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Effect of Bismuth Subsalicylate on Ciprofloxacin Bioavailability

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A single oral dose of 528 mg of bismuth subsalicylate (30 ml of Pepto-Bismol) had no significant effect on the plasma pharmacokinetics of a single oral dose of 750 mg of ciprofloxacin administered to 12 healthy volunteers (six men and six women). These results suggest that ciprofloxacin bioavailability will not be significantly decreased by single doses of bismuth subsalicylate when the two medications are administered simultaneously.

Development of the fluoroquinolones has allowed oral treatment of serious infections which until a few years ago required parenteral therapy (8). Although many of these agents are absorbed well from the gastrointestinal tract, their bioavailability is reduced significantly when administered with antacids containing di- and trivalent metal cations (10, 12, 16, 17). This has resulted in therapeutic failure in at least one instance (11). The exact mechanism of this interaction has not been elucidated fully, although complexation with the metal ions (13–15) and adsorption to the antacids (19, 20) are suggested mechanisms.

Bismuth, a heavy metal, can exist as a trivalent cation. Bismuth subsalicylate (Pepto-Bismol) is commonly used for the symptomatic treatment and prevention of a variety of gastrointestinal disorders. Bismuth subsalicylate decreases the bioavailability of tetracyclines significantly, and recommendations have been made for separation of the dosing times for these two medications (1, 4). However, preliminary studies evaluating the interaction of bismuth salts on norfloxacin and ciprofloxacin absorption have demonstrated only minor reductions in fluoroquinolone bioavailability (3, 18). These data are in distinct contrast to those observed when ciprofloxacin is administered concurrently with other trivalent cations, such as aluminum. Because patients are likely to receive bismuth-containing compounds concurrently with fluoroquinolones, among which ciprofloxacin is well established, this study was conducted to determine the effect of a single dose of bismuth subsalicylate on ciprofloxacin absorption in healthy volunteers.

This study was approved by the Human Experimental Procedures Committee, Ottawa General Hospital, Ottawa, Ontario, Canada. Written informed consent was obtained from 12 healthy volunteers (six men and six women). The mean (± standard deviation) age and weight of the subjects were 35 ± 8 years and 70 ± 11 kg, respectively. Volunteers were excluded on the basis of the following: pregnancy, hypersensitivity reactions to any drug, use of any medications, chronic illness, current infection, abnormal finding on physical examination, abnormal renal or hepatic function tests, and abnormal hematology or urinalysis. On the morning of each study day, subjects were admitted to the Clinical Investigation Unit, Ottawa General Hospital.

The study design was a randomized, two-period, two-treatment, two-sequence crossover with a 7-day washout period. Subjects were instructed to fast overnight and were not allowed to eat until 4 h after administration of the study medications. In one phase of the study, subjects received a single oral dose of 750 mg of ciprofloxacin (Cipro, lot 0GEG; Miles Canada Inc., Toronto, Canada) with 150 ml of tap water. In the other phase of the study, subjects received a single oral dose of 30 ml of bismuth subsalicylate (Pepto-Bismol, lot 2DPZ; Proctor & Gamble Inc., Toronto, Canada), equivalent to 528 mg of bismuth subsalicylate, via syringe, immediately followed by a single dose of 750 mg of ciprofloxacin taken with 150 ml of tap water. The syringe containing the bismuth subsalicylate was weighed before and after delivery to determine accurately the volume of Pepto-Bismol dispensed. The difference between the expected volume (30 ml) and the actual volume ingested was <2%. Blood samples (5 ml) were collected into Vacutainer tubes containing EDTA, immediately before drug administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h after the dose. Samples were allowed to equilibrate for 20 min and were then centrifuged (500 × *g* for 15 min at 24°C). Plasma samples were stored in polypropylene tubes at −70°C until analysis about 2 weeks later.

Ciprofloxacin concentrations in plasma were determined by high-performance liquid chromatography (HPLC) (16). The limit of quantitation was 0.1 μg ml^{-1}. Predicted ciprofloxacin concentrations of individual quality-control samples at three concentrations were less than 6.8% from the nominal value. Within- and between-batch coefficients of variation (CVs) were less than 4.0 and 7.0%, respectively, for the quality-control samples.

The data for ciprofloxacin concentration in plasma (C) versus time (t) were analyzed by nonlinear, weighted ($1/C$), least-squares regression (PCNONLIN 4.0; SCI Software, Lexington, Ky.) to estimate the terminal disposition rate constant (λ_z). The Gauss-Newton fitting algorithm was used for the regression analysis. The model fit, either a one- or a two-compartment model with first-order input, with and without a lag time, and first-order output, was evaluated by Akaike's information criterion and plots of weighted residuals versus time or versus weighted predicted concentration. The highest observed concentration and the corresponding sampling time were defined as C_{max} and t_{max}, respectively. The terminal disposition half-life ($t_{1/2z}$) was calculated from the quotient (ln 2)/λ_z. The area under the plasma drug concentration-time curve from time zero to t_z (AUC_{0-tz}), where t_z is the time of the last measurable concentration, was calculated by the linear

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TABLE 1. Mean pharmacokinetic parameters of ciprofloxacin administered alone and with bismuth subsalicylate (Pepto-Bismol)[a]

Parameter	Value with treatment[b]		ANOVA for crossover design					
	CIP alone	CIP plus bismuth subsalicylate	%Δ[c]	95% Confidence limits	P	Intrasubject % CV	Intersubject pooled % CV	$\%\Delta_{80\%}$[d]
C_{max} (μg ml^{-1})	2.95 ± 0.64	2.57 ± 0.71	−13.9	−31.2, 7.7	0.168	24.6	13.5	−26.9
t_{max} (h)[e]	1.50 (0.75, 2.0)	1.75 (1.0, 4.0)	0.38	−0.25, 1.25	>0.10	NC	NC	NC
AUC_{0-tz} (μg · h ml^{-1})	13.58 ± 3.91	11.81 ± 2.84	−11.6	−32.5, 15.6	0.330	29.6	NM	−31.3
CL_o (liters h^{-1})	55.54 ± 16.22	61.67 ± 12.77	12.7	−12.7, 45.6	0.321	28.1	NM	42.8
$t_{1/2z}$ (h)	4.23 ± 0.73	4.08 ± 0.81	−3.6	−11.0, 3.8	0.299	8.3	16.9	−10.5
λ_z (h^{-1})	0.169 ± 0.030	0.177 ± 0.040	5.1	−4.6, 14.8	0.267	10.4	18.5	13.2

[a] Abbreviations: CIP, ciprofloxacin; NC, not calculated; NM, not measurable.
[b] A 750-mg single dose of ciprofloxacin and a 528-mg single dose of bismuth subsalicylate were used. Values are arithmetic means ± standard deviations (n = 12), except for t_{max} values, which are medians (with minimum and maximum given in parentheses).
[c] Percent change of the least-squares geometric treatment mean (C_{max}, AUC, and CL_o) or the least-squares arithmetic treatment mean ($t_{1/2z}$ and λ_z) of the ciprofloxacin-plus-bismuth subsalicylate treatment relative to the ciprofloxacin-alone treatment. The value for t_{max} is the point estimate of the absolute difference of expected medians, relative to the ciprofloxacin-alone treatment. A negative value refers to a decrease.
[d] Percent change of the least-squares means (see footnote c) that can be detected with a power of 80% at the 5% level of significance (α = 0.05/2).
[e] Analyzed by the nonparametric Wilcoxon rank sum test.

trapezoidal rule. Extrapolations from t_z to infinity were calculated by using the model-predicted concentration in plasma at t_z. The apparent oral plasma clearance (CL_o) was estimated by dividing the dose by $AUC_{0-\infty}$.

Differences in the mean pharmacokinetic parameters of ciprofloxacin (C_{max}, AUC_{0-tz}, CL_o, $t_{1/2z}$, and λ_z) between treatments were evaluated by an analysis of variance (ANOVA) model appropriate for a crossover design (9). Median t_{max} values for the two treatments were compared by using the nonparametric Wilcoxon rank sum test appropriate for a two-period, two-sequence crossover design (7). All pharmacokinetic data except t_{max}, $t_{1/2z}$, and λ_z were logarithmically transformed. The least-squares geometric and arithmetic means were used in the ANOVA calculations. In the ANOVA model, the effects of treatment, treatment-by-gender interaction, and period were tested by the mean-square residual, and the effects of sequence were tested by the subject-within-sequence mean-square term. If there was no treatment-by-gender interaction, then this term was removed in the final model. Calculations of intrasubject CV, intersubject CV, and power have been previously described (6). Statistical significance was defined as $P < 0.05$.

Mean pharmacokinetic data are presented in Table 1, and mean concentration-time data are illustrated in Fig. 1. There were no overall changes in pharmacokinetic parameters between the two regimens ($P > 0.10$). Table 1 shows less than a 15% difference between treatment means for the 12 subjects. Mean and individual AUC_{0-tz} values are shown in Fig. 2. The high intrasubject CV calculated for AUC_{0-tz} (30%) was mainly a consequence of one female subject showing a large increase (of 110%) in AUC and one female showing a large decrease (of 60%) in AUC when ciprofloxacin was taken with bismuth subsalicylate. There was no differential effect of bismuth subsalicylate on the pharmacokinetic parameters of ciprofloxacin in the six males compared with the six females. This study had 80% power at the 5% significance level to detect a 31% decrease in AUC_{0-tz} and a 27% decrease in C_{max} relative to the values for reference ciprofloxacin alone.

Concomitant administration of single doses of aluminum-containing compounds results in a dramatic reduction of ciprofloxacin absorption (5, 10). Also, single doses of ferrous sulfate significantly reduce norfloxacin bioavailability (3). It is generally accepted, therefore, that most multivalent cations decrease the oral bioavailability of the fluoroquinolones (11). The reduction in fluoroquinolone bioavailability in the presence of Ca^{2+}, Mg^{2+}, Fe^{2+}, and Al^{3+} ions has been explained on the basis of a decrease in lipophilicity of the fluoroquinolones following complexation with these ions compared with the lipophilicity of the uncomplexed drug (13). The interaction probably occurs between the cation and the 4-keto oxygen and 3-carboxylic acid groups (11, 14). The degree of interaction appears to be dependent on the solubility and nature of the interacting metal cation-containing agents, the pH at the site of interaction, the fluoroquinolone structure, and the solubility and stability of the cation-quinolone complex (13–15). Additionally, the quinolones adsorb to antacids (19, 20), providing another mechanism by which bioavailability is reduced.

Depending on the concentration of Bi^{3+}, complexation of another fluoroquinolone, lomefloxacin, with Bi^{3+} substantially reduces the aqueous solubility of lomefloxacin at pH 0, leading to precipitation of the complex (14). This suggests that the bioavailability of lomefloxacin, and possibly related fluoroquinolones, such as ciprofloxacin, should be reduced in the presence of bismuth-containing compounds. However, several pilot studies that evaluated the interaction between bismuth-

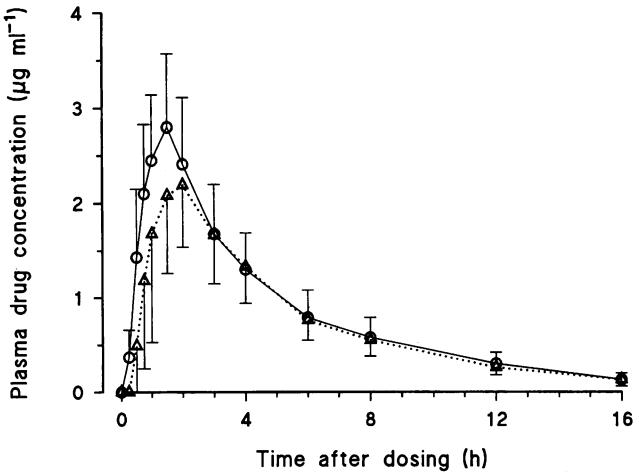

FIG. 1. Mean (± standard deviation) plasma ciprofloxacin concentration-time profiles for a single 750-mg oral dose of ciprofloxacin administered alone (circles) and immediately after a single 528-mg dose of bismuth subsalicylate (Pepto-Bismol) (triangles). Data for mean concentrations that were less than the lower limit of quantitation of the assay (0.1 μg ml^{-1}) are not shown.

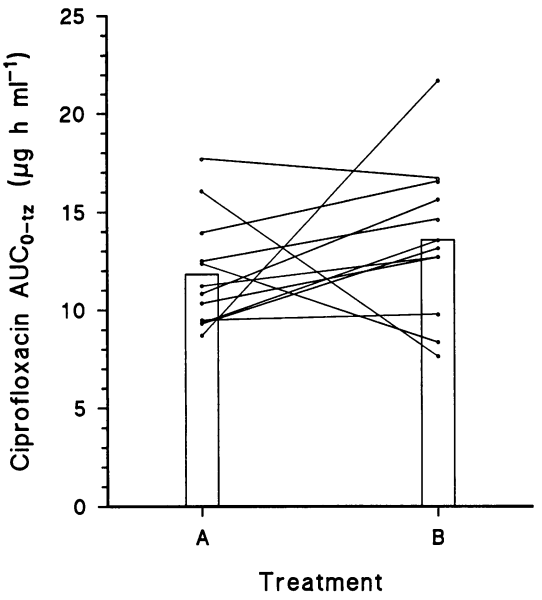

FIG. 2. Individual AUC_{0-tz} values for treatment with ciprofloxacin plus bismuth subsalicylate (A) and ciprofloxacin alone (B). Vertical bars represent mean AUC values for 12 subjects.

containing compounds and ciprofloxacin in small numbers of subjects have resulted in less than a 30% decrease in the bioavailability of ciprofloxacin (2, 18). Also, Campbell et al. (3) did not demonstrate a decrease in norfloxacin recovery from urine when norfloxacin was administered alone compared with when it was coadministered with 30 ml of Pepto-Bismol (recoveries from urine of 153.1 ± 34.7 versus 149.6 ± 26.8 mg/24 h, respectively). However, concentrations of norfloxacin in urine were decreased when the drug was administered with single doses of aluminum and iron salts (3).

Although there was a trend towards a decrease in C_{max} and AUC, we failed to demonstrate a significant interaction between ciprofloxacin and 30 ml of bismuth subsalicylate. All subjects had peak plasma ciprofloxacin concentrations above 1 μg ml^{-1} (range, 1.44 to 3.39 μg ml^{-1}) when the drug was administered with bismuth subsalicylate, which is above the MIC for 90% of strains tested for most susceptible organisms (8).

There are several possibilities for the apparent lack of interaction. Although in vitro studies of the Bi^{3+}-lomefloxacin interaction suggest that complexation does occur, the stability and types of bismuth complexes in vivo, if formed, may be different from those formed in vitro. At least for Ca^{2+} and Mg^{2+}, in vitro, the affinity of the metal for the fluoroquinolone is pH dependent, with the binding of the fluoroquinolone anion > zwitterion >> fluoroquinolone cation (15). The fluoroquinolone cation predominates for ciprofloxacin at the low physiological pH values (<5) expected after ingestion of bismuth-containing compounds (21). Alternatively, displacement of the subsalicylate ligand by ciprofloxacin, a weaker carboxylic acid than salicylic acid, may be unfavorable for formation of a bismuth-ciprofloxacin complex at low pH, or the low solubility of bismuth subsalicylate and the physical barrier of the Pepto-Bismol liquid may hinder complex formation. Adsorption of ciprofloxacin to bismuth subsalicylate is unlikely because ciprofloxacin has a low capacity for adsorption to a related bismuth salt, bismuth oxycarbonate (20).

This study does not provide information on the effect of multiple doses of bismuth on ciprofloxacin absorption, and therefore, we cannot make firm recommendations on dosing of these two agents. Also, bismuth salts may reduce the absorption of smaller doses of ciprofloxacin so that peak concentrations are below the MIC for 90% of strains tested for susceptible organisms.

In this study, in contrast to other studies involving aluminum, a single 30-ml dose of bismuth subsalicylate (Pepto-Bismol) did not substantially decrease ciprofloxacin absorption. The trivalent cations aluminum and bismuth are probably different in their ability to affect quinolone bioavailability.

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