ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1980, p. 199-202
0066-4804/80/02-0199/03$02.00/0

Vol. 17, No. 2

Absorption and Disposition Kinetics of Amoxicillin in Normal Human Subjects

A. ARANCIBIA,[1]* J. GUTTMANN,[1] G. GONZÁLEZ,[1] AND C. GONZÁLEZ[2]

Department of Pharmaceutical Sciences[1] and Department of Biological Chemistry,[2] Faculty of Chemical and Pharmacological Sciences, University of Chile, Casilla 233, Santiago, Chile

Pharmacokinetic parameters of amoxicillin were studied in healthy fasted subjects after both oral and intravenous administration of a single 500-mg dose. Serum levels and urinary excretion rates were determined at various time intervals by a microbiological method. The conventional two-compartment model with elimination occurring from the central compartment was used to analyze the data. Mean values were 3.40 h^{-1} for α and 0.68 h^{-1} for β. Distribution constants k_{12} and k_{21} were 0.92 h^{-1} and 1.99 h^{-1}, respectively. The rate constant for elimination from the central compartment, k_{10}, was 1.16 h^{-1}. The volume of distribution was 20.2 liters (0.30 liter/kg), and the serum clearance was 13.3 liters/h. The absorption rate constant, k_a, in the oral study, calculated by the Loo-Riegelman method, was 1.02 h^{-1}, and the absorption half-life was 0.72 h. Absolute bioavailability after the oral dose was determined by comparing both the areas under the curve (AUC) and fractions of the antibiotic excreted unchanged in the urine. The AUC after oral administration was 77.4% of the intravenous AUC. On the other hand, recovery from the urine was 43.4% after the oral dose and 57.4% after the intravenous dose, indicating 76.5% bioavailability.

Amoxicillin, α-amino-p-hydroxybenzylpenicillin, possesses antimicrobial activities very similar to those of ampicillin. However, absorption of amoxicillin from the intestinal tract is superior to that of ampicillin.

Amoxicillin has been widely studied from the toxicological, microbiological, and clinical points of view (4, 6, 10–13, 17, 19, 21, 23). In contrast, there are few pharmacokinetic studies (8, 18, 20, 26). In only two of these was the antibiotic given intravenously (i.v.) (20, 26). Intravascular administration of a drug makes it possible to calculate disposition parameters more accurately than delivery by the oral or intramuscular route, where an absorption step is needed for the drug to reach the general circulation. The purpose of the current investigation was to study the pharmacokinetic properties of amoxicillin when administered i.v. and its bioavailability after oral dosage.

MATERIALS AND METHODS

Subjects. Nine healthy volunteers, seven males and two females ranging in age from 21 to 45 years old (mean, 28.3 years) and in weight from 46 to 88 kg (mean, 66.4 kg), participated in this study. Written informed consent was obtained, and medical history, physical examination, and various laboratory tests (complete blood count, hematocrit, serum alkaline phosphatase, serum glutamate pyruvate transaminase, serum glutamate oxalate transaminase, creatinine clearance, and urinalysis) were carried out prior to start of the study. The results of these examinations were within normal limits for all volunteers. None had a history of allergy to penicillin or had received any medication for 30 days before the study.

Administration of amoxicillin. The subjects were divided into two groups. Initially, one group received 500 mg of amoxicillin i.v. and the other received the same dose orally. Two weeks later, dosage was repeated with the routes of administration reversed for the respective groups.

A solution of amoxicillin sodium sterile (provided by Beecham Pharmaceuticals, Clifton, N.J.) containing 500 mg of the antibiotic and 25 mg of trisodium phosphate was injected i.v. within 10 s. Blood samples were drawn before injection and at 5, 10, 15, 20, 30, 45, 60, 75, and 90 min and 2, 3, 4, 5, and 6 h thereafter. A 500-mg capsule (Amoxil; Beecham Laboratories, provided by Laboratorios Saval S.A., Santiago, Chile) was administered per os with 250 ml of water. Blood samples were drawn before dosage and at 20, 30, 45, 60, 75, and 90 min and 2, 3, 4, 5, 6, and 7 h thereafter. The antibiotic was administered at 8 a.m. after an overnight fast. Fasting was continued for the first 3 h after i.v. and 4 h after oral administrations. Urine was collected before dosage and then continuously in 1-h periods for 6 h in the i.v. experiments and for 7 h in the oral studies. In both experiments, 24-h urine samples were also collected.

Bioassay. Blood samples were collected in sterile glass tubes without anticoagulant, and serum was obtained by centrifugation. Urine was also collected by aseptic technique, and aliquots were stored for assay. Serum and urine samples were frozen upon collection (−20°C) and assayed within 48 h sampling.

Amoxicillin was determined by the microbiological method of Bennett et al. (3), using a large glass plate (32 by 20 cm) and *Bacillus subtilis* (ATCC 6633) as

the test microorganism. As described elsewhere (28), the sensitivity of this method is 0.25 μg/ml and the precision is ±5%.

Pharmacokinetic analysis. The plasma concentrations of amoxicillin given i.v. decline with time in a biexponential manner. These concentrations (C)-versus-time (t) data were fitted to equation 1:

$$C = A\,e^{-\alpha t} + B\,e^{-\beta t} \quad (1)$$

A nonlinear least-squares regression computer program (1) was used to obtain the best estimates of equation 1. Beta half-life ($t_{1/2\beta}$), body clearance (Cl_B), volume of the central compartment (V_1), apparent volume of distribution ($V_{d\,area}$), volume of distribution at steady state (V_{dss}), distribution rate constants (k_{12} and k_{21}), and the area under the serum concentration-time curve (AUC) were determined by classical pharmacokinetic techniques (9, 24).

Renal clearance (Cl_r) was calculated by two methods, using equations 2 and 3:

$$Cl_r = fu\ Cl_B \quad (2)$$

$$Cl_r = \frac{\Delta Xu/\Delta t}{C_{mid}} \quad (3)$$

where $\Delta Xu/\Delta t$ is the rate of urinary excretion during collection interval t, C_{mid} is the plasma concentration at the midpoint of the collection interval, and fu is the fractional urinary recovery of unchanged amoxicillin. The time at which the amount of amoxicillin in the peripheral compartment reached a maximum (t_{max}) was also calculated, using equation 4:

$$t_{max} = \frac{\ln(\alpha/\beta)}{\alpha - \beta} \quad (4)$$

When amoxicillin was given orally, AUC was calculated by the trapezoidal rule and the absorption rate constant (k_a) was calculated by the Loo-Riegelman method (15). When changes in the terminal log-linear slopes of the serum concentration-time curves between treatments were observed, the elimination rate constant after oral administration (k_{10}) was used in the calculations (24). Bioavailability (F) was determined by two methods, using equations 5 and 6.

$$F = \frac{(AUC)_0^\infty\ (oral)}{(AUC)_0^\infty\ (i.v.)} \times 100 \quad (5)$$

$$F = \frac{fu\ (oral)}{fu\ (i.v.)} \times 100 \quad (6)$$

RESULTS

Mean serum concentrations after i.v. dosage are shown in Table 1. Concentrations 5 min after i.v. injection fluctuated from 52.1 to 30.1 μg/ml and fell to approximately 1 μg/ml at 5 h. This concentration exceeds the minimal inhibitory concentration (MIC) of most amoxicillin-susceptible strains. Mean and individual serum concentration-time curves followed the biexponential pattern described by equation 1. Figure 1 shows a computer-generated curve of the mean serum concentration values of the nine subjects. Mean values for the various pharmacokinetic parameters of the two-compartment model are listed in Table 2. Disposition is characterized by a rapid phase with a $t_{1/2\alpha}$ of 16.2 min, indicating a prompt distribution to the peripheral compartment reaching a maximum at 35.6 min. The $t_{1/2\beta}$ of 1.08 h along with a k_{10} of 1.16 h^{-1} indicates that amoxicillin, like other penicillins, is eliminated rather rapidly from the body. The volume of distribution of 20.2 liters (0.30 liter/kg) is larger than the extracellular fluid volume and consistent with the protein binding approximately 20% (5, 10). The volume of the central compartment was 11.8 liters (0.18 liter/kg). The volume of distribution at steady state was 16.7 liters (0.25 liter/kg).

TABLE 1. *Serum levels after i.v. administration of 500 mg of amoxicillin to nine healthy subjects*

Sampling time (min postinjection)	Concn[a] (μg/ml)
5	42.6 ± 7.7[b]
10	31.5 ± 8.6[c]
15	28.8 ± 7.5[d]
20	22.3 ± 6.9[c]
30	18.7 ± 5.6
45	14.1 ± 4.7
60	11.1 ± 3.7
90	7.7 ± 2.5
120	4.9 ± 1.4
180	2.5 ± 0.9
240	1.3 ± 0.6
300	0.7 ± 0.4
360	0.9 ± 0.6[e]

[a] Mean ± standard deviation.
[b] Mean of six subjects.
[c] Mean of eight subjects.
[d] Mean of five subjects.
[e] Mean of three subjects (amoxicillin was not detectable in the serum of the other subjects).

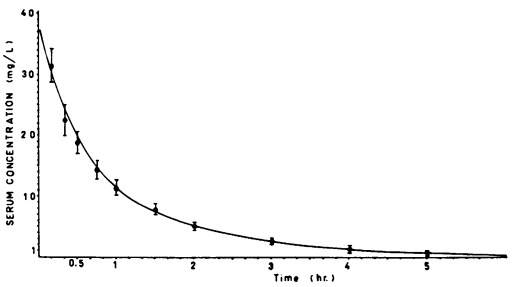

FIG. 1. *Computer-generated plot of serum concentration versus time after a 500-mg i.v. dose of amoxicillin. The serum data of all the subjects at each time were averaged to generate the curve. Bars indicate ± standard error of the mean.*

Table 3 shows that after oral administration, peak serum concentrations were achieved between 1.25 to 2.00 h and ranged from 6.0 to 15.3 μg/ml. Serum levels higher than the MIC were still present 7 h after dosage. Table 4 summarizes the pharmacokinetic parameters and absolute bioavailability of amoxicillin when administered orally. The AUC ranged from 21.0 to 30.3 mg/liter per h, with a mean of 27.4 mg/liter per h. The absorption rate constant was 1.02 h^{-1}. The mean amount of amoxicillin recovered unchanged in the urine over 24 h was 287.0 mg (57.4%) after i.v. dosage and 217.1 mg (43.4%) after oral dosage.

TABLE 2. *Pharmacokinetic parameters for amoxicillin in nine healthy subjects after a 500-mg i.v. dose*

Parameter	Value[a]
β (h^{-1})	0.68 ± 0.16
$t_{1/2\beta}$ (h)	1.08 ± 0.28
α (h^{-1})	3.40 ± 1.88
$t_{1/2\alpha}$ (h)	0.27 ± 0.15
k_{21} (h^{-1})	1.99 ± 0.99
k_{10} (h^{-1})	1.16 ± 0.37
k_{12} (h^{-1})	0.92 ± 0.85
Cl_B (liters/h)	13.3 ± 3.6
V_1 (liters)	11.8 ± 2.5
$V_{d\ area}$ (liters)	20.2 ± 5.8
V_{dss} (liters)	16.7 ± 4.0
AUC, 0–∞ (mg/liter per h)	37.0 ± 9.7
Urinary recovery over 24 h (mg)	287.0 ± 18.0

[a] Mean ± standard deviation.

TABLE 3. *Serum levels after oral administration of a 500-mg dose of amoxicillin to eight healthy subjects*

Sampling time (min post-administration)	Concn[a] (μg/ml)
20	0.3 ± 0.0[b]
30	1.6 ± 0.9[c]
45	4.6 ± 2.1
60	6.9 ± 2.6
75	8.4 ± 3.2
90	9.5 ± 3.8
120	8.8 ± 2.0
180	5.5 ± 1.7
240	3.1 ± 1.1
300	1.5 ± 0.6
360	0.9 ± 0.4
420	0.7 ± 0.4[d]

[a] Mean ± standard deviation. Amoxicillin was not detectable in the serum of subjects not contributing to the mean at 20, 30, and 420 min.
[b] Mean ± subjects.
[c] Mean of six subjects.
[d] Mean of four subjects.

TABLE 4. *Pharmacokinetic parameters and absolute bioavailability of a 500-mg oral dose of amoxicillin*

Parameter	Value[a]
β (h^{-1})	0.73 ± 0.17
$t_{1/2\beta}$ (h)	1.00 ± 0.28
k_a (h^{-1})	1.02 ± 0.15
$t_{1/2\ k_a}$ (h)	0.72 ± 0.12
AUC, 0–∞ (mg/liter per h)	27.4 ± 3.1
Urinary recovery over 24 h (mg)	217.1 ± 47.8
F (%) (using serum data)	77.4 ± 16.9
F (%) (using urine data)	76.5 ± 20.0

[a] Mean ± standard deviation.

DISCUSSION

The various pharmacokinetic parameters found in our study are in good agreement with those reported previously (20, 26). Spyker et al. (20), who administered 500 mg of amoxicillin orally, and Welling et al. (25), who gave two 250-mg capsules, reported peak levels of 11.8 and 10.0 μg/ml, respectively. These values compare with 10.4 μg/ml found in our study, but are higher than the peak level of 7.6 μg/ml reported by Kirby et al. (14). Since there are many factors which influence absorption of drugs from the gastrointestinal tract, this difference is not surprising. It has been recently reported that the volume of water taken with the capsules may significantly influence the amount of amoxicillin absorbed. Reducing the water volume from 250 to 25 ml caused a significant reduction in the serum amoxicillin level in fasted subjects (25).

The AUC for amoxicillin obtained in our oral study is more than given per os (16). Since these antibiotics bind to plasma protein to about the same degree, it is obvious that, at the same doses, amoxicillin would provide more free antibiotic than ampicillin.

At an i.v. dosage of 500 mg, amoxicillin was cleared from serum at an average rate of 221 ml/min. The average renal clearance calculated according to equation 5 was 126.9 ml/min. This value is greater than the average glomerular filtration rate value, considering that the antibiotic is 20% bound to plasma proteins. This suggests that there is active tubular secretion of amoxicillin, as with other penicillins. A possible saturation of the renal clearance mechanism by some antibiotics has been suggested because it has been noted that the renal clearance rates obtained at higher serum concentrations were significantly less than those observed at lower concentrations (2). This would not be the case with amoxicillin, since the renal clearance calculated for the first hour, when the plasma level is high, according to equation 6, gave a value not

less than the average value calculated by using equation 5. The renal clearance accounts for only 57.3% of the total elimination of amoxicillin. It has been reported that after oral administration in humans and rats, amoxicillin is excreted in the form of inactive penicilloic acid in the urine in amounts equivalents to 10 to 25% of the dose given (5, 7), which is considerably higher than the 7 to 11% after ampicillin dosage (7). Amoxicillin, like ampicillin, undergoes biliary excretion (18).

Comparison of urinary recoveries after oral and i.v. dosage (calculated according to equation 5) indicates that bioavailability was 77.4 and 76.5%, respectively. Intersubject variations were similar with both methods, giving a coefficient of variation of 0.26 for the AUC method and 0.21 for the other. From these results, it can be concluded that measurement of urinary recovery is a reliable method for studying the bioavailability and bioequivalence of different amoxicillin dosage forms.

The urinary concentration of amoxicillin is high after either i.v. or oral dosage. One hour after administration the concentration was 1,942.8 μg/ml for the i.v. dose and 146.4 μg/ml for the oral dose. Six and seven hours, respectively, after i.v. and oral doses the concentrations in the urine were 20.7 and 82.0 μg/ml. These values are many times greater than the MIC for most susceptible strains and are in keeping with the demonstrated effectiveness of amoxicillin in treatment of urinary tract infections.

ACKNOWLEDGMENTS

This study was supported in part by a grant from Beecham Pharmaceuticals, Clifton, N.J.

The technical aid of the nurses of the intensive care unit of the J. J. Aguirre Hospital (Santiago, Chile) is gratefully acknowledged. We are grateful to Irene Morales and Osvaldo Pinto from the Computation Center of the Faculty of Medicine, University of Chile.

LITERATURE CITED

1. **Arancibia, A., O. Pinto, and I. Morales.** 1978. Empleo de la computación en la determinación de parámetros farmacocinéticos en un modelo de dos compartimentos. Rev. Comput. Center Fac. Med. Univ. Notre (Chile) **4**: 17.
2. **Barza, M., S. Melethil, S. Berger, and E. C. Ernst.** 1976. Comparative pharmacokinetics of cefamandole, cephapirin, and cephalothin in healthy subjects and effect of repeated dosing. Antimicrob. Agents Chemother. **10**:421–425.
3. **Bennett, J. V., J. L. Brodie, E. J. Benner, and W. M. M. Kirby.** 1966. Simplified accurate method for antibiotic assay of clinical specimens. Appl. Microbiol. **14**: 170–177.
4. **Bodey, G. P., and J. Nance.** 1972. Amoxicillin: in vitro and pharmacological studies. Antimicrob. Agents Chemother. **1**:358–362.
5. **Brodgen, R. N., T. M. Speight, and C. S. Avery.** 1975. Amoxicillin: a review of its antibacterial and pharmacokinetic properties and therapeutic use. Drugs **9**:88–140.
6. **Brush, J. L., M. G. Bergeron, M. Barza, and L. Weinstein.** 1974. An in vitro and pharmacological comparison of amoxicillin and ampicillin. Am. J. Med. Sci. **267**: 41–48.
7. **Cole, M., M. D. Kenig, and V. A. Hewitt.** 1973. Metabolism of penicillins to penicilloic acids and 6-aminopencillanic acid in man and its significance in assessing penicillin absorption. Antimicrob. Agents Chemother. **3**:463–468.
8. **Croydon, E. A. P., and R. Sutherland.** 1970. α-Amino-*p*-hydroxy-benzylpenicillin (BRL 2333), a new semisynthetic penicillin: absorption and excretion in man, p. 427–430. Antimicrob. Agents Chemother. 1969.
9. **Gibaldi, M., and D. I. Perrier.** 1975. Pharmacokinetics. Marcel Dekker, Inc., New York.
10. **Gómez-Lus, R., M. C. Rubio Calvo, L. Gómez López, and M. P. Millán.** 1973. Diez casos de infecciones urinarias tratadas con alfa-amino-hidroxibencilpenicilina. Chemotherapy **18**(Suppl.):47–51.
11. **Guibert, J. M. C., and J. F. Acar.** 1973. Evaluation clinique et bacteriologique de l'amoxicilline en dehors des infections a enterobacteries. Chemotherapy **18**(Suppl.):81–87.
12. **Harding, J. W., and L. J. Less.** 1972. Trial of a new broad spectrum penicillin (amoxicillin) in general practice. Practitioner **209**:363–368.
13. **Kerrebijn, K. F., and M. F. Michel.** 1973. Amoxicillin (BRL 2333) in children. Serum concentration and clinical report. Chemotherapy **18**(Suppl.):92–96.
14. **Kirby, W. M. M., R. C. Gordon, and C. Regamey.** 1974. The pharmacology of orally administered amoxicillin and ampicillin. J. Infect. Dis. **129**(Suppl.):S154–S161.
15. **Loo, J. C. K., and S. Riegelman.** 1968. New method for calculating the intrinsic absorption rate of drugs. J. Pharm. Sci. **57**:918–928.
16. **Mac-Leod, C., H. Rabin, R. Ogilvie, J. Ruedy, M. Caron, D. Zarowny, and R. O. Davies.** 1974. Practical concepts of drug absorption, distribution and loss. Can. Med. Assoc. J. **111**:341–346.
17. **Neu, H. C.** 1974. Antimicrobial activity and human pharmacology of amoxicillin. J. Infect. Dis. **129**(Suppl.):123–131.
18. **Pla Delfina, J. M., J. Moreno, G. Obiols, A. Fillat, E. Puigdellivol, J. Domenech, and J. Lauroba.** 1976. Interpretación farmacocinética de los niveles séricos de amoxicilina y ampicilina en el conejo. I. Ensayos por vía intravenosa. Cienc. & Ind. Farm. **8**:369–384.
19. **Rolinson, G. N.** 1973. Laboratory evaluation of amoxicillin. Chemotherapy **18**(Suppl.):1–6.
20. **Spyker, D. A., R. J. Ruglowski, 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.
21. **Stam, J.** 1973. Preliminary clinical study with amoxicillin (BRL 2333) in complicated lower respiratory tract infections. Chemotherapy **18**(Suppl.):27–33.
22. **Till, A. E., L. Z. Benet, and K. C. Kwan.** 1974. An integrated approach to the pharmacokinetic analysis of drug absorption. J. Pharmacokin. Biopharm. **2**:528–544.
23. **Vallejos, C., V. Rodríguez, J. A. Gottlieb, and G. P. Bodey.** 1973. Amoxicillin therapy of infections. Clin. Pharmacol. Ther. **14**:962–965.
24. **Wagner, J. G.** 1975. Fundamentals of clinical pharmacokinetics, 1st ed. Drug Intelligence Publications, Inc., Hamilton, Ill.
25. **Welling, P. G., H. Huang, P. A. Koch, W. A. Craig, and P. O. Madasen.** 1977. Bioavailability of ampicillin and amoxicillin in fasted and nonfasted subjects. J. Pharm. Sci. **66**:549–552.
26. **Zarowny, D., R. Ogilvie, D. Tamblyn, C. Mac-Leod, and J. Ruedy.** 1974. Pharmacokinetics of amoxicillin. Clin. Pharmacol. Ther. **16**:1045–1051.

ERRATA

Inhibition of Clinically Significant Bacterial Organisms In Vitro by 2-Acetylpyridine Thiosemicarbazones

ARTHUR S. DOBEK, DANIEL L. KLAYMAN, EDWARD T. DICKSON, JR., JOHN P. SCOVILL, AND EDMUND C. TRAMONT

Clinical Investigation Service, Division of Experimental Therapeutics, and Infectious Disease Service, Walter Reed Army Medical Center, Washington, D.C. 20012

Vol. 18, no. 1, p. 35, column 2: The line following line 54 is missing. The sentence should read: "*N. gonorrhoeae* organisms were even more susceptible to the 2-acetylpyridine thiosemicarbazones, some 41% of which have an MIC of ≤ 0.125 μg/ml."

Absorption and Disposition Kinetics of Amoxicillin in Normal Human Subjects

A. ARANCIBIA, J. GUTTMAN, G. GONZÁLEZ, AND C. GONZÁLEZ

Department of Pharmaceutical Sciences and Department of Biological Chemistry, Faculty of Chemical and Pharmacological Sciences, University of Chile, Casilla 233, Santiago, Chile

Volume 17, no. 2, p. 199, column 2, line 33: "within 48 h sampling" should read "within 48 h of sampling."

P. 201: The first sentence of the second paragraph of the Discussion should read: "The AUC for amoxicillin in our oral study is more than twice the value for the same dose of ampicillin (16)."

P. 201, column 2, line 28 under Discussion: "equation 5" should read "equation 2."

P. 201, column 2, line 42: "equation 6" should read "equation 3."

P. 201, Table 3, footnote *b*: "Mean ± subjects" should read "Mean of three subjects."

P. 202, column 1, line 2: "equation 5" should read "equation 2."

P. 202, column 1, line 12: The sentence beginning "Comparison of urinary recoveries" should read "Based on urinary recoveries after oral and i.v. dosage, bioavailability was 77.4% (calculated according to equation 5) and 76.5% (calculated according to equation 6)."

Combined Antibacterial Activity of Amoxicillin with Clavulanic Acid Against Ampicillin-Resistant Strains

M. MATSUURA, H. NAKAZAWA, T. HASHIMOTO, AND S. MITSUHASHI

Department of Microbiology, School of Medicine, Gunma University, Maebashi, and Beecham Yakuhin Co., Ltd., Tokyo, Japan

Volume 17, no. 6, p. 908: The last line of column 1 was accidentally omitted. It should read: "**Media.** Heart infusion agar (Eiken, Tokyo, Japan)."