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THE EFFECT OF SUDANESE DIET ON THE BIOAVAILABILITY OF AMPICILLIN

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SUMMARY

The effect of time of a typical Sudanese diet on the bioavailability of orally administered ampicillin has been examined. Using the urinary excretion method the extent and rate of ampicillin bioavailability from commercially available capsules were determined. Different results were obtained, upon changing the time of ampicillin administration with respect to the food intake. Our results indicate that for maximum absorption of ampicillin the capsules should be taken at least two hours before food.

INTRODUCTION

Ampicillin is a semi-synthetic penicillin derived from the penicillin nucleus (6-aminopenicillanic acid).

The drug is included in a list of drugs whose preparations have differing bioavailabilities or are suspect in this respect (P.S.G.B., Pharmaceutical Journal).

Various reports describing the effect of food on the absorption of ampicillin have been published (Klein and Finland, 1963; Poole, 1968; Kundsen et al., 1961). The oral administration of ampicillin has been reported to be good even if taken with food (Bear et al., 1970). However, in another study evidence was given suggesting that the absorption of the drug might be significantly impaired if it was administered with meals but no mention of the composition of the food was made (Kucers and Bennet, 1972). The nature of the food is of vital importance in this respect, since different foods affect the gastrointestinal absorption of drugs differently (Crounse, 1961; Bates et al., 1966, Moffatt, 1978).

The most popular Sudanese food, which can be considered as a typical meal, is rich in bran (wheat or sorghum) and fibrous substances. Such diets usually shorten the residence time and produce large quantities of faeces (high residue diets). Bran is known to accelerate gastric emptying and might also increase the gastrointestinal motility (Moffatt, 1978). Such an effect may result in shortening of the time for absorption and consequently the amount of drug reaching the general circulation.

TABLE 1

INSTRUCTIONS FOR THE ADMINISTRATION OF ORAL AMPICILLIN PREPARATIONS OBTAINED FROM DIFFFERENT MANUFACTURERS' PACKAGING INSERTS

Brand	Instructions
Ampicillin (Sands)	Oral doses are preferably given 1 hour before meals
Ampilag	It is recommended to take the oral forms of Ampilag half an hour before meals so as to obtain the maximum blood concentrations
Cymbi	The oral administration of Cymbi may be effected independently of meals
Omnipen	Instructions for food intake were not given
Penbritin	All oral preparations of Penbritin should be taken 1/2–1 hour before meals
Pentrexyl	To ensure maximum absorption Pentrexyl should be administered orally to patients at least one hour before or after meals
Ultracillin	To insure maximum absorption Ultracillin should be administered orally at least one hour before or after meals

Certain directions for the oral administration of ampicillin have been recommended by the manufacturers. The statements made by the various manufacturers with respect to the time of diets are not in agreement (Table 1). This non-uniformity of instructions may lead to confusion for both the prescribing doctor and the patient.

We now report the effect of time of a typical Sudanese meal (gorasa and kisra) on the bioavailability of ampicillin from commercially available capsules.

MATERIALS AND METHODS

The ampicillin capsules (Omnipen, 500 mg; lot no. 1781471) and powder were kindly supplied by Wyeth Laboratories, Philadelphia, Pa., U.S.A. The meals were purchased from the local market. The meals were gorasa (made from wheat flour, 11–12% bran) taken with meat gravity as breakfast and kisra (made from sorghum (Dura) flour, 11–13% bran) taken with cooked Lady's Fingers (dried, locally called Waika) as lunch. The brain contents of these meals were determined by the Food Research Centre, Shambat, Khartoum.

Bioavailability studies

The studies were carried out on 4 healthy male volunteers (A, B, C and D; average age and body weight were 26 years and 67 kg respectively). The volunteers did not take any drug a week before and during the trials. A period of 7 days was allowed between each trial. The dose of ampicillin was one gram (2 X 500 mg, Omnipen capsules) taken with 200 ml of water after an overnight fast. The dose of the drug was taken on 4 different occasions as follows: (i) one hour after breakfast; (ii) together with breakfast; (iii) one hour before breakfast; and (iv) 3 h before breakfast. Complete emptying of the bladder, just before taking the drug, was ensured.

Complete urine collections were made hourly for 9 hours post-drug administration. The volunteers were advised to drink water (200 ml) after each urine collection to effect diuresis. The volume of each urine sample was recorded and the samples were kept at

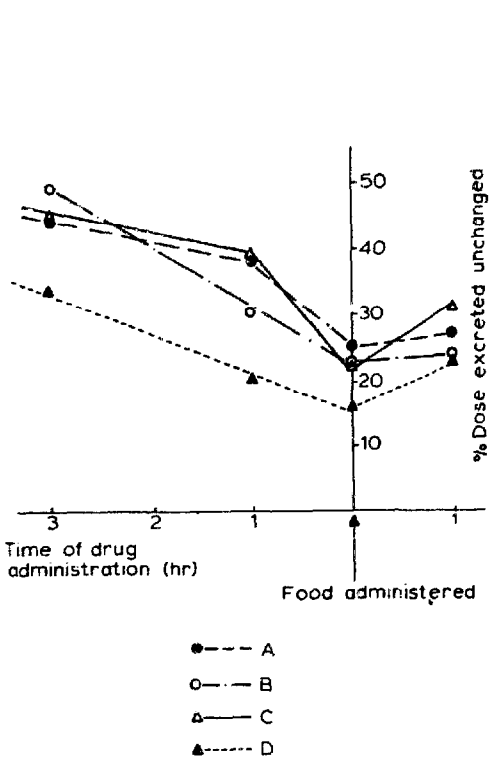
4°C. The urine was analyzed 24 h after the trial. The amount of drug in urine was determined chemically (Smith et al., 1967).

RESULTS AND DISCUSSION

The amount of ampicillin in urine was determined chemically. In agreement with previous findings (Smith et al., 1967; Angelucci and Baldieri, 1971) the method gave reproducible results (Table 2) and therefore proved satisfactory.

The bioavailability of ampicillin was studied using the urinary excretion method. The prerequisites for a valid study were fulfilled, i.e. total emptying of the bladder at each collection, total urine collection until all the drug was almost excreted and frequent urine collection (see Methods). Jusko and Lewis (1973) have previously shown that the urinary excretion method was a satisfactory alternative to the blood method. The total amount of ampicillin excreted in urine over 9 h was used to described the extent of ampicillin's bioavailability (Ritschel, 1971).

The percentage doses of amplicillin excreted unchanged in urine after the administration of the drug at different times with respect to food intake, were 44, 38, 27 and 25 for



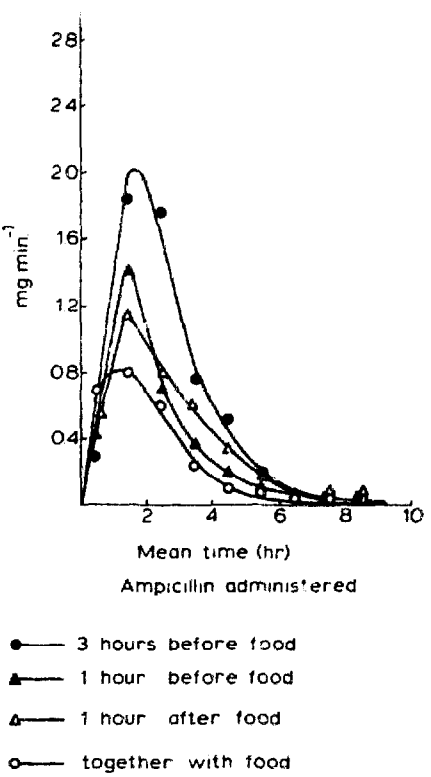


Fig. 1. Effect of time of diet on the urinary excretion of ampicillin after oral administration of ampicillin capsules (2 × 500 mg, Omnipen) to male volunteers (A, B, C and D).

Fig. 2. Effect of time of diet on the urinary excretion rate of ampicillin after oral administration of ampicillin capsules (2 × 500 mg, Omnipen) to a male volunteer (C).

TABLE 2

CALIBRATION CURVES OF AMPICILLIN PREPARED AT DIFFERENT OCCASIONS USING THE CHEMICAL METHOD

Concentration ($mg \cdot ml^{-1}$)	Absorbance								
	Exp. 1	2	3	4	5	6	7	8	S.D.
0.01	0.2757	0.2924	0.2840	0.2840	0.2924	0.3010	0.3098	0.3170	0.01306
0.02	0.5768	0.6383	0.6576	0.6383	0.6383	0.6778	0.6778	0.6737	0.03137
0.03	0.8861	1.0000	1.0000	1.0000	0.9208	1.0458	1.0458	1.0458	0.05607
0.04	1.2007	1.3188	1.3665	1.3468	1.3468	1.3979	1.4202	1.3979	0.06929
Calibration factor	0.0345	0.0316	0.0312	0.0316	0.0319	0.0300	0.0297	0.0296	0.0015
Correlation coefficient	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

* Population standard deviation.

volunteer A; 49, 30, 24 and 23 for volunteer B; 45, 39, 31 and 23 for volunteer C; 34, 20, 22 and 16 for volunteer D (Fig. 1). It could be observed that there was a progressive increase in the percentage dose excreted unchanged upon the administration of the drug together with food, one hour after food, one hour before food and 3 h before (Fig. 1). The maximum peak of excretion followed a similar pattern (Fig. 2). The maximum peak of excretion ($mg \cdot min^{-1}$) for subject D, when the drug was administered together with food, one hour after food, one hour before food and three hours before food, was 0.8, 1.2, 1.4 and 2.0 respectively (Fig. 2). The time to reach that peak was almost identical (1.5 h) for the 4 dietary times (Fig. 2).

The above results indicate that the extent of bioavailability of ampicillin (percentage dose excreted unchanged) depends mainly on the time of the drug administration with respect to the food intake. In addition, there was a drastic reduction in the maximum peak of excretion upon the administration of the drug together with food one hour after food. If one assumes that this peak will reflect the peak blood concentration, such a reduction will correspond to a similar reduction in the inhibitory concentration of ampicillin. If the maximum peak of excretion after the administration of ampicillin capsules 3 h before food ($2.0\ mg \cdot min^{-1}$; Fig. 2) is arbitrarily taken as 100%, a reduction of 60%, 50% and 40% took place when the drug was administered together with food, one hour after food and one hour before food respectively.

The observed differences in the extent of bioavailability and the maximum peak of excretion of ampicillin, when the drug was administered at different dietary times, could be attributed to the varying effect of food on the gastrointestinal tract. The type of food used in this study was known to enhance gastrointestinal motility (Moffatt, 1978) because of its high bran content. The net result of this effect will be a short drug residence time and consequently less absorption of the administered drug. Moreover, this effect will vary according to the time of the meals when the drug is administered. Consequently, one would expect maximum absorption of the drug if sufficient time is given for the drug absorption before such food is taken. Our results are therefore in good agreement with these findings.

The directions made by the various manufacturers of ampicillin capsules (Table 1), apart from being non-uniform, are not in agreement with our observations and also with those described in the Official Monographs (Martindale, 1977). The manufacturers directions, we believe, were based on bioavailability studies carried out in the manufacturers' laboratories. However, the composition of food used in the countries of manufacture is expected to be different from that in Sudan. The European diet consists mainly of a refined low-residue type of food in contrast to the high-residue Sudanese diet. Consequently, one would expect that the effect of such low-residue diet on the gastrointestinal tract (long residence time) will be different. Ampicillin will stay in the gastrointestinal tract longer when administered with a typical European diet and hence the drug will have more time for absorption and consequently more drug will be absorbed than when the drug is administered with a typical Sudanese diet. This may explain the observed difference between our findings and the manufacturers directions.

We think it is important, when preparing directions for the administration of ampicillin capsules, that the manufacturer should consider the nature and composition of diet of the countries where the drug is going to be used. Under the Sudanese dietary conditions,

based on our findings and considering the patients' convenience, we recommend that for maximum absorption of ampicillin the capsules should be administered at least two hours before meals. This may also apply to other countries where similar diets to the Sudanese one (African high-residue diet) are commonly ingested.

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