

Pharmacokinetics of bendazac lysine in 10 Chinese young men

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KEY WORDS bendazac; lysine; pharmacokinetics; high pressure liquid chromatography

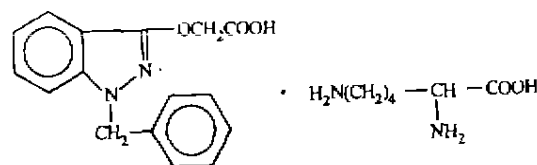
AIM: To compare the pharmacokinetics of domestic and imported tablets of bendaza. lysine (BL).

METHODS: A single oral dose of 500 mg BL of this 2 kinds of tablets was given to 10 Chinese volunteers of Han nationality in a randomized crossover study. Plasma levels were determined with HPLC-UV method. Data were analyzed automatically by using a CAPP program on microcomputer.

RESULTS: The plasma concentration-time curve was fitted to 2-compartment open model, and the major pharmacokinetic parameters of domestic and imported BL tablets were shown respectively as following: C_{max} 66 ± 16 and 65 ± 8 $mg \cdot L^{-1}$; T_{max} 0.98 ± 0.22 and 0.98 ± 0.21 h; $T_{1/2\alpha}$ 6.2 ± 1.8 and 6.2 ± 1.7 h; AUC 335 ± 47 and 337 ± 58 $mg \cdot h \cdot L^{-1}$. There was no significant difference between domestic and imported tablets. The bioavailability of the domestic *vs* that of the imported tablet was 99 ± 12 %. The unchanged BL in urine were about 5.4 % and 5.6 % respectively of the dosage in 24 h after a single oral dose. **CONCLUSION:** The two kinds of tablets had the same biological effects.

Bendazac has anti-inflammatory, antinecrotic, choleric, and antilipemic properties, and its principal action is antidenaturation of protein^[1]. Its lysine salt, bendazac lysine (BL), is better absorbed than bendazac after oral administration and has been used abroad for the treatment of cataract^[1]. In China, the BL tablet, first produced by Nanjing Institute of Materia Medica and Zhejiang Pinghu Pharmaceutical Factory, was permitted to conduct clinical study by the Ministry of Public Health on 1994 Aug 4. In this study we compared the pharmacokinetics between the

imported and domestic BL tablets.



Bendazac lysine

MATERIALS AND METHODS

Drug and reagents BL standard, Nanjing Institute of Materia Medica (lot No 930812), purity >98 %, mp 180 - 181 °C. Domestic BL tablet (200 mg/tablet), Nanjing Institute of Materia Medica and Zhejiang Pinghu Pharmaceutical Factory (tablet lot No 941024). Imported BL tablet (500 mg/tablet), Korea KuKje Pharmaceutical Co Ltd (lot No 93712). XAD-2 macroporous resin (0.3 - 1 mm), Serva Pharmaceutical Co.

HPLC-grade acetonitrile was purchased from Huaiyin Chemical Plants, China. Other chemicals were all of AR. Deionized water was used.

Chromatography condition The HPLC system (Shimadzu Corp, Kyoto, Japan) consisted of an LC-6A solvent delivery unit, a Rheodyne model 7125 injector, an SCL-6A system controller, an SPD-6A UV-VIS spectrophotometric detector, and a C-R6A data processing unit. The analytical column (250 mm × 4.6 mm Dalian Institute of Chemical Physics, China) was packed with Spherisorb C₁₈ 5 μm. The mobile phase was composed of acetonitrile and acetic acid 0.1 mol · L⁻¹ (vol: vol = 47:53), the detector was set at 307 nm and 0.005 AUFS, and the flow rate was set at 1 mL · min⁻¹.

Subjects In accordance with the declaration of Helsinki, 10 healthy male volunteers of Han nationality with free consent, having been informed about the effects of the drug and passed the physical examination, were accepted into the study. They were aged 20.3 ± 0.5 a, weighed 64 ± 6 kg, and all the test results of their blood, urine, liver, kidney, and electrocardiogram were within normal ranges. At least 2 wk before the study, all were kept from medication, tobacco, and alcohol.

Study design After a 12 h fasting, the volunteers

received at 7 AM a single oral dose of domestic or imported BL tablet (500 mg) according to a self-controlled, randomized crossover study design. A uniform diet was supplied after 3 h and water 100 mL was asked to be drunk every 3 h, and physical labor was refrained during that day. The washout period was set to be 1 wk (The Medicine Administration of the Healthy Ministry of China. The guide principle of clinical study of the new medicine. Beijing, 1993; 166).

Plasma and urine sampling Blood samples were collected into the heparinized tubes at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24 h after the medication. The samples were centrifuged at $3000 \times g$ for 10 min to get plasma. After adding acetonitrile 2.5 mL to the plasma (0.5 mL), the mixture was vortexed for a few seconds and spinned at $3500 \times g$ for 5 min. The supernatant was centrifuged at $5000 \times g$ for 5 min. Then the supernatant was injected into HPLC system. The urine was collected 0–24 h after *po* drug. After being filtered, the urine aliquots (10 mL) were poured onto XAD-2 macroporous resin with flow rate $1 \text{ mL} \cdot \text{min}^{-1}$. The washing liquid was composed of methanol and acetone (vol:vol = 1:1) with total volume 35 mL and the washing rate $1 \text{ mL} \cdot \text{min}^{-1}$. The effluent was dried under reduced pressure with the rotating dryer and the residue was dissolved with mobile phase to 5 mL, then diluted to 50 mL and centrifuged at $5000 \times g$ for 5 min. The supernatant was injected for HPLC analysis.

Establishment of standard curves The BL standard was diluted with the normal human plasma and urine to get 2 standard curves in concentration range of 8, 4, 2, 1, and $0.5 \text{ mg} \cdot \text{L}^{-1}$.

Validation procedures To test the inter-day and intra-day reproducibility, 5 aliquots of each sample were assayed within 1 wk and 1 d, accuracy and precision were evaluated by calculating the recovery values from the standard curves and the coefficients of variation among the aliquots, respectively.

Pharmacokinetic analysis The concentration-time curves were analyzed with CAPP program (LUO Jian-Pin, *et al.*, the Department of Mathematics, Nanjing Medical University) on an AST-DX personal computer to determine the compartment models and the pharmacokinetic parameters. All data were analyzed with *t* test (individual comparison).

Bioequivalence analysis To determine of this 2 kinds of BL tablets have the same biological effects, the parameters including T_{\max} , C_{\max} , AUC and the transformation of logarithm $\ln T_{\max}$ and $\ln C_{\max}$ were analyzed with the following methods: ANOVA, Bayesian Method, Westlake Method, two one-sided test and the rank sum test (individual comparison)^[2,3].

RESULTS

Chromatography The retention times of BL

in plasma and urine were 8.86 and 8.5 min, respectively. The peaks were sharp, well-separated, and not interfered by the plasma or urine (Fig 1). The limits of detection were $0.1 \text{ mg} \cdot \text{L}^{-1}$.

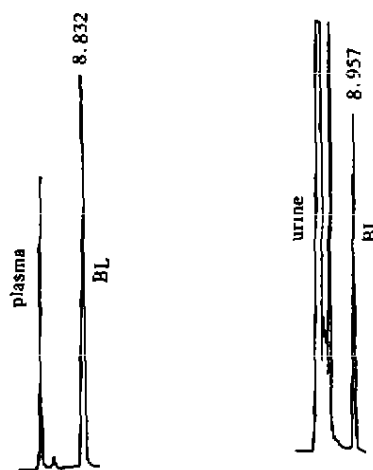


Fig 1. Chromatograms from plasma and urine after *po* 500 mg of BL tablets.

Accuracy and reproducibility The standard curves for plasma and urine range from $0.5 - 8 \text{ mg} \cdot \text{L}^{-1}$ were linear ($r \geq 0.9992$). The inter-day CV was $< 4.7\%$, the intra-day CV was $< 3.7\%$. The mean recoveries of plasma and urine were $99.6 \pm 4.8\%$ and $91.3 \pm 9.4\%$, respectively.

Pharmacokinetics The plasma BL concentration-time curves were fitted to a first order absorption and a 2-compartment open model (Fig 2).

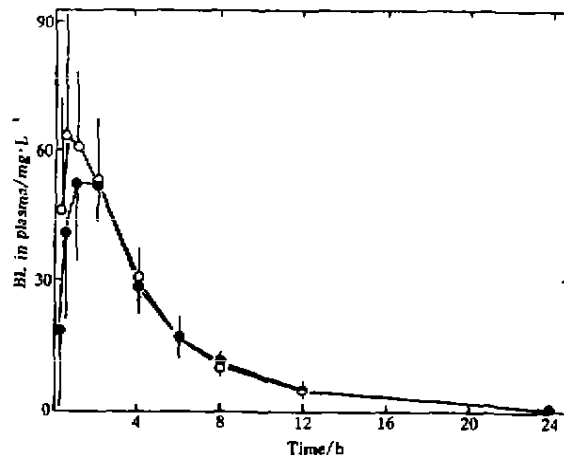


Fig 2. BL in plasma after *po* 500 mg of domestic (○) or imported (●) BL tablets in 10 Chinese young men.

Tab 1 summarized all the PK data of the BL tablets on the same 10 volunteers. The relative bioavailability of the domestic BL vs imported products was $99 \pm 12\%$. About 5.4% and 5.6% of the dosage were recovered as unchanged BL in urine 0-24 h after a single oral dose, respectively.

Tab 1. Pharmacokinetic parameters of BL after a single oral dose of 500 mg of tablets in 10 Chinese volunteers. $\bar{x} \pm s$. * $P > 0.05$.

Parameters	Domestic tablet	Imported tablet
$T_{1/2k_{el}}$ (h)	0.35 ± 0.12	0.35 ± 0.13^a
$T_{1/2\alpha}$ (h)	1.3 ± 0.4	1.3 ± 0.4^a
$T_{1/2\beta}$ (h)	6.2 ± 1.8	6.2 ± 1.7^a
V_d/F (L)	828 ± 327	830 ± 435^a
Cl/F ($L \cdot h^{-1}$)	91 ± 16	91 ± 24^a
K_r (h^{-1})	0.31 ± 0.09	0.31 ± 0.07^a
C_{max} ($\mu g \cdot mL^{-1}$)	66 ± 16	65 ± 8^a
T_{max} (h)	0.98 ± 0.22	0.98 ± 0.21^a
AUC ($mg \cdot h \cdot L^{-1}$)	335 ± 47	337 ± 58^a

DISCUSSION

The HPLC method for measuring plasma and urine BL concentrations was modified from Veleni^[4]. We used the UV-detector instead of fluorescence detector, and our method may be more convenient, more widely used than the old one, and the sensitivity, linearity and reproducibility of our method could satisfy the need of the clinical study.

Amberlite XAD-2 resin, a new nonionic macroporous resin, which has across-linked, polystyrene, macroreticular structure, has a specific absorption for high-molecular weight, lipid-soluble substance^[5]. BL is practically insoluble in water and poorly soluble in methanol, chloroform. So in the study, we could use the XAD-2 resin column to extract BL in the urine, and the results showed that the metabolism was the main form of BL excreted from the kidneys.

According to the ANOVA, no difference was found between the 1st and 2nd medication in the randomized crossover study. In our study, all pharmacokinetic parameters of 2 tablets were in good agreement with each other, the bioequivalence

analysis showed that there was no significant difference between the 2 products. So, the domestic products have the same biological effects as the imported products.

Compared with foreign healthy young subjects ($T_{max} = 1.6$ h, $C_{max} = 41.9$ $mg \cdot L^{-1}$, $T_{1/2} = 3.5$ h)^[11], our domestic products in Chinese people were eliminated more slowly and could obtain higher peak concentration than imported products.

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苄达赖氨酸在 10 名中国青年体内的药物动力学

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关键词 苄达酸; 赖氨酸; 药物动力学; 高压液相色谱法

目的: 比较国产和进口苄达赖氨酸(BL)片在人体内的药物动力学。方法: 10 名男性汉族健康志愿者随机交叉口服单剂量 500 mg 国产和进口苄达赖氨酸(BL)片剂后, 用高效液相-紫外法测定血浆药物浓度。结果: 血药浓度-时间曲线拟合表明该药体内过程符合口服二室开放模型, 国产和进口片剂的主要药代动力学参数: C_{max} 66 ± 16 and 65 ± 8 $mg \cdot L^{-1}$; T_{max} 0.98 ± 0.22 and 0.98 ± 0.21 h; $T_{1/2\beta}$ 6.2 ± 1.8 and 6.2 ± 1.7 h; AUC 335 ± 47 and 337 ± 58 $mg \cdot h \cdot L^{-1}$ 。经 t 检验无显著性差异, 国产片对进口片的相对生物利用度为 $99 \pm 12\%$ 。结论: 两种片剂具有生物等效性。

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