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Application of NONMEM method to evaluation of relative biological availability of ofloxacin[1]

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ABSTRACT The nonlinear mixed effect model (NONMEM) method for analysis of population pharmacokinetics, was applied to evaluate the relative biological availability of 2 ofloxacin (Ofl) products. The data of randomized crossover study of 2 kinds of Ofl tablets in 12 healthy volunteers were analyzed by NONMEM, as well as standard approach. The relative biological availability evaluated by NONMEM ($F = 97.3 \pm 5.0\%$) was close to that by standard approach ($F = 98.2 \pm 3.6\%$). NONMEM was also valid in accurately evaluating the relative biological availability using sparse clinical data ($F = 91.7 \pm 8.0\%$) which could not be analyzed by standard approach. Thus, the usefulness and advantages of NONMEM were ascertained for the evaluation of biological availability using observational or experimental data.

KEY WORDS ofloxacin; pharmacokinetics; biological availability; statistical models

Ofloxacin (Ofl), a fluorinated carboxyquinolone against members of the family *Enterobactericeae* and Gram positive organisms[1], is excellently absorbed and has a long biological half-life[2]. Patients suffering from various diseases often received the drugs postprandially, with multiple doses or coadministered with other drugs. The data were usually collected sparsely with a few sampling points per patient. So it was very difficult for the standard approach to be applied in clinical tests or the routine therapeutic drug monitoring in evaluation of relative biological availability of drug products[3].

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Nonlinear mixed effect model (NONMEM) method was a method of population pharmacokinetics in which the extended least square was used in statistical analysis[4]. It can serve for the evaluation of pharmacokinetic parameters of observational data and experimental data[5], to provide the effects of patients' age, weight, kind of disease, *etc*, on pharmacokinetics, and to help planning the individual dosage regimens[6]. In this paper, NONMEM was applied to evaluate the relative biological availability of 2 kinds of Ofl tablets.

MATERIALS AND METHODS

Drugs The 2 kinds of Ofl products used in the biological availability study were the reference product, Tarivid (Daiichi Pharmaceutical Co, Tokyo, Japan) and test product (Kunshan Pharmaceutical Factory, Jiangshu, China).

Subjects Healthy volunteers (10 M and 2 F), aged 30.4±4.9 a, weighing 61.6±8.6 kg, participated in the study. Patients with respiratory (20 M and 6 F) or urinary tract infections (5 M and 5 F), aged 45.5±17.0 a, and weighing 62.5±8.7 kg, entered the study. Their liver and kidney function tests were all normal.

Study design As for healthy volunteers, after overnight fasting, a single dose of *po* Ofl 300 mg was taken with 200 ml of water. They were not permitted to take food and drink until 4 h after administration. An open randomized crossover study design was adopted. Each dose was followed by a washout period of 1 wk before the next administration. As for patients, after being divided into 2 groups at random, Ofl tablets were administered 300 mg bid and 200 mg once daily for respiratory tract infections and urinary tract infections, respectively.

Serum sampling In healthy volunteers, blood samples (2 ml) were taken prior to dosing and at 1,

1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 24 h after medication. In patients, blood samples were taken before medication and 1—6 points at 1, 2, 3, 4, 6, 8, 10 h after dosing. Serum samples were stored at —20 C until assay.

Assay Serum Ofl concentration was assayed by an improved HPLC method[7]. Instruments consisted of a WGP-6 pump (Zhijiang Technical Instrument Factory, Hangzhou), a Beckman 157 fluorescence detector, a Beckman 427 integrator and an Ultrasphere IP (5 μm) 4.6 mm ID 25 cm column (USA). The mobile phase was methanol: phosphate buffer 8 mmol·L^{-1}: tetrabutylammonium bromide (30:70:20 by volume) with a final pH 2.0. The retention time of Ofl was 6.96 min at a flow rate of 0.7 ml·min^{-1}. The accuracy of detection was up to 0.01 μg·ml^{-1}. The recovery rate was 96.7 ± 5.9%. Calibration curve of Ofl was linear within a range from 0.065 to 2.02 μg·ml^{-1}. Coefficients of variation within a day and between days were 2.5% and 3.3%, respectively.

Standard approach It depended upon a 2-stage analysis requiring individual parameter estimates in the first stage. The pharmacokinetic parameters and peak drug concentration (C_{max}), time of peak (T_{peak}) and area under the Ofl concentration-time curve (AUC) were obtained by PKBP-N1 program carried out on an IBM PC-XT microcomputer through model fitting. It was only for experimental data of healthy volunteers. The t test was carried out to detect any significant difference between the reference product and the test one.

NONMEM method Data sets of healthy volunteers and patients were all analyzed by NONMEM program (version III, level 1.2)[8], running in a SUN model 4/110 work station with a Sun OS Release 4.1 operation system (Unix).

Model: The pharmacokinetic model fitted to the serum drug level-time curves was a one-compartment open model with first-order absorption and first-order elimination[9].

$$C_p=\frac{F\cdot D\cdot k_a}{V_d(k_a-K_e)}(e^{-K_e t}-e^{-k_a t})+C_0\cdot e^{-K_e t} \qquad [1]$$

Where F stood for the relative biological availability of Ofl ($F=1$, in the case of reference product); k_a, absorption rate constant; K_e, elimination rate constant; V_d, the volume of distribution; D, the dosage; C_0, the initial concentration, and C_p, the predicted concentration.

The statistical models[10] were shown in equations 2—6.

$$F_j=F+\eta^F_j \qquad [2]$$

$$k_{aj}=k_a+\eta^{k_a}_j \qquad [3]$$

$$k_{ej}=k_e+\eta^{k_e}_j \qquad [4]$$

$$V_{dj}=V_d+\eta^{V_d}_j \qquad [5]$$

$$C_{ij}=C_{ij}+\varepsilon_{ij} \qquad [6]$$

Where F, k_a, K_e, V_d represented the true pharmacokinetic parameters; η^F_j, $\eta^{k_a}_j$, $\eta^{K_e}_j$, $\eta^{V_d}_j$, ε_{ij}, the random deviations; C_{ij}, the ith observation in jth subject; and C_{ij}, the predicted value.

RESULTS

Standard approach The relative biological availability and pharmacokinetic parameters of Ofl in healthy volunteers showed no significant difference between the 2 Ofl products (Tab 1).

NONMEM analysis The parameters and

Tab 1. Pharmacokinetic parameters of ofloxacin obtained by standard approach (ST) and NONMEM method in healthy volunteers. $^aP>0.05$ *vs* **reference product.** $n=12$. $\bar{x}\pm s$.

Parameter	Reference Ofl		Test Ofl	
	ST	NONMEM	ST	NONMEM
AUC_{0-24}/h·μg·ml^{-1}	25.0±6.9	—	24.5±6.6^a	—
F/%	100.0	100.0	98.2±3.6^a	97.3±5.0^a
k_a/h^{-1}	2.62±3.18	2.39±3.35	2.96±3.34^a	3.17±4.89^a
K_e/h^{-1}	0.114±0.034	0.129±0.036	0.116±0.023^a	0.137±0.019^a
V_d/L·kg^{-1}	1.54±0.40	1.56±0.31	1.52±0.31^a	1.53±0.38^a
T_{peak}/h	0.60±0.97	1.00	0.63±0.51^a	0.87
C_{max}/μg·ml^{-1}	2.9±0.5	2.6	3.1±0.9^a	2.7

relative biological availability of Ofl estimated by NONMEM using the same data obtained from healthy volunteers were very close to those estimated by standard approach. The relative biological availability derived from the 2 methods exhibited no significant difference (Tab 1).

Results of observational data These data had only a few serum levels per patient collected during clinical therapy. NONMEM could be fixed relative biological availability up to 100% (restricted model) and a pharmacokinetic parameter F (full model). It also provided the value of minimum objective function which equaled to minus twice the maximum logarithm of the likelihood of the data[11]. After fitting full and restricted models respectively, difference in minimum objective function between the 2 models (1.01) was approximately distributed Chi-square with 1 degree of freedom. For a 0.05 level test ($\chi^2_{0.05,1}=3.84$), the hypothetic test indicated that F showed no significant difference between the test product and the reference product. Tab 2 showed the results of NONMEM analysis of clinical data.

Tab 2. Population pharmacokinetic parameters of ofloxacin in clinical patients obtained by NONMEM method. $n=36$.

Parameter	$\bar{x}\pm s$	CV (%)
F/%	91.7±8.0	8.7
k_a/h^{-1}	2.49±3.96	159
K_e/h^{-1}	0.144±0.052	36.4
V_d/L·kg^{-1}	1.50±0.40	27.0

DISCUSSION

In healthy volunteers, the reference and test Ofl tablets in biological availability and pharmacokinetic parameters analyzed by the NONMEM method led to almost the same results as those by standard approach (Tab 1). Statistical analysis showed that there were no significant differences between these 2 Ofl products. The results of standard approach and NONMEM were all consistent with literature[13] reports.

Tab 2 showed the superiority of applying the NONMEM method to evaluate relative biological availability and pharmacokinetic parameters to the observational data. Because the NONMEM method using extended least square (ELS) which can explain more complicated error model than the simple nonlinear least square[14]. After collecting a large number of data from patients, accurate estimates could often be obtained by this method. NONMEM is a yet unfamiliar data analysis technique, it requires an explicit statement of a population pharmacostatistical model and a great deal of experience on the part of the analysts. Thus, we had to consider the tradeoffs of the experimental and observational data in the abundance of data, cost of data, complexity of analysis, certainty of conclusions and the relevance of conclusion[15].

The relative biological availability and pharmacokinetic parameters of Ofl products in a well-controlled study using healthy volunteers will sometimes be different from those in clinical patients especially when the type and severity of disease, coadministration of other drugs and other factors affected these values. In this case, the NONMEM method was considerable much more helpful for doctors to determine the dosage regimen for individual patients[16]. So the present study showed the usefulness and advantages of NONMEM in the evaluation of the relative biological availability and pharmacokinetic parameters in routine clinical drug therapy.

REFERENCES

1 Wolfson JS, Hopper DC. The fluoroquinolones: struc-

tures, mechanisms of action, and spectra of activity *in vitro*.
Antimicrob Agents Chemother 1985; **28** : 581—6.
2 Wolfson JS, Hopper DC. Comparative pharmacokinetics of ofloxacin and ciprofloxacin.
Am J Med 1989; **87** : 31S—36S.
3 Graves DA. Application of NONMEM to routine bioavailability data.
J Pharmacokinet Biopharm 1990; **18** : 145—50.
4 Sheiner LB, Beal SL. A note on confidence intervals with extended least squares parameter estimates.
J Pharmacokinet Biopharm 1987; **15** : 93—8.
5 Sheiner LB. Experience with NONMEM; analysis of routine phenytoin clinical pharmacokinetic data.
Drug Metab Rev 1984; **15** : 293—303.
6 Vozeh S, Muir KT, Sheiner LB, Follath F. Predicting individual phenytoin dosage.
J Pharmacokinet Biopharm 1981; **9** : 131—46.
7 Lode H, Hoffken G, Olschewski P, Sievers B, Kirch A, Borner K, *et al*. Pharmacokinetics of ofloxacin after parenteral and oral administration.
Antimicrob Agents Chemother 1987; **31** : 1338—42.
8 NONMEM Project Group. NONMEM user's guide, Part 1—6. University of California, San Francisco 1989.
9 Yuk JH, Nightingale CH, Quintiliani R, Sweeney KR. Bioavailability and pharmacokinetics of ofloxacin in healthy volunteers.
Antimicrob Agents Chemother 1991; **35** : 384—6.
10 Aarons L, Vozeh S, Wenk M, Weiss P, Follath F. Population pharmacokinetics of tobramycin.
Br J Pharmac 1989; **28** : 305—14.
11 Sheiner LB. Analysis of pharmacokinetics data using parametric models. III. Hypothesis test and confidence intervals.
J Pharmacokinet Biopharm 1986; **14** : 539—55.
12 Monk JP, Campoli-Richards DM. Ofloxacin, a review of its antibacterial activity pharmacokinetic properties and therapeutic use. Drugs 1987; **33** : 346—91.
13 Flor S. Pharmacokinetics of ofloxacin.
Am J Med 1989; **87** (6C Suppl) : 24S—30S.
14 Sheiner LB, Beal SL. Pharmacokinetic parameter estimates from several least square procedures; superiority of extended least squares.
J Pharmacokinet Biopharm 1985; **13** : 185—201.
15 Sheiner LB, Grasela TH. An introduction to mixed effect modeling; concepts, definition, and justification.
J Pharmacokinet Biopharm 1991; **19** (3 Suppl) : 11S—25S.
16 Kaniwa N, Aoyagi N, Ogata H, Ishu M. Application of the NONMEM method to evaluation of the bioavailability of drug products. J Pharm Sci 1990; **79** : 1116—20.

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用 NONMEM 法估算氧氟沙星片的相对生物利用度

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摘要 用 NONMEM 法估算国产和日本进口的氧氟沙星片的相对生物利用度(F). 在健康志愿者中两种片剂的生物利用度无显著性差异, NONMEM 法(97.3±5.0%)与传统方法(98.2±3.6%)得到一致的结论. 用 NONMEM 法分析在临床病人中收集的零散数据, 得到呼吸道和泌尿道感染病人国产氧氟沙星片的相对生物利用度为91.7±8.0%.

关键词 氧氟沙星; 药物动力学; 生物利用度; 统计模型