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Amoxicillin-Clavulanic Acid in Treatment of Urinary Tract Infection Due to Gram-Negative Bacteria Resistant to Penicillin

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Twenty-one adult patients with urinary tract infections caused by penicillin-resistant bacteria completed treatment with amoxicillin alone or amoxicillin plus clavulanic acid in a randomized double-blind clinical trial. Of the 13 patients treated with amoxicillin plus clavulanic acid, the absence of bacteriuria within 7 days of therapy was observed in 85%, as compared with only 25% of the 8 patients receiving amoxicillin only. There were no significant side effects nor any clinical, biochemical, or hematological abnormalities related to either treatment. It was concluded that the combination of clavulanic acid and amoxicillin could be useful in the treatment of uncomplicated urinary tract infection caused by penicillin-resistant bacteria.

Clavulanic acid, a natural product of *Streptomyces clavuligerus*, is a potent, irreversible inhibitor of a wide variety of β-lactamase enzymes (5, 7). Although it has little inherent antibacterial activity, it protects the labile penicillins and cephalosporins from destruction by bacterial β-lactamase (4, 6, 8, 9, 13). In vitro studies have demonstrated that clavulanic acid possesses a very wide spectrum of inhibition (3), which results in marked enhancement of β-lactam antibiotics against many β-lactamase-producing organisms (3, 9, 13), including staphylococci and enterobacteria.

Urinary tract infections caused by β-lactamase-producing species are common and often require treatment with antibiotics which are potentially toxic. Since clavulanic acid protects the β-lactam-sensitive antibiotics from enzymatic destruction, it should serve as a useful adjunct to therapy with those agents. Therefore, the purpose of this initial clinical trial was to determine the efficacy and safety of amoxicillin plus clavulanic acid in the treatment of uncomplicated urinary tract infection caused by penicillin-resistant organisms.

MATERIALS AND METHODS

Twenty-one patients presenting with uncomplicated urinary tract infections caused by bacteria resistant to both ampicillin and amoxicillin were considered suitable for this trial. Urinary tract infection was defined as the presence of at least 10^5 bacteria per ml in patients complaining of dysuria, urgency, frequency, and back pain, or by two consecutive urine cultures containing 10^5 or more bacteria per ml of the same species in asymptomatic patients. There was no attempt to differentiate between upper and lower urinary tract infection for the purpose of this trial. All bacterial isolates were identified by standard procedures (2) and tested for susceptibility with a 10-μg ampicillin disk by the Bauer-Kirby method (1). If the isolate was found to be resistant to ampicillin, a tube dilution minimum inhibitory concentration (MIC) to amoxicillin was determined. All patients who were found to have infecting strains with amoxicillin MICs above 10 μg/ml were considered for enrollment in the study. In addition, a further MIC of amoxicillin was obtained in the presence of 10 μg of clavulanic acid per ml. This concentration of clavulanic acid has been shown to be readily obtainable in the urine after oral administration in humans (unpublished data). Patients with known hypersensitivity to penicillins, pregnancy, liver or renal failure, or who presented with life-threatening infections were excluded from this study. In addition to a pretreatment history and physical examination, all of the patients underwent a laboratory evaluation, including complete blood count; urinalysis; blood urea nitrogen and serum creatinine, bilirubin, alkaline phosphatase, glutamic pyruvic, and oxalacetic transaminases tests. The physical examination and laboratory evaluation were repeated at the completion of therapy. Urine cultures were repeated on days 3 and 6 of treatment and within 7 days of completion of therapy.

Patients were then assigned, by a previously prepared random-number code, to one of two treatments. One group, consisting of eight patients, received amoxicillin alone as a 250-mg tablet. Of the eight patients, four were male, and four were female. Their mean age was 47.6 years. Three were symptomatic, and five were asymptomatic. The other group consisting of 13 patients, was treated with a 250-mg amoxicillin tablet containing either 50 or 125 mg of clavulanic acid. Of

the 13 patients, 6 were male, and 7 were female. Their mean age was 46.8 years. Seven were symptomatic, and six were asymptomatic. All medication was given three times a day for 9 days. The trial was completely double blind as the tablets and containers were identical in appearance, and the patients were assigned to each treatment sequentially as they entered the trial. The patients received no other antimicrobial agent during the study. Therapy was discontinued when a urine culture remained positive on either of the two evaluations during treatment.

RESULTS

A total of 21 patients were studied, with 8 receiving amoxicillin alone and the other 13 receiving amoxicillin plus clavulanic acid. The infectious flora with their MICs for amoxicillin plus clavulanic acid, as well as the therapeutic results, are presented in Table 1. The MICs for amoxicillin alone were greater than 160 μg/ml for all isolates. It can be seen that the presence of clavulanic acid at 10 μg/ml resulted in a decrease in the MICs for amoxicillin against all of the isolated bacteria. In the 13 cases treated with the combination of amoxicillin and clavulanic acid, a total of 11 (84.6%) had negative cultures after completion of therapy, whereas in patients treated with only amoxicillin, 2 (25%) had a negative culture (this difference was statistically significant, $P < 0.05$). In the patients with therapeutic failure, the original bacteria persisted in the urine. The small number of cases did not allow an evaluation of a dose-response relationship between patients taking 150 or 375 mg of clavulanic acid per day.

TABLE 1. *Bacterial flora, MICs for amoxicillin plus clavulanic acid, and therapeutic response of 21 patients with urinary tract infection*

Therapeutic regimen	Bacteria[a]	MIC (μg/ml) of amoxicillin-clavulanic acid	Therapeutic result
Amoxicillin	*E. coli*	0.6	Cure
	E. coli	1.2	Failure
	E. coli	1.2	Cure
	E. coli	50.6	Failure
	K. pneumoniae	0.6	Failure
	K. pneumoniae	5.0	Failure
	K. pneumoniae	40.0	Failure
	K. pneumoniae	40.0	Failure
Amoxicillin plus clavulanic acid	*E. coli*	0.6	Cure
	E. coli	0.6	Cure
	E. coli	0.6	Cure
	E. coli	1.2	Failure
	E. coli	1.2	Cure
	E. coli	1.2	Cure
	E. coli	1.2	Cure
	E. coli	20.0	Cure
	K. pneumoniae	0.3	Cure
	K. pneumoniae	1.2	Cure
	K. pneumoniae	40.0	Failure
	C. freundii	40.0	Cure
	Proteus sp. (indole positive)	0.3	Cure

[a] *Escherichia coli, Klebsiella pneumoniae, and Citrobacter freundii.*

Medication was well tolerated in all 21 patients. Two patients who used amoxicillin plus clavulanic acid complained of mild nausea, which did not require discontinuation of therapy. No clinical, biochemical, or hematological abnormalities were detected during or after administration of the two treatments in any patient.

DISCUSSION

Urinary tract infections by β-lactamase-producing species are frequent. In our experience of 284 consecutive bacterial isolates from patients with urinary tract infections, 36% (102 isolates) were resistant to ampicillin or amoxicillin (unpublished data). In view of the significant number of infections by penicillin-resistant species, the combination of amoxicillin with clavulanic acid could be a valuable therapy. In this preliminary study the combination of amoxicillin and clavulanic acid was associated with a negative posttreatment culture in 85% of cases (11 or 13 patients), as compared with only 25% of patients receiving amoxicillin alone (2 or 8 patients). This difference was statistically significant ($P < 0.05$). These data are very similar to another study of urinary tract infection due to ampicillin-resistant bacteria, where 67% of patients had negative urine cultures after amoxicillin plus clavulanic acid, whereas only 27% were negative with amoxicillin alone (10).

The fact that two patients showed a negative culture after amoxicillin therapy, even though the isolate was resistant in vitro to amoxicillin, should not be surprising. It is known that spontaneous disappearance of bacteriuria can occur in urinary tract infections, especially in those of the lower tract. Antibiotic levels attained in the urine may be much greater then the concentration in the disk, and discrepancy between in vitro susceptibility testing and in vivo response may occur (11).

The failure of amoxicillin plus clavulanic acid to cure all of the infections is also not unexpected. A possible cause for treatment failure could be the presence of an upper tract infection, where low cure rates with antimicrobial agents are well known (12). These patients showed no other apparent clinical conditions, such as obstructive uropathy, which could promote a therapeutic failure.

The tolerance and safety of the combination

of clavulanic acid and amoxicillin were considered excellent in this preliminary trial with only mild nausea seen in two cases. Obviously this initial limited therapeutic trial must be extended to a larger group of patients and include long-term follow-up evaluations before a definite conclusion can be drawn. However, it appears that an association of amoxicillin and clavulanic acid may be useful in the treatment of urinary tract infections caused by penicillin-resistant bacteria.

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