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Note

Effect of an antidiarrhoeal mixture on the bioavailability of tetracycline

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Summary

The influence of an antidiarrhoeal mixture, Kaopectate®, on the bioavailability of tetracycline was studied in healthy human subjects. Employing a cross-over design, four subjects in the fasting state were given 250 mg tetracycline HCl as a solution with and without 30 ml Kaopectate®. A drastic and significant decrease (about 50%) in drug absorption resulted. When the antidiarrhoeal mixture was coadministered with a 250 mg capsule, employing a latin-square design with seven subjects, a similar decrease in absorption was observed. The administration of Kaopectate® 2 h before and 2 h after the drug resulted in about 20% decrease in drug absorption.

Concomitant administration of antidiarrhoeals with tetracyclines could lead to a potentially significant drug interaction where relatively high serum antibiotic concentrations are needed. Through many in vitro studies, antidiarrhoeal preparations and/or their ingredients have been shown to possess potential interacting capacity for a large number of drugs, (Bucci et al., 1981; McElnay et al., 1982). It has also been reported that these interactions can often lead to a significant decrease in drug absorption and bioavailability (D'Arcy and McElnay, 1987; Moustafa et al., 1987; Al-Shora et al., 1988).

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Although the effect of concomitantly administered drugs on the absorption of tetracycline has been the subject of considerable research, limited reports are presently available about potential interactions of tetracycline with antidiarrhoeals and other adsorbents (Gouda, 1976; Neuvonen, 1976; Albert et al., 1979; Gugler and Allgayer, 1990; Tatro, 1990).

This study represents a detailed report of previous brief preliminary results on the effect of an antidiarrhoeal mixture, kaolin-pectin (Kaopectate®) on the bioavailability of tetracycline.

All studies were performed under medical supervision. Four healthy adult informed male volunteers participated in the first phase of the study. Two trials were made on each subject in a randomized cross-over fashion. In the first trial each subject received the contents of a 250 mg

tetracycline HCl capsule dissolved in 100 ml of water, and 30 ml of kaopectate plus 70 ml of water were ingested along with the drug. Eight healthy informed volunteers started the second phase of the study; they received the four following treatments (over a period of 4 weeks):

(A) 250 mg tetracycline HCl capsule with 100 ml of water + 100 ml of water;

(B) 250 mg tetracycline HCl capsule and 100 ml of water along with 30 ml of Kaopectate® at the same time + 70 ml of water;

(C) 30 ml of Kaopectate® + 70 ml of water administered 2 h after the capsule which was given with 100 ml of water;

(D) 30 ml of Kaopectate® + 70 ml of water administered 2 h before the capsule which was given with 100 ml of water.

In both studies, all subjects were fasted overnight and no food was permitted until at least 3 h after administration. The subjects were instructed to drink about 100 ml of water every hour in order to stimulate urine output during the first 8 h. Urine was collected immediately prior to, and every hour for 8 h after, the ingestion of the antibiotic, then as necessary for 48 h. The pH and the volumes of the urine samples were measured and the samples were frozen immediately until the time of assay. The unchanged tetracycline in the urine was determined according to a previously described spectrofluorometric method (Kohn, 1961)

Previous reports (Chulski et al., 1963) have established that the urinary excretion rates of tetracycline are directly proportional to serum concentrations. These urinary excretion parameters were, therefore, used to assess the bioavailability of tetracycline when given with and without the antidiarrhoeal mixture, Kaopectate®.

In the first phase, the drug was administered as a solution to eliminate any possible effect due formulation variability on the interaction. The coadministration of the antidiarrhoeal mixture with tetracycline solution leads to a drastic and significant decrease (t-test, $p < 0.01$); about 50%, in drug absorption.

The data for total amount of tetracycline excreted in 48 h for seven subjects who received an intact 250 mg capsule of tetracycline HCl concurrently with and without 30 ml of Kaopectate®, 2 h before and 2 h after the tetracycline capsule are listed in Table 1. A significant (ANOVA, $p < 0.001$) decrease in the absorption of tetracycline was noted. When the drugs were taken concurrently, a 50% decrease in the absorption occurred. When the two drugs were taken 2 h apart, a smaller (20%) but significant ($p < 0.01$) decrease in absorption was still observed.

The mean urinary excretion rate of tetracy-

TABLE 1

Total amount of tetracycline excreted in 48 h [a]

Subject	Sex	Age	Weight	Total excreted (mg) [b]			
				A	B	C	D
1	M	24	135	166.7	71.3	130.9	157.7
2	M	23	150	183.6	96.7	164.6	167.1
3	M	38	145	171.0	101.0	166.7	142.4
4	M	27	210	171.1	99.6	154.9	150.0
5	M	26	140	196.8	77.3	147.5	163.5
6	F	27	115	145.8	76.1	93.1	104.7
7	M	31	138	192.5	67.3	165.3	129.0
8 [c]	F	23	115				
Mean				176.2	84.2	146.3	144.9
RSD				10	17	18	15

[a] Following oral administration of a 250 mg capsule.

[b] A, control; B, concurrent Kaopectate® (30 ml); C, kaopectate® 2 h after tetracycline; D, kaopectate® 2 h before tetracycline.

[c] This subject dropped out after the first day of the study, possibly due to gastrointestinal side effects.

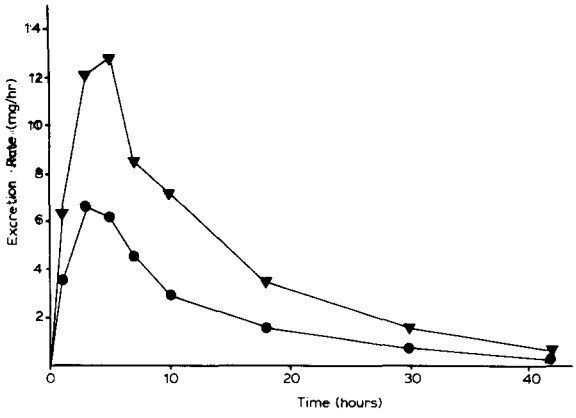

Fig. 1. Mean urinary excretion rate of tetracycline after oral administration of a 250 mg tetracycline HCl capsule (average of seven subjects). (▲) Control; (●) Concurrent Kaopectate® (30 ml).

cline after oral administration of the capsules with and without the antidiarrhoeal is shown in Fig. 1. A drastic decrease in tetracycline bioavailability is observed. The overall first-order elimination rate constant of the drug and thus the biological half-life, as determined from the terminal part of the urinary excretion curve, were found to be essentially the same in the presence and absence of Kaopectate® (9.9 h for control, 9.8 h for experiment). This value is within the range of the biological half-life reported for tetracycline.

The in vivo bioavailability studies correlate well with in vitro adsorption and desorption investigations at simulated gastric and intestinal pH values. A significant amount of tetracycline was adsorbed (32–37 mg/g), of which 75% remained after desorption at simulated intestinal pH. It is worth noting that the 30 ml dose of the antidiarrhoeal mixture is actually half the minimum recommended dose. A higher dose is expected to result in a more drastic decrease in bioavailability.

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