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Bioequivalence studies on two brands of bacampicillin

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Summary

The bioavailability of bacampicillin, following oral administration of two commercially available products to humans, was examined. The extent and rate of bioavailability were determined using the urinary excretion method. Bacampicillin was excreted as ampicillin and the amounts of the latter were measured chemically. The brands, Bacampicin and Penglobe, were compared. The two brands were found to be bioequivalent.

Introduction

Bacampicillin is a newly introduced broad spectrum antibiotic. Chemically, it is the ethoxy-carbonyloxy-ethyl ester of ampicillin which upon hydrolysis in the body produces ampicillin. Therefore, bacampicillin (Rozencweig et al., 1976) is essentially a pro-drug of ampicillin.

Bacampicillin was reported to be more stable in highly acidic media (e.g. the stomach); i.e. more lipophilic and much better absorbed than ampicillin (Magni et al., 1976, 1978).

It was just recently that bacampicillin was introduced in Sudan and only as one brand, under the name Penglobe (Astra) it became commercially available. However, I was able to get another brand, called Bacampicin, from the local agent for Upjohn. The latter brand was not registered in Sudan and was, therefore, not available commercially.

In a previous paper, I have reported a comparative bioavailability study of 8 brands of ampicillin (Ali, 1980). The bioavailability of ampicillin from those brands was varying and almost no two brands were exactly bioequivalent.

With respect to bacampicillin, no report, to the best of my knowledge, on brand bioequivalence has been published previously. Accordingly, I decided to examine the bioavailability of bacampicillin from these two brands to see whether they were bioequivalent or not.

I now report a comparative bioavailability study on two brands of bacampicillin; namely Bacampicin (Upjohn) and Penglobe (Astra).

Materials and methods

Materials

Bacampicin tablets (400 mg; Lot EH 14), Penglobe tablets (400 mg; Batch FF 58) and ampicillin (anhydrous powder) (0.200A/79) were kindly supplied by the local agents for Upjohn, S.A.; Puurs-Belgium, Astra, Sodertalje, Sweden; and the Arab Pharmaceutical Manufacturing Co., (A.P.M.), Sult, Jordan respectively. Bacampicin and Penglobe were both available as the hydrochloride salts of bacampicillin. The meals were similar to those we have described previously (Ali and Farouk, 1980).

Bioavailability studies

Five healthy male volunteers (A, B, C, D and E) participated in the trials. Their ages and body weights were between 22 and 23 years and 48–57 kgs, respectively. They were carefully selected from fourth year students of Pharmacy. The tablets (400 mg; single dose $\equiv$ 278 mg ampicillin) were taken, after an overnight fast, on an empty stomach. Breakfast was allowed 2 h after taking the drug. A wash-out period of 5 days was ensured between the trials for each volunteer. At the start, 3 of the volunteers (A, B and C) took Bacampicin while the other two (D and E) took Penglobe and after the wash-out period this sequence was reversed. All other trial conditions and precautions as well as the analytical procedures were similar to those described previously (Ali, 1980).

Results and Discussion

The bioequivalence studies were based on measuring the amounts of ampicillin excreted in the urine since, immediately after absorption, bacampicillin was completely converted to ampicillin (Bodin et al., 1975).

The total amount of ampicillin excreted in the urine (expressed as a percentage of the equivalent dose, 278 mg, in 6 h) was used to describe the extent of bioavailability; while the maximum peak of excretion (mg/ml) and the time (h) taken to reach that peak were used to describe the rate of bioavailability (Ritschel, 1976).

The percentage dose excreted as ampicillin following the administration of bacampicillin and Penglobe tablets ranged between 51–76 and 49–73, respectively (Table 1). No significant amount of ampicillin could be detected in urine after 6 h. Magni and his co-workers (Magni et al., 1978) reported that over 70% of the dose of bacampicillin was recovered in urine (over 8 h). The maximum peak of excretion (mg/ml; $\bar{X} \pm$ S.E.) was 1.296 ± 0.05 for Bacampicin and 1.198 ± 0.06 for Penglobe (Table 1). The time (h) ($\bar{X} \pm$ S.E.) taken to reach the maximum peak of excretion was 0.9 ± 0.22 for both brands. The urinary excretion rate versus mean time curves for the two brands was quite similar (Fig. 1).

The above results indicated clearly that Bacampicin was almost identical to Penglobe and, furthermore, that ampicillin was biologically available, following the

TABLE I

THE PERCENTAGE DOSE EXCRETED AS AMPICILLIN IN URINE (PDE, OVER 6 h), MAXIMUM PEAK OF EXCRETION (MPE, mg/min) AND THE TIME TAKEN TO REACH THAT PEAK (TTP, h) FOLLOWING ORAL ADMINISTRATION OF BACAMPICIN AND PENGLOBE TABLETS (400 mg BACAMPICILLIN≡278 mg AMPICILLIN) TO VOLUNTEERS A, B, C, D AND E

Brand	A			B			C			D			E		
	PDE	MPE	TTP	PDE	MPE	TTP	PDE	MPE	TTP	PDE	MPE	TTP	PDE	MPE	TTP
Bacampicin	51	1.35	1.5	53	1.19	0.5	71	1.31	1.5	55	1.15	0.5	75	1.48	0.5
Penglobe	49	1.05	1.5	56	1.18	0.5	67	1.32	1.5	53	1.05	0.5	73	1.39	0.5

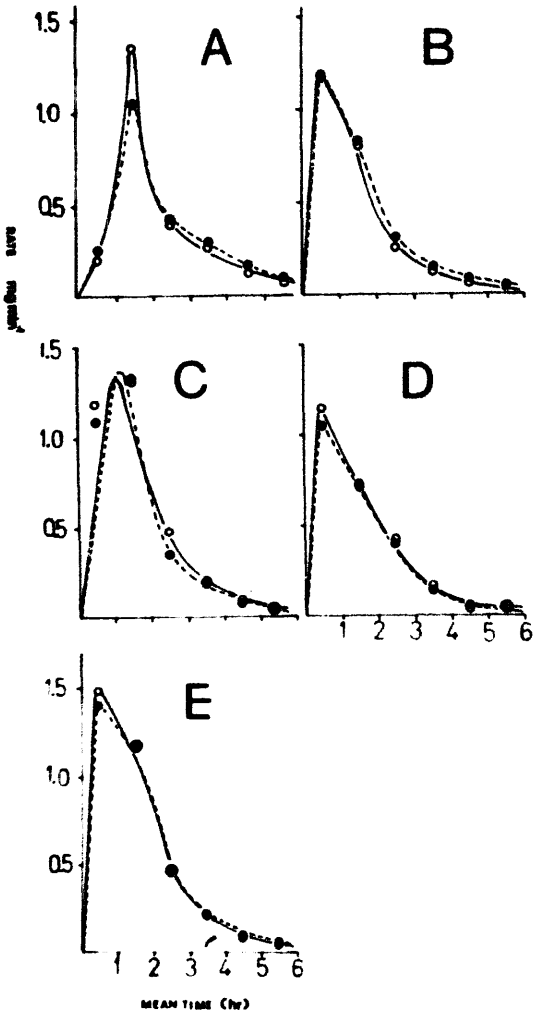

Fig. 1. Urinary excretion profile of ampicillin following oral administration of Bacampicin (O———O) and Penglobe (●———●), to volunteers A, B, C, D, and E.

oral administration of Bacampicin, almost to the same extent and at the same rate as with Penglobe. It could, therefore, be concluded that Bacampicin and Penglobe were bioequivalent with respect to ampicillin bioavailability. Consequently, prescribers may substitute, with more confidence, one brand for the other, unlike the situation of the different brands of ampicillin which I have previously reported on (Ali, 1980).

The urinary excretion rate ($\bar{X} \pm$ S.E.) reached a maximum, 1.247 ± 0.04 mg/ml, after ($\bar{X} \pm$ S.E.) 0.9 ± 0.22 h for Bacampicin and Penglobe indicating a high rate of absorption (Table 1 and Fig. 1), in agreement with previous findings (Bergan, 1978). However, the curves (Fig. 1) showed a sharp decline after the first 2 h and within 6 h the rate was less than 0.10 mg/min (0.04–0.09 mg/min); i.e. the average rate, 0.065 mg/min, was 19 times less than the maximum peak, 1.247 mg/min. These data were in full agreement with those reported by Bergan (1978). Bergan, measuring the serum concentrations of ampicillin after oral administration of bacampicillin, presented data showing that the maximum plasma concentration (10.0 μg/ml, reached after 1 h) was reduced 20 times after 6 h (0.5 μg/ml).

These findings may indicate that the active form of bacampicillin, i.e. ampicillin, is rapidly excreted. Furthermore, the recommended dosage regimen (400 mg every 12 h) needs to be reviewed since the 400 mg (first dose) may not be sufficient to produce adequate body levels for 12 h. One might therefore suggest to increase the frequency of the tablet administration to become 400 mg 3 times daily. Alternatively, modification of the present formulation of bacampicillin, to produce slow release-type tablets (e.g. sustained release) might be worth trying out.

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