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Single-Dose Pharmacokinetics of Intravenous Clavulanic Acid with Amoxicillin in Pediatric Patients

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Pharmacokinetics of a parenteral formulation comprised of 5 parts of amoxicillin and 1 part of clavulanic acid were determined in 12 pediatric patients, 2 to 14 years of age. A single dose amounting to 25 mg of amoxicillin and 5 mg of clavulanic acid per kg of body weight was infused intravenously over 2 min. Mean plasma concentrations 5 min after dosing were 89.4 μg of amoxicillin per ml and 19.5 μg of clavulanic acid per ml. Terminal phase plasma half-lives were 1.2 and 0.8 h, respectively. The data acquired in this study indicate that amoxicillin and clavulanic acid are pharmacokinetically compatible. Moreover, taken with assessment of microbiological activities by others, the present data suggest that intravenous administration of 25 mg of amoxicillin plus 5 mg of clavulanic acid per kg every 6 h is a reasonable starting regimen for assessing the activity of the combined drug formulation in noninvasive childhood diseases caused by *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococci* spp., *Neisseria* spp., *Branhamella catarrhalis*, and other susceptible organisms.

Clavulanic acid, a β-lactam derivative, has comparatively low antibacterial activity but irreversibly inhibits a broad spectrum of β-lactamase enzymes (11). The combination of clavulanic acid with β-lactamase-susceptible antimicrobial agents effects a marked enhancement of the activity of these compounds against many beta-lactamase-producing bacteria (6, 8, 13, 14). In vitro studies, experiments in animal models, and preliminary clinical experience indicate that combinations of clavulanic acid with amoxicillin have a high order of antimicrobial activity (2–4, 6–8, 12–14, 16, 17).

The purpose of the present study was to evaluate the pharmacokinetics of an intravenous (i.v.) formulation of sodium amoxicillin and potassium clavulanate in children. Such pharmacokinetic data should allow the formulation of dosage recommendations for therapeutic trials of this preparation against childhood infections due to susceptible pathogens.

MATERIAL AND METHODS

Study patients. Twelve children, 7 males and 5 females, under treatment for viral infections (8 patients) or neurological diseases (4 patients) at the Department of Pediatrics, University of Berne, Switzerland, were included in the study. Ages ranged between 2 and 14.5 years with a mean of 10 years. None of the 12 patients had received antimicrobial therapy for at least 72 h before the study. Ten received no other drugs and two remained on anticonvulsants during the study period. None had a medical history of previous allergy to beta-lactam compounds, or of renal or hepatic disease. Clinically, their hydration status was judged to be normal. Complete blood cell counts, urine analysis, blood urea nitrogen or serum creatinine or both, and liver enzymes were within normal ranges in all participants. Informed parental consent was obtained for all patients in accordance with the guidelines of the local Institutional Committee on Human Investigations.

Drug administration. The contents of the drug vials (Augmentin injectable, 1.2 g, batch no. C.T. 11075; Beecham Pharmaceuticals, Surrey, England), containing 1,000 mg of amoxicillin and 200 mg of clavulanic acid, were dissolved immediately before use in 40 ml of sterile water, resulting in concentrations of 25 mg of amoxicillin and 5 mg of clavulanic acid per ml. Volumes of this solution equivalent to 25 mg of amoxicillin plus 5 mg of clavulanic acid were administered i.v. over 2 min through a peripheral vein but not through the i.v. line which was used for blood sampling. Local or systemic reactions to the amoxicillin-clavulanic acid formulation were assessed by clinical observation.

Collection of biological specimens. Blood samples for drug assays were collected from an i.v. heparin lock immediately before the dose (predose sample) and at 5, 15, 30, 60, 90, 180, and 360 min after the termination of the infusion (time zero, end of the 2-min drug infusion). The blood was immediately mixed with sodium citrate and centrifuged within 20 min. Plasma samples were stored at −70°C no longer than 96 h before the assays were performed.

The total amount of urine passed was collected from 10 of the 12 study patients at the following time intervals: −2 to 0, 0 to 2, 2 to 4, and 4 to 6 h after dosing. Urine was sampled from either sterile recepta-

TABLE 1. Plasma concentrations and ratios of amoxicillin and clavulanic acid

Drug (dosage)	Mean (±SEM) plasma concn (μg/ml) and ratios at indicated times after dose						
	5 min	15 min	30 min	1 h	1.5 h	3 h	6 h
Amoxicillin (25 mg/kg)	89.36 (4.08)	47.35 (2.78)	27.05 (1.65)	12.63 (1.13)	7.13 (0.55)	1.84 (0.19)	0.43 (0.04)
Clavulanic acid (5 mg/kg)	19.45 (0.91)	11.97 (0.68)	7.83 (0.38)	4.58 (0.23)	2.79 (0.16)	0.80 (0.07)	<0.08
Ratio of amoxicillin to clavulanic acid	4.6	4.0	3.5	2.8	2.6	2.3	>5.4

cles (eight patients) or urinary catheters (two patients). Volumes were recorded, and a 1-ml aliquot from each collection period was mixed with 9 ml of Sorensens citrate buffer (0.1 M, pH 6.5; Mercia-Brocades Ltd., West Byfleet, Surrey, England) and stored at −70°C until assayed within 96 h of collection.

Antibiotic assays. Amoxicillin was assayed by a standard large plate well diffusion microbioassay, using *Sarcina lutea* (NCTC 8340) as the assay organism.

Clavulanic acid activity was measured by the inhibition of the beta-lactamase produced by a strain of *Klebsiella aerogenes* (NCTC 11228). The latter organism is not sensitive to clavulanic acid in the range of concentrations assayed, but the inhibition of its beta-lactamase by clavulanic acid renders this organism susceptible to inhibition by the benzylpenicillin (60 μg/ml) present in the medium. Therefore, penicillinase produced by *K. aerogenes* in the seeded agar is inactivated by clavulanic acid diffusing from the well, causing a zone of inhibition of growth of this organism by the incorporated penicillin. The clavulanic acid concentration was calculated thereafter by reference to the linear regression relationship between zone size and logarithm of the clavulanic acid concentration. The details of this large plate well microbiological agar-incorporation technique are described elsewhere (1; D. Jackson, D. L. Cooper, R. Horton, P. F. Langley, D. S. Staniforth, and A. J. Sutton, Absorption, pharmacokinetic and metabolic studies with Augmentin. *In* E. A. P. Croydon and M. S. Michel (ed.), Augmentin, clavulanate-potentiated amoxicillin. Excerpta Medica, Amsterdam-Oxford-Princeton, in press).

Estimation of pharmacokinetic parameters. Plasma concentrations of both amoxicillin and clavulanic acid declined biexponentially, consistent with a two-compartment, open-system pharmacokinetic model. Although the clavulanic acid plasma concentration-time curves could be fitted to a biexponential equation, the amoxicillin plasma data could not. Therefore, model-independent pharmacokinetic parameters were determined for amoxicillin and clavulanic acid. The terminal phase half-lives were calculated by regression on those data pairs visually determined to be in the log linear phase. The areas under the concentration curves were obtained by the trapezoidal rule.

RESULTS

Plasma concentrations. Mean plasma concentrations of amoxicillin and clavulanic acid are shown in Table 1 (± standard error of the mean). Predose samples were free of either agent. Peak plasma concentrations of 89.4 μg/ml for amoxicillin and 19.5 μg/ml for clavulanic acid were found 5 min after completion of the 2-min infusion. After 6 h, the mean plasma levels had fallen to 0.4 and <0.08 μg/ml, respectively.

Mean ratios of amoxicillin to clavulanic acid are also listed in Table 1. From the initial 5:1 ratio of the infused drug formulation, the values slowly decreased with time to a minimum of 2:3 at 3 h after dosing.

The mean values (± standard error of the mean) of the important calculated pharmacokinetic parameters are shown in Table 2. The mean terminal half-life was 1.2 h for amoxicillin and 0.8 h for clavulanic acid. The average apparent volume of distribution of amoxicillin was approximately twice that of clavulanic acid (746 versus 368 ml/kg). The mean total plasma clearance rate expressed in relation to body surface area for amoxicillin was about 40% larger than the rate for clavulanic acid (360 versus 254 ml/min per 1.73 m^2).

TABLE 2. Pharmacokinetic values[a]

Drug	Dosage (mg/kg)	Plasma half-life (h)	Area under the curve (μg · h/ml)	Vol of distribution (ml/kg)	Total plasma clearance (ml/min per 1.73 m^2)
Amoxicillin	25	1.17 (0.06)	55.9 (2.4)	764 (58)	360 (15)
Clavulanic acid	5	0.81 (0.04)	15.9 (0.7)	368 (14)	254 (13)

[a] Numbers (except dosage) represent means ± standard errors of the mean (in parentheses).

Urine concentrations. The mean values (± standard deviation) of the cumulative percentage of dose recovered in the urine during the three 2-h intervals from time zero to 6 h after dosing are displayed in Figure 1. None of the predose urine samples contained measurable amoxicillin or clavulanic acid. By 6 h, 81.1 ± 17.5% of the dose of amoxicillin and 59.1 ± 17.1% of that of clavulanic acid were recovered in the urine.

Safety. The formulation of amoxicillin plus clavulanic acid administered as a single intravenous dose over 2 min was well tolerated by all of the children, none of whom exhibited local or systemic reactions.

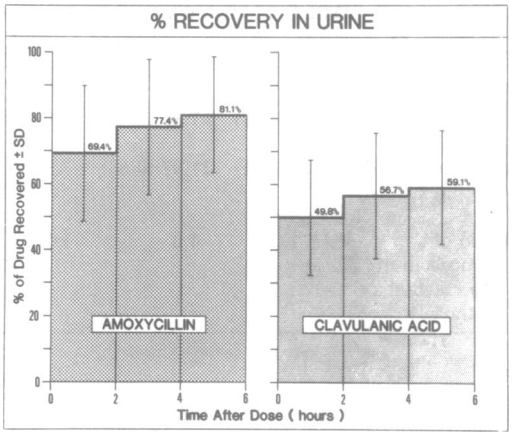

FIG. 1. Recovery of amoxicillin and clavulanic acid in the urine of 10 pediatric patients. Means ± standard deviations (SD) (bars) of cumulative percent excretions of each compound are shown.

DISCUSSION

The pharmacokinetics of an i.v. administration of a formulation of amoxicillin and clavulanic acid (Augmentin) in children are reported in this paper. The observed values for intravenously administered amoxicillin are comparable to those previously reported in pediatric patients (15). In that study, an i.v. amoxicillin dose of 26 mg/kg given over a period of 20 to 30 min resulted in a mean serum half-life of 1.22 h, whereas our mean plasma half-life after 25 mg of amoxicillin per kg was given over 2 min was 1.17 h. No published pharmacokinetic data are available for intravenously administered clavulanic acid. However, our data favorably compare to results with i.v. amoxicillin-clavulanic acid formulations obtained in adult volunteers (data on file, Beecham Pharmaceuticals) and to results with oral amoxicillin-clavulanic acid formulations determined in adult and pediatric patients (2, 9, 10). The terminal plasma half-lives of clavulanic acid are always slightly shorter than those of amoxicillin and amount to values close to 1 h; the average value in our patients was 0.81 h. The mean apparent volume of distribution of clavulanic acid was approximately one-half of that of amoxicillin (368 versus 764 ml/kg), and the mean plasma clearance rate of clavulanic acid was about 70% of the elimination rate of amoxicillin (254 versus 360 ml/min per 1.73 m^2).

The mean fractions of amoxicillin and clavulanic acid excreted unchanged in the urine for the 0- to 6-h period were 81 and 59%, respectively, and are comparable to what was previously found for adults (2, 9).

In general, the observed differences in distribution and elimination characteristics between the two drug constituents were small. This statement is substantiated by the relatively constant ratios of amoxicillin to clavulanic acid measured in plasma at the different sampling times. Therefore, we conclude that amoxicillin and clavulanic acid are pharmacokinetically compatible.

Our data on the concentrations of amoxicillin and clavulanic acid in plasma, coupled with data on the antimicrobial activity of this combination (2, 3, 6, 13, 14, 17), suggest that a parenteral dosage of 120 mg of the studied drug formulation (100 mg of amoxicillin per kg plus 20 mg of clavulanic acid per kg) per kg per day divided into four equal daily doses administered as 2-min infusions should be adequate therapy for various childhood infections caused by *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococci* spp., *Neisseria* spp., *Branhamella catarrhalis*, and other susceptible organisms. Compared with other therapeutic modalities, this regimen has three major advantages. (i) The extensive, favorable clinical experiences with amoxicillin are to be countinued; (ii) the possible bacterial beta-lactamase production is solved by irreversible inactivation of these enzymes by clavulanic acid; and (iii) both parenteral and oral therapy are possible with the same antibacterial drug formulation.

By analogy with single-drug therapy with amoxicillin (5), the dosage schedule suggested above will probably have to be multiplied by two to four times for invasive infections. It must, however, be emphasized that these dosage recommendations are preliminary and only intended for well-controlled clinical evaluations of this investigative antibiotic formulation. Studies to determine adequate dosage formulations for the oral preparation in children are currently under investigation by our department.

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