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Pharmacokinetics of Potassium Clavulanate in Combination with Amoxicillin in Pediatric Patients

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Two dosages of a liquid suspension formulation of amoxicillin and potassium clavulanate were tested in 34 infants and children. The smaller dosage resulted in suboptimal plasma concentrations. With the greater dosage (3.3 mg of clavulanate per kg and 13.3 mg of amoxicillin per kg), the mean peak plasma concentrations were 1.6 μg clavulanic acid per ml and 4.9 μg amoxicillin per ml.

Clavulanic acid is a beta-lactam compound with weak inherent antibacterial activity, but with the capability of binding irreversibly with a broad spectrum of beta-lactamases. When clavulanic acid is combined with beta-lactamase-susceptible antibiotics, such as ampicillin and amoxicillin, its binding properties permit activity of the antibiotic against beta-lactamase-producing bacteria (2). Many childhood infections are caused by *Staphylococcus aureus* and *Haemophilus influenzae* strains which elaborate beta-lactamase and thus are resistant to ampicillin and related drugs. The combination of clavulanic acid with amoxicillin (Augmentin, Beecham Pharmaceuticals) provides a novel approach to increasing the clinical utility of amoxicillin.

A liquid suspension of amoxicillin and potassium clavulanate in a 4:1 ratio by weight was tested in infants and children. The suspension contained 4 mg potassium clavulanate per ml and 16 mg amoxicillin per ml. Two dosages were tested; the smaller was approximately 1.7 mg of clavulanate per kg with 6.6 mg of amoxicillin per kg, and the larger was approximately 3.3 mg of clavulanate per kg and 13.3 mg of amoxicillin per kg. There were 17 children in each group. Each dose was substituted for one dose of the medication the child was receiving for treatment of otitis media or dermatological infections (12 h or more had elapsed since the previous dose of antibiotic).

Blood samples were collected immediately before the dose and at 20, 40, 60, 120, 180, and 240 min thereafter. Plasma was separated and stored at −70°C for no longer than 72 h before the assay was performed.

Clavulanic acid was assayed by a microdisk agar diffusion method by using an overnight seed culture of penicillinase-producing *Klebsiella pneumoniae* (ATCC 29665) grown in tryptose phosphate broth without dextrose. A sample of 1.5 ml of the seed culture was added per 100 ml of nutrient agar, and penicillin G-potassium was added at a concentration of 60 μg/ml. The reference standard was clavulanic acid lithium (Beecham) in pooled normal human plasma. Twenty-μl amounts of standards and samples were added to 6.35-mm disks in triplicate. Amoxicillin trihydrate was incorporated into the standards at a 1:4 ratio of clavulanic acid to amoxicillin. The concentrations of clavulanic acid were doubling dilutions from 1.6 to 0.1 μg/ml.

Penicillinase in the seeded agar is inactivated by clavulanic acid diffusing from the disk, thereby causing a zone of inhibition due to penicillin activity against the assay organism.

Amoxicillin was assayed by a standard disk diffusion microbioassay with *Sarcina lutea* (ATCC 9341).

Mean plasma concentrations of clavulanic acid and amoxicillin are shown in Table 1. Antimicrobial activity was not encountered in predose plasma specimens of 28 specimens assayed for clavulanic acid or in 15 specimens assayed for amoxicillin. In the remaining specimens, the amount of antimicrobial activity was less than 0.1 μg/ml in all except one specimen with 1.7 μg/ml activity in the amoxicillin assay; this effect could have been due to residual antibiotic or to other serum factors.

Peak plasma concentrations of each drug were found in most patients 60 min after the dose, with a range from 40 min to 2 h. The means of peak concentrations of clavulanic acid were 0.78 μg/ml and 1.53 μg/ml with the smaller and larger dosages, respectively. With amoxicillin, the means of peak values were 2.76 and 4.94 μg/ml. The mean ratios of peak values of amoxicillin to clavulanic acid were 3.5 and 3.1 with the smaller and larger dosages, respectively.

After the smaller dose the ratios of amoxicillin to clavulanic acid increased with time. With the larger dose they remained more constant, but mostly less than the 4:1 ratio of ingested drug. The mean ratios for all time periods were 4.6

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

Drug and dosage	Mean (±SEM) plasma concentrations (μg/ml) and ratios at indicated time after dose					
	20 min	40 min	60 min	2 h	3 h	4 h
Clavulanate, 1.7 mg/kg	0.29 (0.14)	0.72 (0.22)	0.67 (0.17)	0.47 (0.11)	0.20 (0.04)	0.09 (0.02)
Amoxicillin, 6.6 mg/kg	0.91 (0.31)	1.65 (0.38)	2.11 (0.39)	2.16 (0.24)	1.23 (0.11)	0.71 (0.08)
Ratio of amoxicillin to clavulanic acid	3.1	2.3	3.2	4.6	6.2	7.9
Clavulanate, 3.3 mg/kg	0.42 (0.10)	1.12 (0.24)	1.45 (0.22)	1.02 (0.14)	0.52 (0.08)	0.25 (0.03)
Amoxicillin, 13.3 mg/kg	1.80 (0.50)	3.56 (0.43)	4.67 (0.39)	3.31 (0.37)	1.95 (0.24)	1.14 (0.16)
Ratio of amoxicillin to clavulanic acid	4.3	3.2	2.1	3.3	3.8	4.6

TABLE 2. Pharmacokinetic values

Drug and dosage	Plasma half-life (h)	Area under the curve (μg.h/ml)	Volume of distribution (ml/kg)	Plasma clearance rate (ml/min/1.73 m^2)
Clavulanate, 1.7 mg/kg	1.10	1.66	1,622	478
Amoxicillin, 6.6 mg/kg	1.25	6.11	1,950	504
Clavulanate, 3.3 mg/kg	1.17	3.54	1,575	435
Amoxicillin, 13.3 mg/kg	1.46	12.90	2,172	481

with the smaller dose and 3.6 with the larger dose. The varying ratios could be due to different absorption and elimination characteristics or to different distribution characteristics of the drugs in body compartments. The amoxicillin concentration (4.7 μg/ml) at 60 min after the 13.3 mg/kg dose is similar to the 5.4 μg/ml value reported by Ginsburg et al. (1) 60 min after a dose of 15 mg/kg. This suggests that the absorption of amoxicillin is not adversely affected by the presence of clavulanate in the mixture.

Calculated pharmacokinetic values are shown in Table 2. The plasma half-life of clavulanic acid is slightly shorter than that of amoxicillin, and half-lives of both drugs are somewhat longer after the larger dose. This may be due to a more prolonged period of absorption of the larger volume of medication. Apparent volume of distribution of clavulanic acid is less than that of amoxicillin, and mean plasma clearance rates of amoxicillin are somewhat more rapid. In general, differences in pharmacokinetic features between the two drugs are small, and the drugs make a suitable pair from that standpoint.

The single dose of the amoxicillin and clavulanic acid combination was well tolerated by all of the children.

Reeves et al. (3) have reported that concentrations of 1 μg of clavulanic acid per ml consistently render beta-lactamase-producing strains of *S. aureus* and *H. influenzae* susceptible to usual blood concentrations of amoxicillin, while Hunter et al. (2) have found that 2.5 μg/ml is required to achieve that effect. It appears that the lower dosage we tested produced suboptimal plasma concentrations of clavulanic acid. We propose that the larger dosage of 3.3 mg of clavulanic acid per ml be the minimum amount used for therapeutic trials with the combination.

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