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Pharmacokinetic Behavior of Ketoconazole in Adult Chinese Males

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ABSTRACT

The pharmacokinetic behavior of ketoconazole (Nizoral-Janssen) in Chinese adults was studied in 14 male volunteers. The pharmacokinetic parameters of ketoconazole obtained after oral administration of 400 mg (two tablets) were AUC (51.4 ± 17.9 mg·h/l, mean ± SD), C_{max} (10.3 ± 2.8 mg/l), T_{max} (1.5 ± 0.3 h), MRT (4.1 ± 0.7 h), VRT (30.9 ± 11.2 h^2), Cl/F/BW (0.138 ± 0.063 l/h/kg) and k^* (slope of terminal phase, 0.330 ± 0.09 h^{-1}). When the plasma concentration data of 14 subjects were fitted to a conventional one-compartment body model, then the first order absorption rate constant was 0.236 ± 0.136 h^{-1}, and the elimination rate constant was 0.172 ± 0.041 h^{-1}. No statistical difference was observed for the parameters CL/F, k^*, C_{max} and AUC between Caucasians in a published study and Chinese in this study ($p > 0.1$). However, the T_{max} in Chinese (1.5 ± 0.3 h) was significantly shorter than that in Caucasians (2.6 ± 1.2 h, $p < 0.01$).

Key words : ketoconazole, pharmacokinetics, Chinese.

INTRODUCTION

Ketoconazole, cis-1-acetyl-4-{4-[2-(2,4-dichlorophenyl)-2-imidazol-1-ylmethyl-1,3-dioxolan-4-ylmethoxy]phenyl}piperazine, is a synthetic imidazole-containing anti-fungal drug. Like other antifungal imidazoles, ketoconazole displays broad spectrum activity against yeasts and filamentous fungi. In its hydrochloride form, ketoconazole is water soluble and is effective after oral administration. This is an important property not shared by most of the other members of the imidazole group. In spite of the popular use of this drug in Taiwan, the available data on the pharmacokinetic behavior of ketoconazole are based on studies which used Caucasian subjects. The current study aims to reveal the pharmacokinetics of ketoconazole in adult Chinese males.

MATERIALS AND METHODS

I. *Drug Product*

Nizoral tablets (Janssen, Lot No. 103162) containing 200 mg of ketoconazole in each tablet were used.

II. *Subjects*

After a review of their personal history, and medical and laboratory examinations, fourteen normal male Chinese aged 24 to 39 were selected

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to participate in this study, which was carried out at the Father Fox Memorial Hospital, Tainan, Taiwan. The subjects' characteristics are summarized in Table 1.

III. *Study Protocol*

The study protocol and written informed consent form were reviewed and approved by the Department of Health, Taiwan. Two tablets (400 mg ketoconazole) and 200 ml drinking water were administered to each subject on the morning following a 12-h overnight fast. Two hours after administration, water was allowed as desired. A standard Chinese lunch was served 4.5 h after the drug administration. Blood (5 - 10 ml) was collected via heparin lock just prior to the drug administration, and at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0 and 24.0 h after the drug administration. The plasma was separated by centrifuge (1500 g for 5 min at 30°C) immediately after the blood had been collected. The plasma was stored in a freezer (-20°C) prior to the assays. The assays were completed within two weeks of collecting the blood samples. A preliminary stability study revealed no appreciable loss of ketoconazole in plasma during two-months' storage in the freezer.

IV. *Determination of Ketoconazole in Plasma*

The high performance chromatographic method (HPLC) reported by Andrews et al[1]. was modified to determine ketoconazole in plasma. Briefly, 1 ml of plasma spiked with 50 µl of clotrimazole stock solution (internal standard, 80 µg/ml in methanol) was alkalified with 75 µl of 0.1 N sodium hydroxide, then diluted with 2 ml of distilled water and injected into a Sep-Pak C18 cartridge (Waters). The Sep-Pak cartridge was then rinsed with 5 ml of distilled water twice.

Table 1. Summary of subjects' characteristics

N	Age (yrs)	Height (cm)	Weight (kg)
14	30.5 ± 4.9	169.1 ± 4.7	65.7 ± 7.9

Mean ± S.D; N: total number of subjects in the study.

After excluding the remaining water with 0.2 ml of methanol, ketoconazole and clotrimazole were eluted with 2 ml of methanol. One hundred microliters of the eluent was injected for the HPLC. In cases where the samples were of low concentration (less than 0.1 µg/ml ketoconazole), the eluent was evaporated to dryness with nitrogen gas at 50°C and the residue was redissolved in 200 µl methanol for injection into the HPLC. The HPLC apparatus consisted of a Shimadzu model LC-6A equipped with SPD-6A detector and CR-6A recorder. The separation was accomplished with a NOVA PAK™ C18 column (3.9 x 150 mm, Waters) and a Zorbax ODS guard column (4 x 12.5 mm, Du Pont). The ketoconazole and clotrimazole were detected at 231 nm. A mobile phase consisting of CH_3CN/CH_3OH/50 mM KH_2PO_4, pH 6.8 in 34/34/32 volume ratio was run at a flow rate of 2 ml/min and a detector attenuation of 0.01 aufs. The ketoconazole assay was calibrated by analyzing 1 ml of plasma to which had been added 0.01 to 15 µg of ketoconazole (USP standard) and 4 µg of internal standard, clotrimazole. A typical chromatogram is depicted in Fig. 1.

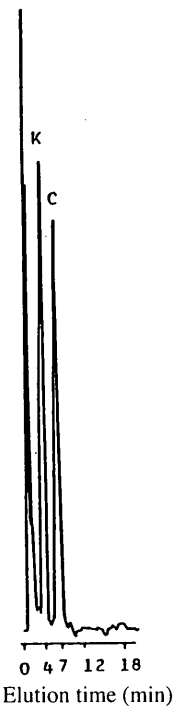

Figure 1. Chromatogram of plasma sample after clean-up (K: ketoconazole, C: clotrimazole).

The linearity of peak height ratio and the ketoconazole concentration in plasma was established for 0.1 to 15.0 μg/ml and for 0.01 to 0.1 μg/ml, respectively. The recovery of ketoconazole in plasma was 102 ± 4.0% (0.1 to 15.0 μg/ml, mean ± SD, n = 26). The intraday and interday variations of the repeatability were less than 1.6 and 2.2% respectively for the samples containing more than 0.1 μg/ml ketoconazole. The limit of quantitation was 0.01 μg/ml; however, in fact no plasma concentration datum fell in the range 0.01-0.1 μg/ml in this study.

V. *Pharmacokinetic Parameters*

The maximum observed concentration, C_{max} and the time to reach peak concentration, T_{max} were recorded for each individual. The AUC_{0-12} values were calculated using the linear trapezoidal method, and the remaining areas were estimated by dividing the last concentration (C_{12}) by the slope of the terminal phase of the plasma concentration-time curve (k*). The plasma concentration data of the 14 subjects were fitted to a conventional one-compartment body model $C = Ae^{-kt} - Be^{-kat}$, to estimate the first order absorption (ka) and elimination (k) rate constants. The mean residence time (MRT) and the variance of residence time (VRT) values were calculated by equations (1) and (2)[2] :

$$MRT = \frac{\int_o^\infty tCdt}{\int_o^\infty Cdt} \quad \text{.....(1)}$$

$$VRT = \frac{\int_o^\infty (t - MRT)^2 Cdt}{\int_o^\infty Cdt} \quad \text{.....(2)}$$

where C is the plasma ketoconazole concentration in μg/ml, and t is the time in h after oral administration. The oral apparent clearance (Cl/F) were estimated by dividing the dose with AUC and are reported here per kg body weight.

VI. *Pharmacokinetics of Ketoconazole in Caucasian and in Chinese*

Pharmacokinetic parameters, C_{max}, k', AUC, T_{max} and Cl/F in Chinese subjects were compared to those reported for Caucasians[3,4].

Table 2. Pharmacokinetic parameters of ketoconazole in Chinese after oral administration (400 mg)

Parameters	Mean ± SD
AUC, μg·h/ml	51.4 ± 17.9
C_{max} μg/ml	10.3 ± 2.8
T_{max}, h	1.5 ± 0.3
MRT, h	4.1 ± 0.7
VRT, h^2	30.9 ± 11.2
Cl/F/BW, l/h/kg	0.138 ± 0.063
k*, h^{-1}	0.330 ± 0.09
A, μg/ml	7.91 ± 1.27
k, h^{-1}	0.172 ± 0.041
B, μg/ml	3.82 ± 1.44
k_a, h^{-1}	0.236 ± 0.136

k*: slope of terminal phase; $C = Ae^{-kt} - Be^{-kat}$; n = 14;
BW : body weight in kg.

RESULTS AND DISCUSSION

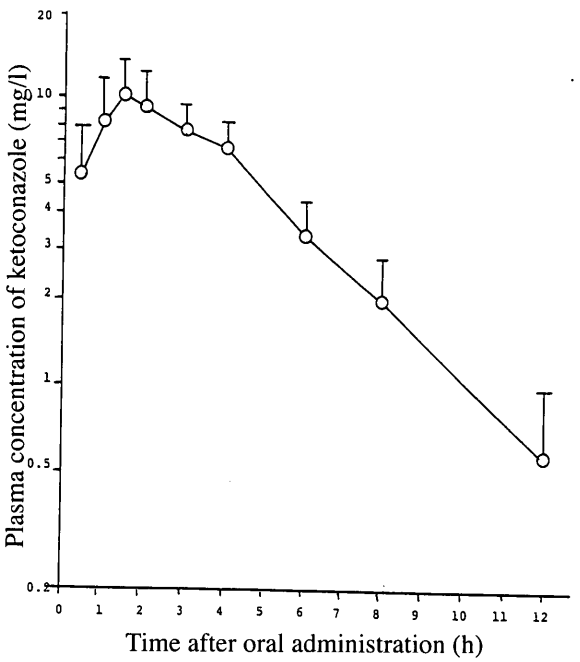

Figure 2. Plasma concentration profile after oral administration of ketoconazole (mean + SD, n=14).

I. *Plasma Concentration Profile*

The plasma concentration profile of ketoconazole after oral administration is depicted in Fig. 2. The plasma concentrations of ketoconazole in all subjects 24 h after the drug was administered were below the limit of quantitation (0.01 μg/ml). The average pharmacokinetic parameters are summarized in Table 2. It is intriguing to note that the observed mean k^* values are significantly larger than the compartment modeling mean k values. The difference may be due to the inadequacy of the model. Besides, the dose per kg body weight is significantly different for each subject, so that fitting the plasma data of 14 subjects to a simple mathematic model would result in large variances. A non-compartment approach therefore seems more appropriate than the conventional one-compartment body model in describing the pharmacokinetics of ketoconazole in a fixed dose study.

II. *Pharmacokinetics of Ketoconazole in Caucasian and in Chinese*

Three of the estimated pharmacokinetic parameters determined in the present study, Cl/F, k^* and T_{max} were compared with those reported by Huang et al[3]. for American college students (Caucasian, oral administration of 400 mg ketoconazole solution). There was no significant difference between the parameters for Americans with oral solutions and those for Chinese taking tablets (Welch t-test, $p > 0.1$). When the parameters, k^*, C_{max}, T_{max}, and AUC from the present study were compared with the corresponding values reported by Baxter et al[4]. for Caucasians (tablets and solutions), the difference of the means for Caucasians and Chinese for k^*, C_{max} and AUC were insignificant ($p > 0.1$). A significant difference was noted, however, for T_{max} after administration of the Nizoral tablets (1.5 ± 0.3 h in Chinese; 2.6 ± 1.2 h in Caucasians; $p < 0.01$). On the other hand, the T_{max} for tablets in Chinese was statistically not different from the T_{max} for the ketoconazole solution in Caucasians (1.5 ± 0.32 h, $p > 0.1$). Gastrointestinal absorption of ketoconazole is known to be influenced by gastric acidity[5], and is impaired by food[6]. The observation implies that the dissolution of ketoconazole in gastric juice might be significantly faster in Chinese. Further studies will be required to elucidate the details.

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ketoconazole在中國人體內的藥物動力學特性

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摘 要

口服投與含 400 mg 之 ketoconazole 錠於十四名健康男性獲得如次的藥物動力學參數：AUC $_\infty$ (51.4 ± 17.9 mg · h / l, mean ± SD), Cmax (10.3 ± 2.8 mg / l), Tmax (1.5 ± 0.3 h), MRT (4.1 ± 0.7 h), VRT (30.9 ± 11.2h^2)，Cl / F / BW (0.138 ± 0.063 l / h / kg) 和 k* (末端相斜率，0.330 ± 0.09 h^{-1})。倘若將十四名受試者之血漿中濃度使用傳統的一室體模式加以歸納，吸收速率常數爲 0.236 ± 0.136 h^{-1}，而消失速率常數爲0.172 ± 0.041 h^{-1}。白種人和中國人間之 Cl / F, k*, Cmax和AUC $_\infty$ 並無顯著差異。唯中國人的Tmax (1.5 ± 0.3 h) 遠比白種人 (2.6 ± 1.2 h, P < 0.01) 爲短，顯示吸收速率明顯地較快速。

關鍵詞：ketoconazole，藥物動力學，中國人。