**提要** 在 Sch 23390 存在时，DA 和 N-0437 以浓度依赖的方式抑制大鼠纹状体突触体 AC 的活性，$D_2$ 受体拮抗剂 spiperone 和 *l*-SPD 拮抗 DA 和 N-0437 的抑制. 在相同条件下，DA 和 N-0437 也显著增加突触体高亲和力 GTP 酶的活性，*l*-SPD 能完全逆转二者的激活效应. 这些结果表明，*l*-SPD 通过逆转 $D_2$ 受体对 GTP 酶的兴奋和 $G_i$ 对 AC 的抑制性调控，从而影响突触前 DA 受体的负反馈调节.

**关键词** 小檗因类；多巴胺受体；腺苷酸环化酶；鸟苷三磷酸水解酶；纹状体；突触体

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# Pharmacokinetics and relative bioavailability of ofloxacin tablets in 12 healthy volunteers

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**ABSTRACT** Single oral dose of tablet A (Daiichi Pharmaceutical Co Ltd, Japan) and B (Jining Pharmaceutical Factory, Shandong, China) of 300 mg ofloxacin (Ofl) were given to 12 Chinese healthy male volunteers in an open, randomized crossover study. Drug concentrations in serum and urine were assayed by HPLC and partial least squares spectrophotometric method, respectively. The serum concentration-time course after medication conformed to a 2-compartment open model with a first order absorption. Pharmacokinetic parameters after tablet B did not differ significantly from the corresponding values after tablet A. The bioavailability of tablet B was comparable to that of tablet A.

**KEY WORDS** ofloxacin; tablets; pharmacokinetics; biological availability

Ofloxacin (Ofl), a fluorinated quinolone, is a new broad-spectrum antibiotic for oral use[1]. Its primary effect is the inhibition of bacterial DNA-gyrase (topoisomerase II). The spectrum of Ofl includes Gram-positive bacteria, highly potent against *Staphylococcus aureus*, as well as Gram-negative bacilli with an efficacy comparable to those of modern parenteral antibiotics. After oral administration, the drug is rapidly absorbed and widely distributed to the body tissues and fluids[2]. Over 90% of Ofl is excreted in the urine unchanged. These properties make Ofl a potential remedy in many types of infections.

The aim of this study was to determine the pharmacokinetics of Ofl in 12 Chinese volunteers upon oral administration, and to investigate the relative bioavailability of tablet B as compared to tablet A.

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## MATERIALS AND METHODS

**Drugs and instrument** Ofl tablet A (lot No AN 549, Daiichi Pharmaceutical Co Ltd, Japan) and B (lot 900315, Jining Pharmaceutical Factory, Jining 272131, China) were compared. Both forms of tablet contained 100 mg Ofl each. The HPLC instrument consisted of Waters 510 HPLC system equipped with a 490 E wavelength adjustable uv detector and a Baseline 810 data processor. The UV-visible recording spectrophotometer was UV-240.

**Subjects** Twelve healthy male Chinese volunteers aged 24 ± *s* 4 a and weighing 64 ± *s* 3 kg entered the study. All volunteers gave their written consents and underwent thorough physical examination. There were no

abnormal findings in liver and kidney functions in particular.

**Study design** After 12 h of overnight fasting, the volunteers received an oral dose of 300 mg Ofl tablet either A or B in an open, randomized crossover study design. Each dosing was followed by a washout period of 1 wk before the next medication.

**Serum and urine sampling** Blood samples (2.0 ml) were taken before medication and after 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 h. Urine was collected at 3, 6, 9, 12, and 24 h.

**Drug analysis** Ofl concentration in serum was determined using HPLC method[3]. The analytical column used was 150 mm × 4.6 mm I.D. packed with Spherisorb C18 (5 $\mu$m). The mobile phase was methanol 0.01 mol · $L^{-1}$, $KH_2PO_4$ 0.5 mol · $L^{-1}$, tetrabutylammonium bromide (35: 65: 4 vol / vol), with a final pH of 2.5. Concentration of Ofl was obtained using the peak height ratio Ofl / norfloxacin. Calibration curve was linear over the range 0.05–4.00 $\mu$g · $ml^{-1}$. The recoveries were 104 ± 4%, 99 ± 3%, and 100 ± 4%, at drug levels of 0.5, 1, and 3 $\mu$g · $ml^{-1}$, respectively. Coefficients of variation were below 5%.

Ofl concentration in urine was assayed by the partial least squares spectrophotometric method. The recovery were 99.3 ± 0.8% and 100.7 ± 0.5% at drug levels of 5 and 10 $\mu$g · $ml^{-1}$, coefficients of variation were < 1%.

**Pharmacokinetic analysis** Compartments model of Ofl serum concentrations were fitted and then pharmacokinetic parameters were calculated with a PKBP–N1 program on a Super XT–III computer. The relative bioavailability (F) was calculated from $F = AUC_{0-\infty}$ (B) / $AUC_{0-\infty}$ (A). Renal clearance ($Cl_r$) was computed from $Cl_r = U_{t1-t2} / AUC_{t1-t2}$, where U was the amount of unchanged Ofl excreted in urine over the indicated time intervals, and AUC was the corresponding area under the Ofl serum concentration curve over the same intervals.

## RESULTS

The changes in serum concentration were best described by a 2–compartment open model with a first order absorption (Fig 1). The corresponding pharmacokinetic parameters were given in Tab 1.

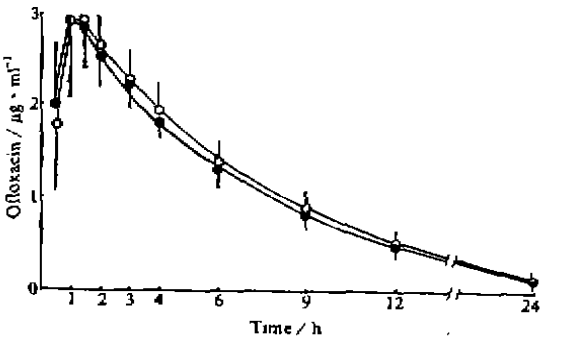


**Fig 1. Ofloxacin concentrations in serum after a single *po* dose of 300 mg of tablet A (○) or B (●). $n = 12$ men.**

**Tab 1. Pharmacokinetic parameters of Ofl after 300 mg tablet A and B in 12 healthy volunteers. $\bar{x} \pm s$, * $P > 0.05$ *vs* tablet B.**

| Parameters | Tablet A | Tablet B |
|---|---|---|
| Lag time / h | 0.22 ± 0.14* | 0.20 ± 0.14 |
| A / $\mu$g · $ml^{-1}$ | 4.4 ± 2.5* | 3.7 ± 2.5 |
| $\alpha$ / $h^{-1}$ | 1.27 ± 0.85* | 1.48 ± 0.95 |
| $T_{\frac{1}{2}\alpha}$ / h | 0.80 ± 0.54* | 0.84 ± 0.81 |
| B / $\mu$g · $ml^{-1}$ | 2.8 ± 0.7* | 2.7 ± 0.9 |
| $\beta$ / $h^{-1}$ | 0.13 ± 0.09* | 0.14 ± 0.02 |
| $T_{\frac{1}{2}\beta}$ / h | 5.37 ± 0.84* | 5.22 ± 0.79 |
| $K_a$ / $h^{-1}$ | 2.49 ± 1.12* | 3.01 ± 1.58 |
| $V_{C\ F}$ / l · $kg^{-1}$ | 1.1 ± 0.2* | 1.1 ± 0.3 |
| $K_{21}$ / $h^{-1}$ | 0.91 ± 0.84* | 1.08 ± 0.89 |
| $K_{10}$ / $h^{-1}$ | 0.21 ± 0.04* | 0.21 ± 0.05 |
| $K_{12}$ / $h^{-1}$ | 0.28 ± 0.19* | 0.32 ± 0.33 |
| $AUC_{0-\infty}$ / h · $ml^{-1}$ | 20.6 ± 5.1* | 20.6 ± 5.4 |
| $T_{max}$ / h | 1.25 ± 0.26* | 1.25 ± 0.34 |
| $C_{max}$ / $\mu$g · $ml^{-1}$ | 3.10 ± 0.55* | 3.11 ± 0.60 |

The relative bioavailability of tablet B was 101 ± 18% as compared to tablet A ($P>0.05$).

The data of Ofl excreted from urine at 3, 6, 9, 12, 24 h were shown in Tab 2.

**Tab 2. Urinary cumulative excretion ratio (%) of ofloxacin after 300 mg tablet A and B in 12 healthy volunteers.** $\bar{x}\pm s$, $^*P>0.05$ *vs* **tablet A.**

| Time / h | Tablet A | Tablet B |
|---|---|---|
| 3 | 19 ± 7 | 22 ± 6* |
| 6 | 40 ± 9 | 42 ± 7* |
| 9 | 54 ± 11 | 52 ± 8* |
| 12 | 59 ± 13 | 57 ± 7* |
| 24 | 66 ± 11 | 65 ± 9* |

The $Cl_r$ were found to be 184 ± 46 and 186 ± 59 ml · $min^{-1}$, and urine concentrations of Ofl in the last collection (12–24 h) were 73 and 52 μg · $ml^{-1}$ for tablet A and B, respectively.

## DISCUSSION

Our findings conformed well with earlier studies[1,2,4,5]. All pharmacokinetic parameters of the 2 tablet forms were in good agreement with each other, there was no significant difference ($P>0.05$) between the 2 forms, The relative bioavailability of tablet B was equivalent to that of tablet A.

Urinary concentrations of Ofl for both tablets even in the last collection (12–24 h after medication) were 73 and 52 μg · $ml^{-1}$, respectively. These were far above the $MIC_{90}$ for most relevant bacterial strains ($MIC_{90}$ for *S. aureus* 1 μg · $ml^{-1}$)[6]. Recovery of the drug in the urine (within 24 h) from the two tablet forms was closely comparable, both in the range of 65%, showing that tablet B was bioequivalent to tablet A. Calculation of AUC also confirmed the same result.

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## 氧氟沙星片剂在 12 名健康志愿者体内的药物动力学及相对生物利用度


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**提要** 12 名健康中国男性志愿者单剂量随机交叉服用 300 mg 氧氟沙星片剂 A(日本第一制药株式会社)及 B(济宁制药厂)后，利用 HPLC 及偏最小二乘法分别测定血清及尿中药物浓度. 服药后药浓度经时过程符合一级吸收的二室模型. 片剂 B 的各药动学参数与片剂 A 相比、无显著性差异. 两种片剂的生物利用度相同.



**关键词** 氧氟沙星; 片剂; 药物动力学; 生物利用度