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The effect of Sudanese food and chloroquine on the bioavailability of ampicillin from bacampicillin tablets

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Summary

The effect of Sudanese food and chloroquine on the bioavailability of ampicillin from bacampicillin was investigated. The bioavailability of ampicillin was determined using the urinary excretion method. The urinary levels of ampicillin were measured chemically. Bacampicillin capsules were administered: (i) under different dietary conditions; and (ii) on an empty stomach together with chloroquine phosphate tablets. Unlike the case of ampicillin capsules, neither food nor chloroquine affected the bioavailability of ampicillin from bacampicillin capsules. The difference between ampicillin and bacampicillin capsules with respect to the effect of food and chloroquine on ampicillin bioavailability is discussed.

Introduction

Bacampicillin, a pro-drug of ampicillin, has been recently introduced in Sudan. The drug is hydrolyzed in vivo to ampicillin (Rozencweig et al., 1976). It was claimed that bacampicillin was almost completely absorbed upon oral administration (Magni et al., 1976, 1978). It was also reported that while over 70% of a dose of bacampicillin could eventually be recovered from urine, only about 40% could be recovered following an oral dose of ampicillin (Magni et al., 1978). Magni and his associates reported that the absorption of bacampicillin was not significantly affected by food.

We have previously shown that the absorption of ampicillin, from commercially available capsules, was greatly reduced when the drug was taken with Sudanese food (Ali and Farouk, 1980). In that report we attributed the reduction in the absorption of ampicillin to the enhanced gastrointestinal motility produced by the high fibre-containing Sudanese food. The absorption of ampicillin was also reduced by the

concurrent oral administration of chloroquine with ampicillin (Ali, 1981; and unpublished data). The chloroquine-induced hurrying effect on the gastrointestinal tract and slowing of the gastric emptying rate were suggested to be the reasons for the reduction in ampicillin absorption.

This present paper reports investigations on the effect of Sudanese food and chloroquine on the bioavailability of ampicillin from commercially available bacampicillin hydrochloride tablets.

Materials and methods

Materials

Ampicillin powder (anhydrous), bacampicillin hydrochloride tablets (Penglobe; Batch FF 58; 400 mg per tablet ≡ 278 mg ampicillin) and chlorquine phosphate tablets (Malvax; Batch 060110; 250 mg per tablet ≡ 150 mg chloroquine base) were kindly supplied by Arab Pharmaceuticals, Sult, Jordan; Astra, Sodertalje, Sweden; and Sudanese Chemicals, Khartoum North, Sudan, respectively. The meals given to the volunteers were similar to those described previously (Ali and Farouk, 1980).

Bioavailability studies

Five healthy male volunteers participated in the trials. Their average age (years) and body weight (kg) were 22 and 56, respectively. The volunteers were instructed not to take any drug a week before and during the trials. A wash-out period of 5 days was ensured. Single doses of 400 mg (one tablet) and 1000 mg (4 tablets) were used for bacampicillin hydrochloride and chloroquine phosphate, respectively. The bacampicillin hydrochloride tablets were taken as shown in Table 1. When chloroquine phosphate was used, the tablets were taken concurrently with bacampicillin hydrochloride tablets after an overnight fast on an empty stomach and breakfast was allowed 3 h after taking the drugs. Complete emptying of the bladder was ensured before taking the drugs and also at each urine sample collection. The samples were analyzed on the same day of the trials. The amount of ampicillin in urine were determined spectrophotometrically (Ali and Farouk, 1980).

TABLE 1

Design of bacampicillin trials

Volunteer	Trial no.			
	1	2	3	4
I	A	B	C	D
II	B	C	D	A
III	C	D	A	B
IV	D	A	B	C
V	B	A	C	D

Trial code: A, drug taken with breakfast; B, drug taken 1.0 h after breakfast; C, drug taken 1.0 h before breakfast; and D, drug taken 2.0 h before breakfast.

Results and discussion

The bioavailability of ampicillin from bacampicillin hydrochloride tablets was studied using the urinary excretion method (Jusko and Lewis, 1973). The percentage dose excreted as ampicillin was used to describe the extent of bioavailability while the maximum peak of excretion (mg/min) and the time taken to reach that peak (h) were used to describe the rate of bioavailability (Ritschel, 1976). The percentage dose excreted as ampicillin, the maximum peak of excretion and the time taken to reach that peak, obtained following the oral administration of bacampicillin hydrochloride tablets (i) under different dietary conditions and (ii) with chloroquine phosphate tablets, are shown in Tables 2, 3, 4 and 5.

Effect of food

Similar values were obtained for the percentage dose excreted as ampicillin in urine (PDEA; Table 2) when bacampicillin was administered at different times with respect to food intake for each subject as indicated by the mean values of PDEA. The means ranged between 59% and 70% (S.E. 1.581–3.027; see Table 2). There was no significant inter-subject variation as indicated by the mean values of PDEA for the different volunteers, under each dietary condition (Table 2). The mean values of PDEA under the 4 dietary conditions, for all the subjects, were almost similar. They ranged between 62.2 ± 3.040 and 68.2 ± 2.267 with an average value of 64.65 ± 1.281 (Table 2).

When the data for the maximum peak of excretion were analyzed (Table 3) a similar picture to that of the PDEA (Table 2) was obtained; i.e. there was no significant difference between the MPEA values when bacampicillin was administrated at different times with respect to food intake.

The above results indicate that the extent (≡ PDEA) and rate (≡ MPEA − TTP) of ampicillin bioavailability from bacampicillin tablets were not affected by food; i.e. the absorption of bacampicillin was independent of food in agreement with previous findings (Magni et al., 1976). However, unlike bacampicillin, ampicillin

TABLE 2

Percentage dose excreted as ampicillin (PDEA) in urine over 6 h after oral administration of bacampicillin hydrochloride tablets (400 mg≡278 mg ampicillin) to male healthy volunteers under different dietary conditions

Volunteer	PDEA under condition				PDEA as $\bar{x}$ + S.E.
	A	B	C	D	
I	62	66	55	53	59 ± 3.027
II	70	63	60	66	65 ± 2.136
III	69	72	66	65	68 ± 1.581
IV	63	75	72	72	70 ± 2.598
V	59	65	58	62	61 ± 1.581
PDEA as $\bar{x}$ ± S.E.	64.6 ± 2.11	68.2 ± 2.267	62.2 ± 3.040	63.6 ± 3.108	64.65 ± 1.281

TABLE 3

The maximum peak of excretion of ampicillin (MPEA; mg/min) and the time taken to reach that peak (TTP; h) after oral administration of bacampicillin hydrochloride tablets (400 mg ≡ 278 mg ampicillin) to male healthy volunteers under different dietary conditions

Volunteer	MPEA (TTP) under condition				MPEA as $\bar{x} \pm$ S.E.
	A	B	C	D	
I	0.812 (2.5)	1.240 (1.5)	1.114 (1.5)	1.140 (1.5)	1.077 ± 0.092
II	1.324 (1.5)	1.208 (1.5)	1.180 (0.5)	1.220 (0.5)	1.233 ± 0.031
III	1.354 (1.5)	1.791 (1.5)	1.502 (0.5)	1.219 (0.5)	1.466 ± 0.123
IV	1.191 (1.5)	1.736 (1.5)	1.966 (0.5)	1.395 (0.5)	1.572 ± 0.173
V	1.350 (0.5)	1.157 (1.5)	1.024 (0.5)	1.140 (0.5)	1.168 ± 0.67
MPEA as $\bar{x} \pm$ S.E.	1.206 ± 0.103	1.426 ± 0.138	1.357 ± 0.172	1.223 ± 0.046	1.303 ± 0.053

absorption was reduced when the drug was administered with food (Ali and Farouk, 1980). This difference between ampicillin and bacampicillin might be attributed to basic differences in the degree of lipophilicity and stability of the two drugs in the gastrointestinal tract. Bacampicillin is more lipophilic and more stable in the gastrointestinal tract than ampicillin (Magni et al., 1978) and hence bacampicillin is expected to be less degraded and so absorbed at a faster rate. Sudanese food, because of its high contents of fibrous matter, usually increases the gut movements (Ali and Farouk, 1980). Bacampicillin but not ampicillin was not influenced by such a food effect, most likely due to bacampicillin's high rate of absorption; i.e. because of its greater lipid solubility bacampicillin diffuses rapidly into the gastrointestinal membrane stucture. In contrast, ampicillin being less lipid-soluble needs to stay longer at the site of absorption before it is completely absorbed and hence the effect of food might be expected to be more pronounced in the case of ampicillin.

Generally, penicillins are known to be absorbed by active transport processes mainly from the duodenum (Bergan, 1978; Sjovall et al., 1978). However, the fact that bacampicillin was almost completely absorbed, and at a fast rate too, might suggest the involvement of simple diffusion processes from a large surface area, e.g. the small intestine, since bacampicillin and not ampicillin will be mostly in the non-ionized form (the free acid group is esterified) and also the simple diffusion processes are known to be responsible for the absorption of highly lipid-soluble drugs. It follows, therefore, that bacampicillin may also be absorbed from the small intestine. Moreover, the ester group in bacampicillin may also play a role in the active transport of the drug; e.g. the presence of such a group may increase the affinity of the drug molecules to an endogenous carrier in an active carrier-mediated transport mechanism.

Effect of chloroquine

The values for the percentage dose excreted as ampicillin in urine, PDEA (Table 4) and the maximum peak of excretion, MPEA (Table 5) obtained when bacampicillin was administered alone were comparable to those when chloroquine

TABLE 4

Percentage dose excreted as ampicillin (PDEA) in urine over 6 h after oral administration of bacampicillin hydrochloride tablets (400 mg≡278 mg ampicillin) to healthy male volunteers: B = alone and BC = with chloroquine phosphate tablets (4×250 mg)

Volunteer	PDEA	
	B	BC
I	49	33
II	56	56
III	67	60
IV	53	62
V	72	50

was administered together with bacampicillin. These results indicate that neither the extent nor the rate of ampicillin bioavailability from bacampicillin tablets was affected by chloroquine. The latter drug is known to produce gastrointestinal irritation in humans such as enhanced gut motility and diarrhoea (Rollo, 1975). In rats, chloroquine has been reported to retard the rate of gastric emptying (Varga, 1966). We have also found that the bioavailability of ampicillin from ampicillin capsules has been reduced upon concurrent administration of ampicillin with chloroquine (unpublished data). Hence, bacampicillin also differed from ampicillin in this respect. Factors such as high degree of lipophilicity, rapid absorption and the involvement of simple diffusion transport processes, in the case of bacampicillin, could be responsible for the observed difference between ampicillin and bacampicillin in a manner similar to that discussed under the effect of food.

Finally, it might be concluded that bacampicillin, unlike ampicillin, was neither affected by Sudanese food nor by chloroquine for the following reasons: (i) bacampicillin was more stable in the acidic environment of the gastrointestinal tract; and (ii) being highly lipid-soluble, bacampicillin was rapidly and completely absorbed and also mechanisms other than active transport processes might have been involved in absorption of the drug.

TABLE 5

The maximum peak of excretion of ampicillin (MPEA; mg/min) and the time taken to reach that peak (TTP; h) after oral administration of bacampicillin hydrochloride tablets (400 mg≡278 mg ampicillin) to healthy male volunteers: B = alone and BC = with chloroquine phosphate tablets (4×250 mg)

Volunteer	MPEA (TTP)	
	B	BC
I	1.05 (1.5)	0.53 (1.5)
II	1.18 (0.5)	1.41 (1.5)
III	1.32 (1.5)	1.10 (1.0)
IV	1.05 (0.5)	1.18 (1.5)
V	1.39 (0.5)	1.10 (1.5)

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