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COMPARATIVE BIOAVAILABILITY OF EIGHT BRANDS OF AMPICILLIN

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SUMMARY

Using a chemical method of assay, the bioavailability of ampicillin in healthy human volunteers has been examined. The urinary excretion method was used to determine the extent and rate of bioavailability following oral administration of 500 mg capsules produced by 8 different manufacturers. The brand Omnipen was used as the reference product. The results indicate that the different brands are not bioequivalent.

INTRODUCTION

Reports from various pharmaceutical organizations have described ampicillin as a drug with which oral preparations were likely to exhibit differences in bioavailability. Various workers have investigated the bioavailability of ampicillin from capsules produced by different manufacturers (MacLeod et al., 1972; Mayersohn and Endrenyi, 1973; Whyatt et al., 1976). However, the results of these studies were conflicting.

Ampicillin is extensively used in Sudan and various brands are commercially available: Ampicillin (Sands Pharmaceuticals), Ampicillin (ICN), Ampilag, Cymbi, Omnipen, Penbritin, Pentrexyl and Ultracillin. Different dosage forms are also available. Studies to compare the bioavailability of ampicillin from these brands have not been carried out previously in Sudan. The choice of the 500 mg strength for this study was based on the observation that the dissolution rates of commercial brands of this strength were more variable than those of the 250 mg strength.

The bioavailability of ampicillin from 500 mg capsules produced by different manufacturers is now reported.

MATERIALS AND METHODS

Materials

The following brands of ampicillin capsules (500 mg) were used:
Ampicillin (B.P.): Lot no. 446 Sands Pharmaceuticals, Toronto, Canada;
Ampicillin (B.P.): Batch no. 9632/1, ICN Pharmaceuticals, Lugano, Switzerland, ICN Arco;

Ampilag: Batch no. 8532, Lagap, S.A., Switzerland;
Cymbi: Batch no. 180101, Ampicillina, Dolorgiet, G.F.R.;
Omnipen: Lot no. 1771883, Wyeth Labs., Pa., U.S.A.;
Penbritin: Batch no. 1678, Beecham Pharmaceuticals, Juron, Singapore, under Licence from Beecham Research Lbs., England;
Pentrexyl: Lot no. MB 8011, Bristol Italiana (Sud.), SPA, Italy, under authority of Bristol Labs., U.S.A.;
Ultracillin: Forte, Batch no. 780306, Arab Pharmaceuticals, Sult, Jordan.

All the brands contain the trihydrate form of ampicillin except Omnipen, which contains the anhydrous form. The brands were coded as A, B, C, D, E, F and G, respectively.

Urinary excretion studies

Healthy male volunteers participated in the trials. Their average body weight (kg) and age (years) were 68 and 28, respectively. Due to difficulties in obtaining the volunteers for the whole period of the trials, it was not possible to compare all the brands on the same panel of volunteers. Each ampicillin brand was therefore separately compared to Omnipen on a number of subjects.

The conditions of the trials were as follows: the capsules (2 X 500 mg) were taken, after an overnight fast, on an empty stomach. A light breakfast was allowed 3 h after taking the drug. A period of 6 days was allowed between the trials for each volunteer. The volunteers were told not to take any drug during this period. Complete emptying of the bladder, just before taking the capsules and at each urine sample collection, was ensured. Urine samples were collected hourly for 8 h and kept at 4°C. The samples were analyzed 24 h after the trial and the amount of ampicillin was determined chemically (Smith et al., 1967).

RESULTS AND DISCUSSION

A previous report has shown that the chemical method of assay of ampicillin in urine was satisfactory with respect to sensitivity and reproducibility (Ali and Farouk, 1980). This method was therefore, adopted throughout the present study.

The bioavailability of ampicillin from the different brands was determined using the urinary excretion method (Jusko and Lewis, 1973).

The extent and rate of ampicillin bioavailability obtained after the oral administration of the brands, A, B, C, D, E, F and G, were compared to the corresponding values for Omnipen. The brand Omnipen (OM) was used as a reference product throughout this study. The choice of Omnipen as the reference product was based on previous findings that ampicillin was more bioavailable from Omnipen than from other brands (Khalil, Ali, Nagib and Farouk, unpublished data). The total amount of ampicillin excreted in the urine over 8 h (Table 1) was used to describe the extent of bioavailability. The maximum peak of excretion and the time taken to reach that peak (Table 3) were used to describe the rate of bioavailability (Ritschel, 1976).

The percentage dose excreted unchanged in the urine obtained following the oral administration of the ampicillin brands OM, A, B, C, D, E, F and G is shown in Table 1.

TABLE 1

PERCENTAGE DOSE EXCRETED UNCHANGED IN URINE AFTER ORAL ADMINISTRATION OF THE AMPICILLIN BRANDS (A, B, C, D, E, F AND G) TO HUMAN SUBJECTS

Volunteer no. *	% dose excreted unchanged						
	A	B	C	D	E	F	G
1	43 (50)	40 (44)	35 (50)	37 (50)	35 (44)	28 (40)	26 (40)
2	39 (41)	35 (49)	50 (55)	44 (50)	31 (49)	31 (43)	21 (43)
3	40 (51)	34 (37)	32 (40)	24 (33)	39 (45)	28 (41)	29 (41)
4	37 (37)	–	35 (41)	40 (46)	42 (50)	–	–
5	39 (41)	–	37 (43)	–	–	–	–

Omnipen (OM) was used as the reference product and its results are given in parentheses.
* Different panels of volunteers were used for the comparison of each brand with OM.

The results indicate that, when each of the brands was compared to Omnipen, (OM) no brand produced a percentage dose excreted unchanged in urine equal to or more than that for Omnipen, except on a single occasion (Brand A, volunteer 4, 37%). It may therefore be concluded that Omnipen offers the greatest extent of ampicillin bioavailability in agreement with our previous findings (Khalil, Ali, Nagib and Farouk, unpublished data). Excluding all other factors, these results may also indicate that the anhydrous form of ampicillin produces a greater extent of bioavailability than the trihydrate form since Omnipen is the only brand, among the 8 tested, containing the anhydrous form of ampicillin. However, previous reports on the bioavailability of ampicillin from the anhydrous and the trihydrate forms have been conflicting (Hill et al., 1975).

The extent of ampicillin bioavailability (percentage dose excreted unchanged, Table 1) could not be used directly to place the different brands in any order or sequence since the trials were not all conducted on the same panel of volunteers (see Methods). The ratio of the extent of bioavailability for each brand to that for the reference product,

TABLE 2

RATIO OF THE PERCENTAGE DOSE EXCRETED UNCHANGED IN URINE FOR EACH BRAND TO THAT OF OMNIPEN (OM)

Volunteer no.	% Ratio (brand/OM)						
	A	B	C	D	E	F	G
1	86	91	70	74	80	70	65
2	95	71	91	88	63	72	49
3	78	92	80	73	87	70	71
4	100	–	85	87	84	–	–
5	95	–	86	–	–	–	–
X	91	85	82	81	79	71	62

TABLE 3

THE MAXIMUM PEAK OF EXCRETION OF AMPICILLIN AND THE TIME TO REACH THAT PEAK AFTER ORAL ADMINISTRATION OF THE AMPICILLIN BRANDS (A, B, C, D, E, F AND G) TO HUMAN SUBJECTS. (THE CORRESPONDING DATA FOR THE REFERENCE PRODUCT (OM) ARE IN PARENTHESES)

Brand	Maximum peak of excretion (mg min^{-1}) for volunteer no.						Time to reach the peak (h) for volunteer no.					
	1	2	3	4	5	$\bar{X}$	1	2	3	4	5	$\bar{X}$
A	2.2 (2.0)	2.3 (1.9)	2.2 (3.2)	2.8 (2.4)	2.5 (2.5)	2.4 (2.4)	1.5 (2.0)	2.5 (2.5)	2.5 (2.5)	1.5 (1.5)	1.5 (1.5)	2.0 (2.0)
B	2.5 (2.6)	1.7 (2.9)	1.9 (2.4)	–	–	2.0 (2.5)	1.5 (1.5)	2.5 (2.5)	2.5 (1.5)	–	–	2.2 (1.8)
C	1.3 (2.2)	2.5 (3.7)	1.6 (2.0)	1.9 (2.2)	2.0 (2.4)	1.9 (2.5)	1.5 (1.5)	1.5 (1.5)	2.5 (3.5)	2.5 (1.5)	1.5 (1.5)	2.0 (2.0)
D	1.9 (2.1)	2.6 (3.2)	1.3 (1.9)	1.9 (2.2)	–	1.9 (2.4)	2.5 (2.0)	2.5 (2.0)	2.5 (2.5)	2.5 (2.5)	–	2.3 (2.4)
E	2.2 (2.6)	1.9 (2.9)	2.1 (2.6)	2.4 (2.2)	–	2.2 (2.6)	1.5 (1.5)	2.5 (2.5)	2.5 (2.5)	1.5 (1.5)	–	2.0 (2.0)
F	1.2 (2.0)	1.2 (2.2)	1.8 (2.4)	–	–	1.4 (2.2)	1.5 (2.5)	2.5 (1.5)	2.5 (1.5)	–	–	2.2 (1.8)
G	1.2 (2.0)	1.5 (2.2)	1.1 (2.4)	–	–	1.3 (2.2)	2.5 (2.5)	2.5 (2.5)	1.5 (1.5)	–	–	2.2 (1.8)

Omnipen, was therefore calculated (Table 2). On the basis of this ratio the following order of superiority could be established:

$$OM > A > B > C > D > E > F > G.$$

The maximum peak of excretion and the time taken to reach that peak for each brand (rate of bioavailability) is shown in Table 3. The brand Omnipen (OM) together with A produced the highest peaks ($\bar{X} = 2.4$ mg min^{-1}, Table 3). The time taken to reach the maximum peak of excretion was almost identical for the brands, A, B, C, D, E, F and G ($\bar{X} = 2.1$ h; Table 3). The corresponding value for the brand Omnipen was 1.7 h. Using the maximum peak of excretion and the time taken to reach that peak to describe the rate of bioavailability compared with that produced by Omnipen (OM), an order describing all the brands, may be drawn up as follows:

$$OM > A > E > B > C \equiv D > F > G.$$

The ranking of the different brands from their rate of bioavailability followed almost a similar pattern to that based on the extent of bioavailability. Using both parameters of bioavailability a general ranking may therefore be established as follows:

$$OM \text{ and } A > B, C, D, E > F \text{ and } G.$$

The observed differences, in the extent and rate of ampicillin bioavailability, between the various brands may be attributed to differences in formulation and manufacturing processes. However, one would expect such differences to be within reasonable limits, otherwise the therapeutic efficacy of the products would be questioned.

Emphasis should be given to the importance of bioavailability testing prior to product registration and marketing, especially if the preparations of the drug(s) in question are likely to produce differences in bioavailability. This is especially important in countries like Sudan, where all medicines are usually imported. One would also think that the time has now come for the official monographs to contain specific limits for the bioavailability of drugs whose existing preparations are shown to vary considerably in this respect.

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