ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 1978, p. 539-543
0066-4804/78/0014-0539$02.00/0

Vol. 14, No. 4
Printed in U.S.A.

Pharmacokinetics of Amoxicillin and Ampicillin: Crossover Study of the Effect of Food

FRED N. ESHELMAN[1] AND DANIEL A. SPYKER[2]

Beecham Laboratories, Bristol, Tennessee 37620,[1] and Department of Internal Medicine, Division of Clinical Pharmacology, University of Virginia School of Medicine, Charlottesville, Virginia 22908[2]

Received for publication 3 April 1978

The effect of food on the absorption of amoxicillin and ampicillin was studied in 16 normal subjects in a double-blind crossover study after each subject was given a single oral 500-mg dose. Serum drug levels were analyzed, assuming a one-compartment linear model with first-order absorption and absorption delay, area under the curve, and urinary recovery. Variations in kinetic parameters were examined by using analysis of variance. The results showed little or no effect of fasting versus nonfasting on amoxicillin absorption, as evidenced by peak serum levels (8.9 μg/ml, fasting, 8.8 μg/ml, nonfasting), area under the curve (26.9 μg/ml per 70 kg, fasting, 22.2 μg/ml per 70 kg, nonfasting), and urinary recovery (47%, fasting; 44%, nonfasting). Ampicillin absorption was significantly decreased in the nonfasted group by the same parameters (peak level: 5.4 μg/ml, fasting, 4.0 μg/ml, nonfasting; area under the curve, 17.4 h·μg/ml, fasting, 12.0 h·μg/ml, nonfasting; urinary recovery, 37%, fasting, 29%, nonfasting). These results confirm the reliable absorption of orally administered amoxicillin in the fed as well as the fasted state.

Although amoxicillin and ampicillin are similar in chemical structure and microbiological activity spectrum, amoxicillin yields higher blood and urine levels at equivalent doses after oral administration (1, 3, 4, 7, 8, 10, 14). Most authors have found the effect of food on the absorption of amoxicillin to be insignificant (6, 9, 12), with the exception of a recent study by Welling et al. (13). The present double-blind, crossover study was designed to quantitate the effect of food versus fasting on the absorption of orally administered amoxicillin or ampicillin.

MATERIALS AND METHODS

Subjects and procedure. Sixteen healthy males 19 to 30 years old and weighing between 65 and 84 kg (mean, 75 kg) were entered into the study after giving written informed consent. All subjects were in good health as judged by physical examination, urinalysis, hematology, and serum biochemistry; negative histories were obtained for allergy to any form of penicillin or cephalosporin. None of the volunteers were taking concomitant medication, nor had any received antimicrobial agents in the 2 weeks preceding the study (1 month for benzathine penicillin).

After an overnight fast, the subjects were not permitted any food or drink until 3 h after dose administration, with the exception of subjects randomly chosen to eat the test meal. Individuals were assigned consecutive numbers on the basis of increasing weight and were randomly assigned to one of two groups balanced according to weight. Medication was administered double blind as 500-mg capsules of amoxicillin or ampicillin (Amoxil or Totacillin, Beecham Laboratories) in a crossover design. All subjects completed each treatment, and there was 1 week between treatments.

Subjects randomized to receive food were given a standard breakfast consisting of orange juice, toast, eggs, bacon, and coffee 15 min before the administration of medication.

At the beginning of the study (zero time), all subjects emptied their bladders, and blood samples were obtained. The assigned capsules were given with 120 ml of water. Additional venipunctures were performed at 1, 2, 3, 6, and 8 h after the medication was consumed. The subjects voided at 8 h and all urine voided during the 8-h study was retained.

Assay. Blood samples were allowed to clot and were centrifuged, and sera were immediately frozen at −5°C until assay. Portions (10 ml each) of the urine collected at zero time and at 0 to 8 h were also frozen until assay. All samples collected at 1, 2, 3, and 6 h were assayed by the large plate microbiological method, with *Staphylococcus aureus* (ATCC 6538P) as the assay organism. Samples collected at 0 and 8 h were assayed by the small plate method, with *Sarcina lutea* (ATCC 9341) as the assay organism. Any samples collected at 1, 2, 3, or 6 h showing levels below 1 μg/ml on large plates were reassayed by the small plate method.

Pharmacokinetic analysis. Data for each subject (available on request) were entered via a computer terminal, stored directly on disk files, and verified. Thereafter, data were manipulated only by pharmacokinetic and statistical computer programs.

Serum level data were well described by a single-compartment open model with first-order absorption process. An iterative least-squares method was used to find the volume of distribution (V_d), absorption rate

constant (K_a), elimination rate constant (K_e), and absorption lag which best described the observed serum levels for each patient (11). As an initial step in the analysis, individual plots of observed and predicted serum levels were generated by computer and examined. We have found this step to be particularly valuable in automated pharmacokinetic analysis.

Subsequent statistical analysis is based on the individual kinetic model for each subject. The area under the curve (AUC) and urinary recovery (UR) were examined for each drug, using least-squares linear regression as a function of measured weight, height, and body surface area (2). We found the coefficient of variation (ratio of within-group standard deviations to means) to be minimized for AUC when corrected by weight. For UR, the coefficient of variation was not improved by correcting for height, weight, or surface area. Subsequent analyses are thus reported for AUC, and peak concentration is corrected for weight, whereas UR is uncorrected.

Statistical analysis. The total area under the serum concentration curve (AUC) is probably the best single measure of drug bioavailability when elimination remains constant. UR provides an independent measure of drug absorption. Our (null) hypothesis was that the test meal would not affect AUC or UR for either drug and that there would be no difference between drugs.

Analysis of variance was applied to each pharmacokinetic parameter. For each dependent variable (AUC, K_e, UR, etc.), the amoxicillin and ampicillin data were examined separately for the effect of food, as well as for the overall drug effect and food effect.

RESULTS

Absorption kinetics. No statistical difference was observed in the K_a for ampicillin or amoxicillin after a meal (Tables 1 and 2), although the average K_a was 1.39/h for ampicillin and 0.99/h for amoxicillin. Absorption delay (lag time) was increased for both drugs with the test meal, as shown in Table 2, possibly reflecting a slower capsule disintegration or increased stomach emptying time.

Serum levels. Time to reach the peak concentration was greater in the nonfasting group with both drugs. This closely parallels the increase in lag time, since the K_a showed little change. Mean peak serum levels of amoxicillin were 8.9 μg/ml in the fasted and 8.8 μg/ml in the nonfasted subjects. Mean peak ampicillin levels were 22% lower after the test meal, with an associated $P = 0.055$ (Table 2). Ampicillin peak levels were 41% of amoxicillin levels.

AUC. The mean AUC for amoxicillin was 5% less after the test meal. Ampicillin AUC was reduced by 31%, with an associated $P = 0.003$. The average AUC for amoxicillin was approximately twice that of ampicillin. A graphical comparison of the two drugs in the fasting versus nonfasting state is presented in Fig. 1. These curves represent the concentrations resulting

TABLE 1. *Summary of pharmacokinetic parameters*[a]

Subject	Absorption				Peak				AUC		UR		K_e	
	K_a		Delay		Time		Concn							
	Amox	Amp	Amox	Amp	Amox	Amp	Amox	Amp	Amox	Amp	Amox	Amp	Amox	Amp
Fasting	0.80	0.58	0.56	0.34	1.86	1.49	8.9	5.9	30.9	19.8	47.1	37.1	0.69	0.61
	(0.21)	(0.31)	(0.25)	(0.36	(0.30)	(0.50)	(2.3)	(2.1)	(5.9)	(5.5)	(22.0)	(12.1)	(0.12)	(0.24)
Non-fasting	0.71	0.57	1.19	1.43	2.40	2.48	8.8	4.6	29.2	13.7	43.3	26.8	0.71	0.75
	(0.20)	(0.20)	(0.37)	(0.61)	(0.41)	(0.74)	(2.0)	(1.6)	(6.1)	(4.9)	(18.2)	8.3	(0.19)	(0.25)
Avg	0.76	0.58	0.87	0.88	2.13	1.98	8.9	5.2	30.0	16.7	45.2	32.0	0.70	0.68
	(0.21)	(0.25)	(0.45)	(0.74)	(0.45)	(0.80)	(2.2)	(1.9)	(6.0)	(6.0)	(19.9)	(11.5)	(0.15)	(0.25)

[a] Values indicate the mean of 16 subjects tested. Values in parentheses indicate standard deviations.

TABLE 2. *Analysis of variance for effect of food and drug*[a]

Determination	Effect (%) of:	
	Food	Drug
K_a		
Amox	−11 ($P = 0.22$)	−24 ($P = 0.0029$)
Amp	−2 ($P = 0.91$)	
Absorption delay		
Amox	114 ($P = 0.00003$)	1 ($P = 0.95$)
Amp	315 ($P = 0.00002$)	
Time to peak		
Amox	29 ($P = 0.00033$)	−7 ($P = 0.62$)
Amp	67 ($P = 0.00026$)	
Peak concn		
Amox	−1 ($P = 0.88$)	−41 ($P < 0.00001$)
Amp	−22 ($P = 0.056$)	
AUC		
Amox	−5 ($P = 0.55$)	−44 ($P < 0.00001$)
Amp	−31 ($P = 0.0026$)	
UR		
Amox	−8 ($P = 0.60$)	−20 ($P = 0.0022$)
Amp	−28 ($P = 0.0089$)	
K_e		
Amox	2 ($P = 0.77$)	−3 ($P = 0.72$)
Amp	22 ($P = 0.12$)	

[a] Amox, amoxicillin; amp,ampicillin.

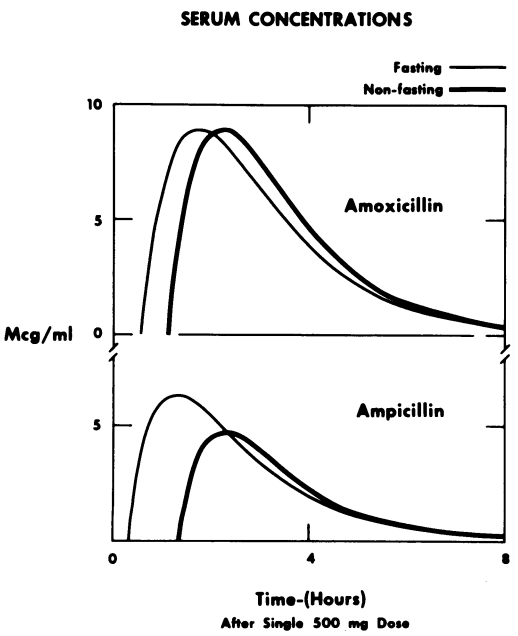

FIG. 1. *Serum concentrations of amoxicillin and ampicillin for fasting and nonfasting subjects. Curves represent the average of individual kinetic parameters within each group.*

from the average pharmacokinetic parameters (Table 1).

UR. The UR results paralleled the AUC data. Excretion of ampicillin was reduced by 28% after eating, whereas amoxicillin excretion was reduced by 8%. Overall average UR was 45% for amoxicillin and 32% for ampicillin. No statistical difference in the K_e values was observed for either drug in the fasting versus nonfasting state. Half-lives yielded by these K_e values would be approximately 1 h for both drugs.

DISCUSSION

Comparison of previous reports of the effect of food on the absorption of amoxicillin and ampicillin is difficult. Only two studies have been found in the literature which measure the two drugs together in regard to fasting versus nonfasting serum levels (8, 13). A crossover study of 12 patients showed amoxicillin peak levels to be unaffected by food, but ampicillin levels decreased; the same pattern held for AUC (8). However, data were not tabulated, and estimates could only be made from figures. Welling and colleagues reported a statistically significant meal effect on both ampicillin and amoxicillin, but the study did not follow a crossover design (13).

Pharmacokinetic parameters for amoxicillin and ampicillin in fasting and nonfasting patients are listed in Table 3. In fasting studies, Philipson et al. noted a sequence effect, with ampicillin levels increasing and amoxicillin levels decreasing in the legs subsequent to the initial dose (10). Differences in AUC values may be due in part to calculation methods; Gordon et al. weighed graphs (3), whereas other authors used computer generation or the trapezoidal rule. Lode et al. noted the scattering of values prevalent in studies of ampicillin absorption, underscoring the importance of crossover design and complete reporting of all experimental conditions (7).

In nonfasting patients, Little and Peddie found no significant meal effect in a multidose study, but the design precludes meaningful comparison with other papers (6). In addition to the data for 500-mg doses, Vitti et al. studied other regimens in nonfasting patients (12). Amoxicillin given as a single 3-g dose was compared to 3.5 g of ampicillin plus 1 g of probenecid. Peak levels and AUC were almost identical. Other reports which involved amoxicillin alone have also demonstrated little or no food effect. Neu and Winshell measured fasting and nonfasting levels of amoxicillin in four patients after a 500-mg dosage and found peak levels of approximately 8 μg/ml in each group (9). The AUC appeared unchanged; interestingly, the time to peak was 1 h after the meal, but occurred 2 h after dose administration in the fasted group. Croydon and Sutherland gave 375 mg of amoxicillin to each subject in a crossover food effect study; the peak level at 2 h was decreased somewhat (7.3, fasting, versus 5.9, nonfasting), but UR was 53% in each group (1).

The present study is comparable only to that of Welling et al. (13), since both were specifically designed to investigate food effect and included ampicillin and amoxicillin. Differences may be explained by several factors, all of which may interact.

In the Welling study, subjects received 250 ml of water 1 h before the dose, and then either 25 or 250 ml with the dose of ampicillin or amoxicillin. Our subjects were given 120 ml only at the time of medication adminsitration. Since the water solubilities of amoxicillin trihydrate and ampicillin trihydrate are 4 and 6.6 mg/ml, respectively, some volume effect might be anticipated. Limited in vitro dissolution data indicate increased dissolution rates for amoxicillin at lower pH, but more definitive studies have not been completed (data on file at Beecham Laboratories). Additionally, the disintegration rates

TABLE 3. *Reported pharmacokinetic parameters for amoxicillin and ampicillin in fasting and nonfasting subjects*[a]

Study	No. of subjects	Ampicillin				Amoxicillin			
		Peak[b]		AUC (h·μg/ml)	UR (%)	Peak[b]		AUC (h·μg/ml)	UR (%)
		Concn (μg/ml)	Time (h)			Concn (μg/ml)	Time (h)		
Philipson et al. (10)	11 F	5.0	2.0	17.5	50.4	6.2	2.3	22.0	56.7
Gordon et al. (3)	8 F	3.2	1.8	50% amox	33.8	8.2	1.2	2× amp	60.2
Lode (7)	13 F	3.8	2.0	12.4	33.6	6.4	2.0	22.2	58.0
Neu (8)	8 F	4.5	1.6		42	9.7	1.8		79
	12 NF	3.2	3.0			7.8	2.0		
Neu and Winshell (9)	21 F	3.8	2		44.5	7.6	2		75.2
	8 F	4.0	2		42	8.3	2		79
Croydon and Sutherland (1)	12 F	6.3	2		40	10.8	2		60
Kirby et al. (4)	8 F	3.2	2	50% amox	30–35	7.6	1.5	2× amp	60
Vitti et al. (12)	8 NF	2.4	2.0	8.17		7.3	2.4	20.1	
Welling et al. (13)	6 F[c]	6.1	3	25.8	66.4	6.6	1.5–2	18.1	49.1
	6 F[d]	6.1	2	19.4	82.8[e]	10.0	2	39.4	85.3
	6 NF[f]	3.0	2.7	11.2	30.6	5.2	3	21.0	44.5
This study	16 F	5.4	1.8	17.4	37.1	8.9	2.1	26.9	47
	16 NF	4.0	2.6	12.0	26.8	8.8	2.6	25.5	43.3

[a] All except Welling study (13) were crossover studies. Each dose was 500 mg, given orally. amp, Ampicillin; amox, amoxicillin; F, fasting; NF, nonfasting.

[b] Peak refers to individual mean peak.

[c] Water volume was 25 ml.

[d] Water volume was 250 ml.

[e] Data for two subjects only.

[f] Average of three meal types; water volume was 250 ml.

of the capsules may have an effect on absorption rate as well as total absorption. Gordon et al. gave 100 ml of water with each 500-mg dose of amoxicillin and noted a peak serum level of 8.24 μg/ml, as compared to our value of 8.04 μg/ml (3). Results of the Lode Study, which used the same dose but with 50 ml of water, were very close to those of the Welling study, in which 25-ml amounts of water were used (peak, 6.41 versus 6.6 μg/ml; UR, 58 versus 49%; AUC, 22.2 versus 18.1 h·μg/ml). When 250 ml was the water volume, Welling et al. found values well above those reported elsewhere for amoxicillin (UR, 85.3%; AUC, 39.4 h·μg/ml). Thus, physiological differences in emptying time, residual volume, and basal pH are additional reasons for crossover, which unfortunately was not the design in the Welling report.

The lag times (time intervals between drug administration and appearance in the blood) found in this study (0.56 h, fasting, and 1.19 h nonfasting) were longer than those previously reported. The lag time in the Welling study was 0.37 h in nonfasting subjects which matches the findings of Spyker et al. (0.31 h) and Zarowny et al. (0.34 h) (11, 14) in fasting patients. However, our absorption rate constants (0.92/h fasting, and 1.05/h nonfasting) fit nicely with the reports on fasting patients of Zarowny (1.08/h) and Spyker (0.90/h), whereas Welling et al. reported values (0.67/h fasting, and 0.34/h nonfasting) that would yield longer absorption half-lives.

As Levy and Hollister have pointed out (5), large intersubject and intrasubject variations in drug absorption and elimination kinetics may be encountered clinically. Interpretation of absorption studies can be confusing, especially when distribution volumes vary and/or K_a is not much greater than K_e. Levy and Hollister suggest that in such cases actual absorption values would permit a more sensitive statistical comparison of drug absorption. Examination of the data of Welling et al. reveals just such a situation in which K_a and K_e are almost indistinguishable. No significant difference was shown in absorption half-life between fed and fasted patients.

Comparison of our results with those of Welling is also difficult in view of the fact that different preparations of amoxicillin were used. Formulation differences may lead to varying results in disintegration and dissolution and, therefore, absorption.

In summary, the results of the present double-blind crossover study in 16 subjects show no significant effect of food on amoxicillin absorption as judged by individual mean serum peak, AUC, and UR. These same parameters were significantly reduced when ampicillin was given after a meal.

LITERATURE CITED

1. **Croydon, E. A. P., and R. Sutherland.** 1971. α-Amino-p-hydroxyldenzyl penicillin (BRL 2333), a new semisynthetic penicillin: absorption and excretion in man, p. 427-433. Antimicrob. Agents Chemother. 1971.
2. **Dubois, D., and E. F. Dubois.** 1916. A formula to estimate the approximate surface area if height and weight be known. Arch. Intern. Med. **17**:863-871.
3. **Gordon, R. C., C. Regamey, and W. M. M. Kirby.** 1972. Comparative clinical pharmacology of amoxicillin and ampicillin administered orally. Antimicrob. Agents Chemother. **1**:504-507.
4. **Kirby, W. M. M., R. C. Gordon, and C. Regamey.** 1974. The pharmacology of orally administered amoxicillin and ampicillin. J. Infect. Dis. **129**:S154-S155.
5. **Levy, G., and L. E. Hollister.** 1964. Inter- and Intrasubject variations in drug absorption kinetics. J. Pharm. Sci. **53**:1446-1452.
6. **Little, P. J., and B. A. Peddie.** 1974. Absorption and excretion of amoxicillin and pivampicillin, two new semisynthetic penicillins. Med. J. Aust. **2**:598-600.
7. **Lode, H., et al.** 1974. Comparative clinical pharmacology of three ampicillins and amoxicillin administered orally. J. Infect. Dis. **129**:S156-S168.
8. **Neu, H. C.** 1974. Antimicrobial activity and human pharmacology of amoxicillin. J. Infect. Dis. **129**:S123-S131.
9. **Neu, H. C., and E. B. Winshell.** 1971. Pharmacological studies of 6 [D(-)α-amino-p-hydroxyphenylacetamido] penicillanic acid in humans, p. 423-426. Antimicrob. Agents Chemother. 1970.
10. **Philipson, A., L. D. Sabath, and B. Rosner.** 1975. Sequence effect on ampicillin blood levels noted in an amoxicillin, ampicillin, and epicillin triple crossover study. Antimicrob. Agents Chemother. **8**:311-320.
11. **Spyker, D. A., R. J. Rugloski, R. L. Vann, and W. M. O'Brien.** 1977. Pharmacokinetics of amoxicillin: dose dependence after intravenous, oral, and intramuscular administration. Antimicrob. Agents Chemother. **11**:132-141.
12. **Vitti, T. G., M. J. Gurwith, and A. R. Ronald.** 1974. Pharmacologic studies of amoxicillin in nonfasting adults. J. Infect. Dis. **129**:S149-S153.
13. **Welling, P. G., et al.** 1977. Bioavailability of ampicillin and amoxicillin in fasted and non-fasted subjects. J. Pharm. Sci. **66**:549-552.
14. **Zarowny, D., R. Ogilvie, D. Tamblyn, et al.** 1974. Pharmacokinetics of amoxicillin. Clin. Pharmacol. Ther. **16**:1045-1051.