Amoxicillin Combined with Clavulanic Acid for the Treatment of Soft Tissue Infections in Children

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We compared responses to amoxicillin combined with clavulanic acid (ACA) with a cefaclor regimen in children with skin and soft tissue infections (impetigo and cellulitis) due to Staphylococcus aureus, Streptococcus pyogenes, and Haemophilus species. All isolates from the 41 patients we were able to evaluate were susceptible to ACA by disk susceptibility testing at the onset of treatment. The 21 children receiving ACA and 18 (90%) of 20 taking cefaclor responded to therapy. Clinical cure was achieved in 18 (86%) of 21 and 18 (90%) of 20 in the two groups, respectively. Bacteriological failure occurred in 2 (10%) patients in the cefaclor group and none in the group receiving ACA; however, there were 2 (9%) relapses and 1 (5%) reinfection among the 21 children taking ACA. Adverse effects, although mild, occurred more commonly (9 of 21 versus 1 of 20; P = 0.005) with ACA than with cefaclor.

Clavulanic acid, a naturally occurring beta-lactamase inhibitor, has been shown to prevent the enzymatic degradation of beta-lactam antibiotics by a number of bacterial species. Combinations of clavulanic acid and amoxicillin (ACA; Augmentin, Beecham Laboratories) show greater activity in vitro against these bacteria than does amoxicillin alone (3, 10, 12). Clinical trials in adults have shown that ACA is effective against respiratory and urinary tract infections caused by ampicillin-susceptible and ampicillin-resistant organisms (1, 2, 5, 6, 11). Thus far, there have been no reports of either the efficacy or the safety of ACA in children. The present study was designed to evaluate these issues in a side-by-side comparison with cefaclor for the treatment of skin and soft tissue infections (4).

MATERIALS AND METHODS

Patient enrollment. Children aged 6 months to 12 years with soft tissue infections, seen in the emergency department of the Children’s Hospital of Philadelphia, from 1 April 1982 until 30 September 1982, were considered for this study. The infections included impetigo, bullous impetigo, and impetigo complicated by cellulitis. Patients were excluded if they had: (i) a history of allergy to penicillin or cephalosporins; (ii) a history of renal or hepatic disease; (iii) evidence of serious infection; (iv) serum creatinine of >2.5 mg/dl; or (v) other significant physical or laboratory abnormalities. Informed consent was obtained from a parent of every child. The patients who enrolled were assigned by the use of a random-number table to receive either ACA or cefaclor. The investigators were blinded as to therapy.

Patients assigned to the ACA group received a liquid preparation (25 mg/kg) each day containing 125 mg of amoxicillin and 30 mg of clavulanic acid per 5 ml. The other group received a liquid preparation (20 mg/kg) each day containing 125 mg of cefaclor per 5 ml. Both drugs were administered three times daily for 10 days.

Clinical and laboratory evaluations. At the time of entry into the study (visit 1), all patients had a culture of their lesions, measurements of blood urea nitrogen, creatinine, and serum glutamic oxalacetic transaminase, and a complete blood count and urinalysis. They returned on study days 3 to 5 (visit 2), 10 to 12 (visit 3), and 17 to 20 (visit 4). Cultures were obtained from any persistent lesions during these visits, a urine-specimen was submitted for compliance testing on study days 3 to 5, and the hematological and chemical tests and urinalysis were repeated upon the termination of drug therapy.

Bacteriological techniques. Specimens of purulent material, obtained by the swabbing of superficial lesions or the aspiration of areas with cellulitis, were inoculated onto sheep blood, chocolate, and MacConkey agars and into cooked-meat medium enrichment broth. Isolates were identified by using standard microbiological techniques (7). Antibiotic susceptibility testing was performed by the standardized disk diffusion method of the National Committee for Clinical Laboratory Standards (8). Included in the battery of antibiotics tested were a disk containing 20 μg of amoxicillin and 10 μg of clavulanic acid and a disk containing 30 μg of cephalothin (class disk to predict cefaclor activity). Gram-positive cocci and Haemophilus spp. were considered susceptible to ACA if the diameter of the zone of inhibition was ≥20 mm and to cefaclor if the diameter of the zone of inhibition around the cephalothin disk was ≥18 mm. The urine specimen obtained during therapy was tested for the presence of an antibiotic by the inhibition of growth of Bacillus subtilis ATCC 6633 in an agar well diffusion
Patient compliance was considered to be acceptable if the urine specimen contained antimicrobial activity which was eliminated by pretreatment with high concentrations of penicillinase.

Assessment of therapy. Patients were considered: (i) clinically cured if the lesions resolved during therapy and did not recur at the time the drug was discontinued or during follow-up; (ii) clinically improved if there was a marked, but incomplete, resolution of the initial infection or a total resolution followed by relapse; or (iii) clinical failures if their infections did not respond to therapy.

Bacteriological success was defined as the elimination of the pathogen during therapy and for the duration of follow-up. If the pathogen was eradicated initially but then recurred during follow-up, we judged the patient to have had a relapse. The subsequent emergence of an organism different from the pretreatment isolate was considered to be a re-infection. Persistent recovery of the initial pathogen during therapy indicated bacteriological failure.

RESULTS

Patient enrollment. Fifty-seven patients were enrolled in the study during the 6-month interval. Of these, 41 were able to be evaluated, 13 did not return for follow-up or were noncompliant with the antibiotic therapy, 2 had negative initial cultures, and 1 withdrew from the study on day 2 for unexplained reasons.

Pretherapy clinical and bacteriological findings. Of the 41 patients evaluated, 21 received ACA and 20 received cefaclor. The two groups were comparable with respect to age (mean, 45 months) and sex (60% were males). Staphylococcus aureus was the most frequently isolated pathogen in both treatment groups, followed by Streptococcus pyogenes (a group A beta-hemolytic streptococcus) and Haemophilus spp. (Table 1). All isolates were susceptible to both ACA and cefaclor by the disk diffusion method; 84% produced beta-lactamase.

Response to therapy. Of the 21 children receiving ACA, 18 (86%) were cured clinically. Of the 21 patients who showed an initial clinical improvement, 3 (14%) subsequently had either a relapse (9%) or a re-infection (5%). On the second visit (days 3 to 5), 18 (86%) of 21 children receiving ACA had residual lesions, and 14 (67%) had positive cultures. Five patients did not have complete resolution locally by the third visit, at the end of therapy, but only two had positive cultures (relapses). The two patients who relapsed were infected by S. aureus susceptible to ACA. The single child who was re-infected was initially infected with an ACA-susceptible S. aureus strain and subsequently with an ACA-resistant strain.

Of 20 children taking cefaclor, 18 (90%) were cured clinically and 2 (10%) were treatment failures. There were no relapses or reinfections.

On the second visit, 16 (80%) had residual lesions and 14 (70%) had positive cultures. As with ACA, five (25%) still had abnormal local findings shortly after the termination of therapy, but all had negative cultures and resolved without further therapy. The two children who were clinical and bacteriological failures were infected with S. aureus, susceptible to cefaclor and ACA.

The clinical cure rates ($P = 0.67$, chi-square test) and response rates ($P = 0.14$, chi-square test) for ACA and cefaclor were the same. The number of patients with lesions or with positive cultures was similar in the two groups at each visit.

Adverse reactions. Nine (43%) of 21 children receiving ACA and 1 (5%) of 20 taking cefaclor experienced adverse reactions; these were limited to diarrhea in nine cases and to vomiting and diarrhea in one. Diarrhea developed during the first 5 days of therapy among five children in the ACA group and during the second 5 days in four others. One child receiving cefaclor had vomiting and diarrhea on day 3 of treatment. The longest duration of diarrhea was 3 days, and all reactions subsided without interrupting therapy. Laboratory studies, including a complete blood count, measurements of blood urea nitrogen, creatinine, and serum glutamic oxalacetic transaminase, and urinalysis, showed no evidence of toxicity.

The difference in the rate of adverse reactions between the two groups was significant ($P = 0.005$, chi-square test).

DISCUSSION

Reading and Cole (12) found that clavulanic acid effectively inhibited the beta-lactamase enzymes of both gram-negative and gram-positive organisms and that the activity of ampicillin against Escherichia coli, Klebsiella spp., and S. aureus could be enhanced by the addition of clavulanic acid. Several reports have described the use of ACA in adults (1, 2, 5, 11). Goldstein and colleagues (5) successfully eradicated amoxicillin-resistant urinary tract pathogens by using a single-dose regimen in five of six adults. Treat-
ing for 1 week, Ball and colleagues (1) achieved cure rates of 30% for amoxicillin-resistant and 70% for amoxicillin-susceptible pathogens in 20 older patients receiving ACA. In the largest study reported to date, Iravani and Richard (6) treated 116 female college students with urinary tract infections. Of the isolates, 19% were resistant to amoxicillin, but all were susceptible to ACA. Cultures after 1 week were sterile in 96.7% of those patients who completed therapy; cures were sustained in 85.6% at 4 weeks after the end of treatment. In respiratory tract infections, Beeuwkes and Rutgers (2) found ACA to be effective, particularly against resistant strains of Haemophilus influenzae.

We have conducted the first controlled trial on ACA for skin and soft tissue infections and the first study of efficacy in children. In vitro testing of our isolates showed ACA to be capable of inhibiting the usual pathogens in children; all isolates of S. pyogenes, S. aureus, and Haemophilus spp. were susceptible to ACA.

Using the dosage established by Nelson and co-workers (9), we found ACA to be effective in the treatment of impetigo and cellulitis. All children receiving ACA responded initially to therapy, and 86% were cured. Although more treatment failures occurred among patients receiving cefaclor than among those taking ACA, the limited number of patients in this study prevents us from reaching any conclusions as to whether ACA is more efficacious than cefaclor. Significantly more patients receiving ACA experienced mild gastrointestinal disturbances. However, these reactions were self-limited in all cases. No child was required to discontinue either medication.

We conclude that ACA has sufficient activity and tolerability to warrant further clinical studies.

LITERATURE CITED

1. Ball, A. P., P. G. Davey, A. M. Gedden, I. D. Farrell, and G. R. Brooks. 1980. Clavulanic acid and amoxicillin: a clinical, bacteriological, and pharmacological study. Lancet i:620–622.

2. Beeuwkes, H., and V. H. Rutgers. 1981. A combination of amoxicillin and clavulanic acid in the treatment of respiratory tract infections caused by amoxicillin-resistant Haemophilus influenzae. Infection 9:244–248.

3. Dumon, L., P. Adriaens, J. Anné, and H. Eyssen. 1979. Effect of clavulamic acid on the minimum inhibitory concentration of benzylpenicillin, ampicillin, carbenicillin, or cephalothin against clinical isolates resistant to beta-lactam antibiotics. Antimicrob. Agents Chemother. 15:315–317.

4. Fleisher, G., S. Ludwig, and J. Campos. 1980. Cellulitis: bacterial etiology, clinical features, and laboratory findings. J. Pediatr. 97:591–593.

5. Goldstein, F. W., M. D. Kitzis, and J. F. Acar. 1979. Effects of clavulanic acid and amoxicillin formulation against beta-lactamase producing gram-negative bacteria in urinary tract infections. J. Antimicrob. Chemother. 5:705–709.

6. Iravani, A., and G. A. Richard. 1982. Treatment of urinary tract infections with a combination of amoxicillin and clavulanic acid. Antimicrob. Agents Chemother. 22:672–677.

7. Lennette, E. H., A. Balows, W. J. Hausler, Jr., and J. P. Truant (ed.). 1980. Manual of clinical microbiology, 3rd ed. American Society for Microbiology, Washington, D.C.

8. National Committee for Clinical Laboratory Standards. 1979. Performance standards for antimicrobial susceptibility tests, 2nd ed. National Committee for Clinical Laboratory Standards, Villanova, Pa.

9. Nelson, J. D., H. Kusmiesz, and S. Shelton. 1982. Pharmacokinetics of potassium clavulanate in combination with amoxicillin in pediatric patients. Antimicrob. Agents Chemother. 21:681–682.

10. Neu, H. C., and K. P. Fu. 1978. Clavulanic acid, a novel inhibitor of beta-lactamases. Antimicrob. Agents Chemother. 14:650–655.

11. Ninane, G., J. Joly, and M. Krayman. 1978. Bronchopulmonary infection due to beta-lactamase-producing Branhamella catarrhalis treated with amoxicillin/clavulanic acid. Lancet ii:257.

12. Reading, C., and M. Cole. 1977. Clavulanic acid: a beta-lactamase-inhibiting beta-lactam from Streptomyces clavuligerus. Antimicrob. Agents Chemother. 11:852–857.