

Effects of Antacids, Ferrous Sulfate, and Ranitidine on Absorption of DR-3355 in Humans

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This study examined the effects of widely used antacids (aluminum hydroxide, magnesium oxide, and calcium carbonate), ferrous sulfate, and ranitidine on the absorption of a fluorinated quinolone, (–)-(S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido-[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hemihydrate (DR-3355), in healthy male volunteers enrolled in three separate randomized crossover studies. Study 1 used 100-mg doses of DR-3355 and concurrent doses of aluminum hydroxide (1 g) or magnesium oxide (500 mg), while study 2 used DR-3355 (100 mg) and concurrent ferrous sulfate (160 mg) or calcium carbonate (1 g). Study 3 used DR-3355 (100 mg) and concurrent ranitidine (150 mg). Each study included control doses of DR-3355 (100 mg) alone. When aluminum hydroxide, ferrous sulfate, and magnesium oxide were coadministered with DR-3355, the relative bioavailability of DR-3355 was decreased to 56, 81, and 78%, respectively, of that for DR-3355 (100 mg) alone. Urinary excretion of DR-3355 was also significantly decreased by coadministration of these drugs. Thus, the magnitude of the decrease in the area under the concentration-time curve for DR-3355 varied among antacids, and the ranking of their inhibitory effects correlated with previously reported rankings of stability constants for chelate formation. DR-3355 bioavailability was not influenced by the concurrent administration of calcium carbonate and ranitidine, indicating that changes in gastric pH do not affect DR-3355 absorption.

DR-3355, a fluorinated quinolone-carboxylic acid derivative, is an optically active (S)-(–)-enantiomer of ofloxacin (OFLX). This compound exhibits marked bactericidal activity by inhibiting DNA gyrase (6, 19). As DR-3355 is 8 to 128 times more potent than (R)-(+)-OFLX and approximately twice as potent as the racemate (±)-OFLX in inhibiting the multiplication of gram-positive and gram-negative bacteria (4), the drug is believed to be largely responsible for the efficacy of racemic OFLX in clinical therapy.

The pharmacokinetics of DR-3355 in experimental animals have been documented (20a). Comparison of the areas under the concentration-time curves (AUCs) of DR-3355 and OFLX revealed a marked stereoselectivity in rats (17). The differences were caused by the stereoselective glucuronidation in favor of (S)-(–)-OFLX (DR-3355) (15). However, the disposition of (S)-(–)- and (R)-(+)-OFLX in humans after an oral dose of racemic OFLX showed little difference (14). With regard to antibacterial activity, therefore, a given dose of DR-3355 should produce the same clinical results as a dose of OFLX twice as large.

Maalox, an antacid containing aluminum and magnesium, is widely used for the treatment of various gastric symptoms and is frequently coadministered with new quinolone antibacterial agents. However, combination therapy with Maalox impairs the bioavailability of new quinolone antibacterial agents (1, 3, 5, 10, 12, 20). Moreover, coadministration with other metal ion-containing drugs also decreases the absorption of some new quinolones, such as ciprofloxacin (CPFX) and norfloxacin (NFLX) given with calcium carbon-

ate (12) and CPFX given with ferrous sulfate (18). This interaction is mainly due to chelate formation (16).

This study compared the effects of aluminum hydroxide and magnesium oxide on the absorption of DR-3355 in healthy male volunteers. We also evaluated the potential for interaction between DR-3355 and the other metal ion-containing drugs, ferrous sulfate and calcium carbonate. In addition, we studied the effect of ranitidine on absorption of the drug.

MATERIALS AND METHODS

Chemicals. DR-3355, (–)-(S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido-[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hemihydrate, was synthesized in our laboratory (Fig. 1). DL-8493, (±)-9-fluoro-3-methyl-10-(4-allyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido-[1,2,3-de][1,4]benzoxazine-6-carboxylic acid, was used as an internal standard for high-performance liquid chromatography (HPLC). All other reagents and chemicals were of analytical reagent grade.

Volunteers. A total of 18 healthy male volunteers ranging in age from 20 to 33 years (mean, 22.4 years) participated in the study. Their heights ranged from 165 to 178 cm (mean, 171.2 cm), and their weights ranged from 53 to 72 kg (mean, 61.5 kg). Each subject was determined to be in good health before the start of the study on the basis of medical history, physical examination, electrocardiogram, and clinical laboratory tests. All subjects abstained from caffeine-containing foods and alcohol during the study. Smoking was forbidden from 10 h before to 4 h after drug administration. Volunteers fasted from 12 h before to 4 h after administration. The

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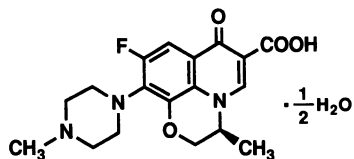


FIG. 1. Chemical structure of DR-3355.

subjects were instructed not to take any medications from 1 week before the study until after the study was completed.

Ethical considerations. The protocol was approved by the Review Committee for Clinical Trials at Kitasato Institute Bio-latric Center. Subjects received written information regarding the aims and procedures of the study. Written consent was obtained from each subject before participation.

Protocol. The study consisted of three separate treatment phases. Six subjects in each group were allocated to each treatment, according to the Latin square crossover design. Study 1 consisted of 100 mg of DR-3355 (100-mg tablet, lot S-1719-PMG; Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan) and simultaneous administration of aluminum hydroxide (1 g of fine granules, lot K9J01; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) or magnesium oxide (500 mg of fine granules, lot 00153; Iwaki Pharmaceutical Co., Ltd., Tokyo, Japan). Study 2 involved 100 mg of DR-3355 and simultaneous administration of calcium carbonate (500 mg, lot VE-9; Kosakai Pharmaceutical Co., Ltd., Tokyo, Japan) or ferrous sulfate (160-mg tablet, lot 00040; Chiba Gaigi Japan Co., Ltd., Tokyo, Japan). Study 3 consisted of 100 mg of DR-3355 and simultaneous administration of ranitidine (150-mg tablet, lot 9Z271; Glaxo Japan Co., Ltd., Tokyo, Japan). Each study included 100 mg of DR-3355 alone. Drugs were ingested with 100 ml of water at 9 a.m. under fasting conditions, and a controlled meal was given 4 h after administration. A 7-day break period was provided between crossover studies in each treatment phase.

Sample collection. Serial blood and urine samples were obtained after administration. Approximately 10 ml of blood was drawn immediately before and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h after dosing. Immediately after collection, each sample was gently inverted a few times for complete mixing with heparin. Each sample was centrifuged within 1 h of collection for 10 min at $1,000 \times g$ to separate plasma. The separated plasma was transferred to another tube and stored at or below -20°C until analysis. Total urine collections were made just prior to dosing and over the intervals of 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h after dosing. To facilitate collection, all subjects took 200 ml of water at 3 h after drug administration.

Drug assay. DR-3355 concentrations in plasma and urine were determined by HPLC as reported previously (13). Portions of plasma (0.1 ml) and urine (0.1 ml) were diluted with 50 mM potassium dihydrogen phosphate containing the internal standard. These samples were applied to a C_8 cartridge column (Bond Elut; Analytichem International, Harbor City, Calif.) and washed with 50 mM potassium dihydrogen phosphate followed by tetrahydrofuran-distilled water (2:8, vol/vol). Elution was performed with tetrahydrofuran-0.5% orthophosphoric acid (2:8, vol/vol), and the eluents were concentrated with a vacuum. The resulting solutions were injected onto the chromatograph. The chromatographic system consisted of an HPLC pump (model CCPM; Tosoh, Tokyo, Japan), a fluorescence detector (model F-1150; Hitachi Ltd., Tokyo, Japan), and a sample

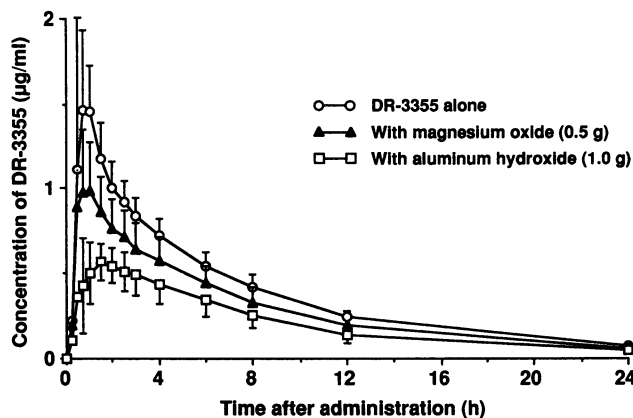


FIG. 2. Plasma DR-3355 concentration-time profiles after a single 100-mg dose of DR-3355 alone and with concurrent doses of aluminum hydroxide (1.0 g) or magnesium oxide (0.5 g) in healthy male volunteers. Values are means \pm standard deviations.

autoinjector. Separation was achieved with a TSK gel ODS-80T (inside diameter, 150 by 4.6 mm; Tosoh) at a flow rate of 1 ml/min. The mobile phase consisted of tetrahydrofuran-50 mM potassium dihydrogen phosphate (pH 2.0, adjusted with orthophosphoric acid)-1 M ammonium acetate (7.5:92.5:1, vol/vol). Detection was performed by spectrofluorimetry at an excitation wavelength of 296 nm and an emission wavelength of 504 nm. Peak area ratios of DR-3355 to an internal standard were linear over the concentration ranges of 0.01 to 1.2 $\mu\text{g/ml}$ in serum and 1 to 200 $\mu\text{g/ml}$ in urine. The intra- and interday coefficients of variation in serum (50 ng/ml) were 4 and 5%, respectively, and in urine (5 $\mu\text{g/ml}$) were 0.3 and 4%, respectively. The determination limits of serum and urine were 10 ng/ml and 1 $\mu\text{g/ml}$, respectively.

Pharmacokinetic analysis. Peak concentration in plasma (C_{max}) and time to peak concentration were determined from data for concentration in plasma versus time. The elimination rate constant was obtained by least-squares linear regression analysis. The terminal log-linear portion of the plasma concentration-time curve was defined by the last n ($n \geq 3$) datum points, where n was selected to minimize the mean square error. Plasma elimination half-life ($t_{1/2}$) was calculated by dividing 0.693 by the elimination rate constant. The AUC for plasma from time zero to the last measured concentration was determined by the linear trapezoidal rule. The AUC from 0 h to infinity was calculated by the trapezoidal rule and extrapolated to infinity by dividing the last observed concentration by the elimination rate constant. Mean residence time (MRT) was computed by dividing the area under the first moment of the drug concentration-time curve by the AUC. The relative bioavailability was calculated by dividing the AUC of each treatment group by that of the control group.

Statistical analysis. Analysis of variance was applied to C_{max} , the AUC, $t_{1/2}$, MRT, and urinary excretion to determine any statistically significant ($P < 0.05$) differences in pharmacokinetic parameters among treatment groups. The initial analysis of variance model included terms for subject, period, carryover, and drug treatment. Statistical significance was assessed at the 5% level.

RESULTS

As shown in Fig. 2, levels of DR-3355 in plasma were

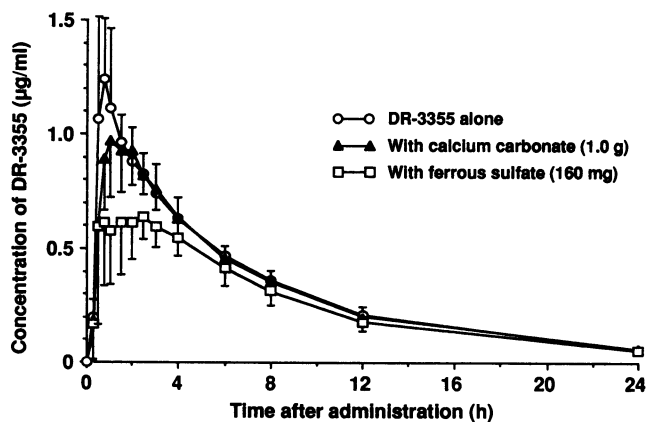


FIG. 3. Plasma DR-3355 concentration-time profiles after a single 100-mg dose of DR-3355 alone and with concurrent doses of calcium carbonate (1.0 g) and ferrous sulfate (160 mg) in healthy male volunteers. Values are means \pm standard deviations.

decreased by concomitant administration of aluminum hydroxide or magnesium oxide. Ferrous sulfate also decreased levels of DR-3355 in plasma, but calcium carbonate had minimal influence on the pharmacokinetics of DR-3355 (Fig. 3). Pharmacokinetic parameters for DR-3355 after each treatment are provided in Table 1. Parameters among the control groups of the three separate studies were almost the same. In study 1, simultaneous administration of aluminum hydroxide resulted in significant reductions in the AUC and C_{max} (44 and 65%, respectively) relative to those for DR-3355 (100 mg) alone. When magnesium oxide was coadministered with DR-3355, small but significant decreases in the AUC (78%) and C_{max} (62%) were observed, whereas time to peak concentration, $t_{1/2}$, and MRT showed no change. In study 2, values for relative bioavailability (97%), C_{max} (1.12 $\mu\text{g/ml}$), $t_{1/2}$ (6.27 h), and MRT (6.69 h) obtained when calcium carbonate was concurrently given did not differ from those for DR-3355 alone. Treatment with ferrous sulfate produced significant reductions in the AUC and C_{max} (19 and 45%, respectively). Thus, the effect of concurrent antacid and ferrous sulfate dosing on DR-3355 bioavailability was largest for aluminum hydroxide and was next largest for magnesium oxide and ferrous sulfate, in that order, while calcium carbonate had no effect on pharmacokinetic parameters. As shown in Fig. 4, ranitidine did not reduce the absorption of DR-3355, nor did its pharmacokinetic parameters differ from those of the control group (Table 1).

The effect of coadministration on cumulative excretion of DR-3355 is presented in Table 1. The effect of treatment on urinary recovery of DR-3355 occurred in a proportion similar to that of changes in the AUC and C_{max} . Coadministration of aluminum hydroxide and ferrous sulfate resulted in significant reductions (28 and 19%, respectively) in the amount of DR-3355 excreted in the urine. Insignificant decreases in urinary recovery for magnesium oxide and calcium carbonate were observed. Urinary excretion for ranitidine treatment was slightly greater than that for the control, but it was not significantly different.

DISCUSSION

The present study showed the bioavailability of DR-3355 to be decreased by concomitant antacid or ferrous sulfate administration. These interactions can be explained primar-

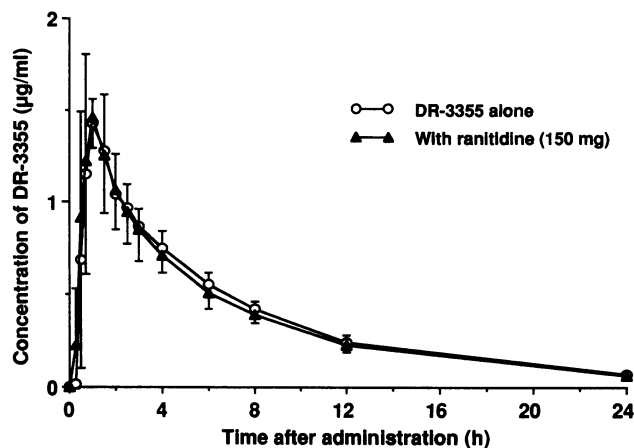


FIG. 4. Plasma DR-3355 concentration-time profiles after a single 100-mg dose of DR-3355 alone and with concurrent doses of ranitidine (150 mg) in healthy male volunteers. Values are means \pm standard deviations.

ily by the inhibition of absorption. However, bioavailability assessed by urinary recovery was not affected to the same extent as that assessed by the AUC. This effect may be caused by incomplete urinary excretion within 24 h, especially in study 1. Previous studies have demonstrated that absorption of orally administered new quinolone antibacterial agents such as OFLX (1, 10, 20), CPMX (5, 11), enoxacin (3, 20), and NFLX (12, 20) is decreased by concomitant administration of aluminum-containing antacids. Currently, it is generally accepted that the mechanism of interaction between metal ion-containing drugs and quinolone antibiotics is chelate formation (8, 16). Okazaki et al. reported that aluminum chloride dramatically enhanced the inhibition of gastrointestinal absorption of OFLX in rats over that by an equivalent amount of aluminum hydroxide (16). The mechanism of the interaction is thought to be stable chelate complex formation between the 3-carboxyl- and 4-oxo-substituents of quinolones and the aluminum ion (8).

In this study, treatment with aluminum hydroxide, ferrous sulfate, and magnesium oxide resulted in 44, 19, and 22% decreases, respectively, in DR-3355 bioavailability, and ranking correlated with the stability constant of the metal chelation complex formed between OFLX and the metal ions (16). Although the stability constants of chelate formation between quinolone antibacterial agents are almost identical (16), the magnitude of the decrease in bioavailability varied, being 44% for DR-3355, 84.0% for enoxacin (20), 97.3% for NFLX (20), and 84.9% for CPMX (11) after concomitant administration of aluminum hydroxide (Alumigel; 1 g) or an aluminum- and magnesium-containing antacid (Maalox, 30 ml [1.8 g of magnesium hydroxide and 3.6 g of aluminum hydroxide]). Consequently, it is supposed that mechanisms other than chelate formation contribute to the interaction between antacids and quinolone antibacterial agents.

Our study showed ranitidine to have no effect on the bioavailability of DR-3355. Since ranitidine has been reported to exhibit its effect on gastric acid secretion for several hours (2), it is doubtful whether the gastric pH actually increased. For CPMX, a 2-h pretreatment with ranitidine has no effect on the bioavailability of CPMX (11). In this study, however, calcium carbonate, which shows

TABLE 1. Pharmacokinetics of DR-3355 alone and with concurrent doses of antacid, ferrous sulfate, and ranitidine^a

Study	DR-3355 treatment	C _{max} (μg/ml)	T _{max} (h)	t _{1/2} (h)	AUC _{0-∞} (μg · h/ml)	MRT (h)	Urinary recovery (% of dose) ^b
1	Alone	1.82 ± 0.89	0.80 ± 0.20	6.44 ± 0.48	9.99 ± 1.55	6.62 ± 0.39	74.4 ± 13.0
	With magnesium oxide	1.13 ± 0.36*	0.08 ± 0.34	6.70 ± 0.62	7.81 ± 2.20*	6.72 ± 0.49	65.4 ± 9.5
	With aluminum hydroxide	0.64 ± 0.20**	1.50 ± 0.70	7.05 ± 0.52*	5.62 ± 1.51***	7.15 ± 0.30	53.3 ± 10.3*
2	Alone	1.45 ± 0.36	1.13 ± 0.93	5.94 ± 0.40	8.42 ± 1.06	6.48 ± 0.26	82.1 ± 3.5
	With calcium carbonate	1.12 ± 0.13	1.33 ± 0.61	6.27 ± 0.31	8.14 ± 0.71	6.69 ± 0.34	79.2 ± 5.5
	With ferrous sulfate	0.80 ± 0.27**	1.33 ± 0.98	6.55 ± 0.57	6.82 ± 1.05***	7.12 ± 0.49**	66.1 ± 3.6*
3	Alone	1.57 ± 0.22	1.00 ± 0.40	6.11 ± 0.72	9.81 ± 1.38	6.60 ± 0.24	85.8 ± 9.4
	With ranitidine	1.65 ± 0.24	0.90 ± 0.30	6.03 ± 0.67	9.45 ± 1.25	6.37 ± 0.30	88.2 ± 10.8

^a Subjects received a single oral dose of DR-3355 (100 mg) alone or with concurrent doses of magnesium oxide (500 mg), aluminum hydroxide (1 g), calcium carbonate (1 g), ferrous sulfate (160 mg), or ranitidine (150 mg) under fasting conditions. Each value represents the mean ± the standard deviation for six subjects. T_{max}, time to peak concentration; AUC_{0-∞}, AUC from 0 h to infinity. *, **, and ***, significantly different from control value at P < 0.05, 0.01, and 0.005, respectively.

^b Cumulative urinary excretion at 24 h.

markedly lower levels of chelation with quinolone antibacterial agents than aluminum ion does, did not change the absorption rate of the drug. This observation indicates that changes in gastric pH may not affect the absorption of DR-3355. Since physicochemical properties such as water solubility and partition coefficient vary among quinolones (7, 9, 21), it is possible that changes in gastric pH reduce absorption by decreasing the solubility of many quinolone antibacterial agents other than OFLX and DR-3355. In fact, ranitidine treatment significantly decreases enoxacin absorption, while that of NFLX is decreased by calcium carbonate (12).

Numerous reports have demonstrated that Maalox (aluminum hydroxide plus magnesium hydroxide), used for treatment of gastrointestinal symptoms, affects the intestinal absorption of new quinolones, resulting in a significant reduction in the bioavailability of these antibacterial agents (1, 5, 11). This mechanism is generally explained by chelate formation with aluminum or magnesium ions (16), but it is not known which metal ion exerts the greater influence on bioavailability of the drug. In this regard, the present study showed that aluminum hydroxide causes a greater decrease in the AUC of DR-3355 than does magnesium oxide and is therefore the main factor in the interaction between new quinolones and Maalox.

DR-3355 is rapidly and completely absorbed from the intestine and is excreted into the urine mainly as the unchanged form. The disposition of DR-3355 in humans is really identical to that of OFLX (10a). The degrees of the effects of concurrent aluminum hydroxide ingestion on the bioavailability of DR-3355 and OFLX were therefore nearly identical (20). For the test drugs containing metal ions, the present study showed the bioavailability of DR-3355 after an oral 100-mg dose to be most influenced by the simultaneous administration of aluminum hydroxide. However, the decrease in relative bioavailability of DR-3355 was only 44%, and the ratio of this decrease was markedly lower than that for other quinolones with the exception of OFLX (20). Moreover, levels of DR-3355 in plasma after coadministration of aluminum hydroxide were maintained at 0.6 μg/ml, considerably exceeding the range of MICs for 90% of strains tested reported for many moderately susceptible pathogens (4). However, further clinical studies are needed to establish specific dosage regimens for coadministration of DR-3355 with metal ion-containing drugs.

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