Effect of Oral Antacids on Disposition of Intravenous Enoxacin

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The effect of an intensive aluminum-magnesium hydroxide antacid regimen (Maalox TC) on the disposition of intravenous enoxacin was studied in six male and six female volunteers. A single 400-mg dose of enoxacin was administered intravenously over 30 min on two occasions separated by a 1-week washout period. Thirty milliliters of Maalox TC was administered at −8, −2.5, −0.5, 1.5, 3.5, 5.5, 7.5, 9.5, 11.5, 13.5, and 15.5 h relative to the start of one enoxacin infusion. The enoxacin dose in which antacid was coadministered was randomly selected. Fourteen plasma samples were collected over 24 h, and urine was collected in two divided intervals over 48 h. Enoxacin concentrations in plasma and urine samples were determined by high-performance liquid chromatographic assays. The intensive antacid regimen did not change the total clearance (P = 0.058) or steady-state volume of distribution (P = 0.516) for enoxacin. However, the nonrenal clearance and half-life were significantly altered (P < 0.05). The mean nonrenal clearance increased from 13.27 ± 3.33 to 15.68 ± 2.35 liters/h (18.2%) following the antacid regimen. This effect of antacid is unlikely to be of clinical significance. Enoxacin may be administered intravenously, but not orally, without regard to antacid treatment.

Antacids containing magnesium and aluminum salts result in marked reductions in concentrations in plasma and the area under the plasma concentration-versus-time curve (AUC) of enoxacin and other fluoroquinolones after concurrent oral administration (1–3). This drug interaction occurs in part because of the reduced amount of absorption of the fluoroquinolone-metal ion complexes. Other mechanisms may increase the elimination rate of fluoroquinolones. After intravenous enoxacin administration to rats, 45% of a dose of 50 mg/kg of body weight was recovered in the feces; however, biliary excretion accounted for only 2.5% of the dose (4). It is likely that either intestinal secretion or diffusion of enoxacin through the gastrointestinal mucosa is responsible. If this is the case, antacids could reduce the reabsorption of drug entering the intestinal lumen and may also promote gastrointestinal dialysis. In the study described here, we examined the effect of an intensive antacid (Maalox TC) regimen on the disposition of intravenously administered enoxacin.

MATERIALS AND METHODS

The study was reviewed and approved by a licensed human research committee, and written informed consent was obtained from all volunteers. The study included 12 subjects (six males and six females). The mean age was 28 ± 5 years and the mean weight was 70.7 ± 12.3 kg. For acceptable subjects, clinical laboratory profiles, a medical history, and physical examination were performed, and the subjects had no evidence of significant diseases or organ dysfunction. Female subjects had a negative pregnancy test and were using a reliable method of contraception. Volunteers had a negative urine screen for drugs of abuse and had not received any medications within 2 weeks of the study.

Enoxacin (400 mg) was administered as a single 30-min intravenous infusion on two occasions, 1 week apart. Thirty milliliters of aluminum-magnesium hydroxide antacid (Maalox TC; W. H. Rorer, Inc., Fort Washington, Pa.) was administered at 8, 2.5, and 0.5 h before and at 1.5, 3.5, 5.5, 7.5, 9.5, 11.5, 13.5, and 15.5 h following one of the enoxacin doses. The subjects were randomized to receive the Maalox TC regimen with either the first or second enoxacin dose in a crossover fashion. Breakfast, lunch, and dinner were of low fat content, and mealtimes relative to the enoxacin dose were standardized.

At 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h following enoxacin administration, serial blood samples were collected in heparinized vacuum tubes. The plasma was harvested and frozen at −20°C.

Concentrations of enoxacin in plasma were determined by high-performance liquid chromatography as described previously (1). For the plasma assay, the relative standard deviations for quality control samples were 5.01, 3.16, and 3.4% for concentrations of 0.2, 0.8, and 4 μg/ml, respectively. Urine samples were assayed for enoxacin by adding 1 ml of urine to 100 μl of distilled-deionized water and 50 μl of methanol. An octadeucsilane cartridge was preconditioned with two 1-ml portions of methanol and water. The urine sample mixture was added, and then 1 ml of phosphate buffer (pH 6.5) and two 1-ml portions of distilled-deionized water were added. Enoxacin was eluted with two 0.5-ml portions of acetone-nitrite-citric acid solution (1:1). The eluent was further diluted 1:1 with citric acid solution and was then injected onto the column. Separation was achieved by using the column described above. The mobile phase consisted of 850 ml of a solution of 21 g of citric acid per liter, 1.15 ml of tetrabutylammonium hydroxide per liter, and 1 g of ammonium perchlorate per liter and 150 ml of HPLC-grade acetone.

The flow rate was 1 ml/min, and detection was at 340 nm. The relative standard deviations for quality control

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samples were 4.58, 2.88, and 0.91% for concentrations of 8, 20, and 80 μg/ml, respectively. The standard curve was linear from 1 to 300 μg/ml.

A two-compartment intermittent infusion model was used to fit plasma concentration-versus-time data. This model was shown to provide the best fit by residual inspection, the runs test, and Akaike’s information criteria (8). Best fits were obtained by using PCNONLIN (7) with a weighting of 1/y² for observed concentrations. Individual AUCs and areas under the moment curve (AUMC) were integrated from the model and parameter estimates. Clearance was determined as dose/AUC. The steady-state volume of distribution was determined as clearance times mean residence time (MRT), where MRT equals AUMC/AUC – (T/2) (T is infusion time). The half-life was determined as ln(2) divided by the terminal elimination rate constant (β). Renal clearance was calculated as the amount of enoxacin excreted in 24 h divided by AUC integrated over the same time interval. Mean total body clearance, renal clearance, nonrenal clearance, steady-state volume of distribution, half-life, and total urine recovery for the two treatments were compared by a two-tailed paired t test. Significance was defined as P < 0.05.

RESULTS

Figure 1 shows the mean plasma concentration-versus-time profiles for the two treatments. The mean values for the pharmacokinetic parameters are provided in Table 1. There were no differences in mean clearance or steady-state volume of distribution between the two treatments. However, an 18.1% increase in nonrenal clearance was observed following the antacid regimen (P = 0.031). The mean half-life for the antacid treatment was slightly shorter than that observed after enoxacin treatment alone (P = 0.016). However, half-life is not an independent pharmacokinetic parameter, and many factors can result in changes. Mean renal clearances were 13.35 and 13.27 liters/h with and without the antacid regimen, respectively (P = 0.409).

Intervenously administered enoxacin was well tolerated in the present study, but there was local venous irritation in three subjects. One female experienced moderate erythema and burning extending 10 cm from the catheter insertion site. The enoxacin infusion was stopped after 15 min and she was removed from the study. She was replaced with an alternate subject. Two additional subjects had mild irritation at the infusion site that did not require any action. Mild to moderate diarrhea was noted in all subjects during the intensive Maalox TC treatment phase.

DISCUSSION

The intensive Maalox TC regimen did not alter the total clearance or steady-state volume of distribution of enoxacin. However, there were significant changes in half-life and nonrenal clearance. Examination of individual plasma enoxacin concentration profiles for enoxacin alone did not reveal any local peaks that may indicate biliary excretion and reabsorption. We initially hypothesized that the antacid may alter the elimination rate by gastrointestinal dialysis or by increased renal excretion. Enoxacin is excreted into bile; however, the total amount excreted in this manner on the basis of concentrations in bile and normal bile flow is less than 2% of the administered dose (6). The changes in observed half-life and nonrenal clearance are compatible with an additional first-order elimination process resulting from the antacid regimen.

In a previous study involving doxycycline (5), a less intensive antacid regimen resulted in a 45% increase in total body clearance, from 2.24 ± 0.39 to 3.25 ± 0.74 liters/h. Thus, the mean additional clearance resulting from antacid treatment was 1.01 liters/h for doxycycline. At least some of this difference was accounted for by decreased enterohepatic recycling. Enoxacin differs from doxycycline in that it has a much larger total clearance (26.54 versus 2.24 liters/h). The Maalox TC regimen resulted in a mean 2.12-liter/h increase (not significant) in the total clearance of enoxacin; therefore, enoxacin may be more susceptible to gastrointestinal dialysis than doxycycline. Since the clearance of enoxacin is relatively fast, the additional clearance caused by antacid did not significantly alter the total clearance. There was also no change in the renal clearance or the steady-state volume of distribution for enoxacin administered with the Maalox TC regimen. It is likely that newer intravenous quinolones with slower clearances would exhibit greater percent increases in total body clearance after oral administration of aluminum and magnesium salts, provided that they interact with metal cations to the same extent.

The present study failed to demonstrate significant

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<th>TABLE 1. Pharmacokinetic parameters for a 400-mg dose of enoxacin given intravenously alone and with 30 ml of Maalox TC every 2 h</th>
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<td>Treatment</td>
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* Statistically significant difference.
changes in the total clearance or steady-state volume of distribution for intravenous enoxacin after an intensive Maalox TC regimen. Enoxacin may be administered intravenously, but not orally, without regard to antacid treatment.

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REFERENCES


