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Original Research

Gender difference in letrozole pharmacokinetics in rats

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KEY WORDS pharmacokinetics; letrozole; gender difference

ABSTRACT

AIM: To study gender difference in letrozole (Letr) pharmacokinetics in rats. **METHODS**: Letr concentrations in plasma and tissues were determined after ig administration of Letr 2 mg/kg. Recoveries of Letr in urine and feces were also analyzed. **RESULTS**: Marked gender differences were found 6 h after ig Letr 2 mg/kg, the plasma concentrations of Letr in male rats were significantly ($P<0.01$) lower than those in female rats. For example, at 24, 36, 48, and 72 h after administration, plasma concentrations in female rats were about 3.3, 5.6, 10.5, and 7.4-fold of that of male rats, respectively. AUC value of Letr in male was only about one-third of that in female rats. Estimated terminal phase half-lives ($T_{\frac{1}{2}}$) were 10.5 and 40.4 h, respectively. In female rats, cumulative excreted fractions of Letr in urine and feces were 5.8 % ± 1.4 % and 6.6 % ± 1.1 % within 120 h after administration, respectively, but in male rats, the excreted fractions of Letr in urine and feces were only 1.30 % ± 0.59 % and 0.87 % ± 0.31 %. Letr concentrations in female rat tissues were significantly ($P<0.01$) higher than those in male rat tissues 24 h after administration. **CONCLUSION**: There are marked gender differences in Letr pharmacokinetics in rats.

INTRODUCTION

Letrozole (Letr, CGS20267), bis-(4-cyanophenyl)-(1, 2, 4-triazolyl) methane, is a potent aromatase inhibitor of estrogen biosynthesis *in vitro* and *in vivo*. It has been established as the optimal second-line agent (after tamoxifen) for the treatment of advanced breast cancer[1,2].

In our preliminary study, large differences in plasma concentrations between male and female rats were found following oral administration of 2 mg/kg. The present describes the gender difference in pharmacokinetics of Letr in rats.

MATERIALS AND METHODS

Chemicals and animals Letr was from Jiangsu Hengrui Pharmaceutical Co Limited. All other reagents were of analytical grade.

Sprague-Dawley rats, Grade Ⅱ, weighing 150-200 g, were supplied by Experimental Animal Center of China Pharmaceutical University, № 98004.

Pharmacokinetics of oral administration of Letr in rats Rats were given Letro 2 mg/kg by gavage (ig), then sacrificed and blood samples were collected in heparinized glass tubes at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 h postdose. Plasma samples were separated by centrifugation. All samples were stored at -20 ℃ until assayed.

Urinary and fecal recoveries of Letr after oral administration Rats were given Letr 2 mg/kg ig and were housed in individual metabolic cages during the study. Urine and feces were collected at 6, 12, 24, 36, 48, 72, 96, and 120 h postdose. Recoveries of Letr in urine and feces were determined.

Distribution of oral administration of Letr in rats Rats were given Letr 2 mg/kg ig, then killed by femoral artery bleeding at 0.5, 3, and 24 h after oral administration. Heparinized blood was collected and centrifuged to obtain plasma. The heart, liver, muscle, kidney, brain, small intestine, spleen, stomach, testis, and ovary were immediately removed, sliced, blotted, and weighed. These tissues were homogenized in 2 mL of distilled water. Letr concentrations were determined.

Assay procedure Letr in biological fluids were

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determined by HPLC[3,4] with fluorescence detection. Briefly, NaOH 0.4 mol/L 0.1 mL was added to plasma and tissue homogenate. The mixture was extracted with of CH_2Cl_2 : diethylether (2:3) mixture 5 mL. The organic phase 4 mL was transferred into a glass tube and evaporated under a stream of nitrogen at 30 ℃. The residue was dissolved in mobile phase 200 μL and 20 μL of the solution was injected into a 5-μm C_{18} Hypersil 200 mm × 4.6 mm column. The mobile phase was 0.01 mol/L phosphate buffer (pH 7.0), acetonitrile and methanol (65:30:5, vol:vol:vol) at a flow rate of 1.5 mL/min. The excitation and emission wavelengths of the fluorescence detection were set at 230 and 295 nm, respectively.

RESULTS AND DISCUSSION

Plasma concentration of Letr after oral administration Fig 1 gives plasma concentration profiles in female and male rats after ig Letr 2 mg/kg.

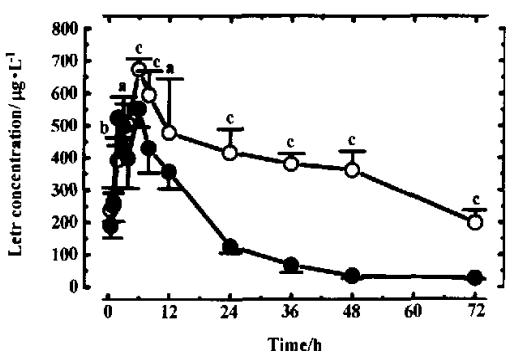

Fig 1. Letr concentration profile in female (○) and male (●) rats after oral Letr 2 mg/kg. $n=5$. $\bar{x} \pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* male rats.

Marked differences were found after ig 2 mg/kg of Letr 6 h postdose, the plasma concentrations of Letr in male rats were significantly ($P<0.01$) lower than those in female rats. For example, at 24, 36, 48, and 72 h post dose, plasma concentrations of female rats were about 3.3, 5.6, 10.5, and 7.4-fold of that of male rats, respectively. The observed C_{max} were also different (552 in male rat *vs* 674 μg/L in female rat), although T_{max} were similar. Estimated AUC[72] values in male and female rats, using trapezoidal rules were 10420 and 27359 $\mu g \cdot h^{-1} \cdot L^{-1}$, respectively. Thus AUC value of Letr in male was only about one-third of that in female rats. The oral apparent clearances (Cl/F) were 0.185 and 0.051 $L \cdot h^{-1} \cdot kg^{-1}$, respectively. Estimated terminal phase half-life in male rat was significantly lower than that in female (10.5 h *vs* 40.4 h). But the apparent distribution volume (V_d/F) was similar (2.80 L/kg in male rats *vs* 3.03 L/kg in female rats). As approximately 90 % of radiolabelled doses were recovered from urine, the F value was around a unity[2], and the V_d/F was almost equal to V_d. This indicates that the marked gender differences in Letr concentration are probably a result of higher elimination rate in male rats.

Recovery of Letr in urinary and feces after oral administration Fig 2 and 3 show excreted fractions of Letr in urinary and feces of female and male rat, respectively.

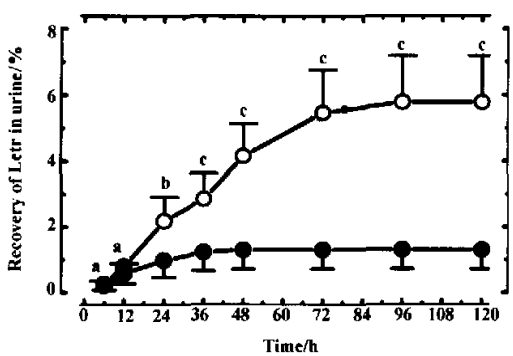

Fig 2. Cumulative excreted fraction of Letr in female (○) and male (●) rat urine after ig Letr 2 mg/kg. $n=5$. $\bar{x} \pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* male rats.

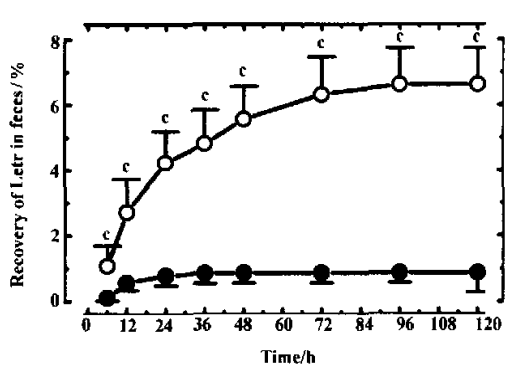

Fig 3. Cumulative excreted fraction of Letr in female (○) and male (●) rat feces after ig Letr 2 mg/kg. $n=5$. $\bar{x} \pm s$. $^cP<0.01$ *vs* male rats.

In female rats, cumulative excreted fractions of Letr

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in urine and feces were 5.78 % ± 1.40 % and 6.61 % ± 1.10 % within 120 h after dose, respectively. The fraction of unchanged drug in female rat urine was in a good agreement with that observed in women (6 %)[5]. But in male rats, the excreted fractions of Letr in urine and feces were only 1.30 % ± 0.59 % and 0.87 % ± 0.31 %. The recovery from male rat feces was smaller than 1 %, which implies that Letr was almost completely absorbed in male rats. This result demonstrated that lower plasma concentration and urine recoveries in male rat were not caused by absorption. In male rats, the urinary and feces excretion was completed after first 36 h of dosage and in female rats, after first 96 h of dosage. This implies that about 12 % of unchanged Letr was excreted via female rat urine and feces, but only 2 % of unchanged Letr was eliminated by the these routes in male rats. The results indicated that Letr metabolized more extensively in male rats than in female rats.

Distribution of Letr after oral administration Comparison of Letr concentrations in female and male rat tissues after ig 2 mg/kg are shown in Fig 4. Twenty-four h after ig administration, large significant differences ($P<0.01$) of Letr concentration were found in male and female rat tissues. Drug concentrations in male rat tissues were about one-third or one-fourth of those in female rat tissues. For example, at 24 h after ig Letr concentra-

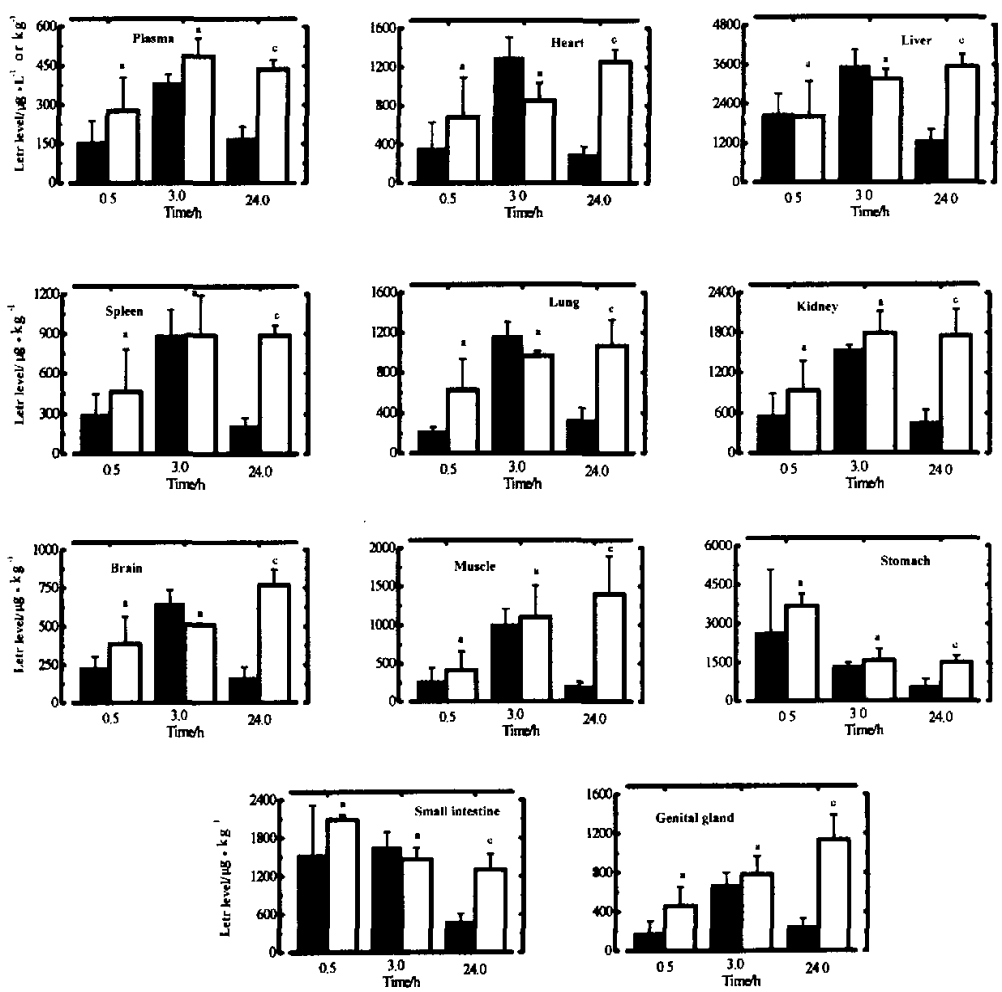

Fig 4. Letr concentrations in female (□) and male (■) rat tissues after ig Letr 2 mg/kg. $n=3$. $\bar{x} \pm s$. $^aP>0.05$, $^cP<0.01$ *vs* male rats.

tions in male and female rat liver were (1273 ± 329) and (3532 ± 361) μg/kgrespectively. In female rats, concentrations in liver, heart, lung, brain, muscle, and ovary at 24 h after ig administration were higher than concentrations at 0.5 and 3 h. This phenomena was not observed in male rats.

In order to investigate whether the difference in concentrations was responsible for concentration difference in plasma, we also calculated the ratios of tissue concentration to plasma concentration as an affinity index to tissues. The results are listed in Tab 1.

Tissue/plasma drug concentration ratios in male rats were higher than in female rats at 3 h postdose, but significance ($P < 0.05$) was only found in heart, liver, and lung. In contrast, tissue/plasma drug concentration ratios in male rats were lower than in female rats 24 h after dosing, and significant differences ($P < 0.05$) were only found in heart, spleen, brain, and genital glands. The difference in tissue/plasma drug concentration ratios was smaller than those of concentrations in tissues. The results show that large gender differences of concentration in plasma mainly accounted for the large gender differences in male and female rat tissues.

Gender has been identified as a risk factor for adverse events due to treatment with drugs[5]. Sex-related factors have also been found to influence pharmacokinetics in compounds such as diltiazem[6], midazolam[7], tirilazad[8], propranol[5], and alcohol[5]. The gender difference suggests that there may exist a gender difference in pharmacology and toxicology of various drugs.

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Tab 1. Tissue/plasma (kg/L) drug concentration ratios of Letr in rat after ig 2 mg/kg. $n = 3$. $\bar{x} \pm s$. $^bP < 0.05$ *vs* male rat.

Tissue	0.5 h		3 h		24 h	
	Male	Female	Male	Female	Male	Female
Heart	2.16 ± 0.56	2.37 ± 0.36	3.43 ± 0.72	1.75 ± 0.44^b	1.72 ± 0.19	2.89 ± 0.38^b
Liver	14.67 ± 4.02	7.39 ± 2.02^b	9.25 ± 0.85	6.53 ± 0.84^b	6.58 ± 1.74	8.16 ± 1.40
Spleen	1.96 ± 0.74	1.53 ± 0.56	2.42 ± 0.61	1.88 ± 0.86	1.21 ± 0.10	2.04 ± 0.22^b
Lung	1.74 ± 0.90	2.23 ± 0.08	3.04 ± 0.26	2.00 ± 0.17^b	1.95 ± 0.44	2.42 ± 0.46
Kidney	3.64 ± 0.29	3.36 ± 0.11	4.04 ± 0.22	3.74 ± 0.93	2.69 ± 0.60	4.06 ± 1.28
Brain	1.58 ± 0.39	1.40 ± 0.02	1.70 ± 0.32	1.06 ± 0.28	0.86 ± 0.33	1.76 ± 0.34^b
Muscle	1.68 ± 0.18	1.49 ± 0.34	2.66 ± 0.66	2.28 ± 0.89	1.23 ± 0.30	3.27 ± 1.46
Stomach	15.23 ± 6.24	15.28 ± 7.26	3.56 ± 0.56	3.29 ± 1.33	3.14 ± 0.90	3.42 ± 0.99
Small intestine	10.15 ± 3.27	8.68 ± 3.70	4.44 ± 0.84	3.08 ± 0.76	2.88 ± 0.59	3.00 ± 0.64
Genital glands	1.12 ± 0.14	1.67 ± 0.30	1.79 ± 0.44	1.63 ± 0.50	1.43 ± 0.23	2.60 ± 0.58^b

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来曲唑在大鼠体内药代动力学的性别差异

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关键词　药物动力学；来曲唑；性别差异

目的：研究来曲唑(Letr)药动学性别差异性．**方法**：ig Letr 2 mg/kg 后，测定在雄、雌性大鼠血浆、组织中浓度及粪、尿中回收率．**结果**：ig Letr 6 h 以后，雄鼠中血药浓度显著低于雌鼠，如给药 24，36，48 和 72 h，雌鼠血药浓度分别为雄鼠的 3.3，5.6，10.5 和 7.4 倍．雄鼠 AUC 也仅为雌鼠的 1/3，其半衰期分别为 10.5 和 40.4 h．120 h 内，雌鼠尿和粪中排泄分数分别为 5.78 % ± 1.40 % 和 6.61 % ± 1.10 %，而雄鼠仅分别为 1.30 % ± 0.59 % 和 0.87 % ± 0.31 %；给药后 24 h，雌鼠组织中药物浓度显著高于雄鼠．**结论**：Letr 在大鼠体内的药动学存在较大的性别差异．

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