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Comparative Bioavailability studies of some oral Amoxycillin Capsules

M. K. HASSANZADEH AND A. DANESHVARI
School of Pharmacy, Mashhad University of Medical Sciences, Mashhad 91775-1365, Iran

Relative bioavailability of four brands of amoxycillin capsules were examined. The absorption of each dosage form was compared in a crossover study of thirteen heathly subjects (6 males and 7 females). Plasma concentrations and urinary excretion rates were employed to evaluate the absorption process. Statistical analysis of the results were carried out to evaluate the significance of differences between dosage forms and subjects. The statistical analysis indicated no significant differences between different tested brands of amoxycillin (except for brand A) while the differences between subject were significant. Although the differences between brand A and other brands are significant, the differences, are within the % ± 20 range and is not clinically important. Comparison between the two different genders indicated no significant differences between the male and female subjects.

Amoxycillin (a - amino-p-hydroxybenzyl penicillin) is a semisynthetic penicillin similar in chemical structure and in spectrum of activity to ampicillin. Following oral administration, amoxycillin appears to be absorbed to a great extent[1-3]. It is well known that all commercially available products do not demonstrate bioequivalence. Therefore, the evaluation of the bioavailability of various solid dosage forms is necessary. The assessment of bioavailability of various solid dosage forms is especially valuable in countries where the pharmaceutical industry is less established and in countries which only have generic products. In this study, the bioavailability of various formulated amoxycillin capsules were compared to a known commercial capsule which is used as a standard.

MATERIALS AND METHODS

Subjects and procedures

Thirteen healthy volunteers, 6 males and 7 females, 20 to 29 years old (mean age 24.9 years) and weighing between 55 to 75 kg (mean weight 63.3.±7.1 kg) were entered into the study after giving written informed consent. All subjects were in good health as judged by physical examination, urine analysis, hematology and serum biochemistry; negative histories were obtained for allergy to any form of penicillin or cephalosporin. None of the volunteers were taken concomitant medication, nor received any antimicrobial agents in the two weeks preceeding the study.

The study was a randomized double-blind complete crossover investigation. Each volunteer receive 500 mg of amoxycillin in four different dosage forms (A, B, C and D) on four separate occasions. Brand D, (Ardin, Antibiotics Pharmaceutical Company, Spain), a commercial amoxycillin capsule was used as a standard to be compared with three local generic dosage forms, brands A and B (Toliddaro Pharmaceutical company, Tehran, Iran), and brand C (Kowsar Pharmaceutical Company, Tehran, Iran).

On the morning of the treatment, each subject drank 250 ml of water at least 1 h before taking the medication. Medication was administered at 8 am, blood samples (5 ml) were collected in heparinized tubes at zero time and at 30, 60, 90 min and 2, 3, 4, 5 and 6 h after ingestion. Urine was collected over intervals of 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 6, and 6 to 8 h.

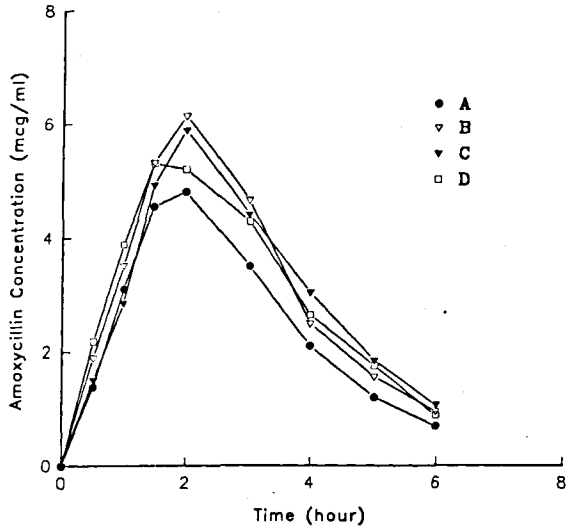

Fig.1: Plasma concentration curve of amoxycillin Mean plasma amoxycillin concentration in thirteen healty volunteers after oral administration of 500 mg of four different brands of amoxycillin capsules.

On each experimental day, the blood samples rapidly centrifuged. The plasma was drawn off using a sterile Pasteur pipittes and stored at -20° until analysed. The volume of urine collected was recorded and aliquots were stored at -20° until analysed.

Analysis

A modified version of the high performance liquid chromatographic procedure of Vree *et al.*[4] was used to assay amoxycillin concentration in plasma and in urine. The assay procedure was shown to produce linear calibration graphs over the range of 85 ng ml $^{-1}$ to 17 mcg ml^{-1} of amoxycilline in plasma and urine.

Data analysis

Amoxycilin elimination half-life was calculated using the method of least squares. Area under the plasma concentration against time curve (AUC) was calculated using the trapezoidal rule with the terminal portion of the curve estimated by dividing the last observed plasma concentration by the elimination rate constant. The ratio of AUC values was used to calculate relative systemic availability. Analysis of variance was applied to each pharmacokinetic parameter.

RESULTS AND DISCUSSION

Plasma pharmacokinetics of amoxycillin

The course of the mean plasma amoxycillin concentration for each formulation tested is graphically illustrated in figure 1. However, all pharmacokinetic parameters were calculated using individual data. Both individual and mean ± standard deviation for the parameters of highest observed plasma amoxycillin concentration (C_{max}), time of the occurrence of C_{max} (t_{max}), amoxycillin elimination half-life and area under the plasma amoxycillin concentration against time curve, are reported separately after each treatment (Table 1). These results were in good agreements with previously reported data[5-7]. Statistical analysis of t_{max} data indicated no significant differences ($P<0.05$) between brands and subjects. Analysis of variance of the C_{max} and $AUC_{0-\infty}$ showed significant differences ($P<0.05$) between four different dosage forms tested. Further statistical analysis indicated no significant differences between brands B, C and D. However, brand A differ significantly from the other brands.

The mean relative bioavailability of tested brands, (A, B and C), in comparison to the brand D, (used as standard, 100% availability assumed), were 83.6, 106, 3, 108, 6 respectively. Only the differences between brand A and other brands were statistically significant. However this differences is less than 20% and could not be considered clinically significant.

Urinary excretion of amoxycillin

Following the administration of amoxycillin capsules, amoxycillin was assayed in urine. The mean values for percent dose excreted during eight hours after administration of each of the four different brands, (A, B, C and D), were 54.0, 53.8, 54.6 and 59.9, respectively. These values are similar to the other previously reported values[5-7]. These urinary data were used to compare the four dosage forms of amoxycillin. The systemic availability of amoxycillin derived from urinary data for brands A, B and C was shown to be 94.3, 94.5 and 95.6 percent relative to brand D,, respectively. These differences were not significant.

Table -1: Pharmacokinetic parameter of oral amoxycillin

Brand	C_{max} (mcg/ml)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (mg.h/l)
A	5.21 ± 0.73	1.77 ± 0.26	1.34 ± 0.21	16.37 ± 1.98
B	6.49 ± 1.48	2.04 ± 0.48	1.31 ± 0.41	21.22 ± 3.6
C	6.28 ± 1.36	2.04 ± 0.48	1.43 ± 0.39	21.22 ± 5.20
D	5.66 ± 0.54	1.81 ± 0.43	1.29 ± 0.33	20.13 ± 4.26
Mean±SD	5.91 ± 0.58	1.91 ± 0.14	1.34 ± 0.05	19.60 ± 2.2

Various amoxycillin capsules were administered to thirteen subjects, blood was collected at different time intervals, analysed for amoxycillin and the data was subjected to pharmacokinetic analysis.

Table - 2 : The ratio of mean bioavailability of four differnt amoxycillin capsules

Brand	A	B	C	D*
Mean Fr				
Plasma	83.6	106.3	108.6	100
Urine	94.3	94.5	95.6	100
Ratio	0.89	1.12	1.14	1

The plasma and urine data of thirteen subjects after oral administration of four different amoxycillin capsules were used to calculate the mean relative bioavailability of various capsules. The ratio of the results obtained from plasma and urine were compared. Asterisk represents standard formulation. Fr is the relative bioavailability.

Comparison of plasma and urinary data

The mean plasma half-life values of amoxycillin in thirteen subjects after oral administration of four different brands of amoxycillin capsules were calculated from plasma data (1/34 ± 0.06) and from urine data (1.40 ± 0.13) which are in good agreement. The ratio of mean relative bioavailability of each brand, calculated from plasma data and urine data, are summarized in Table 2.

Comparison of relative bioavailability (Fr) the area under the plasma concentration time curve (AUC), total urinary recovery of drug, % dose, (Ae_∞), and other pharmacokinetic parameters clearly indicate that the results obtained from urinary data support the information obtained from plasma data.

Comparison between the male and female subjects

It has been established that differences in sex as well as other factors can significantly affect the intersubject variation in drug Bioavailability[8]. Mean pharmacokinetic parameters of different brands of amoxycillin for male (6 subjects) and female (7 subjects) in this study are shown in Table 3. Using the student t-test, differences in bioavailability and other pharmacokinetic parameters, except for the AUC, between the two different groups of male and female subjects were found not to be statistically significant. However, the differences between the bioavailability of various brands of amoxycillin capsuls are not significant between the two groups.

In conclusion, analysis of plasma and urine data in this study demonstrated the bioavailability and other pharmacokinetic parameters of amoxycillin after single oral administration of four different formulation of amoxycillin capsules. Statistical analysis showed no significant differences, ($P<0.05$), between various generic brands (except for brand A) and a known marketed amoxycillin capsule (Ardin)[9]. the results of this study indicated that the

Table - 3 : Pharmacokinetic parameters of amoxycillin

Pharmacokinetic Parameter	C_{max} (mcg/ml)	t_{max} (h)	$AUC_{(0-\infty)}$ (mg.h/l)	(Ae_∞) (% dose)	F [a]
Male	5.61	1.85	17.68	55.10	97.05
	(1.02)[b]	(0.50)	(3.52)	(8.51)	(17.41)
Female	6.17	1.96	21.25	54.57	101.86
	(1.27)	(0.36)	(4.22)	(9.67)	(28.09)

Four different brands of amoxycillin capsules were administered to thirteen subjects, 6 male and 7 female, plasma and urine samples were collected and analysed for amoxycillin and the data were used to calculate various pharmacokinetic parameters. 'a' represents that the F ratio in based on plasma data and b. number in parenthesis represent standard derivation.

behavior of different tested brands of amoxycillin capsules (except brand A) are compatible and bioequivalent. However, it should be mentioned that the differences between bioavailability of brand A and other tested brands is less than 20% which is not considered to be significantly different from a clinical point of view.

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