

Pharmacokinetics of anastrozole in Chinese male volunteers

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KEY WORDS anastrozole; pharmacokinetics; gas chromatography; biological availability

ABSTRACT

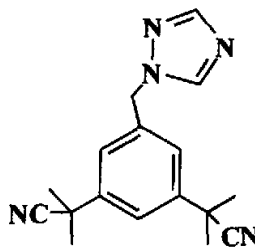
AIM: To compare pharmacokinetics of domestic and imported tablets of anastrozole. **METHODS:** Twenty male Chinese volunteers were enrolled in a randomized crossover study with a single oral dose of 1 mg of the two formulations respectively. The anastrozole in plasma was measured by gas chromatography with electron-captured detector. Area under the drug concentration-time curve was evaluated by variance analysis and two one-side *t*-test. **RESULTS:** A two-compartment model was adopted in anastrozole plasma concentration-time data analysis. The parameters such as C_{max} , T_{max} , $T_{1/2\beta}$, and $AUC_{0-\infty}$ were (10 ± 3) and $(10.2 \pm 2.5) \mu\text{g} \cdot \text{L}^{-1}$, (1.2 ± 0.5) and (1.3 ± 0.4) h, (42 ± 14) and (41 ± 26) h, (443 ± 141) and $(429 \pm 121) \mu\text{g} \cdot \text{h} \cdot \text{L}^{-1}$, respectively, and there were no significant differences between the two formulations. **CONCLUSION:** Domestic and imported anastrozole were of bioequivalence. The relative bioavailability of the domestic tablet was $100\% \pm 9\%$.

INTRODUCTION

Anastrozole [2,2'-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene] bis (2-methylpropanonitrile)] is a potent aromatase inhibitor, which prevents androgen conversion to estrogens^[1]. It is used to treat late-stage breast cancer in postmenopausal women^[2]. The 1 mg per day of anastrozole is highly selective and well toler-

ated by patients^[3,4]. It has a half-life long enough to provide for once-daily dosing and this dose produces the maximum detectable estradiol suppression^[5].

Because of the low plasma concentration of anastrozole, liquid chromatography with detectors of UV, fluorescence, or electrochemistry would not have been an appropriate method of analysis, since these detectors did not have the sensitivity to yield a limit of quantitation low enough to allow full pharmacokinetic profiles of anastrozole in the volunteers or patients from clinical studies. Therefore, we tried gas chromatography with electron-captured detector (GC-ECD) and developed a simple and sensitive procedure which could be employed for the analysis of anastrozole, and compared the data of pharmacokinetics between domestic and imported tablets to see if the two formulations provided the same plasma profile.



Structure of anastrozole

MATERIALS AND METHODS

Drugs and reagents Domestic anastrozole tablets (lot No 000102, Wanma Pharmaceutical Factory, Zhejiang, China), imported anastrozole tablets (Arimidex[®], lot No OA1845A, Zeneca Limited Pharmaceutical Factory, UK), and standard anastrozole (purity 99.87%) were obtained from Wanma Pharmaceutical factory. Each tablet contained 1mg of anastrozole. Internal standard diazepam (purity 99.60%) was offered

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by Institute of Drug Control, Shanghai, China. Other reagents of AR grade were purchased from Shanghai Chemical Reagent Store.

Chromatographic condition Anastrozole was determined by HP6890 GC-ECD. The analytical column was HP-50 + capillary, 30 m × 0.53 mm, 1 μm. The stationary phase was 50 % phenyl-methyl silicone. High pure (purity 99.99 %) N₂ was as carrier gas. Pressure was 200 kPa, and the make-up flow was 45 mL/min. Temperature was 250 °C for sample intaking, 260 °C for detector, and 232 °C for column.

Subjects Twenty male healthy subjects were all students from Shanghai Medical University. Age: (22.5 ± 1.0) a; Weight: (66.4 ± 7.3) kg. Following Helsinki Declaration, informed consents were given to them. They had no allergic history and stopped using any drugs before 15 d. Cigarette and alcohol were forbidden during trial period. Physical examination and laboratory tests including blood, urine, liver, kidney, and electrocardiogram showed no abnormal findings. The scheme was approved by Ethical Committee of Renji Hospital.

Protocol Twenty volunteers in domestic or imported anastrozole group (each n = 20) took part in the study in an open randomized crossover design. Each volunteer was administered orally 1 mg of anastrozole with water 250 mL. Venous blood samples 3 mL were taken before and at 0.33, 0.67, 1, 1.5, 2, 3, 5, 10, 26, 58, 82, and 106 h after medication. The blood samples were collected in heparin-coated tubes and centrifuged at 1600 × g for 10 min. Plasma was stored at -20 °C until assay. Food was not allowed until 3 h postmedication. During the test period they were supplied uniform diets. A crossover study was followed by a washout period of 2 weeks.

Assay of anastrozole To 1.0 mL of a plasma sample, 100 μL of 1.002 mg·L⁻¹ internal standard spiking solution was added, then 7 mL of ether was added. The samples were vortexed for 2 min, the organic layer was transferred to a clean tube and dried in a warm water-bath at 50 °C. The residues were reconstituted in 150 μL of ethyl acetate, and transferred to autosampler vials.

Validation study Control human plasma (1 mL) was spiked with anastrozole and internal standard solutions to achieve a standard curve of anastrozole in concentrations of 0.5 - 20 μg·L⁻¹. The intraday and interday reproducibility were assayed by determining anastrozole in 5 plasma samples with different concentra-

tions for 5 times in a day or in 5 consecutive days. Extraction recovery of anastrozole in plasma was also performed. The limit of detection was defined as three times background noise.

Pharmacokinetic evaluation The pharmacokinetic parameters of anastrozole was calculated and analyzed by 3P87 software. Comparison of pharmacokinetic parameters between domestic and imported tablets was carried out by variance analysis with NDST software. The bioequivalence analysis was evaluated with method of two one-side *t*-test⁽⁶⁾.

RESULTS

Quality control of GC-ECD assay The retention time of anastrozole and internal standard were 6.0 min and 8.9 min, respectively. The peaks were sharp, well-separated, and not interfered by plasma (Fig 1).

The regression equation was: $Y = 0.0178X - 0.0284$, $r = 0.9998$. The sensitivity was 0.01 ng (plasma extract). Anastrozole standard concentrations were 1.0, 10.0, 20.0 μg·L⁻¹, the relative standard deviation (RSD) of intraday were 4.8 %, 2.1 %, and 1.7 %, the RSD of interday were 6.7 %, 3.0 %, and 3.5 %, the extraction recovery were 84 % ± 13 %, 93.9 % ± 0.8 %, and 97.0 % ± 2.8 %, respectively.

Concentration-time course The average concentration-time curves of the two kinds of tablets were fitted with two-compartment model, weight was C⁻² according to parameters of the goodness of fit, AIC, etc. The plasma concentration of 1 mg domestic and imported anastrozole were similar (Fig 2).

Pharmacokinetics Main pharmacokinetic data between the two formulations showed no statistical difference (Tab 1). Relative bioavailability of anastrozole was 100.3 % ± 9.1 %. The *t*₁ and *t*₂ of two one-side *t*-test of the two formulations were: 7.056 and 8.655 in C_{max}; 4.975 and 2.560 in T_{max}; 5.551 and 4.404 in AUC₀₋₁₀₆, respectively. The *t*_(1-0.05)(18) was 1.734, so, the two formulations were of bioequivalence.

DISCUSSION

In this study, triazolam, diazepam, nitrazepam, and estazolam were tried as internal standard. The peak and retention time of diazepam was suitable, and diazepam was easy to obtain. So we used it as the internal

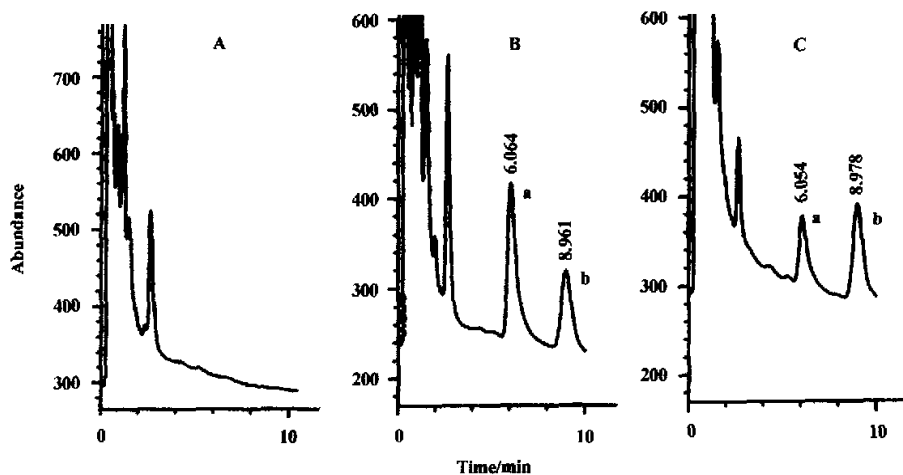


Fig 1. Gas chromatograms of anastrozole in human plasma. A: blank plasma; B: standard anastrozole (a) and internal standard (b) in blank plasma; C: plasma sample after medication.

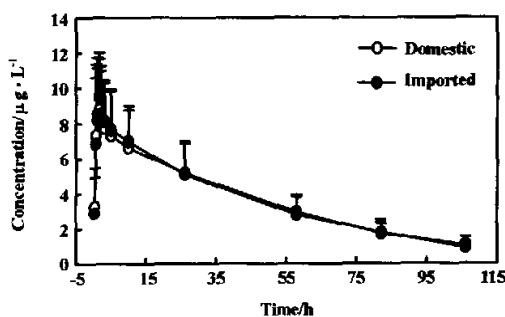


Fig 2. Plasma concentration curves after oral administration of 1 mg domestic and imported anastrozole. $n = 20$ volunteers. $\bar{x} \pm s$.

Tab 1. Pharmacokinetic parameters after oral administration of 1 mg domestic and imported anastrozole tablets in Chinese volunteers. $n = 20$ volunteers. $\bar{x} \pm s$.

Parameter	Domestic	Imported
$T_{1/2\alpha}$ /h	4.7 ± 2.1	4.0 ± 2.3
$T_{1/2\beta}$ /h	42 ± 14	41 ± 26
$V_d \cdot F^{-1}$ /L	106 ± 41	98 ± 41
T_{max} /h	1.2 ± 0.5	1.3 ± 0.4
C_{max} /μg·L ⁻¹	10 ± 3	10.2 ± 2.5
AUC_{0-10h} /μg·h·L ⁻¹	386 ± 117	385 ± 117
$AUC_{0-\infty}$ /μg·h·L ⁻¹	443 ± 141	429 ± 121
$F/\%$	100 ± 9	

method, temperature and pressure program were used for detection, which could lead to the drift of baseline, and the detection limit of anastrozole was $0.5 \mu\text{g} \cdot \text{L}^{-1}$. In our study, the extraction procedure was simple, ie, plasma samples were extracted with only 7 mL ether, and the detection limit was $0.2 \mu\text{g} \cdot \text{L}^{-1}$.

Limited published data were available on the pharmacokinetics of anastrozole. A few trials in healthy women and patients with breast cancer had measured plasma concentrations and the terminal half-life ($T_{1/2\beta}$) of anastrozole after oral administration⁽⁸⁻¹⁰⁾. In healthy postmenopausal women given the 1 mg dose, the mean C_{max} values of anastrozole were $13.1 \mu\text{g} \cdot \text{L}^{-1}$, the maximum plasma concentration occurred within 2 h after oral administration. The terminal $T_{1/2}$ ranged from 38 h to 61 h⁽⁸⁾. These values were similar to that of young men observed in our study.

According to the NDST software and two one-sided t -test, the main pharmacokinetic parameters of the domestic and imported anastrozole tablets were in good agreement with each other. The analysis showed that there was bioequivalence between the two products, and the relative bioavailability was $100\% \pm 9\%$.

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阿那曲唑在中国男性志愿者体内的药代动力学

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关键词 阿那曲唑; 药物动力学; 气相色谱法; 生物利用度

目的: 比较国产和进口阿那曲唑片在健康人体内的药代动力学. **方法:** 二十名志愿者交叉随机分成两组, 单剂量口服 1 mg, 用 GC-ECD 测定血药浓度, 通过方差分析和双单侧 *t* 检验比较两种制剂的药-时曲线下面积. **结果:** 阿那曲唑的体内分布符合二室模型. 国产和进口阿那曲唑的药动学参数 C_{max} 分别为 (10 ± 3) 和 $(10.2 \pm 2.5) \mu\text{g} \cdot \text{L}^{-1}$; T_{max} 分别为 (1.2 ± 0.5) 和 $(1.3 \pm 0.4) \text{h}$; $T_{1/2\beta}$ 分别为 (42 ± 14) 和 $(41 \pm 26) \text{h}$; $\text{AUC}_{0-\infty}$ 分别为 (443 ± 141) 和 $(429 \pm 121) \mu\text{g} \cdot \text{h} \cdot \text{L}^{-1}$, 两者无显著性差别 ($P > 0.05$). **结论:** 两种制剂为生物等效, 国产阿那曲唑片的相对生物利用度为 $100\% \pm 9\%$.

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