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The Effects of Sucralfate, Magnesium Oxide and Sodium Ferrous Citrate on Fleroxacin Pharmacokinetics

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Abstract

The effects of sucralfate, magnesium oxide and sodium ferrous citrate on the bioavailability of fleroxacin were studied in 6 healthy subjects. According to the four-way crossover design, each subject received the following drug combination in a random order : (A) a single 200mg dose of fleroxacin alone ; (B) a single 200mg dose of fleroxacin with 900mg dose of sucralfate; (C) a single 200mg dose of fleroxacin with 1 g dose of magnesium oxide; (D) a single 200mg dose of fleroxacin with 100mg dose of sodium ferrous citrate. The four regimens were performed in fasting subjects. Blood samples were collected for 24 hours period, and plasma concentrations of fleroxacin were determined by high-performance liquid chromatography method. The areas under the plasma concentration-time curve from 0 to 24 ($AUC_{0\text{-}24}$) of fleroxacin for regimen B was significantly different compared with that for regimen A (regimen A vs B : 28.29±5.80 vs 20.57±2.68 μg・hr/mL, mean values ± S.D., $p<0.05$). However, the $AUC_{0\text{-}24}$ for regimens C and D were not significantly different compared with that for regimen A (regimen C and D : 24.27±4.44 and 28.28±5.46 μg・hr/mL, respectively). The peak concentrations in plasma (C_{max}) of fleroxacin for regimens B was significantly different compared with that for regimen A (regimen A vs B : 2.76±0.45 vs 1.64±0.16 μg/mL, mean values ± S.D., $p<0.01$). However, the C_{max} for regimen C and D were not significantly different compared with that for regimen A (regimen C and D : 2.35±0.45 and 2.44±0.39 μg/mL, respectively). These results suggest that drugs containing aluminum should not be given concomitant administration with fleroxacin.

Key words — fleroxacin, metal cation, interaction, pharmacokinetics

Introduction

Fleroxacin is a new fluoroquinolone that has a broad antibacterial spectrum against gram-positive and gram-negative bacteria *in vitro* and *in vivo* [1, 2]. Compared with the other fluoroquinolones, fleroxacin exhibits a long half-life allowing once-daily administration [3].

There have been many reports concerning the effects of antacids, anti-ulcer agents, and other drugs or foods containing metal cations (e.g., aluminum, magnesium, iron, calcium and zinc) on the absorption of fluoroquinolones in healthy volunteers [4-19]. Previously, the interaction between the fluoroquinolones such as norfloxacin [8, 17], ofloxacin [15, 17], ciprofloxacin [4, 5, 6, 7, 10, 11], lomefloxacin [12, 16], DR-3355 (levofloxacin) [13] and sparfloxacin [19] and metal cations has been reported, while the interaction between fleroxacin and metal cations reports only by Lubowski et al. [14] and Bertino, Jr et al. [18].

In the present study, we describe the effects of sucralfate, magnesium oxide and sodium ferrous citrate on the pharmacokinetics of fleroxacin.

Materials and Methods

Materials

Fleroxacin (Megalosin® tablet), fine granules of sucralfate (Ulcermin® fine granule, 1g of Ulcermin® contains 900mg as sucralfate), magnesium oxide (fine granule) and sodium ferrous citrate (Ferromia® tablet) were purchased from Kyorin Pharmaceutical Co. Ltd. (Osaka, Japan), Chugai Pharmaceutical Co. Ltd. (Tokyo, Japan), Yoshida Pharmaceutical Co. Ltd.

(Tokyo, Japan) and Eisai Co. Ltd. (Tokyo, Japan), respectively. Lomefloxacin was kindly donated by Shionogi Pharmaceutical Co. Ltd. (Osaka, Japan). A Molcut Ⅱ® membrane filter was obtained from Millipore Co. (Bedford, MA, USA). All other solvents were used HPLC grade (Wako Pure Chemicals Industries Ltd. Tokyo, Japan). All other reagents and chemicals were purchased from Wako Pure Chemicals Industries or Nakarai Tesque (Kyoto, Japan). All reagents used were analytical grade.

Subjects and Study Design

Six male subjects (age range, 24 to 41years ; weight range, 53 to 70kg) were participated in this study. Each subject was considered to be healthy on the basis of medical history, physical examination and laboratory parameters. None of the subjects were taking any medications, including antacids, within 1 week before and during the study period. The subjects were thoroughly informed, both verbally and in writing, and informed consent was obtained.

Subjects received each of four regimens in a randomized crossover design ; administration of the four regimens was separated by a 7 day washout period. For regimen A, subjects were given a 200mg dose of fleroxacin alone. For regimen B, subjects were given a 200mg dose of fleroxacin and 900mg dose of sucralfate. For regimen C, subjects were given a 200mg dose of fleroxacin and 1g dose of magnesium oxide. For regimen D, subjects were given a 200mg dose of fleroxacin and 100mg dose of sodium ferrous citrate. For all regimens, subjects were given drugs with 200mL of water following an overnight fast. In this study, the amount of medication of each regimen was determined as an amount of daily use of each drug.

Blood samples (5mL each) were obtained by direct venipuncture at 1, 2, 3, 4, 6, 8, 10, and 24hour postdosing. Blood samples were collected into heparinized vacuum tubes and were immediately separated by centrifugation at 1,900×g for 15min, and plasma was stored frozen at −40℃ until analysis.

Assay Methodology

The apparatus used for HPLC system was a Jasco Model PU-880 chromatography pump (Jasco Co. Ltd. Tokyo, Japan) equipped with a Jasco Uvidec 880 ultraviolet detector (Jasco). Plasma concentrations of fleroxacin were determined by direct injection high-performance liquid chromatography with column switching [3]. Briefly, after the plasma sample was filtrated through a Molcut Ⅱ® membrane filter for deprotenization, the filtrate was loaded on the precolumn (C_{18} reverse-phase column, 50× 4.6mm, I.D.) for the elimination of interfering substances in plasma. After washing, fleroxacin and lomefloxacin as an internal standard were eluted from the precolumn and then led to the analytical column by column-switching technique using 0.5% potassium dihydrogenphosphate (pH 2.5)-acetonitrile (84 : 16, v/v) as the mobile phase at a flow rate of 1.0 mL/min. Fleroxacin was detected on an ultraviolet detector at a wavelength of 295nm. The limit of detection was 20ng/mL. Relative standard deviations were less than 2.2%.

Pharmacokinetics Analysis

The peak concentrations of fleroxacin (C_{max}) and the time to reach peak concentrations (T_{max}) in plasma were determined from the observed concentrations. The total area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24}$) was calculated by using the trapezoidal rule. The elimination half-life ($T_{1/2}$)

in plasma was estimated by least-squares regression analysis of the terminal concentration-time curve.

Statistical Methods

Statistical analyses were made with the Excel® software package (Microsoft Co. Ltd., USA). Two-way analysis of variance was used for analysis of the pharmacokinetic parameters. The parameters were then compared with the control values by the Student's t-test for paired values (two tailed), where appropriate. The P values were considered to be statistically significant.

Results

The profiles of the mean plasma concentration of fleroxacin are shown in Fig.1 for four regimens. The observed mean C_{max} for the fleroxacin alone (regimen A), fleroxacin-sucralfate (regimen B), fleroxacin-magnesium oxide (regimen C) and fleroxacin-sodium ferrous citrate (regimen D) were 2.76±0.45, 1.64±0.16, 2.35±0.45 and 2.44±0.39 μg/mL, respectively (Table 1), while the $AUC_{0\text{-}24}$ were 28.29±5.80, 20.57±2.68, 24.27±4.44 and 28.28±5.46 μg·hr/mL, respectively (Table 1). Sucralfate reduced the C_{max} of fleroxacin by 35.7% ($p<0.01$) compared with the control. The C_{max} of fleroxacin were not affected by magnesium oxide and sodium ferrous citrate. The $AUC_{0\text{-}24}$ of fleroxacin was reduced by 27.3% ($p<0.05$) by sucralfate. The reduction of $AUC_{0\text{-}24}$ for magnesium oxide was 14.2%, but this data was no significant differences compared with the control values. The $AUC_{0\text{-}24}$ of fleroxacin was not affected by sodium ferrous citrate. There were no statistically significant differences in the T_{max} or $T_{1/2}$ between the control and the other three regimens.

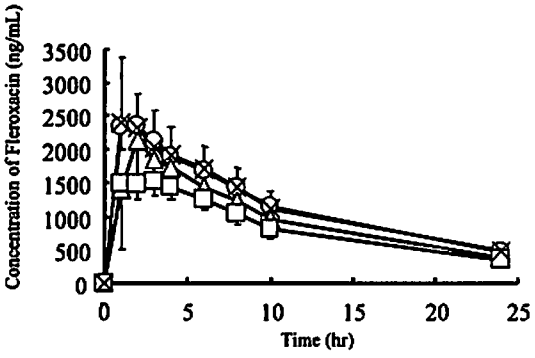

Fig. 1 Plasma fleroxacin concentration-time profiles for fleroxacin (200mg) alone (circles), fleroxacin with sucralfate (900mg ; squares), fleroxacin with magnesium oxide (1g ; triangles), and fleroxacin with sodium ferrous citrate (100mg ; cross). Values are mean values for six subjects ; error bars have been omitted for clarity.

Disccusion

The present study demonstrated the effects of sucralfate, magnesium oxide and sodium ferrous citrate on the pharmacokinetics of fleroxacin. The bioavailability of fleroxacin was significantly reduced by concomitant ingestion of sucralfate. On the other hand, the bioavailability of fleroxacin after concomitant ingestion of magnesium oxide or sodium ferrous citrate was not statistically significant difference compared with that of fleroxacin alone. Previous studies have demonstrated that absorption of orally administered new quinolone antibacterial agents such as norfloxacin [8, 17], ofloxacin [15, 17], ciprofloxacin [4, 5, 6, 7, 10, 11], lomefloxacin [12, 16], DR-3355 (levofloxacin) [13], fleroxacin [14, 18], and sparfloxacin [19] is decreased by concomitant administration of metal cation containing drugs. Therefore, the interaction between fleroxacin and sucralfate can be explained primarily by the inhibition of absorption of fleroxacin.

Lubowski et al. [14] has reported that the relative bioavailability of fleroxacin given with

Table 1 Effects of Sucralfate (900mg), Magnesium Oxide (1g) and Sodium Ferrous Citrate (100mg) on the Pharmacokinetic Parameters of Fleroxacin (200mg)

Regimens	A	B	C	D
	Fleroxacin alone	with Sucralfate	with Magnesium oxide	with Sodium ferrous citrate
C_{max} (μg/mL)	2.76±0.45	1.64±0.16 **	2.35±0.45	2.44±0.39
T_{max} (hr)	1.20±0.45	1.67±0.82	1.50±0.55	1.20±0.45
$AUC_{0\rightarrow 24}$ (μg·hr/mL)	28.29±5.80	20.57±2.68 *	24.27±4.44	28.28±5.46
AUC (% of control)	100.0	72.71	85.79	100.0
$T_{1/2}$ (hr)	9.42±0.57	10.33±2.12	8.98±0.82	9.88±1.43

Data are mean values±S.D. in six subjects.
C_{max} : peak plasma concentration, T_{max} : time to reach maximum plasma concentration,
AUC : area under the plasma concentration-time curve, $T_{1/2}$: elimination half-life.
* $p<0.05$ compared with control
** $p<0.01$ compared with control

sucralfate was 76% compared with that of fleroxacin (400mg) alone. In the present study, it decreased to 72.71% in AUC as compared with fleroxacin alone by co-administration of fleroxacin and sucralfate. This result has suggested that the influence of sucralfate exerted on 200mg dose of fleroxacin and 400mg dose of fleroxacin is the same grade.

It has been considered that the proposed mechanism of the interaction between fluoroquinolones and the metal cation containing drugs was chelation between the metal ion and the 4-keto oxygen, 3-carboxyl group of the fluoroquinolone. Since these groups are required for antibacterial activity, one can anticipate that all of the quinolones will interact with these cations, although there may be differences between the quinolones in the extent of interaction. Mizuki et al. [20] has reported the interaction between the chemical structure of fluoroquinolone derivatives and the metal cation. They have suggested that the 5- and 7-substituents and an 8-fluoro group in fluoroquinolone derivatives may affect the formation ability and stability of chelate with metal cations.

The reduction of fleroxacin bioavailability when sucralfate and fleroxacin were concomitantly administered to healthy subjects in the present study was similar to the results reported by Lubowski et al. [14]. On the other hand, no significant decrease of fleroxacin bioavailability was demonstrated by magnesium oxide or sodium ferrous citrate. Shiba et al. [13] has reported that when aluminum hydroxide, ferrous sulfate, and magnesium oxide were co-administered with DR-3355 (levofloxacin), the relative bioavailability of DR-3355 was decreased to 56, 81, and 78% , respectively, of that for DR-3355 (100mg) alone. This results was similar with our study result. According to previous study, generally, the metal cation which forms more stable chelate is the order of $Al^{3+} > Fe^{2+} \geqq Mg^{2+} > Ca^{2+}$[13]. As a conclusion, fleroxacin has suggested not forming stable chelate with Mg^{2+} or Fe^{2+}, and these results suggest that drugs containing aluminum should not be given concomitantly with fleroxacin.

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