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Comparative studies on the bioavailability of ampicillin anhydrate and trihydrate

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Summary

The relative bioavailability of pure ampicillin (with no additives) anhydrate and trihydrate and two other commercial products marketed in the Sudan was examined in 10 subjects using a cross-over experimental design. Based upon the urinary excretion method the extent and rate of ampicillin bioavailability were determined. Statistically significant differences were found between the products examined. These findings are consistent with previously published reports but in contrast to some other studies.

Introduction

Ampicillin is available in two crystalline forms, the anhydrate and trihydrate, having different properties. For instance, the anhydrous form has greater aqueous solubility and a higher apparent rate of dissolution than the hydrated substance (Poole and Bahal, 1968). It was originally reported that anhydrous ampicillin has better bioavailability than the trihydrate form in adults (Poole et al., 1968) and infants (Silverio and Poole, 1973). However, the comparison which was made in these studies involved the use of commercial dosage forms of anhydrous and trihydrate ampicillin rather than identical formulations of the respective forms of the drug. Thus, the observed 20–30% bioavailability difference may have been related to formulation factors rather than the hydration state of the drug (Mayersohn and Endrenyi, 1973; Hill et al., 1975). Cabana and coworkers (1969) administered capsules of sodium and potassium ampicillin and ampicillin trihydrate to dogs and found no differences in the extent of absorption of these solid dosage forms of the drugs compared to oral solution of sodium ampicillin. Another study by Mayersohn and Endrenyi (1973) has revealed that commercial capsules of ampicillin yield essentially identical bioavailability. On the other hand, MacLeod et al. (1972) have

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shown statistically significant differences in biological availability among certain lots of several commercial brands of ampicillin marketed in Canada. It thus appears that evidence from the literature concerning the comparative degree of absorption from ampicillin capsules has been conflicting.

The present paper is concerned with a re-evaluation of the in vivo performance in man of two identical formulations of pure ampicillin anhydrate and trihydrate. In addition, two commercial dosage forms of anhydrous (Omnipen, Wyeth) and trihydrate (Penbritin, Bristol) ampicillin have been included in the study.

Materials and methods

Ampicillin anhydrate, lot no. GV-50842-1, was kindly supplied by Wyeth Laboratories, Philadelphia, PA, U.S.A. The trihydrate form, lot no. 965-C4, was obtained from Sands Pharmaceuticals, Toronto, Canada. Omnipen capsules, 250 mg, lot no. 1800721 (Wyeth Laboratories, Philadelphia, PA, U.S.A.) and Penbritin capsules, 250 mg, lot no. 3080 (Beecham Research Laboratories, England) were purchased locally. Analysis of 6 capsules of each brand detected no significant difference in equivalent ampicillin content. Powders equivalent to 250 mg ampicillin in either form were loosely filled by hand into hard gelatin capsules and the contents was confirmed by chemical assay.

Bioavailability study

Ten healthy male student volunteers took part in the study. Their ages ranged from 21 to 25 years (average 23) and weights from 110 to 150 pounds (average 130). Informed written consent was obtained from each subject. The volunteers did not take any drug a week before and during the trials. A random cross-over design was used. Each subject fasted for at least 8 h prior to and 3 h after dosing. Each subject ingested 250 mg capsule of ampicillin with 200 ml of water according to the assigned schedule. One week's time elapsed between successive doses. A urine sample was taken at the time of drug administration (time 0), ensuring complete emptying of the bladder, and then hourly for 8 h post-drug administration. In order to stimulate urine output, 200 ml of water were ingested after each urine collection. The amounts of drug in urine were determined chemically according to the method of Smith and coworkers (1967). All samples were analyzed for ampicillin on the same day of their collection to prevent appreciable deterioration of ampicillin which occurs even in the frozen state (Savello and Shangraw, 1971).

Results and discussion

Jusko and Lewis (1973) demonstrated that a relationship exists in man between blood level of ampicillin and its rate of urinary excretion. Hence, it is possible to determine the rate and extent of absorption of this drug by measuring the rate of appearance of unchanged ampicillin in urine. The total amount of ampicillin excreted in urine over 8 h was used to describe the extent of ampicillin bioavailability (Ritschel, 1971).

Table 1 reports the percentage doses of ampicillin recovered as unchanged drug in urine in 8 h for each individual. In addition, the mean percentage doses (average of 10 subjects) of ampicillin anhydrate and trihydrate excreted in urine, and hence absorbed, are shown in the table. The average amount of unchanged ampicillin excreted by the 10 subjects during the experimental time interval for each ampicillin form is summarized in Table 2. Table 2 reveals that the excretion of ampicillin is essentially over by 8 h and that the cumulative amount of unchanged ampicillin excreted in urine in 8 h is a valid estimate of the extent of absorption of the drug from solid dosage forms.

Examination of the excretion data presented in the tables indicates that ampicillin from the experimental capsules containing the pure anhydrous form (with no excipients) was excreted in urine, and therefore absorbed, at both a faster rate and to a greater extent than from either of the other experimental capsule containing the trihydrate form, or the two commercial capsules. Approximately two times as much ampicillin was excreted from the pure anhydrous form as compared with the pure trihydrated drug. The mean percentage doses of ampicillin excreted in urine after oral administration of the drug, were 66, 34, 53 and 42 for the pure anhydrous form, trihydrate form, commercial capsule of anhydrous form (Omnipen) and commercial capsules of trihydrated drug (Penbritin), respectively. The differences between the first and the other 3 capsule formulations were statistically significant (Table 1). This was also true of the means of individuals urinary excretion rates (Table 2). Capsules

TABLE 1

Comparative bioavailability results of ampicillin anhydrous and trihydrate, expressed as cumulative amount of ampicillin equivalents, excreted in 8 h (per cent dose ingested)

Subject code	Ampicillin		Omnipen Anhydrous	Penbritin Trihydrate
	Anhydrous	Trihydrate		
AD	56	38	51	47
AH	74	34	49	38
AS	77	32	49	–
AT	56	22	43	35
FT	88	40	66	55
KG	61	37	50	41
MA	64	41	57	44
OH	53	38	45	42
SH	69	26	54	33
SM	66	31	63	41
Per cent of the dose	66.4 [a] ±(3.5) [b]	34.1 ±(2.1)	52.7 ±(2.4)	41.8 ±(2.2)

[a] Mean of the 10 subjects.
[b] Standard error of the mean in brackets.

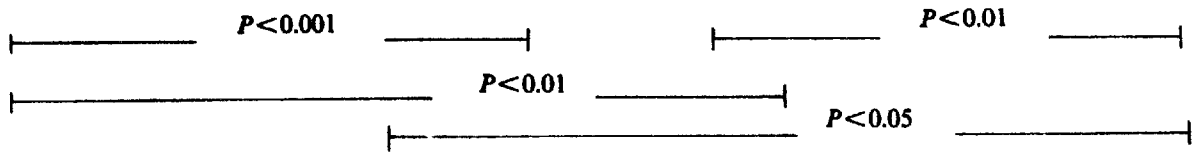

TABLE 2

Ampicillin urinary excretion rates (mg/h) at various times after drug administration

Time (h)	Ampicillin		Omnipen Anhydrous	Penbritin Trihydrate
	Anhydrous	Trihydrate		
0–1	13.3 [a] ±(1.3) [b]	7.5±(1.7)	10.7±(2.1)	8.3±(1.5)
1–2	45.3 ±(5.0)	26.8±(2.8)	36.7±(3.7)	28.5±(2.6)
2–3	33.5 ±(3.7)	19.2±(2.7)	27.7±(3.1)	21.4±(1.8)
3–4	25.4 ±(2.6)	14.4±(1.2)	19.6±(2.7)	17.1±(2.0)
4–5	20.0 ±(1.9)	8.8±(2.0)	16.4±(1.9)	12.7±(1.7)
5–6	16.8 ±(1.6)	6.0±(1.6)	10.8±(1.3)	9.1±(1.7)
6–7	7.9 ±(0.9)	2.4±(0.3)	6.5±(0.9)	5.1±(0.9)
7–8	4.2 ±(0.6)	1.9±(0.7)	3.8±(0.8)	3.3±(0.6)

[a] Each data point represents the mean of 10 subjects.
[b] Standard error of the mean in brackets.

containing the pure anhydrous form gave the highest urinary excretion rates at all time intervals shown in the table. The peak excretion rates (mg/h) were 45.3, 26.8, 36.7 and 28.5 for pure anhydrous form, trihydrate form, Omnipen and Penbritin, respectively. The 4 presentations of ampicillin, however, had reached their maximum excretion rate within 2 h.

Comparing the relative bioavailability of the two commercial brands, Omnipen capsules gave significantly better bioavailability than Penbritin capsules, but it is interesting to note that the commercial dosage form of anhydrous ampicillin (Omnipen) had less bioavailability compared with the pure anhydrous form, while the commercial capsule containing the trihydrate form (Penbritin) gave better bioavailability than the pure trihydrated drug. This suggests that the observed bioavailability differences are related both to hydration state of the drug and its formulation. While the formulation factors have improved the relative bioavailability of the Bristol capsule (from 34 to 42%), they have decreased that of the Wyeth capsule (from 66 to 53%). We have noted that methylcellulose is one of the excipients included in the formulation of Omnipen. The observation by Seager (1968) that delayed absorption and reduced availability occur in man from nitrofurantoin suspension containing 5% methylcellulose, suggests that this polymer may also be responsible for the reduced availability of the Omnipen capsule as compared with the experimental capsule containing pure drug with no additives. However, we are now investigating the effect of methylcellulose on absorption of ampicillin in man.

There is considerable discrepancy in the literature concerning the comparative absorption of ampicillin. It has been reported (Poole and Bahal, 1968; Poole et al., 1968) that suspensions and capsule formulations containing ampicillin anhydrate exhibited superior bioavailability to formulations of the trihydrate, and the authors suggested that the greater aqueous solubility of the anhydrated form was probably the major factor responsible. A study by MacLeod and coworkers (1972) has shown statistically significant differences in biological availability among certain lots of

commercial brands of ampicillin. Our results are in good agreement with these findings but in contrast to others (Cabana et al., 1969; Mayersohn and Endrenyi, 1973; Hill et al., 1975). These authors found that capsules containing either form of ampicillin yield essentially identical bioavailability. They have also stated that the comparison made by Poole and his associates were with formulated products from different manufacturers, and that the results were therefore subject to processing and formulation factors. In the present study, however, the two forms of ampicillin were pure and filled into identical capsules loosely, by hand, with no added excipients. In addition, two commercial formulations containing either form of the drug were included in the study.

Our results suggest that ampicillin absorption is significantly better when the antibiotic is administered in the anhydrated form and that formulation factors might also have a predominent influence.

References

Cabana, B.E., Willhite, L.E. and Bierwagen, M.E., Pharmacokinetic evaluation of the oral absorption of different ampicillin preparations in beagle dogs. Antimicrob. Agents Chemother., 9 (1969) 35–41.

Hill, S.A., Jones, K.H., Seager, H. and Taskis, C.B., Dissolution and bioavailability of anhydrate and trihydrate ampicillin. J. Pharm. Pharmacol., 27 (1975) 594–598.

Jusko, W.J. and Lewis, G.B., Comparison of ampicillin and hitacillin pharmacokinetics in man. J. Pharm. Sci., 62 (1973) 69–76.

MacLeod, C., Rabin, H., Ruedy, J., Caron, M., Zarowny, D. and Davies, R.O., Comparative bioavailability of three brands of ampicillin. Canad. Med. Assoc. J., 107 (1972) 203–209.

Mayersohn, M. and Endrenyi, L., Relative bioavailability of commercial ampicillin formulations in man. Canad. Med. Assoc. J., 109 (1973) 989–993.

Poole, J.W. and Bahal, C.K., Dissolution behaviour and solubility of anhydrous and trihydrate forms of ampicillin. J. Pharm. Sci., 57 (1968) 1945–1948.

Poole, J.W., Owen, G. and Silverio, J., Physicochemical factors influencing the absorption of the anhydrous and trihydrate forms of ampicillin. Curr. Ther. Res., 10 (1968) 292–303.

Ritschel, W.A., In W.A. Ritschel (Ed.), Handbook of Basic Pharmacokinetics, 1st edn., Drug Intelligence, Publication, IL., 1971, pp. 125–147.

Savello, D.R. and Shangraw, R.F., Stability of sodium ampicillin solutions in the frozen and liquid state. Amer. J. Hosp. Pharm., 28 (1971) 754–759.

Seager, H., The effect of methylcellulose on the absorption of nitrofurantoin from the gastrointestinal tract. J. Pharm. Pharmacol., 20 (1968) 968–969.

Silverio, J. and Poole, J.W., Serum concentrations of ampicillin in newborn infants after oral administration. Pediatrics, 57 (1973) 578–580.

Smith, J.W.G., De Grey, G.E. and Patel, V.J., The spectrophotometric determination of ampicillin. Analyst, 92 (1967) 247–252.