164 (182 − H_2O) indicated that the former fragmentation path predominated.

The mass spectral data for the reduced products VI and VIII and their corresponding lactones, although unremarkable, were compatible with the assigned structures. As might be expected for the hydroxymethylbenzoic acids, a major fragment at *m/e* 150 indicated the loss of water with cyclization to the corresponding lactones.

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Bioavailability of Ampicillin and Amoxicillin in Fasted and Nonfasted Subjects

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Abstract □ The influence of various test meals and fluid volume on the relative bioavailability of ampicillin and amoxicillin was studied in healthy human subjects. Serum amoxicillin levels were somewhat, but not always, significantly higher than those of ampicillin from equivalent oral doses. Food ingested immediately before dosing reduced serum levels and urinary excretion of both antibiotics to a similar extent. Reduction of dosed water volume caused a marked decrease in serum amoxicillin levels in fasted subjects.

Keyphrases □ Ampicillin—bioavailability, oral administration, effect of fasting and fluid volume, humans □ Amoxicillin—bioavailability, oral administration, effect of fasting and fluid volume, humans □ Bioavailability—ampicillin and amoxicillin, oral administration, effect of fasting and fluid volume, humans □ Antibacterial agents—ampicillin and amoxicillin, bioavailability, oral administration, effect of fasting and fluid volume, humans

Ampicillin and amoxicillin have similar antibacterial activity against various organisms (1). Amoxicillin has twice the activity of ampicillin against enterococci and *Salmonella* species but is somewhat less active than ampicillin against *Haemophilus* and *Shigella* species (2, 3).

Various reports indicated that, despite the similar antibacterial spectrum of the two compounds, amoxicillin has superior bioavailability properties from oral dosage forms and may, therefore, be the compound of choice when this route of administration is used (4–6). Amoxicillin absorption may be less influenced by food than ampicillin absorption, so less variation in circulating antibiotic levels might be expected during repeated oral doses of amoxicillin (7, 8).

In this study, the bioavailability of ampicillin and amoxicillin was compared in fasted and nonfasted subjects under carefully controlled conditions.

EXPERIMENTAL

The subjects were three male and three female healthy volunteers. Male subjects were 24–30 years old (mean 27) and weighed 64–81 kg (mean 74). Female subjects were 21–27 years old (mean 23) and weighed 50–68 kg (mean 60). All subjects were shown by medical examination to be in good physical condition with normal blood and urine laboratory values. The subjects had no histories of allergic reaction to penicillins.

Protocol—Verbal assurance was obtained from all subjects that they had taken no known enzyme-inducing agents for 1 month and no other drugs for 1 week preceding the study. Subjects were instructed to take no drugs other than the required doses of antibiotic during the study.

The subjects were fasted overnight before each treatment and were permitted to eat no food, apart from test meals, until 4 hr after dosing. On the morning of a treatment, each subject drank 250 ml of water on arising, at least 1 hr before dosing. Medication was administered at 8 am; blood samples (4–5 ml) were collected from a forearm vein into vacuum tubes[1] containing no anticoagulant immediately before dosing and at 20 and 40 min and 1, 1.5, 2, 3, 4, 6, and 8 hr after dosing. Serum was separated and deep frozen at −18° until assayed. Urine was collected through 8 hr

[1] Vacutainers.

Table I—Average Serum Concentrations of Ampicillin and Amoxicillin from All Treatments (±1 *SD*)

Treatment	0.0	20 min	40 min	1.0 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	8 hr
Serum Ampicillin Concentration, μg/ml										
1	0.0	0.0	0.1 ± 0.1	0.4 ± 0.1	1.5 ± 1.1	2.6 ± 1.7	3.4 ± 1.3	3.1 ± 1.3	0.8 ± 0.2	0.4 ± 0.1
2	0.0	0.0	0.2 ± 0.2	0.5 ± 0.2	1.8 ± 0.7	2.7 ± 0.4	2.7 ± 0.4[a]	2.3 ± 0.6	1.3 ± 0.6	0.6 ± 0.3
3	0.0	0.0	0.2 ± 0.1	0.7 ± 0.7	2.1 ± 1.1	2.8 ± 1.1	2.4 ± 0.6[a]	1.8 ± 0.3[a]	0.7 ± 0.2[a]	0.3 ± 0.1[a]
4	0.0	0.6 ± 0.5	2.8 ± 1.4	3.5 ± 1.8	4.0 ± 2.0	4.7 ± 2.1	6.1 ± 2.5	4.2 ± 2.6	2.3 ± 2.1	0.7 ± 0.6
5	0.0	0.2 ± 0.3	3.3 ± 1.6	4.3 ± 1.7	5.4 ± 1.7	6.1 ± 1.7	4.8 ± 1.3	3.3 ± 1.3[a]	1.4 ± 1.5	0.1 ± 0.1
Paired[b] *t*-test		4 > 2,3,5	4,5 > 1–3	4,5 > 1–3	4 > 1,2; 5 > 1–3	4 > 1,2; 5 > 1–3	4 > 2,3; 5 > 1–3	4,5 > 3	NSD[c]	1,2 > 5
Serum Amoxicillin Concentration, μg/ml										
1	0.0	0.0	0.3 ± 0.3	0.9 ± 0.8	2.2 ± 0.7	3.1 ± 2.1	5.0 ± 1.9	4.4 ± 0.7	1.4 ± 0.8	0.6 ± 0.4
2	0.0	0.0	0.3 ± 0.2	1.3 ± 1.1	3.6 ± 2.1	5.0 ± 3.1	5.5 ± 2.3	4.7 ± 1.9	2.2 ± 1.1	0.7 ± 0.4
3	0.0	0.0	0.5 ± 0.6	1.2 ± 0.8	3.0 ± 1.9	4.1 ± 2.3	5.0 ± 1.6	4.3 ± 1.0	2.2 ± 0.8	0.7 ± 0.4
4	0.0	0.5 ± 0.4	2.8 ± 1.3	4.1 ± 1.3	6.6 ± 1.2	6.6 ± 1.7	4.1 ± 1.5	1.9 ± 0.6	0.6 ± 0.2	0.2 ± 0.1
5	0.0	0.1 ± 0.2	3.6 ± 2.7	7.3 ± 5.3	9.6 ± 5.8	10.0 ± 3.3	8.7 ± 2.7	7.0 ± 2.6	3.2 ± 3.2	0.9 ± 0.7
Paired *t*-test		4 > 1–3	4,5 > 1–3	4,5 > 1–3	4,5 > 1–3	4 > 1; 5 > 1–3	5 > 1,2,4	1–3 > 4; 5 > 2,4	1–3 > 4; 2,3 > 1	1–3,5 > 4

[a] Amoxicillin levels significantly higher ($p < 0.05$) than ampicillin levels for this sampling time and treatment. [b] Significant at $p < 0.05$ among treatments. [c] No significant differences.

Figure 1—*Average serum ampicillin levels.*

after dosing, and aliquots were deep frozen until assayed. All assays were carried out within 72 hr of sampling.

Treatments—It is recognized that bioavailability comparisons between compounds are best studied in a crossover fashion. However, the primary aim of the overall study was to compare bioavailability among treatments for each compound. Therefore, the amoxicillin study was done immediately following the ampicillin study. All subjects participated in both studies.

Subjects received single 500-mg doses of ampicillin[2] or amoxicillin[3] as two 250-mg capsules. High carbohydrate, high fat, and high protein test meals were prepared and standardized as described previously (9). Each drug was administered as the following treatments:

Treatment 1—Two capsules with 250 ml of water immediately following a standard high carbohydrate meal.

Treatment 2—Two capsules with 250 ml of water immediately following a standard high fat meal.

Treatment 3—Two capsules with 250 ml of water immediately following a standard high protein meal.

Treatment 4—Two capsules with 25 ml of water on an empty stomach.

Treatment 5—Two capsules with 250 ml of water on an empty stomach.

All subjects received the same treatment at the same time. Treatments were administered 2 weeks apart, and all subjects received all treatments. Capsules were swallowed whole.

Assay—Serum and urine ampicillin and amoxicillin were assayed using a microbiological disk diffusion method with *Sarcina lutea* (ATCC 9341) as the test organism as described elsewhere (10).

Interpretation of Results—Individual serum antibiotic levels were fitted graphically to the standard one-compartment open model with first-order absorption and elimination. With this model, serum concentrations, C, at any time, t, after dosing are described by:

$$C = \frac{FD}{V}\frac{k}{k-K}(e^{-Kt} - e^{-kt}) \qquad \text{(Eq. 1)}$$

where F is the fraction of the dose, D, absorbed, V is the drug distribution volume in the body, and k and K are first-order rate constants for absorption and elimination, respectively. Improved estimates of parameters, together with coefficients of determination, r^2, were obtained by iterative least-squares methods using the program NREG on a digital computer[4] (11). Data fitting was improved in some cases by incorporating a lag time, t_0, representing the time period between dosing and the appearance of the antibiotic in the circulation.

Serum levels at each sampling time, urine data, and pharmacokinetic parameters were examined by analysis of variance. If significant differences due to treatments were obtained ($p < 0.05$), results from individual treatments were compared by a paired t-test.

RESULTS

Serum Levels—Mean serum antibiotic concentrations, together with statistical analysis, are given in Table I; the data are summarized

[2] Ampicillin trihydrate, Polycillin, Bristol Laboratories.
[3] Amoxicillin trihydrate, Polymox, Bristol Laboratories.
[4] Univac model 1110.

Table II—Concentrations and Percentage Recoveries of Ampicillin and Amoxicillin in 8-hr Urine (±1 *SD*)

Compound	Treatment 1	2	3	4	5	Paired *t*-Test
Ampicillin						
Concentration, μg/ml	313 ± 131	781[a]	207 ± 89	1105 ± 411	970[a]	4 > 1,3
Recovery, %	27.2 ± 17.5	42.8[a]	21.8 ± 5.7[b]	66.4 ± 24.9	82.8[a]	4 > 1,3
Amoxicillin						
Concentration, μg/ml	540 ± 278	478 ± 143	341 ± 247	827 ± 289	1491 ± 382	5 > 1–4
Recovery, %	41.3 ± 20.1	55.7 ± 21.4	36.6 ± 25.0	49.1 ± 9.2	85.3 ± 29.7	5 > 1–4

[a] Complete recoveries were obtained from two subjects only. [b] Amoxicillin recoveries significantly higher than ampicillin recoveries.

graphically in Figs. 1 and 2. Urine antibiotic concentrations and recoveries are summarized in Table II, and averaged results from the pharmacokinetic analyses are given in Tables III and IV.

It is clear from Table I and Figs. 1 and 2 that circulating levels of both ampicillin and amoxicillin were significantly reduced by the test meals under conditions used in this study. Treatments 4 and 5 yielded high serum levels of ampicillin compared to the food treatments for the first 3 hr after dosing. After this time, similar serum levels were obtained from all treatments. Serum amoxicillin levels were reduced similarly by the food treatments. These levels also were reduced following the 2-hr postdosing period when amoxicillin was given with 25 ml of water (Treatment 4).

Despite the higher serum levels generally observed with amoxicillin, differences between ampicillin and amoxicillin levels for the same treatment were significant in only a few cases. No significant differences were obtained during the first 2 hr after dosing, due, in part at least, to the scatter between individual serum levels. No significant differences were observed in serum levels among food treatments for either compound.

Urine Recovery—Failure by some subjects to provide complete 8-hr urine samples prevented the statistical comparison of urine concentration and recovery data in some instances (Table II). However, both fasting treatments resulted in higher urine concentrations and recoveries of ampicillin than the food treatments. Whereas Treatment 5 also resulted in increased amoxicillin concentrations and recoveries than the food treatments, values from Treatment 4 did not differ significantly from food treatment values.

Pharmacokinetic Analysis—Analysis of individual serum ampicillin and amoxicillin levels in terms of the simple one-compartment model was complicated by the similar numerical values obtained in many cases for the absorption and elimination rate constants. Almost identical values for these rate constants were reported before for ampicillin and amoxicillin (12). In this type of situation, it is difficult to determine which of the two rate constants, obtained by graphical analysis, represents absorption and elimination. This type of "flip-flop" model was discussed previously (13). Where this problem arose in the present study, the rate constant equivalent to an elimination half-life closest to 1 hr was designated as the elimination rate constant. This arbitrary designation was based on considerable evidence from the literature that both ampicillin and amoxicillin half-lives are close to 1 hr in normal subjects (4–6, 12).

The degree of fit of individual serum levels to the one-compartment model is reflected in the coefficient of determination values in Tables III and IV. Although less than perfect fits were obtained in some cases, this result appeared to be a function of data noise rather than the model. Analysis of the data in terms of the two-compartment model resulted in a greater variance in pharmacokinetic parameter values and no improvement in the coefficients of determination.

From Tables III and IV, it is apparent that the various treatments had little influence on absorption and elimination rates. Ampicillin appeared to be eliminated somewhat faster after Treatment 5 than after all other treatments, although this finding may have been due to the continued absorption of small amounts of antibiotic during the postabsorptive phase in the food treatments resulting in a prolonged apparent elimination half-life.

The influence of food on the overall absorption efficiency of both compounds was reflected in reduced peak heights and FD/V values, reduced areas under serum level–time curves to 2 and 8 hr after dosing, and reduced calculated areas from time zero to infinity. Both fasting treatments yielded significantly greater values for these parameters than the food treatments for ampicillin. In the case of amoxicillin, however, Treatment 5 tended to give higher values than all other treatments. The serum levels, urinary excretion, and pharmacokinetic parameter values from Treatment 5 were similar to reported values in fasted subjects (1–6).

DISCUSSION

Although the superior bioavailability of amoxicillin over ampicillin in fasted subjects is well documented (4–6), there is less comparative information to support the popular notion that amoxicillin absorption is not significantly influenced by food. Neu and Winshell (14) obtained similar serum amoxicillin levels in four fasted and nonfasted subjects. However, the nature of the meal and the actual time relationship between eating and dosing were not described. No comparison was made with ampicillin.

In a subsequent study (2), the times of average peak ampicillin levels were delayed by 2 hr and amoxicillin levels by 1 hr in nonfasting subjects. Peak serum amoxicillin levels were unchanged by food, while peak serum ampicillin levels were reduced by approximately 20%. A third study reported similar serum amoxicillin levels when the drug was administered as repeated doses either before or 0.5 hr after lunch (7). The actual time

Table III—Values of Pharmacokinetic Parameters (±1 *SD*) for Ampicillin

Parameter	Treatment 1	2	3	4	5	Paired *t*-Test
k, hr^{-1}	0.36 ± 0.15	0.34 ± 0.13	0.64 ± 0.25	0.45 ± 0.23	0.57 ± 0.22	NSD
$t_{1/2(abs)}$, hr	2.2 ± 0.8	2.4 ± 1.2	1.2 ± 0.4	0.3 ± 2.0	1.4 ± 0.5	NSD
K, hr^{-1}	0.52 ± 0.13	0.66 ± 0.32	0.46 ± 0.10	0.53 ± 0.18	0.76 ± 0.15[a]	5 > 1–3
$t_{1/2(elim)}$, hr	1.4 ± 0.4	1.2 ± 0.5	1.6 ± 0.4	1.4 ± 0.5	0.9 ± 0.2[a]	1–3 > 5
FD/V[b], μg/ml	9.4 ± 4.9[a]	5.3 ± 1.7[a]	5.7 ± 1.9[a]	18.3 ± 10.0	18.6 ± 3.9	4 > 2,3; 5 > 1–3
Area 0 → 2[c], μg × hr/ml	1.6 ± 1.0	1.8 ± 0.4	2.1 ± 1.0	6.0 ± 2.5	7.1 ± 2.2	4,5 > 1–3
Area 0 → 8[c], μg × hr/ml	13.1 ± 4.6	12.4 ± 2.1[a]	10.1 ± 3.1	26.1 ± 9.3	22.7 ± 6.9[a]	4,5 > 1–3
Area 0 → ∞[d], μg × hr/ml	9.6 ± 4.0[a]	13.2 ± 6.3	10.7 ± 5.7[a]	25.8 ± 8.1	19.4 ± 5.0[a]	4,5 > 1–3
t_0, hr	0.4 ± 0.1	0.5 ± 0.2	0.4 ± 0.2	0.0	0.2 ± 0.2	1–3 > 4
r^{2e}	0.85	0.94	0.93	0.90	0.96	—
Peak height, μg/ml	4.0 ± 1.8	2.9 ± 0.4[a]	2.9 ± 1.0[a]	6.9 ± 2.0[a]	6.5 ± 1.6[a]	4,5 > 2,3
Time of peak height, hr	3.2 ± 0.8	2.5 ± 0.8	2.3 ± 0.5	2.7 ± 0.5	1.9 ± 0.8	1 > 5

[a] Values in this table significantly different from those for amoxicillin (Table IV). [b] Fraction of dose absorbed expressed as concentration in its distribution volume in the body. [c] Obtained by trapezoidal rule. [d] Obtained from FD/VK. [e] $(\Sigma obs^2 - \Sigma dev^2)/\Sigma obs^2$.

Table IV—Values of Pharmacokinetic Parameters (±1 *SD*) for Amoxicillin[a]

Parameter	Treatment 1	2	3	4	5	Paired *t*-Test
k, hr^{-1}	0.29 ± 0.10	0.32 ± 0.18	0.40 ± 0.11	0.69 ± 0.20	0.65 ± 0.35	4 > 1–3
$t_{1/2(abs)}$, hr	2.6 ± 0.7	3.2 ± 2.7	1.9 ± 0.5	1.1 ± 0.3	1.6 ± 1.1	NSD
K, hr^{-1}	0.56 ± 0.16	0.53 ± 0.13	0.41 ± 0.14	0.62 ± 0.10	0.50 ± 0.12	NSD
$t_{1/2(elim)}$, hr	1.3 ± 0.4	1.4 ± 0.3	1.8 ± 0.6	1.2 ± 0.2	1.5 ± 0.4	NSD
FD/V, μg/ml	14.6 ± 4.3	18.4 ± 6.0	12.0 ± 4.7	14.2 ± 4.6	26.4 ± 6.9	5 > 1–4
Area 0 → 2, μg × hr/ml	2.3 ± 1.8	3.7 ± 2.2	3.2 ± 1.8	7.7 ± 1.5	11.5 ± 6.5	4,5 > 1–3
Area 0 → 8, μg × hr/ml	18.8 ± 3.0	23.9 ± 5.8	21.9 ± 5.6	19.2 ± 3.8	42.9 ± 6.4	5 > 1–4
Area 0 → ∞, μg × hr/ml	21.8 ± 8.2	21.7 ± 6.4	19.6 ± 8.0	18.1 ± 5.8	39.4 ± 8.4	5 > 1–4
t_0, hr	0.4 ± 0.2	0.3 ± 0.0	0.4 ± 0.3	0.1 ± 0.1	0.2 ± 0.2	1,2 > 4,5
r^2	0.84	0.90	0.90	0.91	0.92	—
Peak height, μg/ml	5.4 ± 1.3	6.5 ± 2.5	5.4 ± 1.6	7.0 ± 1.3	12.6 ± 3.0	4 > 1; 5 > 1–4
Time of peak height, hr	3.5 ± 0.6	3.7 ± 1.4	3.0 ± 0.6	1.8 ± 0.3	2.5 ± 1.8	1–3 > 4

[a] Symbols are as defined in Table III.

elapsed between the prelunch dose and eating was not indicated, and no comparison was made with ampicillin.

When 500 mg of ampicillin and amoxicillin were given immediately following a standard breakfast, peak serum levels of 2.1 and 5.9 μg/ml were obtained, respectively (8). These values were similar to those obtained from the food treatments in the present study.

During this study, in which nonfasted subjects received the drugs immediately following a standard meal, all food treatments reduced peak serum antibiotic levels by about 50%. However, serum amoxicillin levels in nonfasted subjects were almost identical to ampicillin levels in fasted subjects. Thus, although serum levels of both antibiotics appeared to be reduced to the same extent by food, the reduction was probably of less clinical significance for amoxicillin.

Reducing the dosed water volume from 250 to 25 ml in fasted subjects caused a significant reduction in serum amoxicillin levels, but ampicillin levels were affected to only a small extent. This difference may be explained by comparing the water solubilities of the antibiotics. One gram of ampicillin trihydrate dissolves in about 90 ml of water whereas 1 g of amoxicillin trihydrate dissolves in about 370 ml (15). Thus, any reduction in dosed water volume is likely to reduce the dissolution and subsequent absorption of amoxicillin to a greater extent than ampicillin.

The results of this study indicate that oral absorption of both ampicillin and amoxicillin is reduced to a similar extent when administered immediately following a meal, although the reduction in ampicillin levels may be of greater clinical significance. The bioavailability of amoxicillin is reduced when given with small water volumes in fasted subjects.

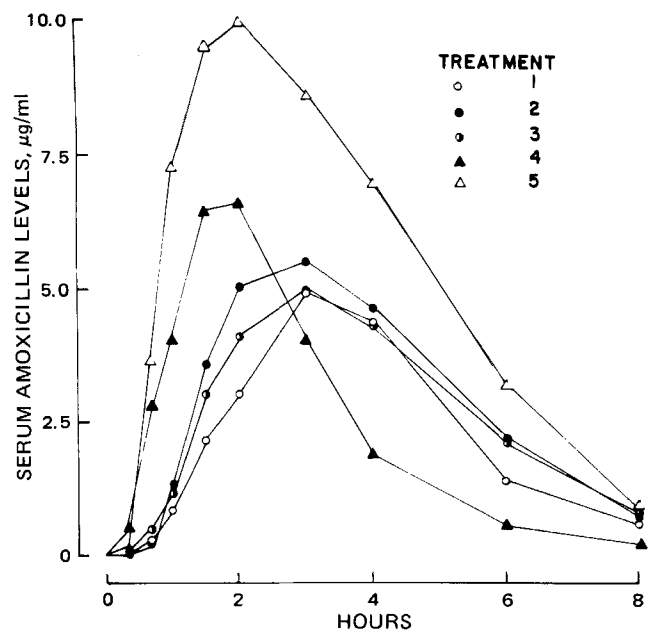

Figure 2—*Average serum amoxicillin levels.*

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