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Comparative Study of Amoxicillin-Clavulanic Acid and Cephalexin in the Treatment of Bacteriuria During Pregnancy

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A comparative clinical trial of amoxicillin-clavulanic acid and cephalexin was carried out in 80 women with bacteriuria of pregnancy. Treatment was randomly allocated and consisted of either one tablet of amoxicillin plus clavulanic acid (250 and 125 mg, respectively) three times daily or cephalexin (250 mg) three times daily for 7 days. Overall bacteriological cure rates at 2 weeks were 77% in the amoxicillin-clavulanic acid group and 74% in the cephalexin group. At 6 weeks the respective rates were 76 and 60%. Twenty-five episodes of infection were with ampicillin-resistant strains; cure rates were 82% (2 weeks) and 80% (6 weeks) in the amoxicillin-clavulanic acid group and 85 and 64%, respectively, in the cephalexin group. Differences in cure rates were not statistically significant. No significant difference in the rate of side effects was found. In particular, no toxicity to the fetus was seen which could be ascribed to either drug. Amoxicillin-clavulanic acid would appear to be a safe and effective treatment for bacteriuria of pregnancy.

Ampicillin and amoxicillin are popular choices for the treatment of bacteriuria of pregnancy. They are active against the majority of commonly isolated infecting organisms and enjoy a low incidence of unwanted effects in the mother, with the further advantage that there is no evidence of toxicity to the developing fetus. Resistance to ampicillin, however, is increasing both in hospitals and in the community; in the main, this is due to plasmid-directed production of β-lactamase. There is therefore a need for antimicrobial agents possessing the same properties as ampicillin and amoxicillin but with activity against β-lactamase-producing organisms resistant to these antibiotics.

Clavulanic acid is an inhibitor of several of the more usual plasmid-mediated β-lactamases (7, 8). It has been shown in vitro that this agent will render an ampicillin-resistant organism susceptible to ampicillin if resistance is due to production of a β-lactamase which is inhibited by clavulanic acid (1, 5, 10, 12). This in vitro effect has been confirmed in vivo in several trials of a combination of amoxicillin with clavulanic acid in the treatment of urinary tract infections (1, 3, 4, 6). The combination is now available in the United Kingdom in a 2:1 ratio, containing 250 mg of amoxicillin and 125 mg of clavulanic acid per tablet. Although amoxicillin-clavulanic acid has been studied extensively in urinary infections, pregnant women have usually been excluded from such studies. We have carried out a clinical trial to compare the efficacy, safety, and tolerance of amoxicillin-clavulanic acid with cephalexin in the treatment of bacteriuria of pregnancy.

MATERIALS AND METHODS

Eighty pregnant women with bacteriuria of pregnancy were entered into the trial. One patient was entered twice, giving 81 episodes of infection. All patients gave informed verbal consent before entry into the trial. Patients were randomly allocated to receive either one tablet of amoxicillin-clavulanic acid three times daily or 250 mg of cephalexin three times daily for 7 days. The physician was not aware of which treatment was given.

Bacteriuria of pregnancy was initially detected by screening midstream urine (MSU) collected at the antenatal clinic. Growth from this specimen was regarded as significant if it yielded more than 10^5 CFU/ml of a single species. Significant pyuria was defined as ≥20 pus cells per μl. Patients with significant growth from this specimen were entered into the trial, but a second MSU was taken before treatment was started; only if the result of this specimen confirmed that of the first were data from that patient used in assessing efficacy. Patients were excluded from the trial if they were known to be hypersensitive to the penicillins or cephalosporins, if the infection was caused by an organism resistant to one of the trial drugs, or if the patient was already taking an antibiotic or had taken one since the first MSU was collected.

Sensitivity testing to cephalexin was carried out by the breakpoint method (11), using diagnostic sensitivity test agar (Oxoid Ltd., Basingstoke, England). The plates incorporated 200 mg of cephalothin per liter (for urine isolates) and were inoculated by multiple replicator with an inoculum of approximately 10^5 CFU. An organism capable of growth on this medium was deemed to be resistant to cephalexin. Sensitivity testing to ampicillin was done in the same way, using a concentration of 100 mg of ampicillin per liter in the plates. Sensitivity testing to amoxicillin-clavulanic acid was carried out by the disk diffusion method on diagnostic sensitivity test agar as described by Stokes and Waterworth (9). This method was preferred to the above breakpoint method because of concern regarding the poor stability of clavulanic acid in agar plates (unpublished data). The disks (Oxoid) contained 20 μg of amoxicillin and 10 μg of clavulanic acid. A semiconfluent inoculum was used.

Follow-up was carried out at 2 weeks after starting treatment with a clinical consultation, at which patients were asked if they had noticed any side effects. They were then questioned specifically about various side effects, including nausea, vomiting, diarrhea, vaginal irritation or discharge, and failure to complete the course of treatment. An MSU was also collected, and a final specimen was obtained at 6 weeks.

The patient was regarded as cured only if both 2- and 6-week follow-up specimens were free from the original infecting organism. If one or both of these specimens contained a demonstrably different organism, this was regarded

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as reinfection. After birth, each child was examined by a pediatrician, who noted any apparent illness or congenital abnormality.

All statistical analyses were by the chi-square test with Yates correction.

RESULTS

Of the 81 episodes of infection, 22 were not included in the assessment of bacteriological cure rates. In 19 cases, this was because the second MSU did not confirm the result of the screening specimen. One patient received an antibiotic from another source shortly after finishing the trial drug; one patient failed to provide follow-up specimens at either 2 or 6 weeks, and the third was catheterized at a maternity hospital shortly after entry into the trial. This resulted in a persistent infection with a multiresistant *Enterobacter* sp.

A total of 59 episodes of infection in 58 patients were therefore included in the assessment of efficacy; 31 episodes were treated with amoxicillin-clavulanic acid, and 28 were treated with cephalexin. Of the 31 patients in the amoxicillin-clavulanic acid group, 17 (55%) had a previous history of urinary infection, 14 (45%) had significant pyuria before treatment was started, and 15 (48%) had symptoms of urinary infection before treatment. In the cephalexin group (28 patients), the respective figures were 15 (54%), 12 (43%), and 12 (43%). Pretreatment infecting organisms are given in Table 1. All isolates were susceptible to both trial drugs. Table 2 shows the bacteriological cure rates at 2 and 6 weeks.

There were 25 episodes of infection with ampicillin-resistant organisms; 11 of these were treated with amoxicillin-clavulanic acid, and 14 were treated with cephalexin. Bacteriological cure rates at 2 and 6 weeks are shown in Table 2.

Overall, there were seven failures in the amoxicillin-clavulanic acid group at 2 weeks, with no additional failures at 6 weeks. In the cephalexin group, there were five failures at 2 weeks and a further five at 6 weeks. In no case was the reason for failure apparent; failure of treatment was never associated with the appearance of resistance to the drug used. One patient in the cephalexin group abandoned treatment after 5 days due to side effects.

There were two reinfections in the amoxicillin-clavulanic acid group and one in the cephalexin group. All of the new infecting organisms were susceptible to both of the trial drugs.

For the assessment of side effects, five patients were not included due to failure to attend follow-up appointments. Side effects in the remaining 76 courses of treatment are shown in Table 3. Thirty-nine patients received amoxicillin-clavulanic acid, and 37 received cephalexin. Twenty-one courses of treatment were given at 14 weeks of gestation or less (10 amoxicillin-clavulanic acid and 11 cephalexin). Of the 80 pregnancies, there was one abortion after amniocentesis; 6 of the remaining 79 babies were lost to follow-up. Only two abnormalities were found in the examination of the newborn babies. One child had a right-sided hydronephrosis, and the second was born prematurely (34 weeks of gestation) with a body weight and head circumference both below the 10th percentile. This latter child was otherwise normal. Both mothers had received cephalexin, at 23 and 15 weeks of gestation, respectively. No reason was found to account for either abnormality.

TABLE 1. Pretreatment infecting organisms

Organism	No. of isolates	
	Amoxicillin-clavulanate	Cephalexin
Escherichia coli	27 (8)[a]	26 (13)[a]
Klebsiella spp.	1 (1)	1 (1)
Staphylococcus aureus	1 (1)	
Staphylococcus epidermidis	2 (1)	
Nonhemolytic streptococcus		1 (0)

[a] Values in parentheses indicate the number of strains that were resistant to ampicillin.

TABLE 2. Bacteriological cure rates at 2 and 6 weeks posttreatment

Week	No. cured/no. infected (%) with:	
	Amoxicillin-clavulanic acid	Cephalexin
All assessable infections		
2	24/31 (77)	22/27[a] (74)
6	22/29 (76)	15/25 (60)
Infections with ampicillin-resistant organisms		
2	9/11 (82)	11/13[a] (85)
6	8/10 (80)	9/14 (64)

[a] One patient failed to provide the 2-week follow-up specimen but provided the 6-week specimen.

DISCUSSION

Bacteriuria of pregnancy is a common condition, and it is important that it be treated to avoid progression to acute pyelonephritis. Problems may occur in the treatment of this condition, however, principally due to infection with resistant organisms and because of the contraindication of certain antimicrobial agents in pregnancy. In particular, nalidixic

TABLE 3. Side effects after the 76 assessable courses of treatment

Side effect	No. of side effects (%) with:			
	Amoxicillin-clavulanate		Cephalexin	
	Volunteered	On questioning[a]	Volunteered	On questioning[a]
None	30 (77)	21 (54)	31 (84)	21 (57)
One or more side effects	9 (23)	18 (46)	6 (16)	16 (43)
Nausea, anorexia, vomiting	2 (5)	4 (10)	2 (5.5)	4 (11)
Diarrhea	2 (5)	7 (18)	0 (0)	3 (8)
Vaginal irritation or discharge	5 (13)	16 (41)	5 (13.5)	11 (30)
Skin rash	0 (0)	2 (5)	0 (0)	1 (3)
Headache	0 (0)	0 (0)	0 (0)	1 (3)
Constipation	0 (0)	0 (0)	0 (0)	1 (3)
Dizziness	1 (2.5)	1 (2.5)	0 (0)	0 (0)
Stopped treatment prematurely	0 (0)	2 (5)	0 (0)	2 (5.5)

[a] Side effects listed in this column are cumulative, i.e., represent volunteered side effects plus those elicited only on questioning.

acid and trimethoprim-sulfamethoxazole are not recommended for use in pregnancy. Pivmecillinam has been shown to be effective but was associated with a significantly higher rate of side effects than ampicillin (2).

The combination of amoxicillin and clavulanic acid (itself a β-lactam) is thus a potentially useful agent for the treatment of this condition. In this trial, the two drugs compared were equally efficacious, there being no significant difference ($P > 0.05$) at 2 or 6 weeks. Although more relapses at 6 weeks were seen in the cephalexin group, this difference was not statistically significant. The bacteriological cure rates were similar to those previously reported (1, 3, 4, 6). When the treatment failed, this was not due to emergence of resistance to either drug.

There were no significant differences ($P > 0.05$) in the frequency of side effects, either in total or if side effects were examined individually. The principal side effect seen with amoxicillin-clavulanic acid was vaginal irritation or discharge. The cause of this is uncertain, since microbiological examination was not performed, but it may have been due to overgrowth of *Candida* spp. The number of patients who abandoned treatment before completion due to side effects was low. No toxicity to the fetus which could be ascribed to either drug was seen.

We conclude that amoxicillin-clavulanic acid is a safe and effective treatment for bacteriuria of pregnancy.

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