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Comparative Efficacies of Ofloxacin, Cefotaxime, and Doxycycline for Treatment of Experimental Epididymitis Due to *Escherichia coli* in Rats

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The in vivo efficacy of ofloxacin was compared with those of cefotaxime and doxycycline in a rat model of epididymitis due to *Escherichia coli*. Treatment was started 24 h after infection and was continued for 7 days. Ofloxacin reduced the numbers of *E. coli* organisms in the epididymides significantly more than the other therapeutic regimens and cured the infection more frequently. Histopathological changes in the epididymides of ofloxacin-treated animals were significantly less severe than those observed in untreated animals. Doxycycline was less effective than ofloxacin but significantly reduced the titers of organisms in rat epididymides. In contrast, despite excellent in vitro activity, cefotaxime failed to reduce the magnitude of infection. The results of this study suggest that ofloxacin may be a very effective antimicrobial agent for the treatment of epididymitis due to *E. coli*.

Acute epididymitis is a common urologic disease which may affect men of all ages. The disease is characterized by a unilateral painful swelling of the epididymis (3). Epididymitis usually results from bacterial infection of the epididymis. Several studies have demonstrated a correlation between the age of patients and the causative organisms. *Escherichia coli* or other common urinary pathogens are most frequently associated with epididymitis in prepubertal children with predisposing structural or neurologic abnormalities and in men over 35 years of age with underlying urinary tract pathology. In contrast, in men up to 35 years of age, epididymitis is commonly caused by sexually transmitted pathogens, e.g., *Chlamydia trachomatis* or *Neisseria gonorrhoeae* (1, 3, 4, 31). Complications of epididymitis include impairment of fertility, abscess formation, testicular infarction, orchitis, and chronic pain. Antibiotic treatment must be initiated immediately, even before the etiology is known, and should be effective against possible etiologic agents. In patients with severe epididymitis, broad-spectrum parenteral antimicrobial therapy is recommended (3, 33).

Tetracyclines have proved to be effective for the treatment of epididymitis due to *C. trachomatis* (12). In contrast, various broad-spectrum antibiotics have been recommended for therapy for epididymitis caused by urinary tract pathogens (3, 30). However, comparative clinical or experimental studies of the treatment of coliform epididymitis have not yet been reported. The present study was undertaken to compare the in vivo efficacies of ofloxacin, cefotaxime, and doxycycline in a rat model of epididymitis due to *E. coli*.

MATERIALS AND METHODS

Animals. Male outbred Wistar rats (Zentralinstitut für Versuchstierzucht, Hannover, Germany), weighing 350 to 450 g, were used.

Organism. The *E. coli* serotype O6 strain (S1) used in these studies was a clinical isolate from a patient with chronic bacterial prostatitis. Stock cultures were made by incubating the organism in Trypticase soy broth (Merck, Darmstadt, Germany) at 37°C for 24 h. This suspension was then diluted 100-fold and again incubated at 37°C for 3 h. One-milliliter samples were stored at −70°C. Fresh inocula were prepared by diluting a stock culture in 3 ml of Trypticase soy broth and incubating it overnight at 37°C. A 100-fold dilution of this culture was grown to a final concentration of approximately 10^7 CFU/ml.

Antimicrobial agents. Ofloxacin (Hoechst AG, Frankfurt, Germany), cefotaxime (Hoechst AG), and doxycycline (Sigma, St. Louis, Mo.) were used.

Susceptibility studies. MICs and MBCs were determined by a broth macrodilution method (25). The media used were Mueller-Hinton broth (Merck) for ofloxacin and cefotaxime and antibiotic broth no. 3 (Merck) for doxycycline. Organisms in the log phase of growth were used at a concentration of 5×10^5 CFU/ml. The MIC was defined as the lowest concentration of antimicrobial agent that inhibited visible growth after 24 h of incubation at 37°C. The MBC was determined by transferring 0.1 ml from tubes with no visible growth to cystine-lactose-electrolyte-deficient agar (GIBCO, Paisley, Scotland) and incubation for 24 h at 37°C. The MBC was defined as the lowest concentration of antibiotic which killed ≥99.9% of the initial inoculum within 24 h.

Time-kill curve studies for ofloxacin and cefotaxime were performed in triplicate in 10 ml of Mueller-Hinton broth with a final inoculum size of 5×10^5 CFU of *E. coli* in the log phase of growth per ml. The antibiotic concentrations used represented 10 times the MIC and the peak blood levels measured in uninfected animals. At 0, 0.5, 1, 2, 3, 4, 8, and 24 h after inoculation of *E. coli* into the antibiotic-containing Mueller-Hinton broth, duplicate 0.1-ml samples as well as serial 10-fold dilutions (to 10^{-7}) were plated on the entire surface of a cystine-lactose-electrolyte-deficient agar plate (94-mm diameter) (8, 18). Colonies were counted after 24 h

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of incubation at 37°C. The minimal accurately detectable number of organisms was 10 CFU/ml.

Pharmacokinetic studies. Antibiotic concentrations in blood, epididymides, and testes were determined for uninfected rats at various time points after a single administration of each drug. Ofloxacin and cefotaxime were administered subcutaneously, and doxycycline was given orally by stomach tube. The concentrations in blood and organs were determined by an agar well diffusion method (2, 11) with the assay organisms *Klebsiella aerogenes* 1082E (Hoechst AG) for ofloxacin, *Streptococcus pyogenes* A77 (Hoechst AG) for cefotaxime, and *Bacillus cereus* ATCC 11778 (American Type Culture Collection, Rockville, Md.) for doxycycline. Standard curves with known concentrations of antibiotics were prepared for blood or tissue homogenates of uninfected animals.

Experimental epididymitis. Epididymitis was induced in Wistar rats by a modification of a method described in detail elsewhere (13, 14). Briefly, male rats were anesthetized by intraperitoneal injection of a combination of ketamine and xylazine. An inguinal incision was made, and the right epididymis and testis were exposed. The lumen of the ductus deferens was punctured with a 27-gauge needle, and 0.1 ml of the *E. coli* suspension containing 10^6 CFU/ml was inoculated. Infected animals were randomly assigned to the different treatment groups.

Evaluation of infection. To determine the numbers of organisms in the epididymal tissue at the initiation of therapy, 10 randomly selected rats were sacrificed 24 h postinfection (p.i.), at the time when treatment was started in the test rats. Epididymides were removed aseptically, weighed, and homogenized in sterile saline. The number of bacteria per gram of epididymal tissue was determined by plating 0.1 ml of serial 10-fold dilutions of the homogenate in triplicate on cystine-lactose-electrolyte-deficient agar, incubating it at 37° for 24 h, and counting the colonies. Results were expressed as $\log_{10}$ CFU of *E. coli* per gram of tissue. This method permitted the detection of 50 CFU/g.

Therapeutic trials. Treatment was started 24 h p.i. and continued for 7 days. Dosage regimens were designed to achieve blood drug levels similar to those observed in humans. Ofloxacin (20 mg/kg) and cefotaxime (50 mg/kg) were given subcutaneously every 12 h, and doxycycline (100 mg/kg) was administered orally every 24 h. Control animals received sterile saline solution subcutaneously at 12-h intervals.

Animals were sacrificed 3 days after the termination of therapy. Epididymides were removed aseptically and cut into halves. One half was fixed in 10% buffered formalin, and the remaining half was weighed and homogenized in sterile saline. The number of organisms per gram of tissue was determined as described above. Bacteria recovered from the infected epididymides of treated rats were stored at −70°C for subsequent MIC determination.

Histopathology. Formalin-fixed tissues were dehydrated in graded alcohols, embedded in paraffin, and cut into 4-μm-thick sections. Mounted sections were stained for light microscopy with hematoxylin and eosin. Sections from the midline of each epididymis were examined in a blinded fashion for histopathological changes. Histopathological parameters were graded from 0 to 5 (0, not present; 5, most severe). All specimens were examined at least four times by the same investigator. Repeated examinations revealed minimal intraindividual variability in scoring.

Statistical analysis. The Kruskal-Wallis two-way analysis of variance was used to compare bacterial counts in tissues statistically. To compare microbiological and histopathological results, the Spearman rank correlation coefficient was used. A statistically significant difference was defined as $P < 0.05$ (7).

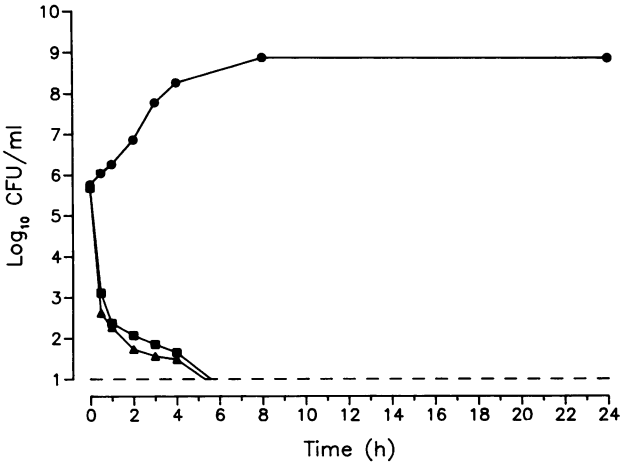

FIG. 1. Time-kill curve studies showing the activity of ofloxacin against *E. coli* at 0.49 μg/ml (■; drug concentration equal to 10 times the MIC) and 3.6 μg/ml (▲; drug concentration equal to the blood peak level) and without antibiotics (●; control).

RESULTS

Susceptibility studies. The MICs for *E. coli* were as follows: ofloxacin, 0.049; cefotaxime, 0.049; and doxycycline, 1.1 μg/ml. The MBC was 0.098 μg/ml for both ofloxacin and cefotaxime.

The results of time-kill curve studies of *E. coli* done with ofloxacin and cefotaxime are shown in Fig. 1 and 2, respectively. For ofloxacin, there was no major difference in the killing rates between 10 times the MIC (0.49 μg/ml) and the peak blood level (3.6 μg/ml). At both concentrations of ofloxacin, the initial inoculum was killed within 8 h. For cefotaxime, a significant difference in the killing rates be-

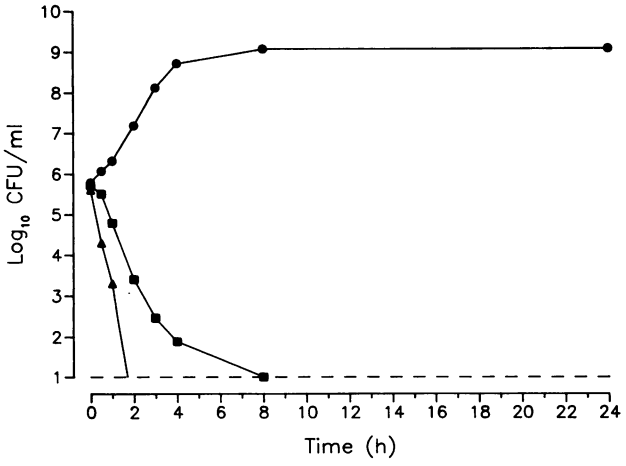

FIG. 2. Time-kill curve studies showing the activity of cefotaxime against *E. coli* at 0.49 μg/ml (■; drug concentration equal to 10 times the MIC) and 50 μg/ml (▲; drug concentration equal to the blood peak level) and without antibiotics (●; control).

TABLE 1. Pharmacokinetic data for ofloxacin, cefotaxime, and doxycycline

Drug (dose [mg/kg])	Site	Peak level (μg/ml [blood] or μg/g [tissue]; mean ± SD)[a]	T_{max}[b] (h)
Ofloxacin (20)	Blood	3.63 ± 0.60	1.0
	Epididymis	4.72 ± 0.60	1.0
	Testis	2.94 ± 0.47	2.0
Cefotaxime (50)	Blood	49.34 ± 7.34	0.5
	Epididymis	14.40 ± 1.60	0.5
	Testis	7.72 ± 1.99	1.0
Doxycycline (100)	Blood	5.05 ± 3.26	6.0
	Epididymis	3.06 ± 0.79	2.0
	Testis	2.71 ± 0.57	4.0

[a] Blood levels were determined with groups of 10 animals. Tissue levels were determined with groups of four animals for each drug.
[b] T_{max}, time to maximum concentration of drug in serum.

tween 10 times the MIC and the peak blood concentration was observed. At a concentration of 50 μg/ml (peak blood level), the bacterial inoculum was killed within 2 h. In contrast, at 0.49 μg/ml (10 times the MIC) a slower fall of viable counts was observed. Decreases of 2.3 and 4.7 $\log_{10}$ CFU/ml were seen within 2 and 8 h, respectively. After 8 h of drug-bacteria contact, 1 $\log_{10}$ organisms were still alive. The whole inoculum was killed within 24 h.

Pharmacokinetic studies. Antibiotic peak levels in the blood and the gonads of uninfected animals after a single administration of 20 mg of ofloxacin, 50 mg of cefotaxime, and 100 mg of doxycycline per kg are shown in Table 1. Peak concentrations of all antibiotics in the blood and the epididymides and testes were high above the MIC for several hours.

State of infection. At the start of therapy (24 h p.i.), the epididymides of all 10 animals sacrificed were infected with a median bacterial count of 4.4 $\log_{10}$ CFU/g (range, 2.8 to 6.8 $\log_{10}$ CFU/g).

Therapeutic efficacy in experimental epididymitis. The results of treatment of experimental *E. coli* epididymitis with ofloxacin, cefotaxime, and doxycycline are shown in Table 2. Ofloxacin was the most effective drug. The numbers of *E. coli* organisms recovered from the epididymides of ofloxacin-treated animals were significantly lower than those for cefotaxime-treated ($P < 0.0001$), doxycycline-treated ($P < 0.01$), and control ($P < 0.0001$) animals. Cure of the infection was observed in 20 of 30 ofloxacin-treated animals, in contrast to 3 of 28 cefotaxime-treated and 3 of 29 doxycycline-treated animals. Doxycycline was less effective than ofloxacin; however, it reduced the bacterial counts significantly compared with the controls ($P < 0.01$). In contrast, despite good in vitro activity, cefotaxime was not effective in reducing the magnitude of infection significantly. In addition, clearance of *E. coli* from the epididymis of any control animal was not observed. The in vitro susceptibilities of *E. coli* strains cultured from epididymides after treatment had not changed from MICs observed in pretreatment studies for all antibiotics.

TABLE 2. Results of treatment of experimental *E. coli* epididymitis

Therapeutic regimen	No. of rats evaluated	No. of rats with sterile epididymides	Median $\log_{10}$ CFU/g of epididymis (range)
Ofloxacin	30	20	<1.0 (<1–5.0)[a]
Cefotaxime	28	3	4.4 (<1–8.8)
Doxycycline	29	3	3.9 (<1–7.9)[b]
Saline	30	0	5.5 (3–8.5)

[a] Significantly lower than the cefotaxime ($P < 0.0001$), doxycycline ($P < 0.01$), and control ($P < 0.0001$) groups.
[b] Significantly lower than the control group ($P < 0.01$).

TABLE 3. Association between therapeutic regimen and histopathological findings

Therapeutic regimen	Histopathological findings (mean severity score[a]/ no. of organs positive [%])			
	Abscess	Inflammation	Fibrosis	Granuloma
Ofloxacin	0.38/13[b]	1.13/79[b]	1.00/63[b]	1.30/67
Cefotaxime	0.52/24	1.84/88	1.68/88	1.72/76
Doxycycline	0.28/12[b]	1.48/76	1.52/84	1.76/72
Saline	1.06/48	2.08/92	1.96/92	1.60/64

[a] Severity scores graded from 0 (absent) to 5 (most severe).
[b] Significantly lower than the control group ($P < 0.05$).

Histopathological findings. Abscess formation, inflammation, fibrosis, and sperm granuloma were the most frequent histopathological findings in the epididymides of both treated and untreated rats (Table 3). These changes were most prominent in the epididymides of the control animals. In contrast, mean severity scores for abscess formation, inflammation, and granuloma of the ofloxacin-treated animals were significantly lower than those of the control animals. Doxycycline had a significant effect only on the severity score for abscess formation. Pathology scores of the cefotaxime-treated rats were not different from those of the control animals. No treatment regimen had a significant effect on the occurrence of sperm granuloma. Histopathological changes were not observed in any of the left epididymides.

The numbers of bacteria recovered from the epididymides were significantly associated with the severity scores for abscess formation ($r = 0.352$; $P < 0.001$), inflammation ($r = 0.453$; $P < 0.001$), fibrosis ($r = 0.356$; $P < 0.001$), and granuloma formation ($r = 0.280$; $P < 0.01$).

DISCUSSION

In this study, the in vivo efficacies of ofloxacin, cefotaxime, and doxycycline were assessed both microbiologically and histopathologically in a rat model of epididymitis due to *E. coli*.

When treatment was started at 24 h p.i., the median level of infectious organisms was 4.4 $\log_{10}$ CFU/g of epididymal tissue. Spontaneous cure of the infection was never observed. Three days after the termination of therapy, *E. coli* organisms were recovered at a median concentration of 5.5 $\log_{10}$ CFU/g from the epididymides of all control animals. Histopathological changes in the epididymides caused by infection with *E. coli* were characterized by abscess formation, inflammation, fibrosis, and the occurrence of sperm granuloma. These changes are similar to those described for the human disease (15, 20, 23).

Among the three therapeutic regimens, ofloxacin was most effective for the treatment of experimental epididymitis due to *E. coli*. Ofloxacin was significantly more efficacious than the other therapeutic regimens in reducing the numbers of bacteria in the epididymides and cured the infection more frequently (in 66% of cases compared with 10% with cefo-

taxime and 10% with doxycycline). These findings obviously reflect the excellent in vitro activity against the challenge strain and the good penetration into the epididymal tissue (9, 19, 30–32). In addition to its excellent bacteriologic efficacy, ofloxacin treatment significantly reduced the severity of histopathological changes in the epididymides. Abscesses, inflammatory changes, and fibroses were less prominent in ofloxacin-treated animals than in controls. These findings indicate that effective antimicrobial therapy may prevent or reduce the rate of complications associated with epididymitis.

The results of this experimental study are in agreement with those of previous clinical trials with ofloxacin. In an open study, ofloxacin therapy for epididymitis due to common urinary tract pathogens or *C. trachomatis* cured 17 of 18 patients (17). In a similar trial, bacteriologic cure, as determined by culture of midstream urinary tract specimens or urethral swabs, was achieved with ofloxacin for 16 of 20 patients. However, in six patients clinical symptoms were still present at 10 weeks after the completion of therapy (31).

An unexpected finding in this study was the therapeutic failure of the β-lactam cefotaxime. Despite good in vitro activity and tissue penetration, cefotaxime did not significantly reduce the numbers of bacteria in the epididymides. This observation cannot be explained by the selection of β-lactam-resistant mutants of *E. coli*, since MICs for bacteria recovered from the epididymides after treatment were identical to those found in pretreatment studies. In our study, cefotaxime was administered at 12-h intervals. The dosing regimen was designed to achieve peak blood levels in the experimental animals that mimic those observed in humans. However, this dosing scheme was found not to be effective. This finding may be attributed to the different pharmacokinetics of β-lactams in humans and in laboratory animals. In experimental animals, clearance of antibiotics is more rapid than in humans (6). The bacteriologic in vivo efficacy of β-lactam antibiotics is mainly influenced by the time during which levels in serum exceed the MIC (16, 29). Fractional dosing with β-lactams, which results in active serum drug levels for prolonged periods of time, has been shown to be superior to single-bolus injections in experimental animals (10). Therefore, it seems likely that shorter dosing intervals or continuously administered doses of cefotaxime would have been effective. In addition, a poor penetration of the drug into epididymal abscesses might explain the failure of cefotaxime. In a similar experimental study, cefotaxime was effective only when administered before or immediately after the infection of rats (21).

Doxycycline has been recommended for the treatment of epididymitis caused by sexually transmitted pathogens, e.g., *C. trachomatis* or *N. gonorrhoeae* (3, 22, 27). This antibiotic exhibits broad activity against many gram-positive and gram-negative organisms (5). Further properties of this drug are a high lipid solubility resulting in excellent tissue penetration and a long half-life allowing once-daily dosing (24). In this study, doxycycline was less effective than ofloxacin with respect to the cure rates. However, this treatment reduced the concentrations of *E. coli* in the epididymides significantly when compared with those in the controls. Previous animal studies have shown an enhanced penetration of antibiotics into the inflamed epididymal tissue (26). Concentrations of doxycycline in infected epididymides were found to be 200% greater than those in uninfected epididymal tissues (28). Unfortunately, modern fluoroquinolones or broad-spectrum β-lactams were not included in these studies. The enhanced penetration of antibiotics into the inflamed epididymis is probably caused by a disturbance of the blood-epididymis barrier (26).

In conclusion, results of this study demonstrate that ofloxacin is highly effective for the treatment of experimental epididymitis due to *E. coli*. Since this drug possesses good activity against most pathogens associated with acute epididymitis, it may be used for initial blinded therapy. Clinical trials are needed to study the efficacy of this antibiotic for the treatment of acute epididymitis.

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