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Dose related pharmacokinetics of ofloxacin in healthy volunteers

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SUMMARY

OBJECTIVE: To evaluate the pharmacokinetic profile of ofloxacin in healthy volunteers after single oral doses of 600 and 800 mg.

DESIGN: Seven healthy volunteers were administered 600 and 800 mg of ofloxacin on two occasions with an interval of one week. Paired samples of blood and saliva were collected after 1, 2, 3, 6, 9, 12, 24, 32 and 48 hours post-dose. Urine samples were collected over a period of 0–6, 6–12 and 12–24 hours. Concentrations of ofloxacin in plasma, saliva and urine were assayed by high performance liquid chromatography.

RESULTS: Increases of 22% in peak plasma concentration (C_{max}) and 40% in area under the concentration-time curve ($AUC_{0–24}$) were observed with the 800 mg dose. The other parameters, namely time to attain C_{max}, half-life, the apparent volume of distribution, plasma and renal clearance and percentage of dose excreted in urine over 24 hours were independent of doses. The mean ratios of the concentration in saliva to the concentration in plasma ranged from 0.4–0.6, and the correlation coefficient was 0.94.

CONCLUSIONS: Dose proportionality was observed in C_{max} and $AUC_{0–24}$ when 600 and 800 mg doses of ofloxacin were given. Ofloxacin determined in saliva seems to be suitable for therapeutic drug monitoring.

KEY WORDS: pharmacokinetics; saliva to serum concentration ratio; urinary excretion; ofloxacin; tuberculosis

THE FLUOROQUINOLONES are the most recent class of drugs to offer hope in the treatment of tuberculosis. Among the quinolones, the drug most commonly used against *Mycobacterium tuberculosis* is ofloxacin (OFX). Ofloxacin has high antibacterial activity against gram-positive and gram-negative bacteria in vitro and in vivo, and it has shown good antituberculosis activity under in vitro conditions.[1] It is as useful as ethambutol in the treatment of pulmonary tuberculosis when either drug is combined with isoniazid and rifampicin.[2] The other important findings related to OFX include its effectiveness in the retreatment of patients with multidrug-resistant tuberculosis (MDR-TB) who have failed on retreatment with rifabutin, and its superior activity at higher doses.[3,4] In vitro studies on bactericidal activity against *M. tuberculosis* have suggested that OFX is likely to be most useful in the early stages of treatment and in preventing the emergence of resistance to other drugs.[5] A multicentre study of the early bactericidal activity (EBA) of anti-tuberculosis drugs showed a moderately high mean EBA for OFX, ranging from 0.130 to 0.391.[6]

In a recent controlled clinical trial undertaken at the Tuberculosis Research Centre (TRC), Chennai, India, the efficacy of a daily regimen of 3–5 months' duration, using OFX as one of four drugs in the intensive phase, was studied in the treatment of patients with smear-positive pulmonary tuberculosis. The results indicated greater than 95% efficacy, with no increased incidence of adverse reaction and minimal relapses.[7] The encouraging results of this trial led us to study its efficacy in intermittent regimens. Intermittent regimens have several potential advantages of facilitating fully supervised drug administration as well as reducing drug costs and toxicity.[8] Monitoring of OFX concentrations in body fluids is beneficial in assuring that maximum peak concentration (C_{max}) to minimal inhibitory concentration (MIC) ratios are being achieved.[1] This information may be valuable to guide chemotherapy, as good antimicrobial activity against *M. tuberculosis* is associated with pharmacodynamic values calculated on the basis of C_{max}/MIC and area under concentration-time curve (AUC)/MIC ratios.

The purpose of the present study was to determine the pharmacokinetic parameters of OFX in healthy volunteers after administration of single oral doses of 600 and 800 mg. Ofloxacin concentrations were monitored simultaneously in blood and saliva to examine

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whether the concentration of this drug in saliva can replace plasma for therapeutic monitoring. The urinary excretion of OFX was also studied. There are limited data in the literature of the oral pharmacokinetics of 600 mg OFX in volunteers,[9–11] and none for 800 mg.

MATERIALS AND METHODS

Study design

Seven healthy male volunteers with a mean age of 34.5 years (range 22–50 years) and a mean body weight of 59.2 kg (range 44–78 kg) participated in the study. The volunteers were determined to be healthy on the basis of medical history and hepatic and renal function tests. The study protocol was approved by the institutional ethics committee, and informed written consent was obtained from all the volunteers. After an overnight fast, 600 mg of OFX (FDC Ltd., Goa, India) was administered orally to all the volunteers on the first occasion; after a washout period of 1 week, 800 mg of OFX was given on the second occasion to the same volunteers. The exact content of the drug in the lots used was determined spectrophotometrically, and the results were found to be within the acceptable limits of 5%.

Sampling

Paired samples of heparinised blood and saliva were collected at 1, 2, 3, 6, 9, 12, 24, 32 and 48 hours after oral administration of OFX. Saliva was collected after rinsing the mouth with water before starting and with the help of unsweetened chewing gum. Blood specimens were centrifuged immediately and plasma separated and stored at −20°C. Saliva samples were frozen at −20°C; they were thawed the next day, centrifuged and the supernatant stored at −20°C until assay. Urine samples were collected from 0–6, 6–12 and 12–24 hours after dosing. The volume was measured and an aliquot was stored at −20°C until assay.

Assay of ofloxacin

Ofloxacin concentrations in plasma, saliva and urine were determined by high performance liquid chromatography (HPLC) according to the method of Immanuel and Hemanth Kumar.[12] The Shimadzu HPLC system used (Shimadzu Corporation, Kyoto, Japan) was equipped with two pumps (LC-10AT*vp*), a spectrofluorometric detector (RF-10AXL) and a system controller (SCL-10A*vp*). A rheodyne manual injector (Rheodyne, Cotati, CA, USA) attached with a 20 μL sample loop was used for loading the sample. Briefly, the method consisted of the separation by a reverse-phase column and fluorescence detection. The mobile phase consisted of 50 mM phosphate buffer (pH 2.6 adjusted with 1.5 M disodium hydrogen phosphate)-acetonitrile (82:18 v/v). A C18 5 μ Luna, 250 × 4.6 mm ID (Phenomenex, Torrance, CA, USA) reverse-phase column with a matched guard column was used for the assay. Plasma was deproteinised with 7% perchloric acid and the supernatant injected. Saliva was centrifuged in the microcentrifuge filters (Millipore, Tokyo, Japan) and the filtrate was injected. The urine samples were appropriately diluted in MilliQ water followed by direct injection. The fluorescence detector was operated under the following conditions: excitation 290 nm, emission 460 nm; the sensitivity ranges for plasma and saliva assays were set at low combined with gain of ×4 and for the urine assay it was set at low ×1. Under these conditions, the assay was linear from 0.1–10 mg/L for all the body fluids. The coefficient of variations for the within-day and between-day performance were lower than 5%.

Plasma standards for the calibration graph were prepared by using blood bank plasma. The saliva standards were prepared in pooled human saliva passed through the microcentrifuge filters. There was no non-specific binding in the membrane of the filters, and the recovery was 100%. Urine standards were prepared in pooled human urine diluted with Milli-Q water. The chromatogram was run for 7 minutes at a flow rate of 1.5 ml/min. The retention time for OFX was 5 minutes.

Pharmacokinetic analysis

Maximum concentrations (C_{max}) and the time to attain C_{max} (T_{max}) were determined by direct visual inspection of data. Ofloxacin concentration–time data were analysed by a non-compartmental model using WinNonlin software (Pharsight Corp, Mountain View, CA, USA). The linear trapezoidal rule was used to compute the AUC; the elimination rate constant (K_{el}) was calculated from the terminal log-linear decline of concentration; the terminal elimination half-life ($t_{1/2}$) was calculated as $0.693/K_{el}$; and $AUC_{0-\alpha}$ was calculated by adding the sum of AUCs obtained from time zero until 32 h concentration to the last quantifiable concentration (at 32 h) divided by K_{el}. The apparent volume of distribution (V_{oral}) was calculated as dose/($AUC_{0-\alpha} \times K_{el}$) and plasma clearance ($CL_{tot}$) as dose/$AUC_{0-\alpha}$. The amount of unchanged OFX excreted in the urine at 24 h (Ae_{24}) was calculated as the product of urine volume and OFX concentration in urine. The percentage was calculated as (Ae_{24}/dose) × 100. The renal clearance (CL_R) of OFX was calculated as Ae_{24}/AUC_{0-24}.

Statistical evaluation

Data were expressed as mean with 95% confidence intervals (CI). The significance of differences in the pharmacokinetic parameters between doses was evaluated by using Student's paired *t*-test. A *P* value of ≤ 0.05 was considered statistically significant. Correlation between plasma and salivary concentrations of OFX was assessed by linear least-squares regression

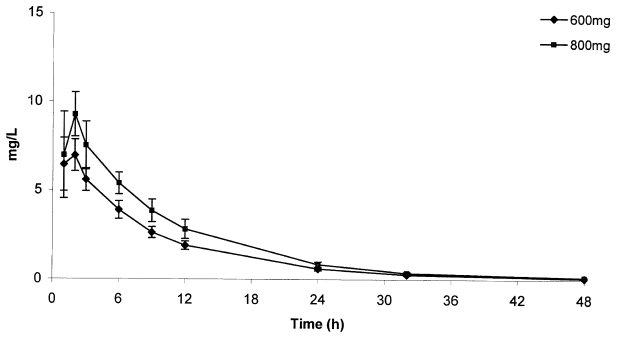

Figure 1 Mean plasma concentrations following administration of 600 and 800 mg of OFX in seven healthy volunteers.

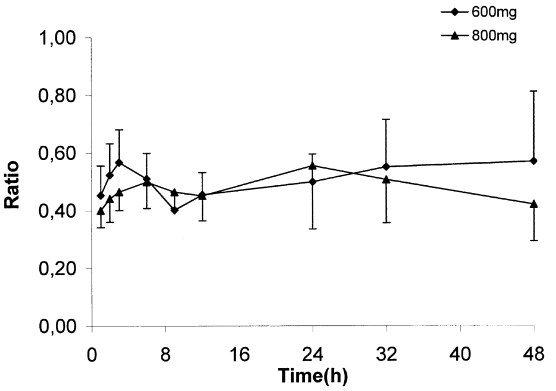

Figure 2 Mean saliva to plasma OFX concentration ratios after the administration of 600 and 800 mg.

analysis by plotting the plasma concentrations against those of saliva at all time points for both doses ($n = 126$).

RESULTS

The mean dosage was 11.9 mg/kg (range 7.7–13.8) for the 600 mg dose and 15.8 mg/kg (range 10.3–18.3) for the 800 mg dose of OFX. Mean concentrations of OFX in plasma at different time points after 600 and 800 mg of doses are depicted in Figure 1. The higher dose of 800 mg resulted in higher concentrations at all time points except at 1 hour. The differences were statistically significant ($P < 0.05$). The mean trough levels for thrice weekly dosage (48 hours) were 0.10 mg/L for the 600 and 0.13 mg/L for the 800 mg doses.

The pharmacokinetic parameters calculated on the basis of plasma and urine concentrations for the 600 and 800 mg doses are given in Table 1. The mean C_{max} was 8.0 mg/L for the 600 mg and 9.8 mg/L for the 800 mg dose ($P = 0.03$). With an increase in dose, the T_{max} was slightly longer, but not statistically significantly so. There were no changes in the apparent volume of distribution and half-life between the doses. The mean $AUC_{0–24}$ was 60.8 and 85.8 mg.h/L for 600 and 800 mg, respectively ($P = 0.02$). The mean plasma clearance was 156 ml/min for the 600 mg and 151 ml/min for the 800 mg doses. Renal clearance accounted for 68% and 61% of the corresponding plasma clearances for the 600 and 800 mg doses, respectively. The proportion (%) of dose excreted in urine over a 24-hour period seemed to be slightly lower for the higher dose, but this difference was not significant (62% and 57% for 600 and 800 mg, respectively).

The OFX concentrations in saliva were much lower than those in plasma, as corresponding C_{max} values were 4.1 and 8.0 mg/L for the 600 mg dose and 4.2 and 9.8 mg/L for the 800 mg dose, respectively. The ratios of OFX concentration in saliva to plasma were calculated for all time points (Figure 2). The results showed that the ratios ranged from 0.40 to 0.57 for the 600 mg and from 0.40 to 0.56 for the 800 mg dose. The correlation coefficient between plasma and saliva concentrations was 0.94. The mean saliva $AUC_{0–24}$ was 29.7 mg.h/L for 600 mg and 40.2 mg.h/L for 800 mg (48% of the plasma $AUC_{0–24}$ for both doses).

DISCUSSION

The dosage of OFX used to treat tuberculosis varied. Once-daily administration of this drug is possible, as

Table 1 Pharmacokinetic parameters for OFX in seven healthy volunteers

	600 mg		800 mg	
Parameters	Mean (95%CI)	CV %	Mean (95%CI)	CV %
C_{max} (mg/L)	8.0 (7.4–8.6)	11	9.8 (8.2–11.4)	22
T_{max} (h)	1.4 (1.0–1.8)	37	1.9 (1.6–2.2)	20
V_{oral} (L)	86 (78–94)	13	83 (72–94)	18
$T_{1/2}$ (h)	6.7 (6.2–7.2)	11	6.5 (6.1–6.9)	8
$AUC_{0–24}$ (mg.h/L)	60.8 (54.2–67.4)	13	85.3 (69.4–101.2)	23
$AUC_{0–\alpha}$ (mg.h/L)	67.9 (60.9–74.9)	14	93.1 (79.7–106.5)	19
CL_{tot} (ml/min)	149 (135–163)	12	147 (128–166)	18
CL_R (ml/min)	105 (88–122)	22	92 (74–110)	26
Ae_{24} (%)	63 (56–69)	14	57 (52–61)	10

CI = confidence interval; CV = coefficient of variation; C_{max} = maximum concentration; T_{max} = time to attain C_{max}; V_{oral} = volume of distribution; $T_{1/2}$ = terminal elimination half-life; AUC = area under the concentration-time curve; CL_{tot} = total plasma clearance; CL_R = renal clearance; Ae_{24} = amount of unchanged OFX excreted in the urine at 24 h.

the generation time of *M. tuberculosis* is 24 hours.[1] In the controlled clinical trial undertaken at the TRC, 600 mg of OFX was given daily along with isoniazid, rifampicin and pyrazinamide to patients with a body weight of more than 40 kg.[7] Other authors have used up to 800 mg of OFX once daily.[4] The present study was performed to obtain information on the pharmacokinetic profile when 600 and 800 mg of OFX were given orally.

The pharmacokinetics of OFX displayed a 22% increase in the C_{max} and a 40% increase in the AUC with the 800 mg dose compared to the 600 mg dose. This study also demonstrated that inter-individual differences in these parameters were greater for the 800 mg dose, with C_{max} values ranging from 8 to 13 mg/L (CV 22%) and $AUC_{0–24}$ values ranging from 64.7 to 126.5 mg.h/L (CV 23%). The highest values in both the parameters were recorded in the volunteer with the lowest body weight (43.6 kg), with a dosage of 18.3 mg/kg. These values were reflected in both plasma and renal clearance, which were lowest in this volunteer.

The lack of difference in renal clearance between doses implies that the secretory process has not been saturated. Our finding of urinary excretion independent of doses is also corroborated by other studies where oral administration of 100, 300 and 600 mg of OFX resulted in 70% excretion.[9] Dose proportionality was observed in C_{max} and AUC for 600 and 800 mg doses when compared with lower dose.[11] The apparent volume of distribution was dose-independent, consistent with other findings.[9–11]

Use of saliva instead of blood for pharmacokinetic investigations has obvious practical advantages. It is a non-invasive procedure, which avoids venipuncture, and is therefore more suitable for the collection of multiple specimens. Pharmacokinetic studies have shown that OFX penetrates into saliva and that its concentration correlates well with serum levels.[13] However, the data available in the published studies are inconsistent. Variable results have been reported for the ratio of saliva to serum concentrations. Koizumi et al. reported a ratio of 1.0 between 2 and 8 hours after administration of a 300 mg dose.[14] Fujita et al. in their studies on patients with renal impairment reported a 1:1 ratio of saliva to serum concentrations.[15] However, Warlich et al. reported a ratio of 0.6 and a close relation of levels in saliva and serum ($r = 0.99$).[16] These results are consistent with our findings. In the present study the ratio was around 0.5, T_{max} and half-life were similar to plasma, and there was a good correlation coefficient of 0.94 with respect to drug concentrations. OFX determination in saliva therefore seems to be suitable for therapeutic drug monitoring.

From the published data, it can be inferred that the clinical response to OFX appears to be dose-related. The drug is most effective when the C_{max} to MIC and or AUC to MIC ratios are maximised.[1] The MIC_{90} value of OFX against *M. tuberculosis* is 1.0 mg/L.[17–19] The pharmacodynamic parameters calculated on the basis of the AUC could be useful for predicting the efficacy of a drug. In the present study, the AUC to MIC ratio for 800 mg dose was significantly higher than that with the 600 mg dose. The coverage, i.e., the time above the level of MIC, was 24 hours for 800 mg as against 20 hours for the 600 mg dose (Table 2). These results are in agreement with the recent study by Zhu et al., who reported simulated pharmacokinetic (PK)/pharmacodynamic (PD) estimates for 600 and 800 mg doses of OFX in tuberculosis patients.[20] Another putative pharmacodynamic parameter that could be of help in the design of an optimal dosing schedule is the post antibiotic effect (PAE) of a drug against *M. tuberculosis*. Studies on OFX tested at a C_{max} value of 8 mg/L suggested the use of OFX daily, but it could have synergistic activity when given in combination with rifampicin.[21] Hence, the recommendation was that it should be given intermittently only when rifampicin is included in the regimen. The extended period of coverage and the higher ratio of AUC to MIC for the 800 mg dose could be beneficial for intermittent chemotherapy. Clearance is not affected be-cause of the higher dose. However, it was observed that subjects weighing <50 kg when given 600 mg attained an AUC similar to that of 800 mg given to the subjects weighing >50 kg. Therefore, the dosage for intermittent therapy may be adjusted accordingly.

Table 2 Pharmacodynamic values of OFX against *M. tuberculosis*

Dose	Time ⩾ MIC_{90}* hour	C_{max}/MIC_{90}	$AUC_{0–24}/MIC_{90}$
600 mg	20	8	61
800 mg	24	9.8	85

* MIC = 1.0 mg/L.
OFX = ofloxacin; MIC = minimum inhibitory concentration; C_{max} = peak plasma concentration; AUC = area under the concentration-time curve.

The limitation of this study was the participation of a small number of volunteers. However, the information is still valid because the same volunteers were given both doses.

Pharmacokinetic knowledge about a drug enables the clinician to choose the dosage schedule, the optimal size and the frequency of individual doses. The use of the AUC is particularly appropriate because it provides an integral measure of drug exposure and therefore an individual indicator of the therapeutic value of the drug. We must, however, understand the assumptions on which it relies; the pharmacokinetic parameters must therefore be interpreted by relating the concentration-time profile to clinically important end-points. The ultimate answer must come from clinical trial in patients with tuberculosis.

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RÉSUMÉ

OBJECTIF : Evaluer le profil pharmacocinétique de l'ofloxacine chez des volontaires sains après des doses orales uniques de 600 et 800 mg.

SCHÉMA : On a administré à un intervalle d'une semaine à deux reprises des doses de 600 mg et de 800 mg d'ofloxacine à sept volontaires bien portants. Des échantillons appariés de sang et de salive ont été prélevés 1, 2, 3, 6, 9, 12, 24, 32 et 48 heures après la prise. Les échantillons d'urines ont été recueillis sur une période de 0–6, 6–12 et 12–24 heures. Les concentrations d'ofloxacine ont été déterminées par chromatographie liquide de haute performance dans le plasma, la salive et l'urine.

RÉSULTATS : Avec la dose de 800 mg, on a observé une augmentation de 20% du pic de concentration plasmatique (C_{max}) et de 40% de la zone sous la courbe temps-concentration ($AUC_{0–24}$). Les autres paramètres, en l'occurrence la durée nécessaire pour atteindre C_{max}, la demi-vie, le volume apparent de distribution, la clairance plasmatique et rénale et le pourcentage de la dose excrété dans les urines sur une période de 24 heures ont été indépendants des doses. Les ratios moyens de concentration dans la salive par rapport au plasma ont été de 0,4–0,6 et le coefficient de corrélation de 0,94.

CONCLUSIONS : On a observé pour la C_{max} et pour la $AUC_{0–24}$ une proportionnalité à la dose en administrant soit 600 soit 800 mg d'ofloxacine. La détermination de l'ofloxacine dans la salive paraît une méthode valable pour le suivi thérapeutique du médicament.

RESUMEN

OBJETIVO : Evaluar el perfil farmacocinético de la ofloxacina en voluntarios sanos después de una dosis única de 600 y 800 mg.

DISEÑO : Se administró 600 y 800 mg de ofloxacina, con un intervalo de una semana, a 70 voluntarios sanos. Se recolectaron muestras pareadas de sangre y saliva 1, 2,

3, 6, 9, 12, 24, 32 y 48 horas después de la administración de cada dosis. Se midió la concentración de ofloxacina en el plasma, saliva y orina por cromatografía líquida de alto rendimiento.

RESULTADOS: Con la dosis de 800 mg se observó un aumento de 22% de la concentración plasmática máxima (C_{max}) y de 40% del área bajo la curva tiempo-concentración ($AUC_{0–24}$). Los otros parámetros, principalmente el tiempo para alcanzar la C_{max}, la vida media, el volumen aparente de distribución, el clearance plasmático y renal y el porcentaje de la dosis excretado por la orina en 24 horas, fueron independientes de la dosis. Los coeficientes promedio de concentración en la saliva en relación a la concentración en el plasma fueron de 0,4–0,6 y el coeficiente de correlación fue de 0,94.

CONCLUSIÓN: Se observó una proporcionalidad en la C_{max} y en la $AUC_{0–24}$ cuando se administraba 600 u 800 mg de ofloxacina. La determinación de la ofloxacina en la saliva parece ser un método conveniente para el control terapéutico de la droga.