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SHORT COMMUNICATION

THE INFLUENCE OF COFFEE WITH MILK AND TEA WITH MILK ON THE BIOAVAILABILITY OF TETRACYCLINE

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ABSTRACT

The effect of milk added to coffee or black tea on the bioavailability of tetracycline was evaluated in 12 healthy volunteers according to a crossover design. Results showed that even a small volume of milk containing extremely small amounts of calcium severely impair the absorption of the drug, so that the presence of this metal ion should be carefully controlled in order to avoid decreasing the available tetracycline. ©1997 by John Wiley & Sons, Ltd.

KEY WORDS: coffee; tea; milk; tetracycline

INTRODUCTION

Some drugs contain electron-donor groups that bind metal ions occurring naturally *in vivo*. Among these, tetracycline antibiotics have long been known to behave as relatively efficient chelating agents with metallic ions, to form six-membered rings.[1] These complexes formed are either insoluble or highly charged and thus can hardly be absorbed from the gastrointestinal tract.[2]

It has been well demonstrated that milk and other dairy products containing considerable amounts of calcium or magnesium impair the absorption of tetracycline. Mattila *et al.*[3] reported that the ingestion of 300 mL whole milk with 500 mg tetracycline reduced serum levels by 50–60%. Considering that these studies were performed with a large volume of milk, the present study was carried out to determine whether a small volume of milk added to coffee or tea would influence the bioavailability of tetracycline.

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MATERIALS AND METHODS

The study was performed on twelve healthy volunteers, six male and six female (age, 22–30 years; weight, 47–75 kg; height, 150–180 cm) according to a Latin square design. Each subject gave written consent to participate in the study. Subjects did not take alcohol or any other medication for at least 10 d prior to and throughout the entire study. Subjects were randomly divided into three groups and each group received a single oral dose of 250 mg tetracycline (Tetrex, Bristol, Mexico) with 200 mL water (treatment A), 200 mL coffee containing 16 mL evaporated milk (treatment B), or 200 mL black tea containing 16 mL evaporated milk (treatment C) according to the day of the study. To ensure adequate hydration, each subject ingested 200 mL water 2 h prior administration and subsequently 100 mL water were given at 1, 2, 3, and 4 h after dosing. Every subject fasted overnight prior to the experiment and food was withheld for 4 h after dosing, then a standard lunch, free of dairy products, was ingested by all subjects.

Blank urine samples were obtained prior to dosing. Quantitative urine collections were obtained during each of the following time intervals: 0–1, 1–2, 2–3, 3–4, 4–6, 6–8, 8–12, 12–24, 24–36, 36–48, and 48–60 h. Two 10 mL aliquots of each sample were frozen at $-20\,^{\circ}C$ until the time of assay. At least 7 d elapsed between each trial.

The chromatographic method of Hermansson[4] was used to assay tetracycline in urine. Samples were diluted with *o*-phosphoric acid 0·1 M, and injected directly to the chromatographic system using a μBondapak-C18 column and phosphate buffer added with 20% acetonitrile V/V as mobile phase at $0{\cdot}8\,mL\,min^{-1}$ flow rate. All samples were monitored spectrophotometrically at 359 nm. A linear relationship was observed in the range of $0{\cdot}5–10\,\mu g\,mL^{-1}$. The maximum intra-day assay coefficient of variation was 5·39% at $0{\cdot}5\,\mu g\,mL^{-1}$. It was found that samples remained stable for at least 4 weeks when stored at $-20\,^{\circ}C$.

STATISTICAL ANALYSIS

The analysis of variance for complete crossover design was used to determine whether or not there were differences in the bioavailability among treatments. The cumulative amount of tetracycline excreted at each time and apparent elimination rate constant were statistically analysed.

SPECIATION ANALYSIS

Metal ions in food or biological fluids exist, either as protein bound or as low-molecular-weight complexes. The nature and relative concentrations of these complexes (speciation) are of considerable interest. Current analytical methods

are incapable of measuring concentrations of low-molecular-weight complexes in biological fluids due to the multicomponent nature of the latter and the extremely low concentrations of the former. For these reasons, handling the problem with programs to calculate the desired concentrations is unavoidable. Because tetracycline absorption is controlled by a passive process, the availability of the neutral species should be responsible for the total amount of tetracycline absorbed; therefore, in order to account for the available tetracycline in each of the several stages involved in the gastrointestinal absorption of the drug, computer simulation of the Ca–tetracycline system was performed with the program COMICS.[5] The values for ionization and complexation constants of calcium and tetracycline as obtained by Brion *et al.*[6] were used. The input concentrations used in the simulation ranged from zero to ten (total calcium–total tetracycline ratio), using a concentration of 250 mg tetracycline in 200 mL solution.

RESULTS AND DISCUSSION

The tetracycline capsules used in this study are the most used in Mexico. The product met all USP XXIII specifications including the dissolution test. Figure 1 shows the mean cumulative amount of tetracycline excreted in urine after the

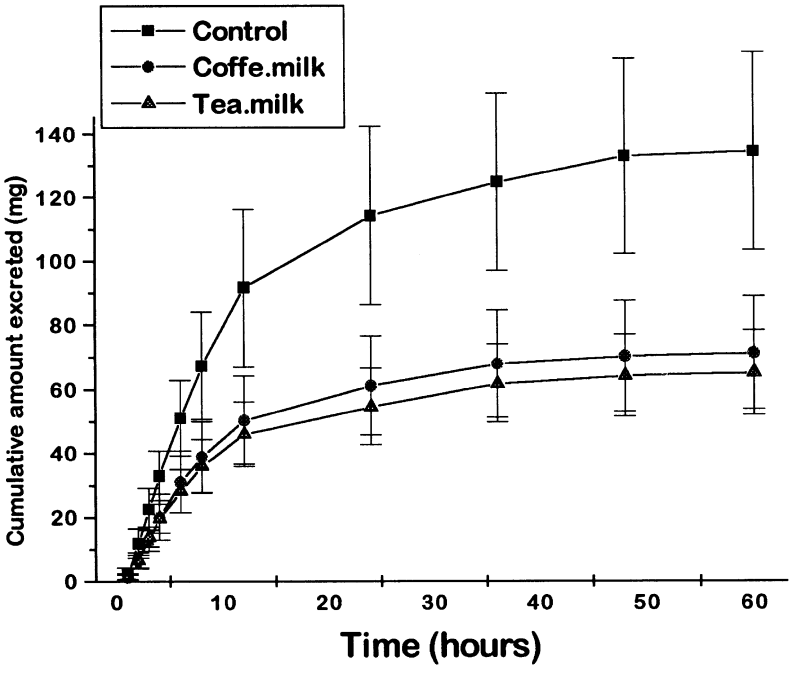

Figure 1. The mean cumulative amount of tetracycline excreted in urine for each treatment

Table 1. Bioavailability parameters (average and standard deviation) of tetracycline from twelve healthy volunteers following a 250 mg oral dose

Bioavailability parameters	Treatment A	Treatment B	Treatment C	Significance level
Cumulative amount excreted in 60 h (mg)	134·5 (31·0)	71·4 (17·5)	65·3 (13·1)	$p<0·05$
Elimination rate constant (h^{-1})	0·079 (0·014)	0·075 (0·013)	0·071 (0·009)	NS
Peak excretion rate (mg)	11·52 (2·25)	8·98 (2·78)	7·49 (1·19)	$p<0·05$
Peak excretion time (h)	4 (1·5)	4 (1·5)	3 (0·60)	NS

three treatments. It can be seen that the cumulative amount of tetracycline excreted was lower when administered with coffee or tea with milk. Significant differences were found in the cumulative amounts excreted at 6, 8, 12, 24, 36, 48 and 60 h between the fasting state ($p<0·05$) and the other treatments. Data from Table 1 show that bioavailability was reduced by about 40–50% after the milk treatments; also, statistical differences were found in the peak excretion rate; however, no statistical differences were found in the elimination rate constant.

It is well known that absorption of tetracycline is severely impaired when administered with milk and dairy products,[7] with antacids containing aluminum hydroxyide gels,[8] and with iron[9] or copper salts. Also when calcium is present as free ion or as slightly bonded complex in the diet, reduction of the bioavailability of tetracycline is observed.[10] The presence of citric and ascorbic acid which show higher affinity for calcium, as in the case of orange juice,[11] avoid the influence of calcium on tetracycline bioavailability. Our results obtained from speciation analysis showed that a very small amount, such as 37·5 mg of calcium (contained in the 16 mL milk), decreased substantially the amount of species to be absorbed. It can be argued that lactic acid might complex the calcium present; however, this compound is a very ineffective calcium complexing agent compared to tetracycline. On the other hand, when tea was administered, even greater reduction in the tetracycline bioavailability was observed. Differences between the two treatments (tea against coffee) can be understood considering the fact that tea leaves are exposed to aluminum compounds in the process of drying. In this way, there is another complexing agent contending against the bioavailable forms of tetracycline.

As could be observed, according to these results, even the presence of extremely small amounts of calcium will act upon the bioavailable tetracycline. It becomes quite clearly apparent that the presence of any metal ion should be carefully controlled to avoid decreasing the available tetracycline.

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