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# Some aspects of the bioavailability of orally administered ofloxacin in healthy human volunteers

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Ofloxacin is a recently developed fluoro-quinolone carboxylic acid derivative, structurally related to nalidixic acid, and is claimed to exert excellent antibacterial activity against a wide spectrum of organisms (Wittenberger, 1986). Its reported pharmacokinetic features include high absorption rate, low serum protein binding, good body tissue and fluid penetration, and high urinary contents of the drug in the mostly unmetabolised form.

There have, however, been conflicting data on the pharmacokinetics of ofloxacin. For example, while Leroy et al. (1987) found that food and the dose of the drug had no influence on the serum half-life of the drug, Kalager et al. (1985) observed that half-life was nearly 50% higher in fasting than non-fasting subjects. In order to shed more light on the pharmacokinetics of the drug, the effect of food and the gender of individuals on the availability of orally administered ofloxacin tablets in the saliva and urine of healthy volunteers has been examined.

The ofloxacin (purity: 99%) used in the preparation of standard solutions was kindly supplied by Nigerian Hoechst (Ikeja, Nigeria). The nutrient agar used was manufactured by Oxoid (Basingstoke, U.K.). *E. coli* NCTC 10418 was the indicator strain employed in bioassay.

Ten healthy and informed university students, composed of 5 males and 5 females, voluntarily enrolled in this study programme which had ethical approval. They were non-smoking and had not taken any medication in the preceding fortnight. Their mean age was 20.9 years (range 19–24 years); mean weight 59.9 kg (range 45–75 kg); and mean height 1.71 m (range 1.58–1.88 m). Details of these subject parameters according to gender as well as fasting and non-fasting states are provided in Table 1. All the subjects fasted overnight and were then divided into two equal groups – fasting and non-fasting. Those in the fasting group were each administered a single dose of 200 mg film-coated ofloxacin tablet (Nigerian Hoechst) orally with 150 ml of water and then fasted for at least another 2 h. The drug was similarly administered to those in the non-fasting group immediately after a standardized breakfast of bread and fried eggs.

Saliva and urine samples were collected from the subjects at 0 (i.e. just before drug administration), 1, 2, 4, 6 and 9 h, and stored at $-16\,^{\circ}C$

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TABLE 1

*Subject parameters classified according to gender, fasting and non-fasting states*

| | Age (years) | | Weight (kg) | | Height (m) | |
|---|---|---|---|---|---|---|
| | Mean | Range | Mean | Range | Mean | range |
| Male | 22.2 | 21–24 | 63.4 | 59–66 | 1.77 | 1.65–1.88 |
| Female | 19.6 | 19–20 | 56.4 | 45–75 | 1.65 | 1.58–1.80 |
| Fasting | 20.4 | 19–22 | 60.2 | 45–75 | 1.71 | 1.58–1.84 |
| Non-fasting | 21.4 | 19–24 | 59.5 | 45–65 | 1.72 | 1.63–1.88 |

pending analysis of their ofloxacin content. Ofloxacin levels were determined by bioassay using the agar ditch diffusion method with *E. coli* as the indicator organism. The lower limit of assay sensitivity was 0.2 $\mu g \cdot ml^{-1}$ and the regression coefficients of the standard curves were generally not lower than 0.99.

The profile of ofloxacin in saliva has previously been shown to closely parallel that in serum (Uematsu et al., 1985). This indicates that following absorption, the drug in serum not only rapidly distributes into salivary fluid but also speedily attains distribution equilibrium with the drug in saliva. This explains, in addition to convenience,

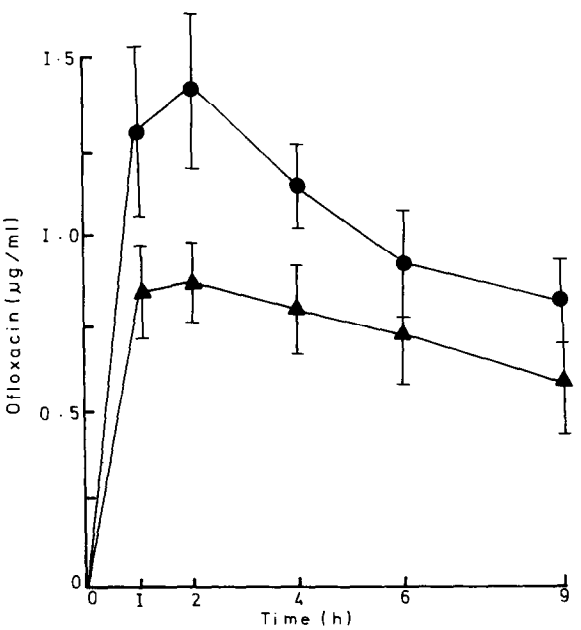


Fig. 1. Saliva ofloxacin concentration in fasting (●) and non-fasting (▲) states. (Error bars indicate S.E.M.).

why saliva rather than serum was chosen along with urine for bioavailability evaluation in the present work. Pharmacokinetic data for saliva were obtained by the two-compartment model. The saliva parameters assessed include elimination half-life ($t_{1/2}$), peak saliva concentration ($C_{max}$) and the trapezoidal area under the saliva drug concentration versus time curve ($AUC$). The peak drug levels in urine were also determined.

*Saliva.* The drug profile in saliva is illustrated in Fig. 1. Peak concentrations of ofloxacin were achieved in 1–2 h in both fasting and non-fasting individuals which implies that the food ingested did not delay the onset of absorption of the drug. The times taken to attain saliva peak levels are generally similar to the values previously reported for serum (Hoffler and Koeppe, 1987; Leroy et al., 1987) which confirms rapid saliva penetration by the drug following absorption.

Generally, ofloxacin levels were higher in fasting than in non-fasting subjects. The difference was significant at the 95% confidence level only up to the fourth hour after drug administration. It is generally believed that the gastrointestinal absorption of a majority of orally administered drugs is favoured by increased gastric emptying which in turn is promoted by a fasting state (Gibaldi, 1977; Hoener and Benet, 1979). On the other hand, lipids, which were present in significant quantities in the breakfast ingested by the non-fasting subjects, usually hinder gastric emptying (Gibaldi, 1977). It is likely, therefore, that reduced gastric emptying rate was a major factor in the lower saliva drug contents seen in the non-fasting state within the first 4 h of drug administration, a period which falls within the normal range of gastric residence time. However, the $AUC$ data

TABLE 2

*Some pharmacokinetic data ( ± S.E.M.) derived from the saliva and urine results*

| | Saliva | | | | Urine |
|---|---|---|---|---|---|
| | $t_{1/2}$ (h) | $C_{max}$ ($\mu g \cdot ml^{-1}$) | $AUC_{0-9}$ ($h \cdot \mu g \cdot ml^{-1}$) | $AUC_{0-\infty}$ ($h \cdot \mu g \cdot ml^{-1}$) | $C_{max}$ ($\mu g \cdot ml^{-1}$) |
| Fasting | 6.2 ± 1.3 | 1.42 ± 0.30 | 9.17 ± 2.10 | 16.53 ± 2.33 | 439 ± 46 |
| Non-fasting | 12.0 ± 2.2 | 0.87 ± 0.12 | 6.41 ± 1.74 | 16.41 ± 2.71 | 670 ± 58 |
| Male | 6.8 ± 1.2 | 1.14 ± 0.29 | 7.07 ± 1.59 | 12.82 ± 2.02 | 507 ± 69 |
| Female | 9.4 ± 1.7 | 1.25 ± 0.25 | 8.55 ± 1.71 | 19.50 ± 3.08 | 578 ± 75 |

(Table 2) show that although the extent of bioavailability ($AUC_{0-9}$) was lower in the non-fasting state during the sampling period, extrapolation of the data to infinity ($AUC_{0-\infty}$) clearly demonstrate that the food ingested had no influence on the overall amount of drug absorbed. Saliva half-life of ofloxacin (see Table 2) in non-fasting conditions was approximately twice that in the fasting state. The drug in saliva was also apparently more slowly eliminated in female than male subjects.

The results shown in Fig. 2 indicate that salivary ofloxacin concentration was higher in female than in male volunteers but the difference was found to be insignificant at the 95% confidence level. However, the $AUC_{0-\infty}$ results (Table 2) suggest that the extent of bioavailability was significantly greater (95% level) in females than in males; this could be attributed to the longer elimination half-life in the former. Nonetheless, irrespective of the gender of the subjects, and in both fasting and non-fasting condition, salivary ofloxacin levels were higher than 0.5 $\mu g \cdot ml^{-1}$ throughout the 9-h sampling period, a level which is greater than the minimum inhibitory concentration (*MIC*) of the drug for a number of bacteria commonly implicated in upper respiratory tract infections, e.g. *Staph. aureus* and *Haemophilus influenzae*.

*Urine*. The urine data (Figs. 3 and 4) indicate peak concentrations of ofloxacin in urine within one hour after oral administration and, like the

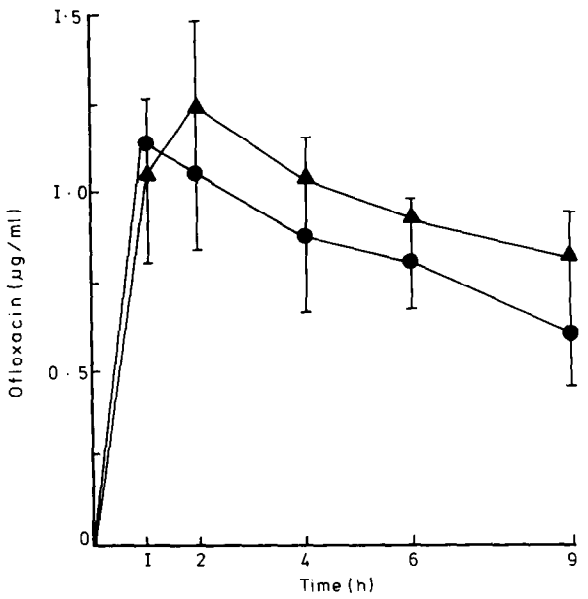


Fig. 2. Saliva ofloxacin levels in male (●) and female (▲) subjects. (Error bars represent S.E.M.).

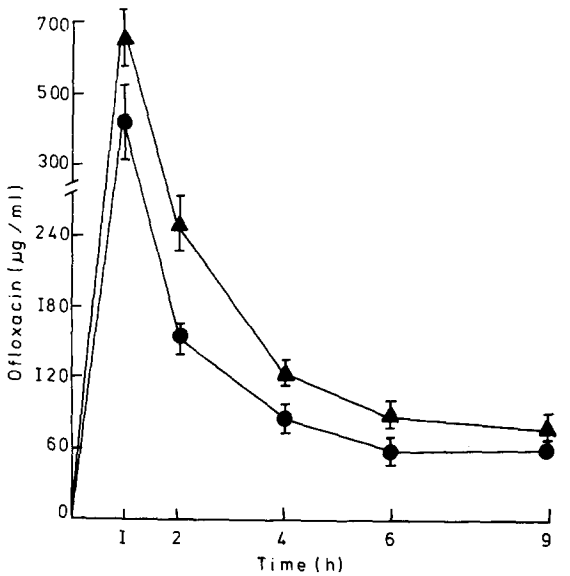


Fig. 3. Urine ofloxacin levels in fasting (●) and non-fasting (▲) conditions. (Error bars represent S.E.M.).

TABLE 3

*Comparison of some pharmacokinetic data for saliva (from present study) with published serum data after oral administration of a single 200 mg dose of ofloxacin ( ± S.E.M. for saliva data and ± S.D. for serum data)*

| Data source | $t_{max}$(h) | $C_{max}$($\mu g \cdot ml^{-1}$) | $t_{1/2}$(h) | $AUC_{0-\infty}$($h \cdot \mu g \cdot ml^{-1}$) |
|---|---|---|---|---|
| Present study [a] | 1–2 [c] | 1.42 ± 0.30 [c] | 6.2 ±1.3 [c] | 16.53 ± 2.33 [c] |
| | 1–2 [d] | 0.87 ± 0.12 [d] | 12.0 ±2.2 [d] | 16.41 ± 2.71 [d] |
| Leroy et al. (1987) [b] | 0.83 ± 0.31 [c] | 2.24 ± 0.90 [c] | 7.86 ± 1.81 [c] | 13.18 ± 3.12 [c] |
| | 1.85 ± 1.15 [d] | 1.56 ± 1.00 [d] | 8.00 ± 1.71 [d] | 11.26 ± 2.98 [d] |
| Hoffler and Koeppe (1987) [b] | 1.3 ±0.6 [c] | 2.42 ± 0.60 [c] | 5.43 ± 0.95 [c] | 16.6 ±2.6 [c] |

[a] Saliva. [b] Serum. [c] Fasting. [d] Non-fasting.

saliva results, the time ($t_{max}$) taken to attain peak drug level appeared not to be influenced by the gender of the subjects and food. There was also no significant difference (95% confidence limits) between peak urine drug contents in male and female volunteers. Unexpectedly, however, urine ofloxacin levels were significantly higher in non-fasting than in fasting conditions (Table 2 and Fig. 3). Why this was so is not clear at the moment, but this observation has no clinical significance since the *MIC*s of ofloxacin for practically all susceptible bacteria found in urinary tract infections (e.g. *Chlamidia trachomatis, Neisseria gonorrhoea, E. coli* and *Pseudomonas aeruginosa*) are less than 8 $\mu g \cdot ml^{-1}$ and this figure is considerably lower than the urine drug levels seen in this study.

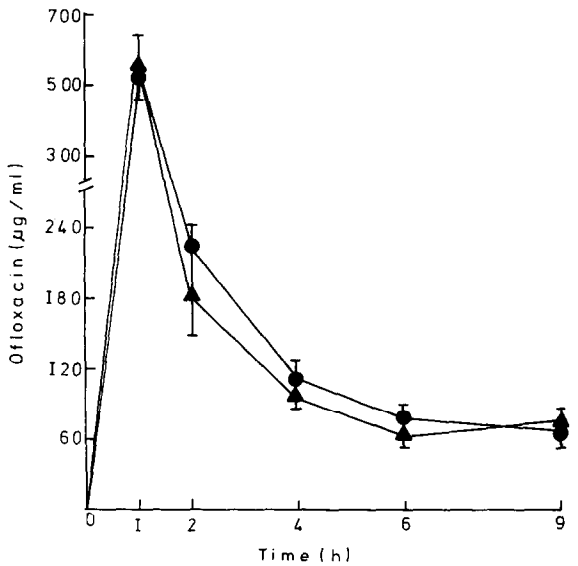


Fig. 4. Urine ofloxacin concentration in male (●) and female (▲) volunteers. (Error bars indicate S.E.M.).

Concluding, both saliva and urine data show that ofloxacin is rapidly and well absorbed after oral administration. High urinary concentrations of the drug are also quickly achieved. Although the extent of bioavailability was initially higher in fasting than non-fasting subjects, the total amount of drug ultimately absorbed was unaffected by food. Generally, the results did not demonstrate significant gender differences in both the saliva and urine levels of ofloxacin. It is noteworthy, as shown in Table 3, that there is a high degree of equivalence of saliva pharmacokinetic data with those of serum. A similar observation has been made by Uematsu et al. (1985). Saliva may therefore be substituted for serum in bioavailability evaluation of ofloxacin.

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