Amoxicillin Plus Clavulanic Acid in the Treatment of Recurrent Urinary Tract Infections

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Forty-four patients (43 female, 1 male), all with a history of recurrent urinary tract infections, were treated with 250 mg of amoxicillin plus 125 mg of clavulanic acid (one tablet of Augmentin) every 8 h for 7 days. The microbiological cure rates were 84% 1 week after the end of treatment and 67% 1 month later. Side effects, which were reported by 20% of the patients, were mild and in no case caused interruption of treatment. In view of the increasing trend in resistance to agents commonly used for the treatment of urinary tract infections in outpatients, the combination of amoxicillin and clavulanic acid may now be considered a first-line drug in patients with recurrent urinary tract infections.

The incidence of resistance to amoxicillin among bacteria causing urinary tract infections has increased over the years, and in our area the figure reached about 20% during 1980-1981 (6, 7). This resistance is due for the most part to the presence of the TEM plasmid (16, 19), which results in the production of a β-lactamase which destroys amoxicillin. This type of β-lactamase is inhibited by clavulanic acid (18); as a result, these resistant strains are almost all susceptible to Augmentin, the combination of amoxicillin and clavulanic acid which has recently been marketed in the United Kingdom. There is, as yet, little information on the efficacy of Augmentin in the treatment of recurrent urinary tract infections (14). Therefore, we decided to carry out a trial of this preparation in patients who suffer recurrent urinary tract infections and who pose difficult therapeutic problems.

MATERIALS AND METHODS

Patients. Patients attending the Urinary Infection Clinic at the Royal Free Hospital, London, had been referred by family doctors or a consultant from this hospital. All have a history of recurrent attacks of symptoms referable to the urinary tract, such as frequency, dysuria, and urgency. Not all symptomatic attacks are accompanied by bacteriuria, nor are all bacteriuric episodes symptomatic. For entry into the trial, patients had to satisfy the following criteria: at least four attacks during the preceding 12 months and at least one with a previously documented significant bacteriuria, no allergy to β-lactam antibiotics, and an infecting organism susceptible to Augmentin. A full history was taken, and a clinical examination was carried out on all patients. Full details of the management of patients attending the Urinary Infection Clinic have been described elsewhere (10).

Treatment and follow-up. Patients with \( \geq 10^5 \) bacteria per ml in a properly taken mid-stream urine specimen (MSU) were treated with Augmentin, one tablet (250 mg of amoxicillin plus 125 mg of potassium clavulanic acid) every 8 h. Particular attention was paid to ensure that patients cleansed themselves thoroughly. Patients were asked to attend the clinic within 7 days after finishing the treatment (a 2-week follow-up) and again 1 month later (a 6-week follow-up). They were questioned about side effects and symptoms.

Bacteriological methods. Quantitative counts were made from MSUs within 20 min after they were passed, by methods previously described (10), onto cystine-lactose-electrolyte-deficient agar. Susceptibility testing was carried out on IsoSensitest agar (Oxoid Ltd., Basingstoke, England) with an inoculum of 10⁴ colonies per plate with the following disks: 200 μg of sulfafurazole, 5 μg of trimethoprim, 30 μg of Augmentin (20 μg of amoxicillin plus 10 μg of clavulanic acid), 30 μg of ampicillin, 30 μg of cephradine, 200 μg of nitrofurantoin, 30 μg of tetracycline, and 30 μg of mecillinam. Bacteria were identified to the species level by the API 20E system, and Escherichia coli strains were further defined by O serotyping (2) and biotyping (11).

The presence of antibody-coated bacteria in the urine was looked for by a technique developed in this laboratory (12). If 1% of the organisms in the urine was coated with antibody, the test was regarded as positive.

Definitions. Definitions follow the recommendations of the Medical Research Council (15). Microbiological cure rates were determined from the results of the MSU cultures collected at the 2-week and the 6-week follow-up. Cure was defined as the disappearance of the original infecting organism from the urine. If the original infecting organisms were present in the 2-week follow-up MSU, this was recorded as persistence and regarded as a treatment failure. Reinfection—the appearance of a different pathogen either at 2 or 6 weeks—was regarded as a bacteriological cure, since the antibiotic had successfully removed the original infecting pathogen. Relapse was defined as the reappearance of the original pathogen after it had been cleared from the urine at the 2-week follow-up and was recorded as a treatment failure. The relapse rate was calculated as the proportion of patients apparently cured at 2 weeks who subsequently relapsed. Symptomatic cure rates were assessed by direct questioning of patients with a standardized questionnaire.

RESULTS

Patients. Forty-four patients were entered into the trial; 43 were female, 1 was male. The mean age of the patients was 47.4 (±18.3, standard deviation). Of 39 patients, 12 (31%) showed abnormal radiology; 4 had residual urine, 5 had chronic pyelonephritis, 2 had a duplex system, 1 had a ureteric diverticulum, and 1 had a bladder pouch. Of 29
patients, 9 (31%) showed the presence of antibody-coated bacteria. Of the 44 patients, 5 (11%) showed a presence of chemical or hematological abnormalities; when treatment started, 2 had a raised aspartate transaminase, 1 had raised urea and creatinine, 1 had raised urea only, and 2 had raised electrolyte sedimentation rates. None became further elevated during therapy. A relatively high proportion of the infections (36%) were asymptomatic when bacteriuria was detected: these patients were attending the clinic for periodic monitoring. The symptomatic patients complained of frequency (61%), dysuria (54%), loin pain (25%), urgency (21%), suprapubic pain (14%), fever (11%), and nausea (4%).

**Infecting organisms and resistance patterns.** Thirty-seven of the organisms isolated from infected patients (82%) were E. coli. The rest of the infections were due equally to gram-positive cocci (two Staphylococcus epidermidis, one Streptococcus milleri, one S. faecalis) and to gram-negative bacilli other than E. coli (two Proteus mirabilis, one Klebsiella pneumoniae, one Acinetobacter odorrhans). All the infecting strains were susceptible to Augmentin but only 64% were susceptible to amoxicillin. The incidence of resistance to other antibiotics tested were: mecillinam, 2%; nitrofurantoin, 4%; cephradine, 7%; tetracycline, 33%; sulfonamide, 51%; and trimethoprim, 49%. The reason for the high incidence of trimethoprim resistance is discussed below.

**Cure rates.** (i) **Eradication of infection.** At 1 week after the end of treatment, 30 of the 44 patients had sterile urine. Of the 14 who had significant bacteriuria, 7 had an organism other than that which had caused the original infection; these 7 had therefore become reinfected and were scored as having been cured, in view of the fact that the original infecting species had been eliminated. The microbiological cure rate at 2 weeks was therefore 37 of 44 (84%). Of the 30 patients who had sterile urine at the 2-week follow-up, 28 attended the 6-week follow-up; 21 proved to have sterile urine. Of the seven patients with significant bacteriuria at this time, three had become reinfected and four had relapsed. Thus, the microbiological cure rate at 6 weeks was 24 of 35 (67%), and the relapse rate was 4 of 28 (14%). The 14 patients who had significant bacteriuria at the 2-week follow-up were retreated (not necessarily in the context of the present study).

(ii) **Disappearance of symptoms.** There was a good (but not absolute) correlation between relief of symptoms and eradication of bacteriuria. Of the 28 patients who had been treated for a symptomatic infection, 20 reported at the 2-week follow-up that their symptoms had gone (usually within 3 days of starting the treatment). Of the 20, 17 were bacteriuric at this point, whereas 2 patients had become reinfected asymptptomatically. In the remaining patient, the original infecting organism had persisted even though the symptoms were no longer present. Eight patients were still symptomat-
ic at the 2-week follow-up; one was bacteriuric, two had been reinfected, and five still had significant bacteriuria with their original infecting organism.

**Side effects.** Nine patients (20%) reported mild side effects. There were four complaints of vaginal irritation or discharge (yeasts were isolated from high vaginal swabs taken from two of these patients), three complaints of gastrointestinal problems (diarrhea, nausea and indigestion, and upset stomach, respectively), and three complaints of a neurological type (sleepiness, slight blurring of vision, and problems with balance, respectively). In no case did a patient have to stop taking the prescribed treatment because of side effects, which were therefore judged to have been mild. Side effects of a neurological type are well recognized as occurring in a small proportion of patients taking amoxicillin (1, 17).

**DISCUSSION**

Patients with a history of recurrent urinary tract infections usually respond well in the very short term to conventional antibiotic treatment; the cure rate 1 week after treatment has end ranges between 70 and 86% (7). The success rate at this time should thus be similar to those observed (2) in simple dysuria and frequency associated with infection (85 to 90%) and in bacteriuria in pregnancy (70 to 80%).

However, although cure rates for the latter two groups hardly changed at the 6-week follow-up, a characteristic feature of the “difficult” patients, such as those treated here, was that many relapsed during the month after the end of therapy. This means that cure rates at 6 weeks were substantially lower than those at 2 weeks and may be as low as 40% (6). We now have some evidence that points towards certain antibiotic regimens as being superior to others in respect to the rate of relapse observed in difficult patients. Thus, trimethoprim alone (7), trimethoprim-sulfamethoxazole (10), and cephradine (1 g every 12 h) (3) all give a relapse rate of less than 15%, as did Augmentin in the present study. On the other hand, other antibiotic regimens may give relapse rates as high as 30%. The most likely explanation for relapse is that not all the original infecting organisms are completely eliminated by the antibiotic but persist within the tissues of the urinary tract so that the urine contains <10⁵ organisms per ml at the 2-week follow-up. However, during the following month, the residual organisms multiply in the bladder urine to reach significant numbers once again.

On this hypothesis, it is attractive to suppose that those antibiotics which give rise to the lower rate of relapse are those which most often bring about complete sterilization of the urine during the course of the 7 days of treatment. It is interesting that in a study (6) carried out with the same protocol as that used in the present investigation, in which an almost exactly identical group of patients was treated, amoxicillin alone (250 mg, every 8 h; the same dose as is given when one tablet of Augmentin is taken every 8 h) did not give such good results. The relapse rate with amoxicillin alone was 33% compared with 14% here. Clavulanic acid is a weak antibacterial agent in its own right (9), and a synergistic activity with amoxicillin may occur over and above its effect of inhibiting β-lactamase (13).

Many physicians who lack a rapid laboratory service are compelled to treat symptomatic patients with an antibiotic selected on a “best-guess” basis; i.e., the antibiotic most likely to be active against the type of pathogen most commonly isolated from urinary tract infections.

We found a very high incidence of resistance (49%) to trimethoprim in this study. We assume this is because the patients we treated had been given many courses of trimethoprim-sulfamethoxazole in the fairly recent past, which has selected for resistant bacteria. By contrast, in an unselected population, we have found the incidence of trimethoprim resistance among urinary isolates to be 13% from hospital patients and 6% from patients outside the hospital (8).

Resistance to amoxicillin has now risen to about 30% in our experience but virtually all resistant strains are susceptible to Augmentin (4). The latter must therefore be a good candidate for best-guess therapy. The most common urinary pathogens that we found to be resistant to Augmentin are Enterobacter spp. (5), which comprise only 2.5% of the organisms isolated from urine samples in this laboratory. Other bacterial species which are resistant to Augmentin, such as indole-positive Proteae, Citrobacter freundii, Serra-
tia marcescens, and Pseudomonas aeruginosa, are in our experience even less common than Enterobacter spp. Thus, in view of its broad spectrum and great efficacy, combined with a low incidence and mild nature of side effects, we consider that physicians could reasonably use Augmentin as a first-line treatment for patients with recurrent urinary tract infections. An alternative choice would be one of the oral cephalosporins, which are broad spectrum and clinically effective (3, 10). However, Augmentin is not as expensive as oral cephalosporins and may be chosen partly for this reason.

LITERATURE CITED