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Pharmacokinetics of ofloxacin through three administration routes

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ABSTRACT This paper reports the pharmacokinetic characteristics of ofloxacin (Ofl) through 3 administration routes in 42 patients with respiratory tract infections. The concentration-time data were fitted with a two-compartment model for infusion (inf) and im, and a one-compartment model for *po*. The pharmacokinetic parameters of Ofl through inf, im and *po* were: $T_{\frac{1}{2}\beta}$ or $T_{\frac{1}{2}K}$ 6.0±1.3, 5.0±1.0, and 5.0±0.7 h; V_c or V_d 58±16, 68±27 and 94±25 L; C_{max} 3.9±1.0, 2.8±0.9, and 1.9±0.7 $\mu g \cdot ml^{-1}$; AUC 16±5, 15±4, and 15±4 $h \cdot \mu g \cdot ml^{-1}$; *Cl* 13±4, 14±4, and 14±3 $L \cdot h^{-1}$, respectively.

KEY WORDS ofloxacin; pharmacokinetics; drug administration routes; high pressure liquid chromatography

Ofloxacin (Ofl) is an antimicrobial agent with broad antibacterial spectrum. When first introduced, Ofl was administered orally, and its pharmacokinetics was described[1-4]. Recently, an iv preparation was developed[5,6], but its im formulation was not mentioned. The purpose of this study was to investigate the pharmacokinetic differences of Ofl through 3 routes in 42 patients with respiratory tract infections.

MATERIALS AND METHODS

Drug and reagents Ofl standard and tablets were made by Kunshan Pharmaceutical Factory, Jiangsu; Ofl injection by Changzheng Pharmaceutical Factory, Suzhou (for inf), and Nanjing 3rd Pharmaceutical Factory (for im).

Study design Forty-two patients suffering from respiratory tract infections with normal liver and kidney functions were divided into 3 groups: Group 1 for *po*, 14 patients (all males), aged 47±17 a; Group 2 for inf, 16 patients (4 females and 12 males), aged 51±17 a; Group 3 for im, 12 patients (4 females and 8 males), aged 47±16 a. Drug dosage was 200 mg of Ofl for all 3 groups. Blood samples were collected from antecubital vein before and 0.5, 1, 1.5, 2, 3, 4, 8, 10, and 12 h after dosing. Urine samples were collected for 24 h for calculating cumulative excretion rate.

HPLC analysis The Ofl concentrations in serum and urine were determined by HPLC[7]. Beckman HPLC system included 114 M pump, 157 fluorometric detectors (λ_{ex} 305—395 nm, λ_{em} 420—650 nm), and 427 data processors. The Beckman Ultrasphere ™"IP" column (250 mm×4.6 mm ID) was used. The mobile phase consisted of methanol and pH 2.5 phosphate buffer solution (32:68, vol:vol) and tetrabutyl ammonium bromide 5 $mmol \cdot L^{-1}$. The flow rate was 0.8 $ml \cdot min^{-1}$.

Serum sample (0.2 ml) mixed with methanol 0.8 ml was centrifuged at 10 000×*g* for 10 min. The supernatant was evaporated to dryness at 45 ℃ with air stream. The residue was dissolved in 0.4 ml of mobile phase for HPLC analysis. Urine sample was analyzed after being diluted 1000 times with distilled water.

Data analysis The data were fitted with one or two-compartment model with the software 3P87. The pharmacokinetic parameters were estimated by least-square nonlinear regression analysis[8].

RESULTS

Quality control of HPLC assay The retention time of Ofl was 6.68 min (Fig 1).

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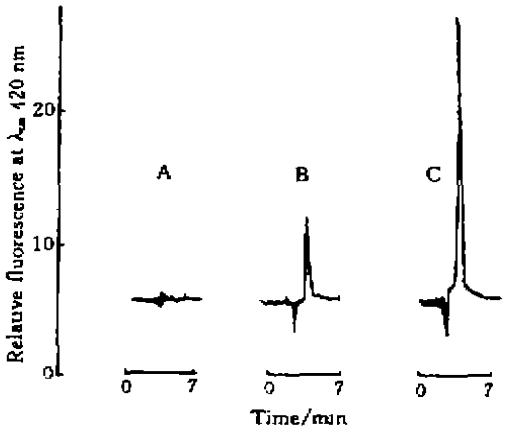

Fig 1. HPLC of ofloxacin. (A) blank serum sample; (B) ofloxacin; (C) serum sample after *po* ofloxacin.

The calibration curve was linear within a range from 0.01 to 8 $\mu g \cdot ml^{-1}$ ($r = 0.9997$). The detection limit was 5 $ng \cdot ml^{-1}$. The recovery rate was 98 ± 5 %. Coefficients of variation within a day and between days were 2.5 % and 3.3 %, respectively (Tab 1).

Tab 1. HPLC assay of ofloxacin. $n = 5$, $\bar{x} \pm s$.

Added/ $\mu g \cdot ml^{-1}$	Found/ $\mu g \cdot ml^{-1}$	Recovery/%	CV/ %
Within-day			
0.126	0.132±0.005	104.8	3.8
0.252	0.247±0.004	97.9	1.6
0.504	0.473±0.014	93.8	2.9
1.008	0.933±0.015	92.5	1.6
Between-day			
0.126	0.130±0.007	103.2	5.4
0.252	0.250±0.008	99.2	3.2
0.504	0.473±0.009	93.3	2.0
1.008	1.000±0.025	99.2	2.5

Pharmacokinetic analysis In cases of 30 min after inf and im Ofl 200 mg, the pharmacokinetic characteristics showed an open two-compartment model (Tab 2). The pharmacokinetic profile after *po* Ofl 200 mg could be described with an one-compartment model (Fig 2). The mean cumulative excretion rate of Ofl in 24 h was 83±19 % for inf; 73±10 % for *po*; and 77±9 % for im. The mean concentration of Ofl in urine in 24 h was 91±21 $\mu g \cdot ml^{-1}$, 91±34 $\mu g \cdot ml^{-1}$, and 113±43 $\mu g \cdot ml^{-1}$ for inf, *po*, and im, respectively.

Tab 2. Pharmacokinetic parameters of ofloxacin after inf, im or *po* 200 mg in 42 patients with respiratory tract infections. $\bar{x} \pm s$.

Parameters	inf ($n=16$)	im ($n=12$)	*po* ($n=14$)
$T_{\frac{1}{2}\beta}$ or $T_{\frac{1}{2}K}$/h	6.0±1.3	5.0±1.0	5.0±0.7
V_c or V_d/L	58±16	68±27	94±25
$C_{max}/\mu g \cdot ml^{-1}$	3.9±1.0	2.8±0.9	1.9±0.7
T_{max}/h		1.0±0.4	2.8±0.9
$AUC_{0-12}/h \cdot \mu g \cdot ml^{-1}$	17±5	15±4	15±4
$Cl/L \cdot h^{-1}$	13±4	14±4	14±3

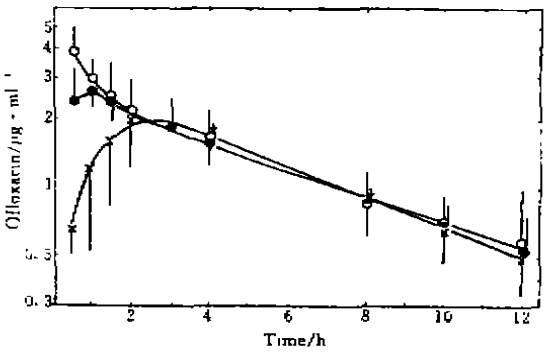

Fig 2. Ofloxacin concentration in serum after inf (○, $n=16$), im (●, $n=12$), and *po* (×, $n=14$) 200 mg in patients. $\bar{x} \pm s$.

DISCUSSION

The HPLC method were specificity and sensitivity. No interference of any endogenous substance or other concomitantly used drugs was detected. The assay was successfully applied to the measurement of concentrations of Ofl[2,9], ciprofloxacin[10], and lomefloxacin in serum and urine samples collected

from patients and healthy volunteers.

The pharmacokinetics of Ofl in respiratory infection patients was similar to that in normal volunteers[1-5], but significantly different from that in patients with chronic renal failure[11]. The AUC values of Ofl were found to be nearly the same through 3 routes in 42 patients with respiratory tract infection ($P > 0.05$).

The bioavailabilities were 92.5 % for im and 93.8 % for *po*, similar to values reported elsewhere[3]. The mean serum concentrations before 12 h were all higher than the minimum inhibitory concentration (MIC) of most kind of bacterial[12]. The results showed the same biological equivalence and effectiveness in all 3 formulations.

The concentration of Ofl was very high (50—160 $\mu g \cdot ml^{-1}$) in urine within 24 h. The concentration range was 20—100 times of MIC in most kind of bacterial[12]. This implied that Ofl is a effective drug for the treatment of urinary infection.

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氧氟沙星三种给药途径的药物动力学

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摘要 本文报道42例呼吸道感染病人用 inf，im 和 *po* 三种途径给氧氟沙星后的药物动力学特性. 血药浓度经3P87程序拟合，inf 和 im 药物动力学模型符合二房室，*po* 为一房室. inf，im，*po* 后氧氟沙星的主要药物动力学参数为：$T_{1/2\beta}$6.0±1.3，5.0±1.0和 $T_{1/2K}$5.0±0.7 h；V_c58±16，68±27和 V_d94±25 l；C_{max}3.9±1.0，2.8±0.9 和 1.9±0.7 $\mu g \cdot ml^{-1}$；Cl 13±4，14±4和14±3 $L \cdot h^{-1}$.

关键词 氧氟沙星；药物动力学；给药途径；高压液相色谱法