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Decreased bioavailability of ampicillin and amoxycillin in presence of kaolin

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Substantial evidence is available to show that the absorption characteristics and ultimately the therapeutic performance of drugs can be significantly altered by the presence of adsorbents (Stockley, 1981). Kaolin, when ingested alone or with pectin, reduced the bioavailability of lincomycin (McCall et al., 1967; McGehee et al., 1968), clindamycin (Albert et al., 1978b), digoxin (Brown and Juhl, 1976; Albert et al., 1978a) and oral hypoglcyaemic agents (Said and Al-Shora, 1980). One report showed that the concomitant administration of a kaolin–pectin mixture with ampicillin had no significant effect on its bioavailability (Gouda, 1976). Many OTC antidiarrhoeal products contain kaolin and thus its co-administration with drugs is not uncommon. In bacterial diarrhoea and food poisoning, kaolin is sometimes prescribed with antibiotics including ampicillin. A commerical product containing 1.88% ampicillin, 25% kaolin and 5% sulphadimidine has been on the market [1].

The objective of the present study has been to examine the influence of kaolin on the bioavailability of the two structurally-related antibiotics, ampicillin and amoxycillin, when both the drug and adsorbent were ingested concomitantly and when their time of administration was separated by 2 h.

Ampicillin anhydrate and amoxycillin trihydrate powders (B.P. grade) were used and white light kaolin (DAB7) was supplied by E. Merck, Darmstadt.

Bioavailability testing was carried out using 6 healthy volunteers (3 males and 3 females), their ages ranging from 24 to 40 years (average 31) and body weights from 62 to 82 kg (average 71). The volunteers were instructed not to take any drug a week before and during the trials. Each subject fasted for at least 8 h prior to and 3 h after dosing. Each subject ingested a single dose (500 mg of either ampicillin or amoxycillin) with or without kaolin according to the following treatments.

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[1] Known as Penbritin KS (Beecham Research, U.K.)

Treatment A: the drug (500 mg) in 200 ml of water (control).
Treatment B: the drug in 200 ml of water and, 2 h later 4 g kaolin in 200 ml of water.
Treatment C: the drug and kaolin (4 g) in 200 ml of water at the same time.
Treatment D: kaolin (4 g) in 200 ml of water and 2 h later the drug in 200 ml of water.

A week elapsed between successive treatments. Urine was collected at the time of administration of the drug (0 time), ensuring complete emptying of the bladder, and then hourly for 8 h post-administration. In order to effect diuresis, 200 ml of water were ingested after each urine collection.

To study the effect of administration of two successive doses of both the drug and kaolin on the bioavailability, the following procedure was followed.

Treatment A *. At zero time, the first dose (500 mg) of either drug was ingested in 200 ml of water. After 4 h, the second dose of the drug (500 mg) was ingested. Urine samples were collected hourly for 10 h starting from zero time.

Treatment D *. Kaolin (4 g) was ingested with 200 ml of water and 2 h later, the first dose (500 mg) of either drug was taken in 200 ml of water (zero hour). After 4 h from the first adsorbent dose, kaolin (4 g) was again ingested in 200 ml of water and 2 h later the second dose (500 mg) of either drug was ingested in 200 ml of water. Urine samples were collected hourly for 10 h starting from the time of administration of the first dose of the antibiotic.

Urine samples were frozen immediately after collection and assayed within 24 h of sampling. The amounts of either drug in the urine samples were determined chemically according to the method of Smith et al. (1967). For ampicillin, a good correlation between the chemical and microbiological methods of assay was confirmed by Ali et al. (1981).

The urinary excretion data obtained following Treatments A, B, C and D showed that values for amoxycillin were approximately double those for ampicillin. Contrary to Treatments B and C, the ingestion of kaolin 2 h prior to either drug (Treatment D) produced statistically significant reduction ($P < 0.001$) in both the 8 h cumulative amounts excreted and the peak excretion rates. The results of Student's *t*-tests are shown in Table 1.

All the volunteers showed reduced drug bioavailability following Treatment D. Based on the 8-h cumulative amounts excreted, the relative bioavailability for ampicillin ranged from 51.2 to 76.3 (mean $\pm$ S.E., 63.2 ± 3.66) and for amoxycillin 63.6 to 80.6 (74.5 ± 3.10). Analysis of variance, based on the 8-h cumulative amounts excreted, showed no statistically significant difference between the three Treatments A, B and C ($P = 0.01$). However, when Treatment D was included in the analysis, a statistically significant difference ($P < 0.01$) between the treatments was found. Inter-subject variability was not statistically significant following the 4 treatments with ampicillin but with amoxycillin a significant difference ($P < 0.05$) was found.

Table 2 shows the urinary excretion data and the calculated pharmacokinetic parameters of ampicillin and amoxycillin following Treatments A, B, C and D. The elimination rate constants (K_{el}) did not significantly differ following the 4 treatments. Also, the calculated values are in good agreement with those previously

TABLE 1

STUDENT'S *t*-TEST APPLIED TO EXCRETION DATA AFTER ORAL ADMINISTRATION OF 500 mg AMPICILLIN OR AMOXYCILLIN, FOLLOWING TREATMENTS A, B, C AND D (n = 6)

Data analyzed	Treatments [a]	*t*-values		Significance	
		Ampicillin	Amoxycillin	Ampicillin	Amoxycillin
Peak excretion rate ($mg \cdot h^{-1}$)	A,B	1.11	0.997	N.S. [b]	N.S.
	A,C	2.25	0.938	N.S.	N.S.
	A,D	9.29	9.920	S [c]	S [c]
Cumulative 8-h amounts excreted (mg)	A,B	0.49	0.810	N.S.	N.S.
	A,C	2.81	1.030	S [d]	N.S.
	A,D	9.43	7.820	S [c]	S [c]

[a] For key to Treatments A–D, see text.
[b] Not significant.
[c] Significant ($P < 0.001$).
[d] Significant ($P < 0.05$).

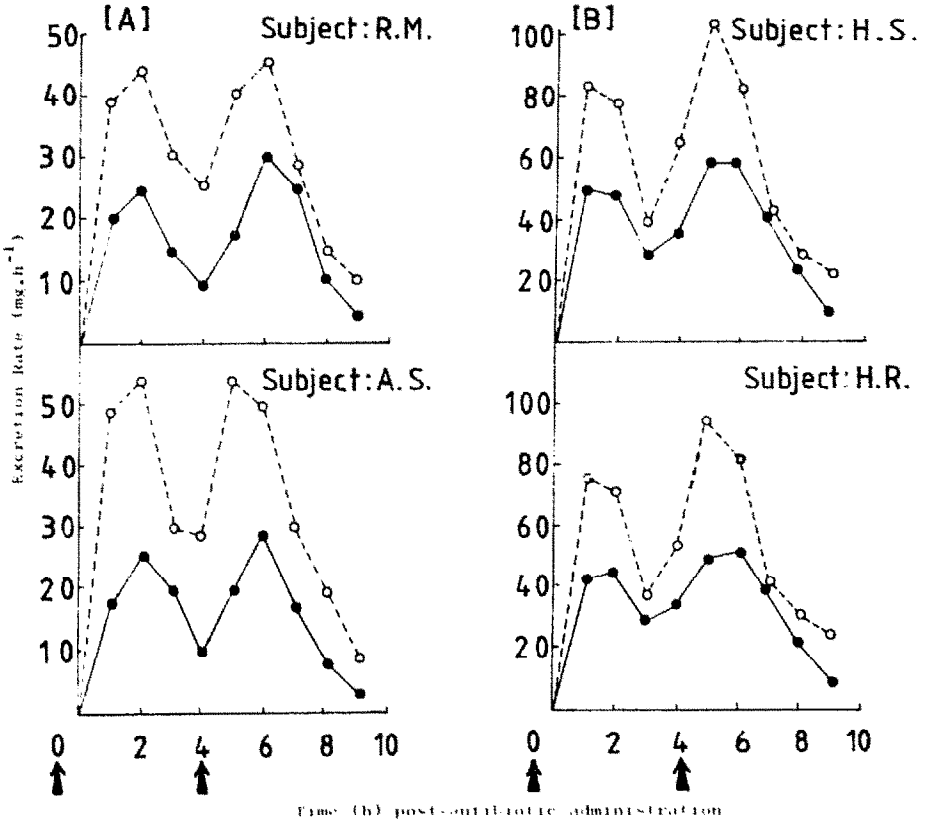

Fig. 1. Urinary excretion rates of (A) ampicillin and (B) amoxycillin following the administration of two successive doses (2×500 mg) of either drug 4 h apart (○------○) Treatment A *; or (●———●) Treatment D *. (Arrows indicate time of antibiotic administration, kaolin was administered 2 h before the antibiotic.)

TABLE 2

MEAN VALUES OF CUMULATIVE AMOUNT EXCRETED (C.A.E.), PERCENT DOSE EXCRETED, PEAK EXCRETION RATE (P.E.R.), PEAK EXCRETION TIME (P.E.T.), ELIMINATION RATE CONSTANT (K_{el}), ELIMINATION HALF-LIFE ($t_{1/2el}$) AND ABSORPTION RATE CONSTANT (K_a) FOR AMPICILLIN AND AMOXYCILLIN FOLLOWING TREATMENTS A, B, C AND D (n = 6)

Parameter	Ampicillin				Amoxycillin			
	A	B	C	D	A	B	C	D
C.A.E. (mg) [a]	153.5	155.9	140.5	96.8	273.4	278.3	281.5	203.4
	(3.4) [b]	(4.9)	(3.8)	(5.4)	(6.5)	(4.1)	(10.0)	(9.6)
Dose excreted (%) [c]	30.7	30.9	28.2	19.4	54.7	55.7	56.3	40.7
P.E.R. ($mg \cdot h^{-1}$)	41.8	41.7	39.3	27.8	81.4	80.9	77.4	57.0
	(1.22)	(0.88)	(0.90)	(1.53)	(1.00)	(1.40)	(2.00)	(3.00)
P.E.T. (h)	2.0	2.0	2.0	2.0	1.16	1.0	1.5	1.5
K_{el} (h^{-1})	0.57	0.53	0.56	0.59	0.61	0.66	0.56	0.61
	(0.05)	(0.02)	(0.04)	(0.06)	(0.03)	(0.02)	(0.04)	(0.01)
$t_{1/2el}$ (h)	1.22	1.31	1.24	1.18	1.14	1.05	1.24	1.14
K_a (h^{-1})	0.73	0.70	0.76	0.84	0.78	0.82	0.78	0.80

[a] After 8 h.

[b] Values in parenthesis are ± S.E.

[c] Based on a dose of 500 mg.

reported (Welling et al., 1977; Lee et al., 1979) hence suggesting that the interactions of kaolin with both drugs influenced only absorption and not disposition.

Fig. 1 shows the influence of kaolin (Treatment D *) on the excretion rates of ampicillin and amoxcillin ingested as two successive doses (2 × 500 mg) after the adsorbent. Similar reduction in the excretion rates, to those occurred with the single dosing, was found. The extent in reduction was similar after the first and second doses.

Calculation of the pharmacokinetic parameters obtained after the two successive dosings showed no significant differences following Treatments A * or D *.

To test whether the observed reduction in bioavailability was due to adsorption of the drugs by kaolin, the possible in vitro uptake was examined during dissolution testing of capsules containing either ampicillin or amoxycillin (Khalil et al., 1984). The results obtained suggest that the presence of 4 g kaolin in the dissolution medium had no significant effect on the in vitro availability of the drugs. Almost identical dissolution rate plots were obtained with and without kaolin in the medium. If in vivo adsorption had taken place, Treatment C (concurrent administration of the drug and kaolin) would have resulted in a reduction in the rate and/or extent of absorption. This was the case for kaolin–pectin interactions with lincomycin (Wagner, 1966) and digoxin (Brown and Juhl, 1976; Albert et al., 1978a). A suggested explanation for the observed reduction in the rate and extent of absorption of ampicillin and amoxycillin in the presence of kaolin following Treatment D is based on possible coating of gastric mucosa by the adsorbent. The ability of some antacid preparations to coat gastric mucosa has been reported by a number of authors (see Ihamäki, 1979 and refs. cited). It is probable that gastric coating by kaolin resulted in a reduction in the fraction of dose absorbed due to kaolin acting as a physical barrier to absorption.

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