ISSN 1671-4083 Acta Pharmacol Sin 中国药理学报 2002 Apr; 23 (4): 381 - 384
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Pharmacokinetics of multiple intravenous instillation of levofloxacin in Chinese healthy subjects

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KEY WORDS levofloxacin; high pressure liquid chromatography; pharmacokinetics; intravenous infusions

ABSTRACT

AIM: To study the pharmacokinetics of multiple doses intravenous infusion of levofloxacin instillation in Chinese healthy volunteers. **METHODS**: Intravenous infusion of levofloxacin instillation 200 mg within 60 min was given to 10 male healthy volunteers for 7 d, on d 1 and d 7, once-daily, from 2 - 6 d twice-daily dosing. The concentrations of levofloxacin in serum and urine were assayed by HPLC. **RESULTS**: The main pharmacokinetic parameters after the first dosing were as follows: C_{max} was (2.4 ± 0.4) mg/L; $AUC_{0-\infty}$ was (16.1 ± 1.4) mg·h·L^{-1}; $T_{\frac{1}{2}\beta}$ was (6.3 ± 0.3) h. The concentration in serum reached steady state within 72 h. The main parameters after the last dosing were as follows: C_{ssmax} was (2.9 ± 0.4) mg/L; C_{ssmin} was (0.71 ± 0.19) mg/L; C_{av} was (1.40 ± 0.29) mg/L; AUC_{ss0-12} was (17 ± 3) mg·h·L^{-1}; $T_{\frac{1}{2}\beta}$ was (6.2 ± 0.8) h. The 24-h cumulative urinary excretion rate was (88 ± 5) %. From the calculation, the cumulative rate was 1.20; the fluctuation index was 1.30. The difference of $T_{\frac{1}{2}\beta}$ and AUC between the first dosing and the last dosing was not significant, and the elimination rate of levofloxacin was not changed after multiple dosing. No clear adverse events were noted during this study. **CONCLUSION**: There was no accumulation of drug after the repeated intravenous infusion with 200 mg levofloxacin instillation for 7 d.

INTRODUCTION

Levofloxacin, a new antibiotic agent of quinolone, inhibits the normal function of bacterial DNA topoisomerase Ⅱ. The single oral dose results showed that levofloxacin is well absorbed, the bioavailability is above 95 %, $T_{1/2}$ is about 6 h, and 70 % - 80 % excretes into the urine[1-3]. Some study results for quinolones showed that AUIC (AUC : MIC, minimum inhibitory concentrations) was near 100 and C_{max} : MIC was 10 which can reach the best clinical and bacteria response[4,5]. From the results of administration of levofloxacin 200 mg, the AUIC and C_{max} : MIC could reach these levels; in addition, the interval of giving medicine should be 1.44 times of half life time, do it like this, medicine can not produce accumulation in bodies as usual, then it is reasonable for levofloxacin 200 mg twice daily dosing. The purpose of this study is to evaluate the safety and pharmacokinetics of infusion of multi-dose of levofloxacin instillation (200 mg) twice daily in Chinese healthy volunteers and to guide clinical use.

MATERIALS AND METHODS

Drugs and reagents Levofloxacin instillation (2 g/L), working standard compound, purity 100.1 %, supplied by Daiichi Pharmaceutical Co Ltd.

HPLC-grade acetonitrile was purchased from Tianjin Siyou Chemical Reagent Company, analytical grade (AR). All other chemical reagents were of AR. Distilled water was used.

Chromatography Waters HPLC system consisted of a 2487 absorbency detector, a 717 autosampler, and a 515 pump. The column was Alltech Alltima C18 (4.6 mm × 150 mm). The mobile phase was composed of H_3PO_4 0.04 mol/L-acetonitrile-triethylamine (8.4 : 1.6 : 0.04, v : v : v) at a flow rate of 1.0 mL/min[1,6]. The UV wavelength was 295 nm.

Sample processing Serum 0.35 mL and 0.7 mL $HClO_4$ solution 0.33 mol/L was mixed thoroughly, centrifuged for 5 min at 2910 × g, and 30 μL of the supernatant was taken for analysis. The urine samples

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Received 2001-05-18 Accepted 2001-12-29

ISSN 1671-4083 Acta Pharmacol Sin 中国药理学报 2002 Apr; 23 (4)
E-mail aps@mail.shcnc.ac.cn Phn/Fax 86-21-6474-2629

were diluted 40 times and injected directly.

Subjects The study protocol was approved by Independent Ethics Committee of Peking University Medical Unit. A total of 10 healthy adult male volunteers (20.0 a ± 0.8 a and 63 kg ± 6 kg) were included in this study. They had normal physical examination and laboratory profiles. The volunteers abstained from other drugs including alcohol and tobacco for 2 weeks before the study and signed a written informed consent.

Study design After a 12-h fasting, ten volunteers received 12 total doses of 200 mg levofloxacin instillation in 7 d. They took only one dosing on d 1 and d 7, twice daily on d 2 – 6 with a dosing interval of 12 h. The drug was infused within 60 min. During this study a uniform diet was supplied.

Sample collection Blood samples were collected before and at 0.5, 1 (end of infusion), 2, 4, 6, 8, 12, and 24 h after the morning dose on d 1 and d 7. On d 2 – 6, blood samples were taken before and 1 h after dosing. Serum was separated by centrifuging. Urine samples were collected before and during 0 – 2, 2 – 6, 6 – 12, and 12 – 24 h after the morning dose on d 1 and d 7. All samples were stored at −20 ℃.

Pharmacokinetic analysis The results were expressed as $\bar{x} \pm s$. All data were analyzed with paired t test. The main pharmacokinetic parameters were calculated by the program of 3p97. C_{max} were obtained from the observed values of determination. R (Cumulative urine excretion rate) = $(\Sigma C_i V_i)/D$

C_i: urine concentration

V_i: urine volume

D: dosage of administration

RESULTS

Evaluation of HPLC method The peaks in serum or urine were well-separated and the impurity did not affect determination results. The retention time of levofloxacin in serum was about 4.1 min, and in urine was 4.2 min (Fig 1). The calibration curve in serum was 0.078, 0.15625, 0.3125, 0.625, 1.25, 2.5, and 5 mg/L ($r = 0.9990$), in urine was 0.15625, 0.3125, 0.625, 1.25, 2.5, 5, and 10 mg/L ($r = 0.9996$). The limit of quantification in serum was 0.078 mg/L and in urine was 0.1 mg/L. The inter-day and intra-day coefficient of variation in serum and urine were lower than 10 % (Tab 1). The average absolute recovery of levofloxacin was 83.5 % in serum and 99.2 % in urine (Tab 2).

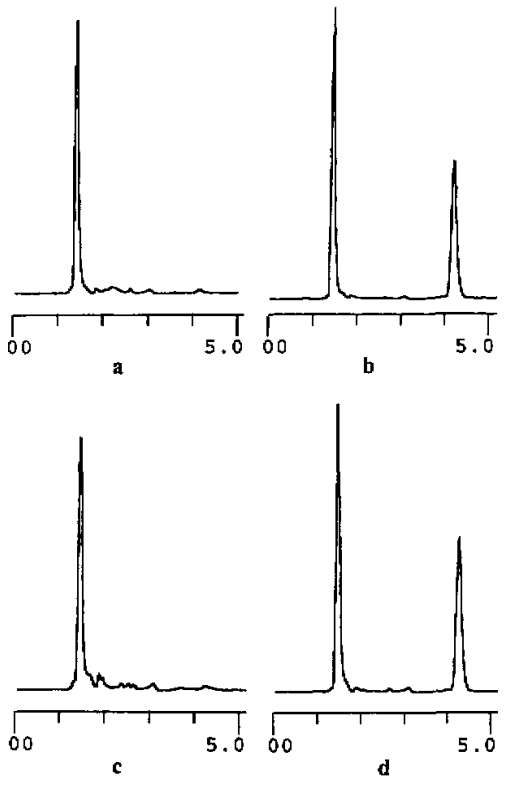

Fig 1. Levofloxacin HPLC chromatograms in serum and urine. (a) blank serum; (b) serum sample; (c) blank urine; (d) urine sample.

Tab 1. Precision of levofloxacin in serum and urine. $n = 5$.

	Concentration/ mg·L^{-1}	Inter-day RSD/%	Intra-day RSD/%
Serum	5.0	3.04	2.95
	1.25	3.51	4.20
	0.156	5.24	6.12
Urine	10	4.61	4.19
	2.5	3.04	4.74
	0.625	3.23	5.28

Safety In the infusion multi-dose study, volunteers tolerated well. Vital signs, hematology, blood chemistry, and urianalysis showed no abnormal changes attributable to the trial medication. Only one subject showed transitory phlebitis after the first dosing.

Pharmacokinetics The concentrations of levo-

floxacin in serum were shown in Fig 2, which reached steady state within 72 h.

Tab 2. Absolute recovery of levofloxacin in serum and urine. $n=5$.

	Concentration/ mg·L^{-1}	Recovery rate/ %	Mean value/ %
Serum	5.0	85.0	
	1.25	83.9	83.5
	0.15625	81.7	
Urine	10	97	
	2.5	100.8	99.2
	0.625	99.8	

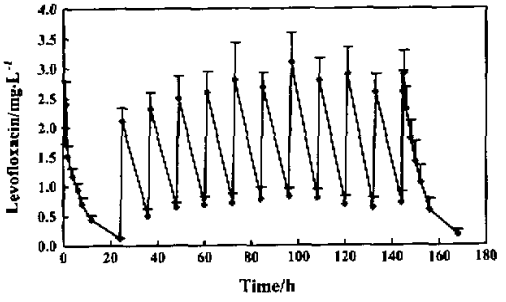

Fig 2. Mean concentration-time curve after multiple doses in 7 d. $n=10$. $\bar{x} \pm s$.

The C_{max} and $AUC_{0-\infty}$ of the last dosing were greater than that of the first dosing ($P<0.05$), but the area under curve of steady state (AUC_{ss0-12}) had no significant difference from the $AUC_{0-\infty}$ of the first dosing. The $T_{\frac{1}{2}\beta}$ showed no significant difference ($P>0.05$). The average concentration at steady state was (1.40 ± 0.29) mg/L (Tab 3). From the calculation, the cumulative factor was 1.20; the fluctuation index (FI) was 1.30. For the last dosing, the 24-h cumulative urinary excretion rate was (88 ± 5) % (Tab 4). The pharmacokinetic results suggested that there was no clear accumulation after levofloxacin infusion for 7 d.

Tab 3. Main parameters of multi-dose levofloxacin 200 mg instillation on d 1 and d 7. $n=10$. $\bar{x} \pm s$.

Parameters	Levofloxacin	
	d 1	d 7
$T_{\frac{1}{2}\beta}$/h	6.3 ± 0.3	6.2 ± 0.8
C_{max}/mg·L^{-1}	2.4 ± 0.4	2.9 ± 0.4
C_{min}/mg·L^{-1}	–	0.71 ± 0.19
C_{av}/mg·L^{-1}	–	1.40 ± 0.29
Cl/L·h^{-1}	12.6 ± 1.2	9.3 ± 2.1
V_c/L	33 ± 18	39 ± 19
$AUC_{0-\infty}$/mg·h·L^{-1}	16.1 ± 1.4	23 ± 6
AUC_{ss0-12}/mg·h·L^{-1}	–	17 ± 3

Tab 4. Urinary concentrations and cumulative excretion rate of levofloxacin for the last dosing. $n=10$. $\bar{x} \pm s$.

Period	Concentration/ mg·L^{-1}	Cumulative excretion rate/%
0 – 2 h	215 ± 89	24 ± 6
2 – 6 h	309 ± 179	49 ± 9
6 – 12 h	154 ± 66	71 ± 8
12 – 24 h	81 ± 45	88 ± 5

DISCUSSION

Levofloxacin has potent and broad antimicrobial activity against gram-positive and gram-negative bacteria, and it has been used to treat various infectious illnesses in clinic. Levofloxacin can completely enter into blood and rapidly distribute to tissues and organs by intravenous infusion.

Theoretically, if the drug can be completely utilized, the interval of administration is equal to $T_{1/2}$, then the steady state will be established after six $T_{1/2}$ and accumulation could not be produced. During multiple-dose infusion, the concentrations of levofloxacin in serum reached a steady state within 3 d and the measured concentrations in serum were close to the stimulated value which reflected the persistence of the linear pharmacokinetics of levofloxacin and the interval of dosing was above 1.44 times of $T_{1/2}$, which showed that there was no significant accumulation. It was similar to that of some abroad studies[1,7].

The fact that at the steady state the concentrations in serum were well above the MIC at which 90 % of the bacterial strains tested for most levofloxacin-susceptible pathogens are inhibited, which supported the twice daily dosage regimen[1,8-10]. The clinical trials of levofloxacin have been done mainly with the twice daily dosing. In addition, the high concentrations in urine indicated that effect of levofloxacin against urinary tract infections might be expected at a dose of 200 mg.

Pharmacokinetic study of levofloxacin in patients with renal dysfunction showed that as the degree of renal impairment aggravated, the AUC was greater, $T_{1/2}$ was prolonged (about 18 – 30 h), and Cl decreased more.

ISSN 1671-4083 Acta Pharmacol Sin 中国药理学报 2002 Apr; 23 (4)
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Then, the reduction of dose and prolongation of intervals should be considered for levofloxacin in the treatment of the patients with chronic renal failure[11].

Throughout the entire test period, no abnormalities were observed for the subjective and objective symptoms, such as vital signs, routine laboratory tests, and other test items, which indicated that levofloxacin instillation was well tolerated in the healthy subjects.

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中国健康受试者多剂量静脉滴注左氧氟沙星注射液的药物动力学

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关键词 左氧氟沙星; 高压液相色谱; 药物动力学; 静脉内输注

目的: 研究左氧氟沙星注射液多剂量给药在健康人体内的药代动力学. **方法**: 10名健康男性受试者给予左氧氟沙星注射液 200 mg, 注射时间为 60 min, 连续给药 7 天, 其中第 1 天及第 7 天给药 1 次, 第 2 到 6 天每天给药 2 次, 间隔 12 h. 采用反相高效液相色谱法测定血及尿药浓度. **结果**: 第一次给药的主要药物动力学参数: C_{max} (2.4 ± 0.4) mg/L; $AUC_{0-\infty}$ (16.1 ± 1.4) mg·h·L^{-1}; $T_{\frac{1}{2}\beta}$ (6.3 ± 0.3) h. 血药浓度于第 3 天达稳态, 稳态后最后一次给药的主要药物动力学参数: C_{ssmax} (2.9 ± 0.4) mg/L; C_{ssmin} (0.71 ± 0.19) mg/L; C_{av} (1.40 ± 0.29) mg/L; AUC_{ss0-12} (17 ± 3) mg·h·L^{-1}, $T_{\frac{1}{2}\beta}$ (6.2 ± 0.8) h. 24 h 内平均尿累积排泄百分率为(88 ± 5) %. 累积比为 1.20, 波动系数为 1.30. 第一次给药与最后一次给药 $T_{\frac{1}{2}\beta}$ 及 AUC 差异无显著性($P > 0.05$). 整个试验期间, 受试者未出现明显的不良反应. **结论**: 左氧氟沙星注射液 200 mg 连续给药 7 天, 药物在体内无明显蓄积.

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