 國防醫學院藥學系　台北市民權東路六段161號

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摘　要

12名健康自願華人男性，以單劑量口服投予兩種Tranilast膠囊製劑（Tranpro®和Rizaben®）之交叉試驗進行其藥物動力學及相對生體可用率之試驗。試驗前及試驗後適當時間之血液檢體收集至24小時，血漿中藥物濃度是以高效能液相層析儀進行分析。口服這二種不同處方膠囊製劑的藥動學參數並無顯著差異，故Tranilast的藥動性質是將其合併起來計算：C_{max}, T_{max}, $t_{1/2}$及Cl/F分別為42.2 ±5.92 μg/ml, 2.79 ±1.14 h, 7.58 ±1.44 h及8.12 ±1.31 mL/h/kg。口服Tranpro®和Rizaben®之AUC_{∞}分別為431 ±97和412 ±60 μg·h/mL，經統計分析之結果顯示二種Tranilast膠囊具生體相等性。

關鍵詞：Tranilast，藥物動力學，生體相等性，華人