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BIOAVAILABILITY OF EIGHT BRANDS OF AMPICILLIN CAPSULES

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ABSTRACT

An *in vivo* absorption study was performed in a crossover fashion on 6 healthy volunteers (4 males and 2 females) to compare the bioavailability of 8 brands of ampicillin capsules. Absorption was assessed by a urinary excretion method in which the drug was assayed chemically. Statistical analysis of the results was carried out to evaluate the significance of differences between brands and between subjects. Results of the analysis of variance indicated no significant differences between the tested brands of ampicillin capsules. However, significant differences between brand A and brand B were found on using the student t-test. A significant intersubject variation was also found between the volunteers participated in the present study.

INTRODUCTION

It is a well established fact that not all commercially available products containing a given drug will neces-

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sarily exhibit equivalent bioavailability eventhough their compendial assay methods may indicate essentially identical content. It was, therefore, deemed valuable to assess the bioavailability of various solid dosage forms especially those produced in developing countries, where the pharmaceutical industry is relatively new, and compare these products with those imported from multinational firms. Along this line of research, the bioavailability of different brands of tetracycline capsules (1), griseofulvin tablets (2) and nalidixic acid tablets (3) have been studied by our research team.

Ampicillin, a highly potent antibiotic with a relatively low toxicity and side effects, was reported to exhibit differences in bioavailability (4,5). The wide spread use of ampicillin specially in serious infections, its presence in the A.Ph.A. list of drugs with potential risk of incomplete bioavailability (6) as well as the conflicting reports (7-9) concerning the bioavailability of ampicillin from capsules produced by different manufacturers, initiated its selection in the present study.

The bioavailability of ampicillin is relatively easy to assess. As about 90% of the absorbed drug is usually excreted in the urine (10), the total urinary recovery of the drug should be an almost direct indication of the extent of ampicillin absorption. Although many of the bioavailability studies reported were based on drug blood concentration (11,12), urine data were also used to study the effect of food (13), type of food (14), influence of particle size (15), hydration state (16,17), variation in dosage forms (18), and variation in brands (19) on the bioavaila-

bility of ampicillin. As the urinary excretion methods is easier and possesses the advantages over method based on blood data that it does not trouble the subjects with veinpuncture, the bioavailability of 8 brands of ampicillin capsules was assessed in a crossover fashion, in the present study, using urinary excretion data.

EXPERIMENTAL

Materials

Citric acid, anhydrous disodium hydrogen phosphate, copper sulphate and trichloroacetic acid used were of analytical grade. Eight brands of ampicillin capsules were chosen; 4 locally made (B, C, D and G); 1 brand locally made under licence from an international firm,(E); and 3 brands were imported (A, F and G). Pure anhydrous ampicillin BP[1] was also used in the present study.

Protocol for Urine Collection

Six healthy normal adult volunteers participated in the present study; four males and two females. Their average age was 37.7 years (range 23-56 years) and their average weight was 77.3 kg (range 68-95 kg). All subjects were instructed to abstain from taking any medications one week prior and during each study. A single 500 mg capsule or two 250 mg capsules were administered with approximately 250 ml of water on an empty stomach following an overnight fast. No food or liquids other than water were permitted for 4 hours following ingestion of the dose. The urine was collected quantitatively after

1. Courtesy of the Alexandria Co. for Pharmaceuticals and Chemical Industries, Alexandria, Egypt.

1,2,3,4,6,8, and 12 hr. Blank urine was collected before drug intake. The collected urine was refrigerated immediately until analyzed after 24 hr from the first sample collection. The urine samples were analyzed chemically according to the procedure proposed by Angelucci and Baldieri (20). Three standard concentrations of ampicillin (20,30 and 40 μg/ml) were assayed side by side with the samples to overcome the effect of any fluctuation in the conditions of the assay.

RESULTS

In man, a relationship was reported to exist between blood level of ampicillin and its rate of urinary excretion (21). 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. To compare the relative bioavailability of the eight brands of ampicillin capsules tested, five parameters describing the urinary excretion curves were evaluated: (a) the cumulative mg of ampicillin excreted after 8 hours, (b) the urinary peak height (mg/hr), (c) the time to reach that peak (hr) or the time of peaking, (d) the urinary concentrations after 2 hours following oral administration (mg/ml), and (e) the elimination and absorption rate constants (hr^{-1}).

(a) Cumulative mg of Ampicillin Excreted after 8 Hours

It is well doccumented that the cumulative urinary excretion data describe the extent of bioavailability of drugs that are mostly eliminated in the unchanged form (22). The rapid absorption and elimination of ampicillin limit the duration of urine collection to about eight hr in normal adult (11). In the present study, urine was collected for

12 hr to ensure complete clearance of the drug. The concentration of ampicillin in the urine sample collected at 12 hr. showed negligible value, hence, the cumulative mg excreted after 8 hr. would be a proper indication of the extent of ampicillin absorption.

The cumulative mg excreted after 8 hr for the various brands are shown graphically in Fig. 1. Tables 1 and 2 show the average pharmacokinetic parameters per brand and per subject respectively. From Table 1, it can be observed that the average mg excreted after 8 hr for all the tested brands is 139.1 mg (range 107.9 - 172.4 mg). Statistical analysis of variance (23) of these data revealed no significant differences ($p = 0.05$) between the different brands evaluated. However, significant intersubject variation was observed (Table 3).

(b) Urinary Peak Height (mg/hr) and (c) the Time Necessary to Reach that Peak

The peak serum concentration was suggested to be a function of both the rate and extent of drug absorption, while the time necessary to reach that peak is only a function of the rate of drug absorption (22). Similarly, in the present study, the peak height of the urinary excretion rate curve, as well as the time to reach that peak, could also be used as suitable parameters to describe the rate and extent of ampicillin absorption.

The average urinary excretion rate curves of the various brands tested are shown in Fig. (2). The average value of the urinary peak height for all the tested brands was 39.4 mg/hr (range from 28.5-51.1 mg/hr) (Table I). Analysis of

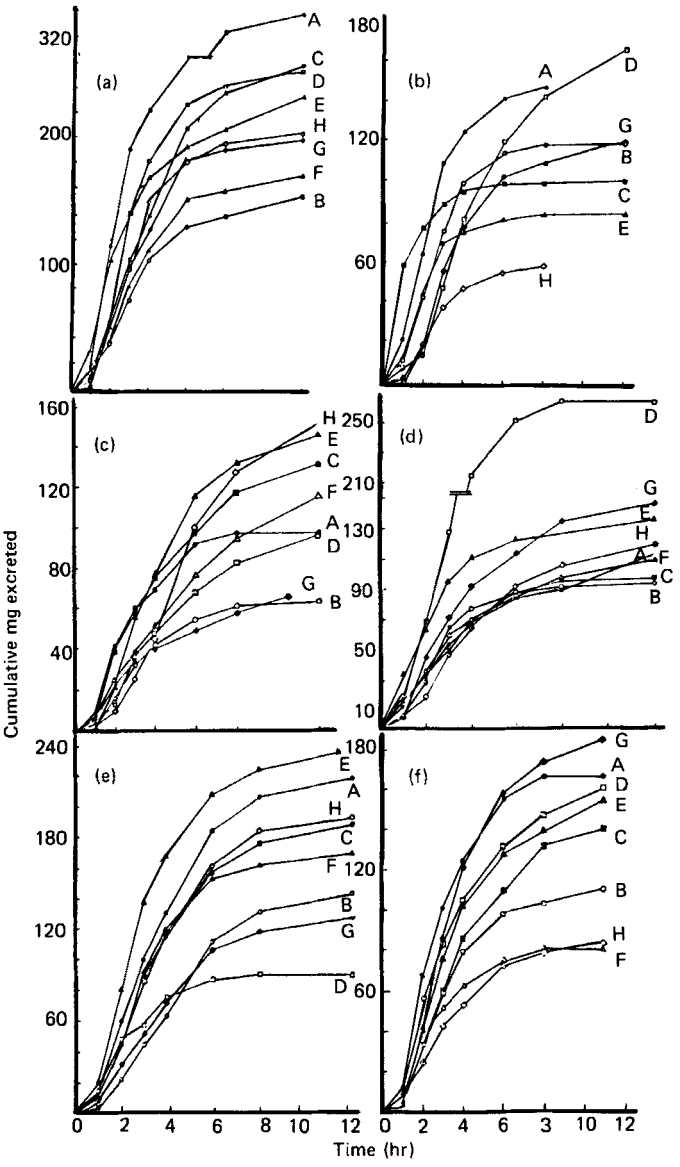

Figure 1

Cumulative mg ampicillin excreted following oral administration of 8 brands of ampicillin capsules to 6 subjects.

TABLE 1

Average Pharmacokinetic Parameters per Brand Following Oral Administration of 8 Brands of Ampicillin Capsules to 6 Subjects.

Brand	Cumulative mg excreted after 8 hr	Urinary peak height (mg/hr)	Time of peaking (hr)	Urinary concentration after 2 hr (mg/ml)	K_e^b (hr^{-1})	K_a^c (hr^{-1})
A	172.4	51.1	1.83	0.99	0.358	0.518
	(35.3)[a]	(11.3)	(0.21)	(0.20)	(0.05)	(0.05)
B	107.9	28.5	2.92	0.50	0.480	0.496
	(11.8)	(3.1)	(0.38)	(0.11)	(0.03)	(0.03)
C	143.2	40.0	2.00	0.63	0.354	0.470
	(22.2)	(6.1)	(0.43)	(0.04)	(0.09)	(0.04)
D	161.9	51.1	2.33	0.63	0.374	0.538
	(31.1)	(11.6)	(0.31)	(0.24)	(0.06)	(0.04)
E	151.6	45.5	1.50	0.86	0.429	0.676
	(21.9)	(7.0)	(0.26)	(0.18)	(0.06)	(0.08)
F	118.9	32.3	2.10	0.68	0.329	0.506
	(17.1)	(5.9)	(0.26)	(0.14)	(0.04)	(0.02)
G	131.1	35.8	2.00	0.50	0.369	0.483
	(19.5)	(5.1)	(0.24)	(0.14)	(0.06)	(0.02)
H	125.6	31.1	2.92	0.55	0.374	0.487
	(22.7)	(5.8)	(0.49)	(0.14)	(0.04)	(0.06)
Mean	139.1	39.4	2.20	0.67	0.380	0.520
	(7.82)	(3.17)	(0.18)	(0.06)	(0.03)	(0.02)

a. Numbers in parentheses represent the standard error of the mean.

b. Elimination rate constant

c. Absorption rate constant

TABLE 2

Average Pharmacokinetic Parameters per Subject Following Oral Administration of 8 Brands of Ampicillin Capsules to 6 Subjects.

Subject	Age (year)	Weight (kg)	Cumulative mg excreted after 8 hr	Urinary peak height (mg/hr)	Time of peaking (hr)	Urinary concentration after 2 hr (mg/ml)	K_e (Kr^{-1})	K_a (hr^{-1})
L.M(F[a])	37	75	211.7	62.7	2.38	1.02	0.379	0.494
			(20.4)	(8.5)	(0.23)	(0.14)	(0.04)	(0.02)
N.A(F)	23	68	108.5	37.4	2.07	0.58	0.557	0.620
			(11.9)	(4.8)	(0.29)	(0.16)	(0.06)	(0.06)
S.K(M[b])	47	95	95.9	25.4	2.31	0.30	(0.271)	0.425
			(9.9)	(3.1)	(0.42)	(0.06)	(0.04)	(0.02)
M.H(M)	25	78	126.4	35.3	2.38	0.49	(0.377)	0.588
			(20.6)	(7.1)	(0.34)	(0.06)	(0.05)	(0.06)
A.M(M)	38	78	162.4	40.6	2.19	0.75	(0.375)	0.423
			(16.1)	(4.2)	(0.42)	(0.16)	(0.02)	(0.02)
A.H(M)	56	70	128.0	35.7	1.88	0.85	(0.349)	0.519
			(13.0)	(4.2)	(0.17)	(0.11)	(0.04)	(0.04)
Mean			138.8	39.5	2.20	0.67	(0.382)	0.522
			(17.2)	(16.1)	(0.08)	(0.11)	(0.04)	(0.02)

Numbers in parentheses represent the standard error of the mean.

(a) Female
(b) Male

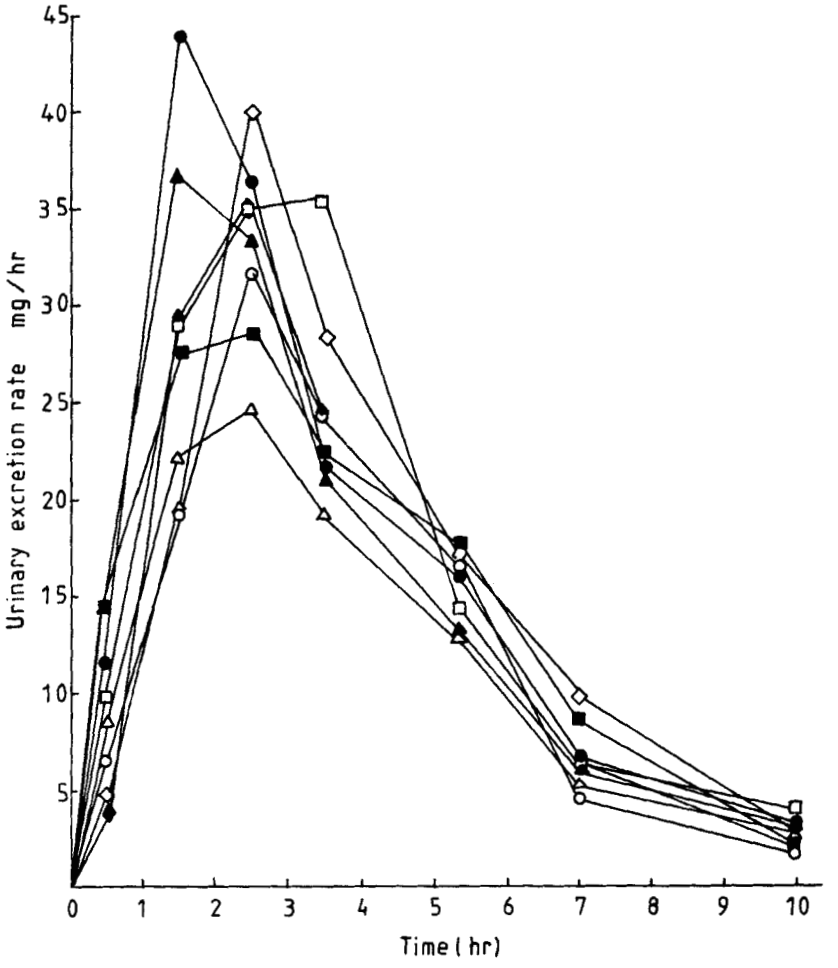

Figure 2

Average urinary excretion rates following oral administration of 8 brands of ampicillin capsules to 6 subjects. (●) brand A, (○) brand B, (■) brand C, (□) brand D, (▲) brand E, (△) brand F, (◆) brand G and (◇) brand H.

TABLE 3

Analysis of Variance for the Cumulative mg Excreted after 8 hr.

Source of variance	Sum of squares	Degree of freedom	Mean of squares	F ratio
Between brands	20643.90	7	2949.13	1.67(N.S)[a]
Between subjects	71202.16	5	14240.43	8.1 (S)[b]
Error	61866.29	35	1767.61	

a- Insignificant at p= 0.05

b- Significant at p= 0.05

TABLE 4

Analysis of Variance for the Urinary Peak Height (mg/hr)

Source of Variance	Sum of squares	Degree of freedom	Mean of squares	F ratio
Between brands	9747.80	7	1392.54	6.49(S)[a]
Between subjects	6220.64	5	1244.13	6.21(S)
Error	7014.66	35	200.42	

a- Significant at p= 0.05

variance for the urinary peak height data showed statistically significant differences (p= 0.05) between brands and between subjects (Table 4).

The average time taken to reach the peak urinary concentration of all the tested brands was 2.2 hr(range 1.50-2.92 hr) (Table 1). No statistically significant differences (p= 0.05) between brands and between subjects were observed from the time of peaking data (Table 5).

TABLE 5

Analysis of variance for the time to reach the peak (hr)

Source of variance	Sum of squares	Degree of freedom	Mean of squares	F ratio
Between brands	10.63	7	1.52	2.13(N.S)[a]
Between subjects	1.60	5	0.32	0.45(N.S)
Error	24.92	35	0.712	

a- Insignificant at p= 0.05

TABLE 6

Analysis of Variance for the Urinary Concentration after 2 hr

Source of variance	Sum of squares	Degree of freedom	Mean of squares	F Ratio
Between brands	1.32	7	0.19	2.11(N.S)[a]
Between subjects	2.96	5	0.59	6.56 (S)[b]
Error	3.18	35	0.09	

a-Insignificant at p= 0.05 , b= Significant at p= 0.05

(d) Urinary Concentration After 2 hr from Oral Administration of Ampicillin Capsules

Absorption of ampicillin usually occurs within 2 hr after oral administration of the capsule (11). Urinary concentration after 2 hr was, therefore, chosen to compare the rate of absorption of the various ampicillin brands. The average urinary concentration after 2 hr for all the tested brands was 0.67 mg/ml (range 0.50-0.99 mg/ml) (Table 1). No significant differences between brands were observed at the 5% level of confidence (Table 6). However, intersubject variations were still statistically significant (p= 0.05).

TABLE 7

Analysis of Variance for the Rate Constants (hr^{-1})

Source of Variance	K elimination			K absorption		
	df[a]	M.S[b]	F ratio	df	M.S	F ratio
Between brands	7	0.02	0.5(N.S)[c]	7	0.03	3 (N.S)
Between subjects	5	0.07	2.3(N.S)	5	0.05	5 (N.S)
Error	35	0.03		35	0.01	

a. Degree of freedom, b. Mean of squares, c. Not significant

(e) The Elimination and Absorption Rate Constants

Individual urine ampicillin levels were fitted graphically to the standard one-compartment open model with first-order absorption and elimination. Improved estimates of parameters were obtained using regression analysis. The average data of the calculated elimination and absorption rate constants per brand and per subject are shown in Table 1 and 2 respectively. The mean K elimination for all the tested brands using six volunteers was 0.38 hr^{-1} (SE 0.03); the average half-life calculated was 2.08 hr (SE 0.11). In addition, the mean K absorption was found to be 0.52 hr^{-1} (SE 0.02); the average half-life calculated was 1.39 hr (SE 0.49). The calculation of the rate constants was based on the equation suggested by Nelson et al (24). Analysis of variance revealed no significant differences in both the rate constants ($p = 0.05$) between brands and between subjects (Table 7).

In general, from the data present in Table 1, brand A can be considered to have the highest rate and extent of absorption, while brand B shows the lowest bioavailability characteristics. The mean relative bioavailability of brand B/A, based on the cumulative amount excreted after 8 hr, was

found to be 62.6%. The significance of differences between the two brands was tested using the student t-test. The difference between brand A and B, regarding the cumulative percent excreted after 8 hr, was statistically significant at p= 0.05. However, the differences resulting from peak height, time of peaking and the urinary concentration after 2 hr data were statistically significant at p= 0.10 and insignificant at p= 0.05.

DISCUSSION

Comparison Between Brands

It is well estabilished that ampicillin suffers from partial absorption ranging from 20-70% of the dose (11), and consequently considered as a drug of potential risk of incomplete bioavailability (6). An average of 27.8% (S.E= 1.57) of the dose of ampicillin was excreted after eight hr by the subjects of the present study as calculated from Table 1. This finding agrees with the data of Jusko and Lewis (21), who reported a 32±8% absorption from ampicillin capsules on studying ampicillin bioavailability in eight fasting subjects.

With the exception of the peak height analysis, no significant differences between the tested brands were observed in the present study. These results are similar to previous reports on bioavailability of ampicillin capsules (9,12). However, on using the student t-test, differences in bioavailability characteristics between brand A and brand B were statistically significant. Variations in the *in vivo* behaviour of brand A and B, may be attributed to differences in formulation and/or processing factors which

control the release of the capsule content. It was found that *in vivo* dispersion time, using the external scintigraphy (25), is dependent on the solubility of the capsule content. If proper storage conditions of the capsules are maintained (26, 27), the gelatin shell appears to play little part in controlling the behaviour of the dosage form *in vivo* (28). Improper storage conditions may cooperate in lowering bioavailability of brand B. Preliminary visual observation of the capsule content of this brand showed a hard slug-like mass on opening the capsule shell. Storage at high relative humidity may induce accumulation of moisture in the encapsulated powder and probable cementing of the capsule content with possible reduction of dissolution and consequently drug availability. In addition, the state of hydration of the drug may be partially responsible for the observed differences of bioavailability of both brands. Ampicillin in brand A was in the anhydrous form, while that in brand B was in the trihydrate form. Previous studies (29,30) indicated that anhydrous ampicillin was approximately 8-17% better absorbed than the trihydrate form. *In vitro* study of the behaviour of these brands (burst time, deaggregation and dissolution rates) may explain the *in vivo* differences exhibited between brand A and brand B (31).

Inspection of the results of the cumulative urinary excretion of ampicillin capsules for each individual volunteer (Fig. 1) reveals that a significant difference in excretion of brand A and B is also observed in most subjects. Subject L.M. exhibited extremely high excretion behaviour for brand A compared to brand B (Fig. 1 A). This superiority of brand A over brand B was also evident in most of the other

subjects (Fig. 1;B,C,E and F). However, both brands showed almost similar excretion pattern in case of subject M.H (Fig. 1,D). Brand F, in most cases, also exhibited relatively low excretion behaviour. The excretion patterns of the remaining brands were highly variable among the various subjects.

Comparison Between Subjects

The absorption of ampicillin has been reported to exhibit considerable variability between subjects following oral administration (4,5). The present study showed significant intersubject variation ranging from 19.2 to 42.3% for the cumulative percent excreted after 8 hr as calculated from Table 2. This agrees with the finding of Swahn (5) who reported that the absorption of ^{35}S-ampicillin by six healthy subjects, ranged from 25 to 67% (mean 44%), as calculated from the excretion of radioactivity in urine. MacLeod et al (4) also found that the percentage of ingested drug that was absorbed varied among individuals from 32 to 64%. From Table 2, it can be observed that subject L.M. exhibits superior excretion behaviour, compared to the other subjects. On the other hand, subjects, S.K. and M.H. are considered to have low excretion characteristics. About 65% of ampicillin from brand A was excreted by subject L.M. compared to 18.4 and 19.4% by subjects, M.H. and S.K. respectively. In addition, the cumulative percent excreted after 8 hr, for brand B, was about 28% for subject L.M., compared to 12 and 19% for subjects S.K. and M.H. respectively. A considerable intersubject variation in capsule bursting was reported by Alpesten et al (32) who studied the disintegration of gelatin capsules in fasting volunteers using a

profile scanning technique. This fact may be partially responsible for the variation between subjects taking ampicillin capsules in the present study.

It is well known that differences in age, weight,health conditions and sex between volunteers, contribute significantly to intersubject variations in drug bioavailability (33). Although the age of human beings can affect the rate and extent of drug absorption in both pediatrics and geriatrics (34), no age effect was found in the present study. On comparing the most aged subject (A.H. 56 years old), with the youngest one (N.A. 23 years old) (Table 2), having approximately the same weight, no apparent differences in ampicillin bioavailability was observed. Since none of the volunteers, in the present work, was considered to be in the geriatric level ($>$ 70 years old), the effect of age was not pronounced.

By observing the effect of weight variation on ampicillin bioavailability, it appears that obesity suppressed both the extent and the rate of ampicillin absorption. Subject S.K. (95 kg) showed the lowest pharmacokinetic parameters; as regarding the cumulative amount excreted after 8 hr (95.9 mg), the peak height (25.4 mg/hr), the K elimination (0.271 hr^{-1}) and the K absorption (0.425 hr^{-1}) (Table 2). However, the time of peaking (2.31 hr) did not deviate drastically from the mean time of peaking (2.2 hr) of the six subjects contributing in this study. Due to the limited number of volunteers in the present study, no decisive conclusion can be drawn on the effect of obesity on ampicillin bioavailability.

Reported person to person variation in ampicillin bioavailability was confirmed in the present study. However,

since the recommended dose for the therapeutic use of ampicillin is sufficiently high to give therapeutic concentrations in most cases, there are likely to be few therapeutic failures as a consequence of low bioavailability in certain subjects (35). This is well examplified when ampicillin is used as a urinary tract disinfectant. The concentrations of ampicillin attained in urine are much higher than the minimum inhibitory concentrations (M.I.C.) on microorganisms causing acute and uncomplicated urinary tract infections (36). In the present work, the lowest urinary concentration of ampicillin observed after 2 hr, for example, was 110 µg/ml for subject S.K. This concentration is still much higher than the M.I.C. for Escherichia coli (5 µg/ml), Proteus mirabilis(1.25 µg/ml) and Streptococcus feacalis (1-5 µg/ml) which commonly cause urinary infections. But in some clinical situations, as diarrhea or other signs of malabsorption, cases suffering from low bioavailability will be subjected to therapeutic failure.

CONCLUSION

It could be concluded from the previous results that no significant differences between the tested ampicillin brands were observed. However, significant differences between brand A and brand B were found on using the student t-test. On the other hand, significant intersubject variation was observed in this study.

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