Effects of Ten Milligrams of Ampicillin per Day on Urinary Tract Infections

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A total of 20 patients with symptomatic urinary tract infections (>10^5 colony-forming units of Escherichia coli per ml of urine in addition to pyuria) received 10 mg of ampicillin and 2 liters of fluid daily for 3 days. After 2 days, 16 patients had culture-negative urine without pyuria. A total of 18 similar patients received only 2 liters of fluid for 3 days. On day 4, all had >10^5 colony-forming units of E. coli per ml of urine and >10^4 leukocytes per mm^3 of urine.

Gram-negative bacilli, when exposed to beta-lactam antibiotics at concentrations lower than the minimum inhibitory concentration (MIC), elongate and produce filaments (5, 9, 18). Concentrations of ampicillin as low as 1/16 of the MIC elongate Escherichia coli (7). Exposure of E. coli for 5 h to ampicillin at a concentration of 1/20 of the MIC decreases the bacterial population by one log (99%) as compared with a control grown without the drug (8). Bacterial adherence to epithelial cells is an important factor in virulence (1). It has been shown that urinary tract infections produced by E. coli are closely related to the binding capacity of E. coli to periurethral epithelial cells (4). Sub-MICs of antibiotics inhibit bacterial adherence to epithelial cells (11, 15), and sub-MICs of ampicillin have been shown to significantly inhibit the adherence of E. coli to epithelial cells of the urine sediment (14). Sub-MICs of ampicillin increase the survival rate of rabbits infected with E. coli (17). Exposure of E. coli to sub-MICs of ampicillin results in an alteration of morphology, an inhibition of growth, an inhibition of adherence to epithelial cells, and an increase in the survival rate of infected animals. This investigation was intended to determine whether the effects of sub-MICs of antibiotics on bacteria, as seen in vitro and in animals, can also be observed in patients.

A total of 38 patients admitted to the Charles Nicolle Hospital, Tunis, Tunisia, with symptomatic urinary tract infections were investigated. The age of the patients ranged from 7 to 79 years with a mean of 42.7, a median of 42, and a mode of 60. With six exceptions (three treated and three control), no patient had a history of urinary tract infection. None of the patients had signs of upper urinary tract infection as evidenced by lack of fever, flank pain, and tenderness in the costovertebral angle upon examination. All patients produced urine containing >10^6 E. coli per ml which were susceptible to ampicillin. All patients gave informed consent to participate in this study.

Two consecutive clean-catch urine specimens collected 2 h apart were plated with a calibrated loop (2) on MacConkey agar. Colonies were counted after 20 to 24 h of incubation; identification and a disk susceptibility test were performed by a rapid method (6, 10), and the results were reported within 5 h of isolation. The MICs of ampicillin for each strain of E. coli were determined by the twofold broth dilution method (16). Ampicillin in the urine was assayed by the agar diffusion method with Sarcina lutea (3). Leukocytes in the urine were counted by the chamber method (2).

The patients were assigned alternately to a group receiving ampicillin or to a control group. Each patient in the ampicillin group received 10 mg of ampicillin (Bristol Laboratories, Syracuse, N.Y.) per day for 3 days. The ampicillin was dissolved in 6 ml of water and was administered 2 ml each time together with a glass of water in the morning, after lunch, and before dinner. The control group received only the three glasses of water. All patients were given a total of 2 liters of liquids per day. During the first 3 days and on day 7 after the investigation began, all who received the 3-day course of ampicillin were monitored for the number and species of organisms in the urine, the presence of filaments in the sediment, and the number of leukocytes and the concentration of ampicillin in the urine. The control patients were tested in the same manner during the first 3 days. The patients who showed no decrease in the number of organisms after day 3 of ampicillin treatment, and also the control patients, were given conventional antibacterial treatment on day 4 of the investigation.
ampicillin in the urine were between 0.5 and 4 μg/ml. Most of these concentrations represented one-fifth to one-half the MIC of the \textit{E. coli} strain of the patient (Fig. 1). After 24 h of treatment with ampicillin, 8 of the 20 patients showed a colony-forming unit (CFU) count of $<10^5$ per ml. On days 2, 3, and 7 after the start of treatment, 16 patients showed negative urine cultures ($<10^4$ CFU/ml) (Fig. 2). Filaments 10 to 50 μm long were observed on eight occasions in the urine sediment after 24 h of ampicillin treatment. The decrease in the number of \textit{E. coli} in the urine in the group receiving ampicillin was closely followed by a decrease in the number of leukocytes in the urine. On days 3 and 7, the number of leukocytes was practically normal. The control patients not receiving the drug showed little or no change in the number of leukocytes in the urine.

The four treatment failures were one tumor, one cystitis owing to a neurological bladder, one cystitis secondary to calculi, and one cystitis in a woman 7 months pregnant.

The purpose of this investigation was not to evaluate a new method of treatment, but to determine whether the effects of sub-MICs of antibiotics on bacteria as observed in vitro (4, 11, 14, 15) and in animals (17) can also be observed in patients.

The prompt drop in the number of organisms in patients receiving 10 mg of ampicillin per day shows that this dosage produces significant antibacterial activity in the urine. Since the urine cultures remained negative 4 days after the termination of treatment (in the absence of ampicillin in the urine), the activity of this dosage was confirmed. A follow-up limited to 7 days was considered adequate for the purpose of this investigation.

There were twice as many female patients as males, and the group receiving ampicillin had a higher proportion of females. The clinical types of urinary infection were similar in both groups. Acute cystitis represented about one-half of the total. The other half consisted of cystitis secondary to calculi, and one patient had a tumor compressing the urethra. The MICs of ampicillin for the isolated \textit{E. coli} ranged between 1 and 4 μg/ml; most were 4 μg/ml. The concentrations of ampicillin in the urine.
investigation. Leukocyte counts decreased in the urine of the bacteriologically negative patients but remained high in the patients who did not respond to treatment with ampicillin as well as in most control patients not receiving ampicillin.

These results are attributed in part to the reduction in the number of organisms produced by sub-MICs of ampicillin (8). Another factor to be considered is the effect of sub-MICs of ampicillin on the adherence of E. coli to urinary epithelial cells (14). The nonadhering E. coli could have been simply washed away by the large volume of excreted liquid. In a retrospective study, gentamicin was shown to produce the same cure rate for gram-negative bacteremias regardless of whether the serum concentration was below or above one-eighth of the MIC of the infecting organism (12, 13).

The data show that a low dosage of an antibiotic, resulting in sub-MICs at the site of infection, produces a significant decrease in the number of organisms. In the urinary tract infections investigated, the very low dosage resulted at least in a temporary bacteriological cure.

LITERATURE CITED