Effect of Attapulgite on the Oral Bioavailability of Ciprofloxacin

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Abstract
Adsorption nature of attapulgite may inhibit the absorption of ciprofloxacin after oral administration. As a result, this drug-drug interaction may reduce ciprofloxacin bioavailability. This study was aimed to determine the effect of attapulgite on the bioavailability of a single orally-administered ciprofloxacin. Six New Zealand white rabbits received each of the following treatments in a randomized, three-way crossover sequence, separated by a 7-day washout period: (i) ciprofloxacin (23 mg/kgBW) alone; (ii) ciprofloxacin (23 mg/kgBW) given simultaneously with attapulgite (28 mg/kgBW); (iii) ciprofloxacin (23 mg/kgBW) given 2 hours after attapulgite (28 mg/kgBW). Blood samples (1 mL) were collected from the marginal ear vein up to 240 minutes postdose. The plasma concentrations of ciprofloxacin were determined by a validated high-performance liquid chromatography method. The maximum concentration and oral bioavailability ($AUC_{0\text{-}240\ min}$) of ciprofloxacin were significantly decreased by 49% and 32% when administered concomitantly with attapulgite ($p<0.001$). Attapulgite appeared to have no significant effect on the bioavailability of ciprofloxacin when administered 2 hours before ciprofloxacin. In conclusion, the oral bioavailability of ciprofloxacin is markedly reduced when administered concomitantly with attapulgite. This drug-drug interaction may decrease clinical efficacy and promote microbial resistance to ciprofloxacin. However, the interaction could be minimized by separating the adminsitration of these drugs at least 2 hours.

Key words: Attapulgite, bioavailability, ciprofloxacin, drug-drug interaction

Pengaruh Atapulgit pada Ketersediaan Hayati Siprofloksasin Oral

Abstrak
Kemampuan absorpsi atapulgit dapat menghambat absorpsi siprofloksasin pada pemberian per oral. Sebagai hasilnya, interaksi obat-obat ini dapat menurunkan ketersediaan hayati siprofloksasin. Penelitian ini bertujuan untuk mendeterminasi efek atapulgit pada ketersediaan hayati obat siprofloksasin yang diberikan secara oral. Sebanyak 7 kelinci putih Selandia Baru menerima perlakuan secara random dengan desain *three-way crossover sequence*, yang dipisahkan dengan periode *washout* 7 hari. (i) siprofloksasin (23 mg/kgBB); (ii) siprofloksasin (23 mg/kgBB) diberikan secara simultan dengan atapulgit (28 mg/kgBB); (iii) siprofloksasin (23 mg/kgBB) diberikan 2 jam setelah pemberian atapulgit (28 mg/kgBB. Sampel darah (1 mL) dikumpulkan pada *marginal ear vein* setelah 240 menit pemberian obat. Konsentrasi siprofloksasin plasma dihitung dengan metode kromatografi cair kinerja tinggi tervalidasi. Konsentrasi maksimum dan ketersediaan hayati oral ($AUC_{0\text{-}240\ min}$) siprofloksasin secara signifikan berkurang 49% dan 32% ketika dikombinasikan bersamaan dengan atapulgit ($p< 0{,}001$). Atapulgit tidak memiliki pengaruh signifikan pada ketersediaan hayati ketika diberikan 2 jam sebelum siprofloksasin. Ketersediaan hayati siprofloksasin berkurang secara signifikan ketika diberikan bersamaan dengan pemberian atapulgit. Interaksi obat dengan obat ini dapat mengurangi efikasi obat dan meningkatkan resistensi mikrob terhadap siprofloksasin. Namun, interaksi dapat dikurangi dengan pemberian obat pada jarak waktu minimal 2 jam.

Kata kunci: Atapulgit, interaksi obat dengan obat, ketersediaan hayati, siprofloksasin

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Introduction

Ciprofloxacin is a second-generation of fluoroquinolone which exhibits in vitro minimum inhibitory concentrations (MICs) of 1 μg/mL against most (≥90%) strains of aerobic Gram-positive and Gram-negative microorganisms.[1] Ciprofloxacin given as an oral tablet is well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is 70 to 80% with no substantial loss by first pass metabolism.[2] Maximum serum concentrations are attained 1 to 2 h after oral dosing and its serum concentration after oral administration is similar to the intravenous route.[2]

Food and drugs which have divalent (Ca^{+2}, Fe^{+2}, Mg^{+2}, Zn^{+2}) or trivalent (Al^{+3}, Fe^{+3}) cations may interact with ciprofloxacin by forming chelate complexes thus reducing the rate and amount of ciprofloxacin absorption in the upper gastrointestinal tract.[1,3,4] A research by Garrelts et al.[5] showed a decrease in the bioavailability of ciprofloxacin in healthy humans after a concurrent use of 500 mg ciprofloxacin with 1 gram sucralfate which has 16 aluminum ions per molecule. A sucralfate-ciprofloxacin interaction causes a decrease in the area under the concentration-time curve (0 to 12 h) of 8.8 to 1.1 μg.h/mL ($p<0.005$) and the maximum concentration of ciprofloxacin in the serum of 2.0 to 0.2 mg/mL ($p<0.005$).[5] Another study revealed that the bioavailability of 750 mg ciprofloxacin reduced respectively by 7%, 20% and 95% when given sucralfate consecutive 6 h before, 2 h before and at the same time.[6] Further results of reduced bioavailability of this drug may impact to the effectiveness of therapy, even though the study does not address any impact on antibiotic therapy outcomes.

A drug-drug interaction with a chelate formation mechanism may also occur when ciprofloxacin is concurrently administered with attapulgite. Attapulgite, a hydrated magnesium aluminum silicate, has aluminum cations which can bind to the carboxylic acid and ketone groups at positions 3 and 4 on the ciprofloxacin nucleus thus forming nonabsorbable chelate complexes. Furthermore, adsorption nature of attapulgite may also inhibit the absorption of ciprofloxacin after oral administration. As a result, this drug-drug interaction may reduce ciprofloxacin bioavailability. However, there are no recent studies reported on the issue. Therefore, the purpose of this study was to determine the effect of attapulgite on the bioavailability of a single orally-administered ciprofloxacin.

Methods

Six New Zealand white rabbits received each of the following treatments in a randomized, three-way crossover sequence, separated by a 7-day washout period: (i) ciprofloxacin (23 mg/kgBW) alone; (ii) ciprofloxacin (23 mg/kgBW) given simultaneously with attapulgite (28 mg/kgBW); (iii) ciprofloxacin (23 mg/kgBW) given 2 h after attapulgite (28 mg/kgBW). The rabbits were fasted overnight prior to treatments and given free access to water. Blood samples (1 mL) were collected from the marginal vein of the ear at 0, 20, 40, 60, 90, 120, 180, and 240 minutes postdose. Samples were collected into sterile vacuum tubes and centrifuged at 4,000 rpm for 15 minutes. Plasma was obtained and stored in a sterile microtube at -20°C until analyzed.

The plasma concentrations of ciprofloxacin were determined by a validated high-performance liquid chromatography assay and a modification of the method reported by USP.[7] Briefly, 200.0 μL of spiked standards (ciprofloxacin 3.0 μg/mL) was added to 200.0 μL of plasma, and the mixture was vortexed for 60 s. Next, 200.0 μL of acetonitrile and 100.0 μL of H_3PO_4 0.02 M (pH 3.0, adjusted with triethanolamine) were added to the

mixture and then centrifuged at 4,000 rpm for 20 minutes. The supernatant was filtered by a 0.2 µL filter membrane and then 10.0 µL of solution was injected into the HPLC system.

The chromatographic system was composed of a HPLC-DAD Agilent 1100 series, diode array detector, and Licrospher ODS @ 100 RP-18 column. The detector wavelength was set to 280 nm. Mixtures of acetonitrile:H_3PO_4 0,02 M (pH 3, adjusted with triethanolamine) (13:87, v/v) were used as the mobile phase at a flow rate of 1.5 mL/min. The retention time is 9.2 min. The calibration curve of ciprofloxacin was linier within range 0.25 to 10.0 µg/mL (r=0.9997). Detection limit was 0.02 µg/mL and quantification limit was 0.06 µg/mL. The within-day (n=5) and day-to-day (n=5) coefficient of variation was 1.98±0.65%. Recovery (%) was assessed from replicate analysis (n=6) and shown 99.54±7.13%.

The maximum concentration and the time of maximum concentration of ciprofloxacin in plasma were obtained directly from the plasma concentration-time curve for each subject. The area under the plasma concentration-time curve from 0 to 240 min (AUC_{0-240}) was calculated by using the linear trapezoidal rule method. Differences in the mean $AUC_{0-240min}$ and the maximum ciprofloxacin concentrations among the treatment groups were analyzed for significance by a two-way ANOVA with an alpha value of 0.05.

Results

The plasma concentrations of ciprofloxacin after the oral administration of ciprofloxacin alone, co-administered with attapulgite, and 2 hours after attapulgite to rabbits are shown in Table 1 and Figure 1.

The plasma concentrations of ciprofloxacin were altered when ciprofloxacin was given concomitantly with attapulgite. The maximum concentration and bioavailability ($AUC_{0-240\ min}$) of ciprofloxacin decreased by 49% and 32% when attapulgite was administered concomitantly ($p<0.001$). However, concurrent administration of attapulgite did not affect the time to reach maximum plasma concentration of ciprofloxacin after oral administration. Furthermore, attapulgite appeared to have no significant effect on the bioavailability of ciprofloxacin when administered 2 h before ciprofloxacin.

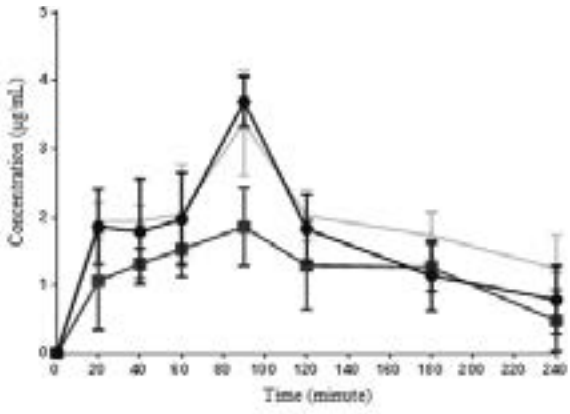

Figure 1 Mean Plasma Ciprofloxacin Concentration-versus-time Profiles for Ciprofloxacin 23 mg/kgBW Alone ( ), Ciprofloxacin 23 mg/kgBW with Attapulgite 28 mg/kgBW ( ), and Ciprofloxacin 23 mg/kgBW 2 h after Attapulgite 28 mg/kgBW ( ). Values are Means±Standard Errors

The plasma concentrations of ciprofloxacin were altered when ciprofloxacin was given concomitantly with attapulgite. The maximum concentration and bioavailability ($AUC_{0-240\ min}$) of ciprofloxacin decreased by 49% and 32% when attapulgite was administered concomitantly ($p<0.001$).

However, concurrent administration of attapulgite did not affect the time to reach maximum plasma concentration of ciprofloxacin after oral administration.

Table 1 Pharmacokinetic Parameters of Ciprofloxacin in Rabbits After a Single Oral Dose of 23 mg/KgBW Given Alone, with 28 mg/KgBW Attapulgite, and 2 Hours After Attapulgite

Treatment Group	C_{max}		t_{max} (min	AUC_{0-360}	
	µg/mL	% decrease (compared to control)		µg.min/mL	%decrease (compared to control)
Ciprofloxacin alone (control)	3.69 ± 0.37		90	12.68 ± 1.66	
Ciprofloxacin with attapulgite	1.86 ± 0.57	49.6b	90	8.57 ± 1.92	32.4b
Ciprofloxacin 2 h after attapulgite	3.38 ± 0.77	8.40c	90	9.67 ± 0.58	23.7c

Note: a Data are mean values (± standard deviations as appropriate) for six subjects
b Significantly different ($p < 0.001$) from control
c No significantly different ($p > 0.001$) from control

Furthermore, attapulgite appeared to have no significant effect on the bioavailability of ciprofloxacin when administered 2 h before ciprofloxacin.

Discussion

The absorption process plays an important role in achieving maximum concentrations and bioavailability of drugs in the systemic circulation.[8] If there are either drug-drug or drug-food interactions during an absorption phase, it will reduce the amount of drug that enters the body hence reducing the bioavailability of drug. The present study demonstrated that the effects of concomitant ingestion of attapulgite were pronounced decreases in maximum concentrations (C_{max}) and bioavailability ($AUC_{0-240min}$) of ciprofloxacin.

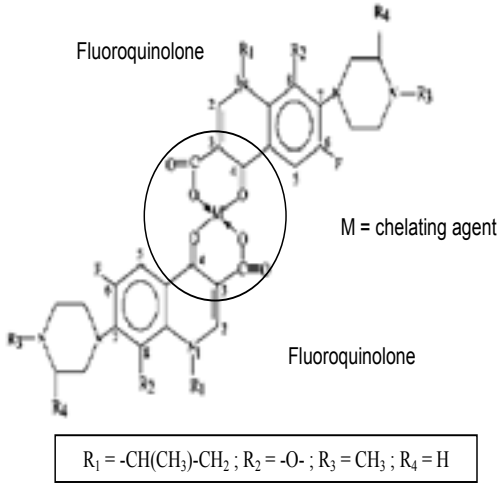

Figure 2 Chelate Formation between a Chelating Agent which Has Cations and Fluoroquinolones
From: El-Kommos et al.[9]

The most plausible explanation for attapulgite-ciprofloxacin interaction is the formation of chelate complexes.[9] Attapulgite which acts as an adsorbent in the gastrointestinal tract has a capacity to bind drug molecules to its surface area. Next, its aluminum cations (Al^{+3}) may interact with the 4-keto and 3-carboxyl groups of ciprofloxacin to form chelate complexes thus reducing the rate and amount of ciprofloxacin absorption in the gastrointestinal tract.[1,4,5] Figure 2 shows the possible mechanism of chelate formation between attapulgite and ciprofloxacin. When ciprofloxacin was given concomitantly with attapulgite, there were many aluminum cations available to interact with the 4-keto and 3-carboxyl groups of ciprofloxacin. Only a small amount of ciprofloxacin was left to be absorbed into the systemic circulation hence

reducing the bioavailability and maximum plasma concentration of ciprofloxacin.

Some investigators have evaluated the effect of staggered dosing of fluoroquinolones and sucralfate on the extent of drug-drug interaction.[5,6] Sucralfate which has aluminum cations appeared to reduce the bioavailability of ciprofloxacin by 88% (with 1 g of sucralfate administered four times on the day before the study and the fifth dose given with ciprofloxacin). However, when a 1 g dose of sucralfate was given 6 and 2 h before ciprofloxacin, only a 30% decrease in the bioavailability of ciprofloxacin was observed.[5] Clearly, not only the time interval between administrations of these interacting drugs, but also the sequence in which they are given, is important when trying to prevent this potential interaction.

Of additional importance, when attapulgite was administered 2 h before ciprofloxacin, it failed to significantly affect the bioavailability of ciprofloxacin. It means that the amount of attapulgite contained in the rabbit stomach may begin to diminish as the process of gastric emptying (3 to 6 h).[10] As a result, this potential drug-drug interaction could be minimized by separating the intake of these drugs at least 2 h. Moreover, the maximum concentration of ciprofloxacin in plasma was achieved in less than 2 h, so it is reasonable to assume that the absorption process was completed before ciprofloxacin came into contact with released aluminum ions when ciprofloxacin given 2 h before attapulgite.

This present study does not investigate the impact of drug-drug interaction on decreasing the effectiveness of therapy. Nonetheless, further studies on assessing the clinical outcomes from the concomitant use of attapulgite and ciprofloxacin are needed to address this issue. Ciprofloxacin exhibits in vitro minimum inhibitory concentrations (MICs) of 1 μg/mL against most (≥ 90%) strains of aerobic gram-positive and gram-negative microorganisms.[1] Therefore, if plasma concentrations of ciprofloxacin fall below its MICs then the effectiveness of ciprofloxacin in treating clinical infections will be questioned.

Conclusions

The oral bioavailability of ciprofloxacin was markedly reduced when administered concomitantly with attapulgite. This drug-drug interaction may decrease clinical efficacy and promote microbial resistance to ciprofloxacin. However, the interaction could be minimized by separating the adminsitration of these drugs at least 2 h.

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