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Chronic Salmonella Bacteriuria with Intermittent Bacteremia Treated with Low Doses of Amoxicillin or Ampicillin

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Amoxicillin and ampicillin were compared at a dose of 250 mg twice daily for 4 weeks to treat *Salmonella typhi* or *Salmonella paratyphi* A chronic bacteriuria with intermittent bacteremia. Eleven patients received amoxicillin, and 15 received ampicillin. Concentrations of the two drugs were measured in the urine and serum on treatment days 1, 2, and 7. The urine levels of both antibiotics were maximal 2 h after administration, and minimal levels were 80-fold higher than the *S. typhi* minimal inhibitory concentration and 20-fold higher than the *S. paratyphi* A minimal inhibitory concentration. The serum level of amoxicillin was below the minimal inhibitory concentration of *S. paratyphi* A 6 h after administration on each of the testing days. The serum antibiotic levels of the two drugs showed no cumulative effect at day 2 or day 7. Of the 11 patients treated with amoxicillin, 1 had positive urine cultures during treatment, and 1 treated with ampicillin continued to be symptomatic. Recurrence of bacteriuria occurred in three of seven patients with persistent bladder calcification. None of the 26 patients in this study had positive blood culture during or after treatment. Amoxicillin and ampicillin at a dose of 250 mg twice daily were equally successful in treating chronic salmonelluria.

The finding of chronic bacteriuria requires evaluation for structural abnormalities of the urinary tract and identification of the bacteria and its antibiogram to prescribe specific therapy. Nephrocalcinosis, nephrolithiasis, and obstructive lesions of the urinary tract contribute to chronic bacteriuria (6). In Egypt, infection with *Schistosoma haematobium* leads to obstructive lesions of the urinary tract due to granulation tissue, fibrous tissue, or calcification of the bladder or ureters (13); chronic bacteriuria with *Salmonella typhi* or *S. paratyphi* A is associated with these obstructive changes (8, 12).

Ampicillin given orally four times daily at a dose of 100 mg/kg per day for 4 weeks has been shown to be successful in treating chronic salmonelluria (1), and 250 mg of amoxicillin given orally four times daily for 4 weeks was found to be equally effective (5). This study compares the effectiveness of ampicillin and amoxicillin when given at the same dose of 250 mg twice daily for 4 weeks.

MATERIALS AND METHODS

Twenty-six male patients from 8 to 59 years of age (median 15 years) were studied. All patients had had repeated attacks of fever for 3 to 12 months before hospitalization, and 12 had received various courses of several antibiotics.

Urine cultures were done twice weekly, and blood cultures were done twice weekly and on every fever spike in all patients. All 26 patients demonstrated persistent bacteriuria (three or more consecutive positive urine cultures for the same species); urine cultures showed *S. typhi* in 9, *S. paratyphi* A in 16, and a *Salmonella* species in 1. Bacterial colony counts were greater than 100,000 per ml of urine in each case. Twenty-four of the patients had intermittent bacteremia (mean of two of six blood cultures taken at twice weekly intervals were positive) with the same species as identified from the urine.

Twelve of the patients had active *S. haematobium* infection, and the other 14 had evidence of previous infection as shown by characteristic abnormalities on intravenous pyelography, by an enzyme-linked immunosorbent assay test of serum (using a crude adult worm schistosomal antigen), or by *S. haematobium* eggs demonstrated on rectal valve biopsy. The patients were divided into two treatment groups: 11 patients received amoxicillin, one 250-mg capsule every 12 h for 4 weeks; and 15 patients received ampicillin, one 250-mg capsule every 12 h for 4 weeks.

All patients were observed closely for clinical response and side reactions. Both serum and urine antibiotic concentrations were measured in all patients treated with amoxicillin and in six patients treated with ampicillin. Serum and urine samples were collected before starting antibiotic treatment and 1, 2, 6, and 12 h after the morning dose on day 1 and day 2 of

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treatment, as well as 6 h after the morning dose on day 7. The concentrations of the drugs were determined by the agar well diffusion method of Bennett et al. (2) with *Bacillus subtilis* spore suspension (Difco Laboratories, Detroit, Mich.) as the test species. The minimal inhibitory concentrations (MICs) of amoxicillin for 27 *Salmonella* isolates from the urine and blood of the 11 patients were determined by the inocula-replicating method of Steers et al. (15). The MICs of ampicillin for *S. typhi* and *S. paratyphi* have previously been reported (11). Blood and urine cultures were repeated twice weekly and on every fever spike throughout the treatment and in hospital follow-up periods. Treatment of schistosomiasis with niridazole (25 mg/kg per day for 6 days) was started from 1 to 3 weeks after the start of the antibiotic therapy. All of the patients were hospitalized during the investigation period, therapy, and the follow-up period.

RESULTS

The mean MICs for *S. typhi* were 0.4 μg/ml for amoxicillin and 0.1 μg/ml for ampicillin. The mean MICs for *S. paratyphi* A were 2.4 μg/ml for amoxicillin and 0.6 μg/ml for ampicillin (Table 1). The mean peak serum level (Fig. 1) occurred 2 h after administration for both antibiotics—3.1 μg/ml for amoxicillin and 1.9 μg/ml for ampicillin. The serum antibiotic levels showed no cumulative effect at day 2 or 6 h after administration on day 7 (0.9 μg/ml for amoxicillin and 1.5 μg/ml for ampicillin) (Table 2). The mean serum levels of amoxicillin were below the MIC of *S. paratyphi* A 6 h after administration on each day measured.

TABLE 1. *MICs of amoxicillin and ampicillin for S. paratyphi A and S. typhi*

Species[a]	MIC (μg/ml)[b] of:	
	Amoxicillin	Ampicillin[c]
S. paratyphi A (19)	2.4 (1.6–3.1)	0.6 (0.4–0.8)
S. typhi (7)	0.4	0.1 (0.1–0.2)
Salmonella spp. (1)	0.4	

[a] Number of isolates tested with amoxicillin is given in parentheses.
[b] Range is given in parentheses.
[c] Reference 11.

The urine levels of both antibiotics were maximal after 2 h from administration (Fig. 2), and because of active renal tubular transport and urine concentrating, the lowest individual minimum urine antibiotic level was 80-fold higher than the highest *S. typhi* MIC and 20-fold higher than the highest *S. paratyphi* A MIC.

All but one patient in the amoxicillin treatment group had clearance of bacteriuria, and he continued to have urine cultures positive for *S. paratyphi* A during and after treatment in spite of adequate urine amoxicillin levels. The MIC of this species was 1.60 μg/ml. The species was not tested in vitro with the patients' urine. One patient in the ampicillin treatment group remained febrile and toxic after 5 days of treatment, so therapy was switched to chloramphenicol with good resolution. No patient had a positive blood culture during treatment, and there was no evidence of endocarditis, hepatic abscess, or other focus of systemic infection as a result of the subinhibitory antibiotic levels.

The 24 patients whose bacteriuria was cleared on the protocol treatment were followed from 1 to 12 (median 3) months after therapy. One patient in the amoxicillin group had recurrence after 1 year, and two patients in the ampicillin

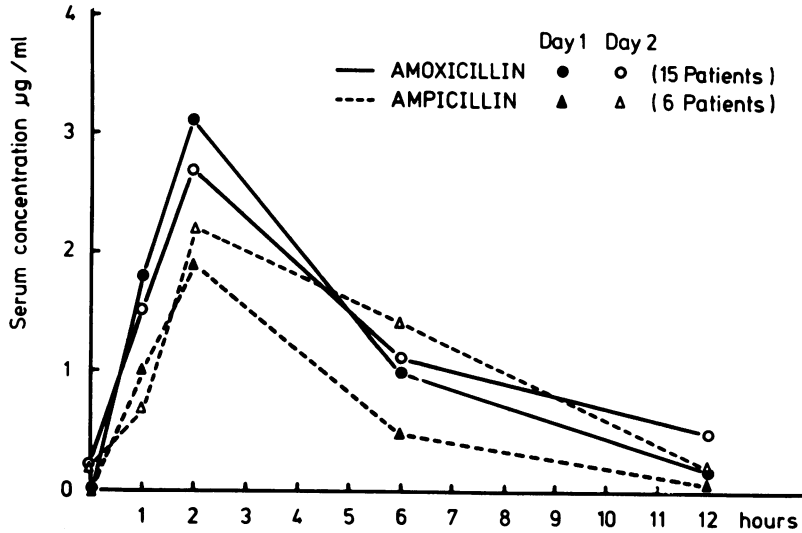

FIG. 1. *Mean concentrations of amoxicillin and ampicillin in sera of patients with S. typhi or S. paratyphi A bacteriuria.*

group had recurrence of bacteriuria (one at 2 months and one at 1 year). The same species of bacteria with the same antibiogram was cultured in each case. Phage typing was not done. All three patients had persistent bladder calcification. There were four other patients (two in each group) who had bladder calcification and had no recurrence of bacteriuria. Niridazole cured the active *S. haematobium* infection in all treated patients.

TABLE 2. *Amoxicillin and ampicillin concentrations in the serum of patients with chronic salmonellosis*

Time	Concn (μg/ml) of:					
	Amoxicillin			Ampicillin		
	Mean	Median	Range	Mean	Median	Range
Day 1						
1 h	1.9	2.2	0–3.4	0.9	1.4	0.1–1.6
2 h	3.1	3.2	1.7–6.0	1.9	2.1	0.4–3.1
6 h	1.0	0.5	0.1–4.1	0.5	0.7	0.1–1.3
12 h	0.2	0	0–1.5	0.1	0	0–0.3
Day 2						
1 h	1.5	1.5	0–4.5	0.7	0.4	0.2–1.5
2 h	2.8	3.0	0.2–5.8	2.2	2.4	1.4–2.9
6 h	1.1	1.1	0.2–1.5	1.4	0.6	0.2–4.6
12 h	0.5	0	0–3.0	0.2	0	0–0.9
Day 7						
6 h	0.9	0.6	0–2.9	1.5	1.3	0.3–2.9

DISCUSSION

Chronic bacteriuria presents both diagnostic and therapeutic challenges. In Egypt where *S. haematobium* infection leads to obstructive changes in the urinary tract (10), a 5% incidence of bacteriuria in boys aged 5 to 16 years has been reported (9), and chronic bacteriuria with intermittent bacteremia with *S. typhi* and *S. paratyphi* A has been described (4).

Recurrent urinary tract infections respond poorly to conventional 2-week treatment regimens, but some increased success has been noted with 6-week regimens (7). The importance of urinary antibiotic levels in achieving a cure in cases of urinary tract infections has been demonstrated (14).

Our study clearly shows that a twice daily dosage of amoxicillin or ampicillin achieves adequate urine levels for a prolonged time and can be used to clear urinary tract infections caused by sensitive species. Recurrent bacteremia secondary to a urinary tract focus of infection can be prevented by antibiotic therapy which eradicates the urinary focus even though serum antibiotic levels are blow the MIC. Reversing the obstructive lesion is essential to prevent recurrence of both the urinary infection and the bacteremia. Treatment with niridazole has been shown to decrease the schistosomal obstructive lesions (3). In previous studies we showed that

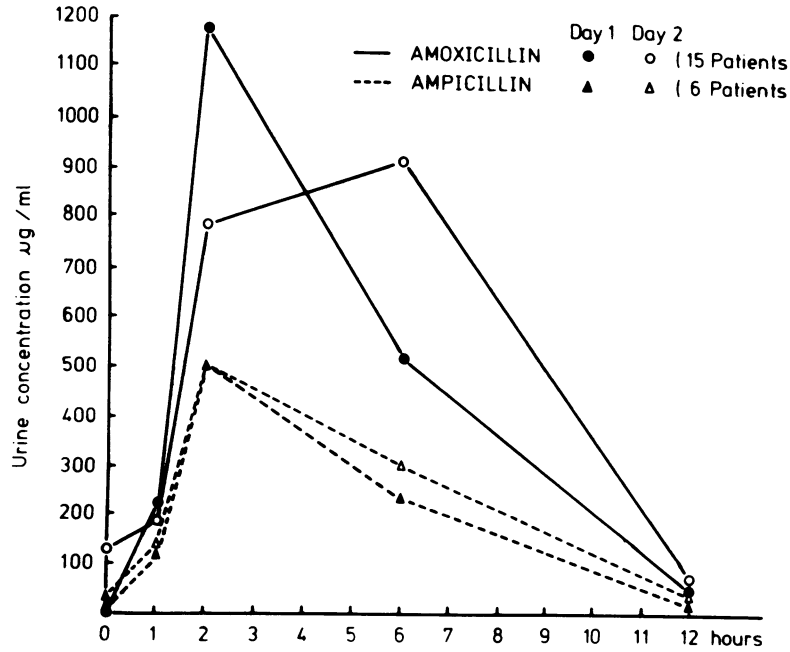

FIG. 2. *Mean concentrations of amoxicillin and ampicillin in urine of patients with S. typhi or S. paratyphi A bacteriuria.*

if niridazole is given without antibiotic therapy, bacteriuria persists. Conversely, treating the bacteremia is of little benefit so long as the obstructive lesions remain. Antibiotic treatment for 4 weeks provided adequate urinary levels during the time the urinary obstructive lesions were resolving.

Previously, ampicillin used at a high daily dose of 100 mg/kg of body weight resulted in a relapse of 5 of 14 patients (1). Those had advanced irreparably damaged urinary tracts. In this study 21 of the 26 patients were cured and did not relapse during a follow-up period of 1 to 12 months. The three patients with recurrent infection all had persistent bladder calcification. Amoxicillin and ampicillin were equally effective, and a single capsule twice daily was economical, enhanced patient compliance, and resulted in successful therapy.

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LITERATURE CITED

1. **Bassily, S. B., Z. Farid, J. S. Lehman, Jr., D. C. Kent, W. R. Sanborn, and S. D. Hathout.** 1970. Treatment of chronic urinary salmonella carriers. Trans. R. Soc. Trop. Med. Hyg. **64**:723–729.
2. **Bennett, J. V., J. L. Brodie, E. J. Benner, and W. M. M. Kirby.** 1966. Simplified accurate method for antibiotic assay of clinical specimens. Appl. Microbiol. **14**: 170–177.
3. **Farid, Z., S. Bassily, M. F. Abdel-Wahab, J. S. Lehman, Jr., A. Hassan, and D. C. Kent.** 1970. Urinary schistosomiasis treated with niridazole (Ambilhar): a quantitative evaluation. Trans. R. Soc. Trop. Med. Hyg. **64**:122–129.
4. **Farid, Z., S. Bassily, D. C. Kent, W. R. Sanborn, A. Hassan, and M. F. Abdel-Wahab.** 1970. Chronic urinary salmonella carriers with intermittent bacteremia. J. Trop. Med. Hyg. **73**:153–156.
5. **Farid, Z., S. Bassily, I. A. Mikhail, D. C. Edman, A. Hassan, and W. F. Miner.** 1975. Treatment of chronic enteric fever with amoxicillin. J. Infect. Dis. **132**:698–701.
6. **Fass, R. J., A. S. Klainer, and R. L. Perkins.** 1973. Urinary tract infection practical aspects of diagnosis and treatment. J. Am. Med. Assoc. **225**:1509–1513.
7. **Gleckman, R., M. Crowley, and G. A. Natsios.** 1979. Therapy of recurrent invasive urinary tract infections of men. N. Engl. J. Med. **301**:878–880.
8. **Hathout, S. D., Y. A. Ghaffar, A. Y. Awny, and K. Hassan.** 1966. Relationship between urinary schistosomiasis and chronic enteric urinary carrier state among Egyptians. Am. J. Trop. Med. Hyg. **15**:156–161.
9. **Laughlin, L. W., Z. Farid, N. Mansour, D. C. Edman, and G. I. Higashi.** 1978. Bacteriuria in urinary schistosomiasis in Egypt. Am. J. Trop. Med. Hyg. **27**:916–918.
10. **Lehman, J. S., Jr., Z. Farid, J. H. Smith, S. Bassily, and N. A. El-Masry.** 1973. Urinary schistosomiasis in Egypt: clinical, radiological, bacteriological, and parasitological correlations. Trans. R. Soc. Trop. Med. Hyg. **67**:384–399.
11. **Mikhail, I. A., D. C. Kent, K. Sorensen, W. R. Sanborn, and J. Smith.** 1972. Concentrations of ampicillin and chloramphenicol in the serum of patients with acute salmonella enteric fever. Antimicrob. Agents Chemother. **2**:336–339.
12. **Miller, W. S., and T. M. Floyd.** 1954. Chronic urinary salmonella carriers. Lancet **i**:343–344.
13. **Smith, J. H., A. S. Kelada, A. Khalil, and H. A. Torky.** 1977. Surgical pathology of schistosomal obstructive uropathy: a clinico-pathologic correlation. Am. J. Trop. Med. Hyg. **26**:96–108.
14. **Stamey, T. A., W. R. Fair, M. M. Timothy, M. A. Millar, G. Mihara, and Y. C. Lowery.** 1974. Serum versus urinary antimicrobial concentrations in cure of urinary tract infections. N. Engl. J. Med. **291**:1159–1163.
15. **Steers, E., E. L. Foltz, and B. S. Graves.** 1959. An inocula replicating apparatus for routine testing of bacterial susceptibility to antibiotics. Antibiot. Chemother. **9**:307–311.