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# Effect of Food on Enoxacin Absorption

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**Fifteen subjects received a single 400-mg oral dose of enoxacin in the fasting state and after carbohydrate and high-fat meals. The carbohydrate meal delayed the time to peak enoxacin concentration in plasma by an average of 0.92 h. The extent of enoxacin absorption was not altered by food.**

Enoxacin is a member of a relatively new class of antibacterial agents, commonly referred to as the fluoroquinolones (2). These drugs have bactericidal activity particularly against gram-negative bacteria and have the added advantage over similar classes of agents of being active after oral administration. Coingestion of food can have divergent effects on the extent and rates of antibiotic absorption, depending on the physicochemical properties of the antibiotic and the composition of the food (7). Antibiotic efficacy can be substantially altered by concomitant food intake. The aim of this study was to evaluate the influence of two different types of food on the gastrointestinal absorption of enoxacin in humans.

(Part of this study was reported previously [Proc. 14th Int. Congr. Chemother., p. 1733–1734, 1985].)

Fifteen healthy subjects agreed to participate after being fully informed of the purpose and risks associated with the study. Written consent was obtained, and the study was approved by the Research Review Committee of the Royal Adelaide Hospital and the Committee on the Ethics of Human Experimentation, University of Adelaide. The subjects included 13 males and 2 females, whose ages ranged from 19 to 37 (mean, 24) years, and they weighed between 55 and 108 (mean, 74) kg. Six of the subjects were tobacco smokers, and the two females were taking oral contraceptives. Apart from these, the subjects took no medication 2 weeks before and throughout the study period. The subjects were in good health as judged by physical examination and biochemical, hematological, and urological screening tests. These tests were repeated at the end of the study.

Each subject ingested a single 400-mg oral dose of enoxacin as two 200-mg capsules (batch WLI-PK-5-T 1; Parke Davis Pty. Ltd.) with 100 ml of water on three occasions, with a 7-day washout period between study days. The study design was of a randomized, open, three-way crossover type, with the subjects receiving enoxacin after (i) a 12-h overnight fast, (ii) a standard carbohydrate breakfast, and (iii) a high-fat breakfast. Enoxacin was taken within 5 min of the completion of breakfast. The carbohydrate meal contained 2,533 kJ, comprised 108 g of carbohydrate, 15 g of fat, and 13 g of protein, and was made up of orange juice, cornflakes, toast with jam, and tea or coffee. The fat meal contained 2,562 kJ, comprised 39 g of carbohydrate, 42 g of fat, and 20 g of protein, and consisted of orange juice, fried bacon and eggs, toast, and tea or coffee. For the fast, no food was permitted until 4 h after drug administration, but a cup of tea or coffee was permitted after 2 h. Lunch was provided after 4 to 5 h, and an evening meal was provided after 9 to 10 h. The subjects were encouraged to drink dilute fruit juice to maintain an adequate urine flow rate. From an indwelling intravenous catheter and stylet (Jelco; Critikon Corp., Tampa, Fla.) placed in a forearm vein, blood samples (7 ml) were collected at the following times after enoxacin administration: 0, 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 10, and 12 h. Blood was also collected by separate venipuncture at 24, 30, and 33 h. Urine was collected between 0 and 33 h. Plasma and urine samples were stored at −20°C before analysis, and all samples were analyzed within 4 weeks of collection. Enoxacin was measured in plasma

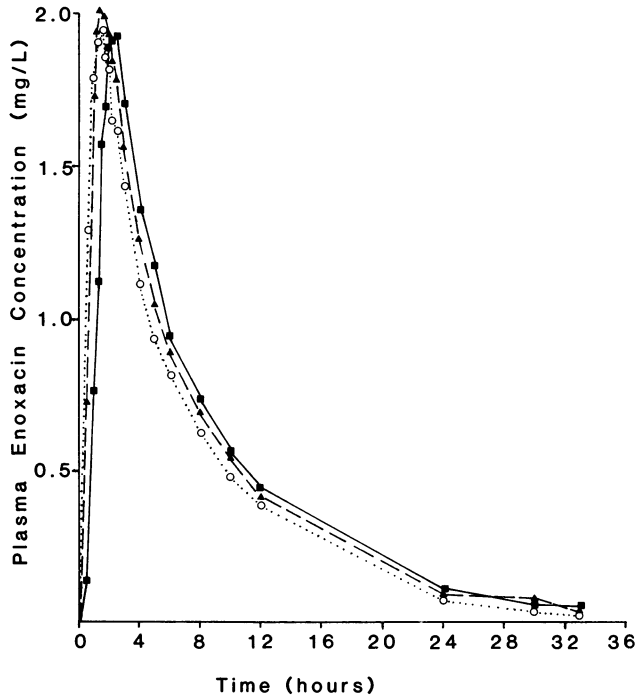


FIG. 1. Mean plasma enoxacin concentration-time profile in 15 subjects after a 400-mg oral dose in the fasting state (○), after a carbohydrate meal (■), and after a high-fat meal (▲).

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TABLE 1. Pharmacokinetic data for enoxacin after single-dose administration with different food coingestion in 15 subjects[a]

| Study | $T_{max}$ (h) | $C_{max}$ (mg/liter) | $AUC_{0-33}$ (mg · h/liter) | $AUC_{0-\infty}$ (mg · h/liter) | $t_{1/2}$ (h) | fe (%) | $CL_R$ (ml/min) |
|---|---|---|---|---|---|---|---|
| Fasting | 1.38 ± 0.51 | 2.39 ± 0.69 | 14.45 ± 4.21 | 14.75 ± 4.27 | 5.71 ± 0.72 | 44.3 ± 9.7 | 220 ± 76 |
| Carbohydrate | 2.33 ± 0.89 | 2.16 ± 0.61 | 15.71 ± 4.53 | 16.03 ± 4.56 | 5.66 ± 0.63 | 46.6 ± 5.2 | 214 ± 68 |
| Fat | 1.68 ± 0.60 | 2.53 ± 0.78 | 15.43 ± 4.03 | 15.72 ± 4.09 | 5.68 ± 0.64 | 47.6 ± 8.4 | 217 ± 67 |
| Statistical significance ($P$) | <0.005 | >0.05 | >0.05 | >0.05 | >0.05 | >0.05 | >0.05 |

[a] $T_{max}$, Time to maximum concentration in plasma; $C_{max}$, maximum concentration in plasma; $AUC_{0-33}$, area under the curve from 0 to 33 h; $AUC_{0-\infty}$, area under the curve from time zero to infinity; $t_{1/2}$, terminal half-life; fe, urinary recovery; $CL_R$, renal clearance. Values are means ± standard deviation.

samples by minor modifications to the high-performance liquid chromatography method of Nakamura et al. (5). Urine samples were diluted 1 in 10 with water before direct injection onto the column. Assay coefficients of variation were less than 5%. The following pharmacokinetic parameters were calculated by conventional methods: the maximum concentration in plasma, the time to reach the maximum concentration in plasma, the area under the plasma concentration-time curve from 0 to 33 h ($AUC_{0-33}$), the area under the plasma concentration-time curve from time zero to infinity, the terminal half-life, urinary recovery of enoxacin as a percentage of the dose (fe), and renal clearance. The latter parameter was calculated as (fe × 400)/($AUC_{0-33}$ × 100). The linear trapezoidal method was used to calculate the area under the curve, and linear regression analysis was used to calculate the slope and, hence, the terminal half-life. Analysis of variance with Tukey's honestly significant difference (HSD) test (1) was used to test for statistical significance ($P < 0.05$) in the various pharmacokinetic parameters between the three occasions. All data are tabulated as means ± standard deviation.

The average concentrations of enoxacin in plasma after the three treatments are shown in Fig. 1, and the resultant pharmacokinetic analysis is shown in Table 1. There were no statistically significant ($P > 0.05$) differences in the maximum concentrations in plasma, areas under the plasma concentration-time curves, terminal half-lives, renal clearances, or urinary enoxacin recovery. However, the time to reach the maximum concentration in plasma was significantly ($P < 0.005$) longer after the carbohydrate meal than after (i) the fasting state (mean difference, 0.92 h; range, −0.43 to +3.27 h) and (ii) the high-fat meal (mean difference, 0.65 h; range, −0.77 to +2.77 h). There was no difference in this parameter between the fasting state and the high-fat meal. No subject experienced any adverse effects attributable to the study, and biochemical, hematological, and urological test results all remained within normal limits.

This study showed that coingestion of food has minimal effects on the pharmacokinetics of a single oral dose of enoxacin. When given on an empty stomach, enoxacin was very rapidly absorbed, with the time to reach the maximum concentration being approximately 1.5 h. The sole statistically significant finding was that the carbohydrate meal delayed the time to reach the peak concentration in plasma by an average of 1 h. This is interpreted as a reduction in the rate of enoxacin gastrointestinal absorption. Although statistically significant, the result is of minimal clinical significance in light of the small absolute difference found. Importantly, the extent of enoxacin absorption was not altered by the two different meals. This was assessed as unaltered areas under the plasma concentration-time curves and fractional urinary excretion. Food also had no effect on the disposition of enoxacin, for which the values of half-life, renal clearance, and fractional urinary recovery were similar to those previously reported (6, 8). The results reported here for enoxacin are similar to those for ciprofloxacin of Ledergerber et al. (4), who found that a standard breakfast reduced the time to achieve the maximum ciprofloxacin concentration, and those of Kalager et al. (3) for ofloxacin, in which food reduced the rate of absorption, both meals being closer in composition to the carbohydrate meal than the high-fat meal of the present study. Because of the similarity in results, it might be anticipated that most of the quinolones will behave in a similar manner with regard to absorption after food ingestion.

In conclusion, this study showed that food does not alter enoxacin absorption. Therefore, patients have the option of taking enoxacin with or without food.

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