ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1994, p. 1490–1495
0066-4804/94/$04.00+0

Vol. 38, No. 7

Effects of Ciprofloxacin, Norfloxacin, and Ofloxacin on In Vitro Adhesion and Survival of *Pseudomonas aeruginosa* AK1 on Urinary Catheters

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Received 22 December 1993/Returned for modification 28 February 1994/Accepted 25 April 1994

Pretreatment of urinary silicone latex catheters in vitro with 0.1 and 0.5 μg of ciprofloxacin per ml for 1, 24, and 48 h significantly reduced the adhesion and survival of the clinical isolate *Pseudomonas aeruginosa* AK1. UV spectroscopy and high-performance liquid chromatography confirmed the presence of ciprofloxacin adsorbed onto the catheters and showed that up to 56% of the drug leached into the surrounding fluid within 24 h. Scanning electron microscopy demonstrated that the adherent organisms were malformed and elongated after exposure to ciprofloxacin. Transmission electron microscopy showed the presence of fimbriae on the bacterial surfaces, but there was no conclusive evidence of changes in the fimbriae upon exposure to ciprofloxacin. It was found that a significant eradication of 24-h *Pseudomonas* biofilms could be achieved with ciprofloxacin as well as with ofloxacin and norfloxacin. Preincubation of catheters with 50- and 100-μg/ml concentrations of ciprofloxacin resulted in up to a 99% reduction in the number of adherent bacteria in comparison with the reduction on control catheters. In addition, adherent biofilms were eradicated by 24 h of challenge with 50 and 100 μg of ciprofloxacin per ml at pH 7.0 and 5.5. Results of these in vitro studies suggest that there could be a clinical role for fluoroquinolones in preventing and treating urinary tract infections associated with *P. aeruginosa* adherence to prosthetic devices.

Infections related to the insertion of medical devices in the body are common, although in relation to the numbers of devices used, the actual percentage of people infected is small (19). The net effect on infected patients, however, can be serious and even fatal.

The process in relation to urinary catheterization involves the adhesion of urethral organisms onto the devices, multiplication of the organisms, biofilm formation, and the seeding of the bladder mucosa and urine by planktonic bacteria. Clinical and in vitro evidence suggests that certain antibiotics (trimethoprim-sulfamethoxazole, ampicillin, nalidixic acid, gentamicin, nitrofurantoin, cephalexin [Kelfex], tobramycin, amoxicillin, cefazolin [Ancef], cloxacillin, cefuroxime) eradicate the planktonic organisms from the urine but do not eradicate the biofilms that adhere to body cells and devices (15, 21–23). The potential of agents which do penetrate biofilms or which can prevent the adhesion of pathogens to prostheses and cells for use against such infections has been an area of growing interest. In the former case, altered substrate surface chemistry (8), incorporation of the disinfectants iodine (9) and salicylic acid (7), and coating of biomaterial surfaces with silver (10, 12) and silver oxide (10, 26) have been used as strategies to prevent bacterial adhesion and biofilm formation. The selection of antibiotics effective against bacterial biofilms must take into account their activities against organisms in that mode of growth; otherwise, the treatment will be inadequate (1).

The new fluoroquinolones (6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids) are highly potent, broad-spectrum agents which penetrate bacterial cell walls and inhibit DNA gyrase (bacterial topoisomerase II) activity, rapidly killing susceptible organisms (5, 25). Of these, ciprofloxacin is among the most potent clinically, especially against members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa*, providing a standard against which other compounds are compared (25). In a previous study (24), it was found not only that ciprofloxacin could be used to reduce the level of adhesion and survival of *Escherichia coli* but also that it had a capacity to penetrate young biofilms, which constitute newly formed microcolonies (less than 48 h old) (2). The latest study was undertaken to test the effectiveness of ciprofloxacin, ofloxacin, and norfloxacin against a strain of *P. aeruginosa*, because organisms of this species are highly adherent to various biomaterial surfaces (11–14) and are invariably more difficult to eradicate clinically because of drug resistance and virulence properties that include slime production.

MATERIALS AND METHODS

Bacterium. A uropathogenic isolate, *P. aeruginosa* AK1, was selected as being typical of adherent *P. aeruginosa* in that it was hydrophobic (water contact angle, >50°) and expressed a capsule and fimbriae (6, 11, 30). This strain had been passaged only a few times since its isolation, and experimentation in a flow system showed that its adherence was significantly reduced after exposure to ciprofloxacin (18a). The organisms were cultured overnight at 37°C in brain heart infusion (BHI) broth (Difco, Detroit, Mich.) and were used at concentrations of 10^8 CFU/ml in phosphate-buffered saline (PBS; pH 7.1). The MIC of ciprofloxacin for this organism was 0.38 μg/ml, and therefore, antibiotic concentrations were selected to examine the effects of sub-MICs and concentrations greater than the MICs.

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Adhesion assay. A static adhesion assay was used as described previously (24), and modifications were made to the assay after preliminary experiments were carried out with different sonication times and rinses and after light and scanning electron microscopies confirmed the effective detachment of adherent organisms. In the first series of experiments, a section of silicone latex urinary catheter (length, 1 cm; Rusch Pilling, Scarborough, Ontario, Canada) was placed in a test tube with 0.1, 0.5, and 1.0 μg of the appropriate solutions per ml for 1, 12, and 24 h at room temperature. Then, the catheter sections were placed in another tube with a 5-ml suspension of *P. aeruginosa* AK1, and the mixture was incubated for 1, 24, and 48 h at 37°C. In the second series of experiments, the catheter section was first incubated with the bacteria for 24 h, and then the bacteria were challenged with ciprofloxacin, norfloxacin, and ofloxacin. In both series of experiments, at the conclusion of each experiment, the catheter sections were rinsed in PBS and were sonicated for 2 min, and then the organisms were quantitated on BHI agar.

Additional experiments were carried out with 50 and 100 μg of ciprofloxacin per ml because these concentrations can be present in the urine of patients given the agent orally (16). Furthermore, because fluoroquinolones generally exhibit a biphasic response between pH and solubility and because urinary pH is often less than 7.0 and is frequently 5.5, the effect of pH was examined.

HPLC and UV Spectroscopy. High-performance liquid chromatography (HPLC) analysis was carried out on an HP 1090 II high-performance liquid chromatograph equipped with a photodiode array detector and a Lichrosphere 100-RP-18 column (4 mm by 12.5 cm). The oven temperature was maintained at 40 ± 1°C. The flow rate was 1.0 ml/min. A filtered and degassed mixture of 0.0025 M phosphoric acid (adjusted to a pH of 3.0 ± 0.1 with triethylamine) and acetonitrile (40:60), was used as the mobile phase. Ciprofloxacin hydrochloride, obtained from Miles Pharmaceuticals Canada, was dissolved in water to obtain a 1-mg/ml solution. This solution was further diluted in PBS (pH 7.1 ± 0.1) to obtain a concentration of 0.1, 0.5, or 1.0 μg/ml. UV spectrophotometric analysis for the experiments was carried out at 278 nm in triplicate on a UV Beckman DU-65 spectrophotometer and showed an excellent correlation coefficient with the results obtained for the controls by the HPLC-photodiode array detector.

Sections of 1-cm-long silicone latex urinary catheter were placed in a test tube with 0.1, 0.5, or 1.0 μg of ciprofloxacin hydrochloride per ml for 1 or 24 h of incubation at room temperature. The preincubated catheter was gently washed with 2 ml of PBS (pH 7.1 ± 0.1). The wash solution was used to determine the amount of ciprofloxacin adsorbed onto the catheter surface by either HPLC-photodiode array detector analysis or UV determination. The catheter segment was incubated in 2 ml of PBS (pH 7.0 ± 0.1) for an additional 1 or 24 h. The solution was analyzed by HPLC by using the photodiode array technique to determine the leaching of ciprofloxacin from the catheter surface.

All of the solutions were filtered through 0.2-μm-pore-size acrodisc filter units into Wheaton liquid chromatograph vials. PBS solutions of 20 μl were injected into the chromatograph, and the quantity of ciprofloxacin hydrochloride was calculated by using a maximum A_{278} values. All experiments were carried out in triplicate.

Electron microscopy. Scanning electron microscopy was performed on selected specimens to examine the effects of ciprofloxacin on the *P. aeruginosa* AK1 that adhered to the catheters. The specimens were fixed in alcohol–5% glutaraldehyde, sputter coated with gold, and examined under an International Scientific Instruments Inc. model DS-130 (Tokyo, Japan) electron microscope. In addition, suspensions of *P. aeruginosa* AK1 were placed on a Formvar carbon-coated grid and were negatively stained with uranyl acetate (5%) and ammonium molybdate (2%). The organisms were then examined for fimbriae under a CM10 Philips transmission electron microscope.

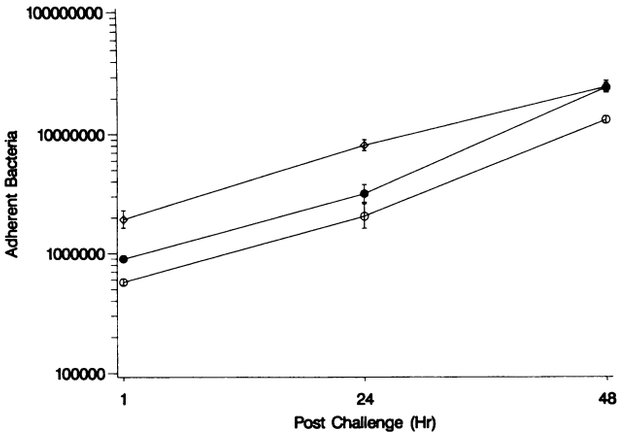

FIG. 1. Counts of viable *P. aeruginosa* AK1 bacteria adhering to a urinary catheter pretreated for 1 h with 0.1 and 0.5 μg of ciprofloxacin per ml and then challenged for 1, 24, and 48 h. ◇, control; ●, ciprofloxacin at 0.1 μg/ml; ○, ciprofloxacin at 0.5 μg/ml.

RESULTS

Figure 1 presents the number of viable *P. aeruginosa* AK1 recovered from a catheter surface preexposed for 1 h to ciprofloxacin in comparison with the number of bacteria recovered from a control catheter treated with buffer. A statistical analysis was undertaken by using Dunnett's test of the geometric means of the raw data. Ciprofloxacin at 0.1 and 0.5 μg/ml had a significant effect ($P = 0.0006$) after 1, 24, and 48 h postchallenge in reducing the number of *P. aeruginosa* AK1 which adhered to the catheters (however, there was not a significant effect of ciprofloxacin at 0.1 μg/ml versus the control at 48 h).

The HPLC and UV spectroscopy analyses did not detect the percent adsorption of ciprofloxacin at a concentration of 0.1 μg/ml, possibly because the UV detection method was not sensitive enough. However, a refractive index method did confirm the adsorption of ciprofloxacin. After 1 h of incubation with a 0.5-μg/ml suspension of ciprofloxacin, 70.18% of the drug had adsorbed onto the catheter (Table 1). After a subsequent 1 h of incubation in PBS, 29.82% of this adsorbed drug had leached from the surface. With a longer (24-h) reaction time and a greater concentration of ciprofloxacin (1.0 μg/ml), more drug adsorbed onto the catheter (up to 87.88%).

Significantly fewer bacteria adhered to catheters preincubated with ciprofloxacin for 24 h than to control catheters, as shown in Fig. 2 (for control catheters versus catheters pretreated with ciprofloxacin at 0.1 and 0.5 μg/ml, $P = 0.01$ at 1 h, $P = 0.003$ at 24 h, and $P = 0.01$ at 48 h; overall analysis, $P = 0.012$ for concentration versus postchallenge) and those pretreated for 48 h for control catheters versus catheters pretreated with ciprofloxacin at 0.1 and 0.5 μg/ml, $P = 0.03$ at 1 h, $P = 0.003$ at 24 h, and $P = 0.01$ at 48 h; overall analysis, $P = 0.005$) (Fig. 3).

As Fig. 4 shows, the three fluoroquinolones significantly

TABLE 1. Summary of HPLC results for catheter segments incubated with ciprofloxacin and then challenged in buffer to determine amount of leaching

Concn (μg/ml)	Reaction time (h)	Leaching time (h)	% Adsorbed	% Leached
0.5	1	0	70.18	0
	1	1	70.18	29.82
	24	0	87.88	0
	24	1	87.88	12.12
	24	24	68.70	31.30
1.0	1	0	87.38	0
	1	1	87.38	12.62
	24	0	84.72	0
	24	1	84.72	15.28
	24	24	44.31	55.69

killed adherent *P. aeruginosa* AK1. There was a trend toward ciprofloxacin being the most effective agent ($P = 0.045$ for analysis of control catheters versus catheters pretreated with ciprofloxacin at 0.1, 0.5, and 1.0 μg/ml) in comparison with the effectiveness of norfloxacin ($P = 0.059$) and ofloxacin ($P = 0.089$). However, there was no statistical difference between the effectiveness of the three drugs ($P = 0.4326$). There was a significant difference ($P = 0.0023$) attributed to the antibiotic concentration, with the greatest penetration effect found at the highest concentration tested, namely, 1.0 μg/ml.

Additional experiments showed that *P. aeruginosa* AK1 adhered equally well in PBS at pH 7.0 and PBS at pH 5.5 (mean, 6×10^6 and 3.3×10^6 organisms, respectively) and that subsequent challenge with 50 and 100 μg of ciprofloxacin per ml completely eradicated the bacteria. When the catheters were precoated for 24 h with 50 and 100 μg of ciprofloxacin per ml and then challenged for 24 h with *P. aeruginosa* AK1, there were 96 and 95% reductions, respectively, in viable bacterial adhesion at pH 7.0 and 95 and 99% reductions, respectively, at pH 5.5. Thus, the pH of the fluid in which the organisms were suspended did not interfere with the killing effect of the antibiotic.

The scanning electron micrographs illustrate dramatically the effect of exposing control bacteria (Fig. 5) to catheters

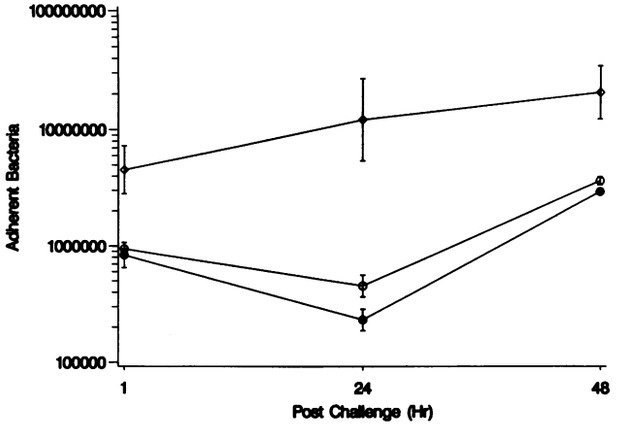

FIG. 2. Counts of viable *P. aeruginosa* AK1 bacteria adhering to a urinary catheter pretreated for 24 h with 0.1 and 0.5 μg ciprofloxacin per ml and then challenged for 1, 24, and 48 h. ◇, control; ●, ciprofloxacin at 0.1 μg/ml; ○, ciprofloxacin at 0.5 μg/ml.

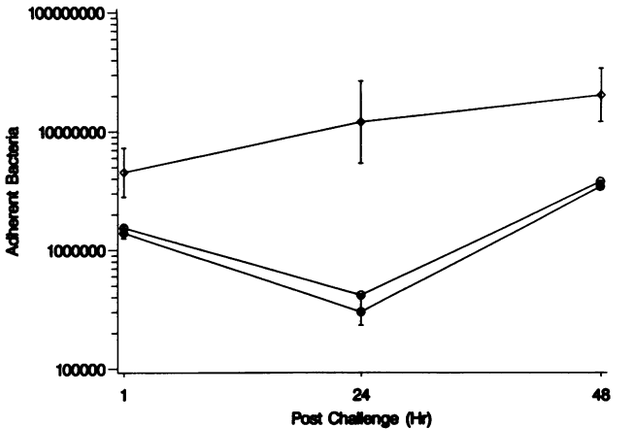

FIG. 3. Counts of viable *P. aeruginosa* AK1 bacteria adhering to a urinary catheter pretreated for 48 h with 0.1 and 0.5 μg of ciprofloxacin per ml and then challenged for 1, 24, and 48 h. ◇, control; ●, ciprofloxacin at 0.1 μg/ml; ○, ciprofloxacin at 0.5 μg/ml.

treated for 1 h with 0.5 μg of ciprofloxacin per ml (Fig. 6). Not only were fewer organisms adherent to the treated surfaces, but those which were found to adhere were visibly elongated (as expected from treatment with a drug which interferes with DNA gyrase) and malformed.

To determine if there were visible differences in the fimbriation of the bacteria exposed to ciprofloxacin, samples were studied under a transmission electron microscope. In essence, no significant differences could be seen between control samples and those treated with ciprofloxacin. In all specimens, fimbriation tended to be sparse and located at the tips of the organisms.

DISCUSSION

The present in vitro study demonstrated that ciprofloxacin could adsorb from a liquid suspension onto urinary catheters, and over a period of 1 to 48 h it significantly reduced the number of *P. aeruginosa* AK1, a hydrophobic, encapsulated,

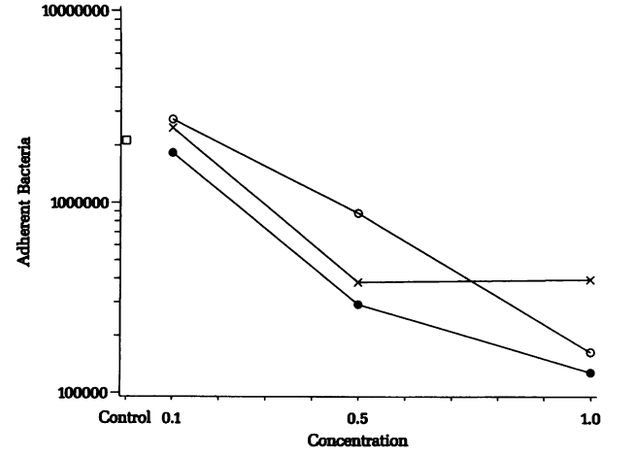

FIG. 4. Number of viable *P. aeruginosa* AK1 adhering to urinary catheter material after 24 h of treatment with ciprofloxacin (●), norfloxacin (×), and ofloxacin (○) in comparison with the number on untreated control catheters (□).

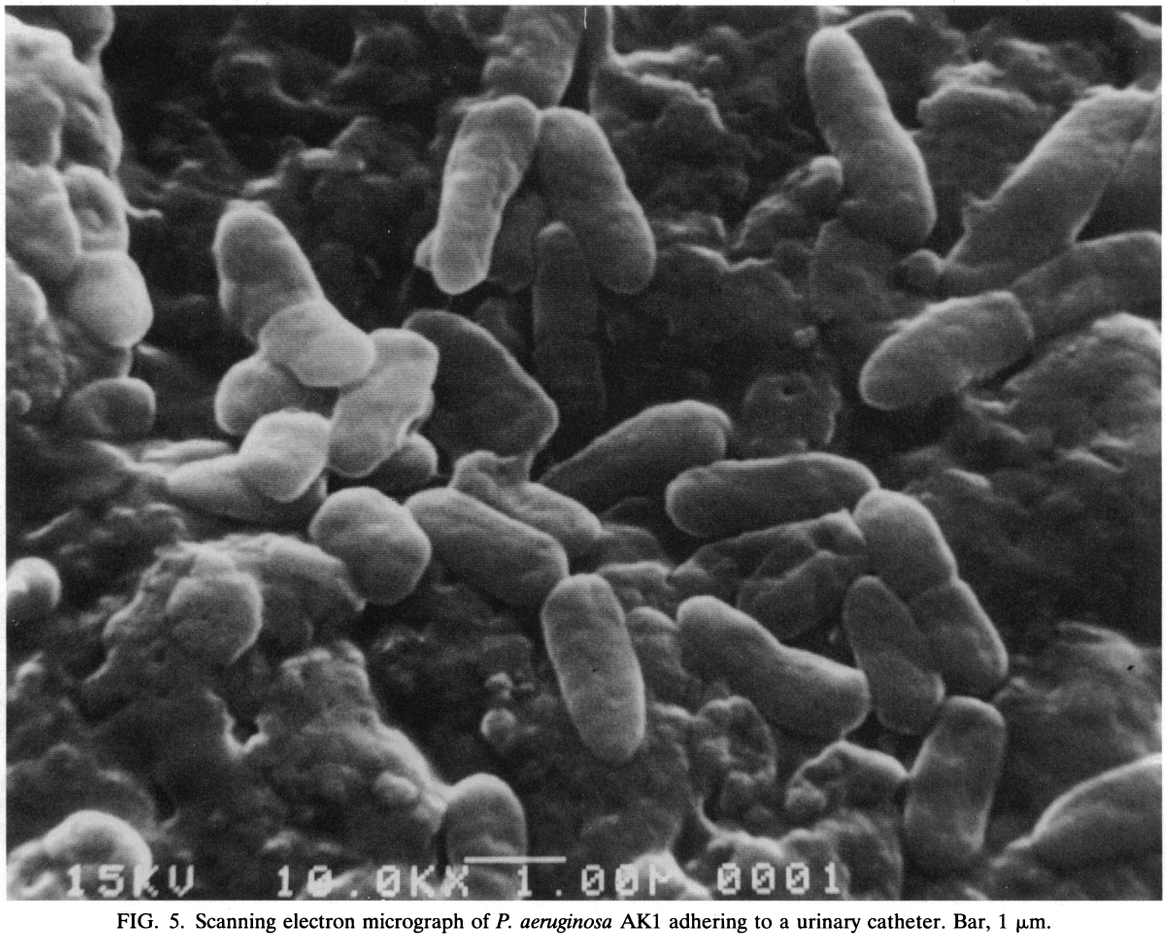

FIG. 5. Scanning electron micrograph of *P. aeruginosa* AK1 adhering to a urinary catheter. Bar, 1 μm.

and fimbriated strain, able to adhere to the surfaces of the devices. A similar result was obtained previously against uropathogenic *E. coli* (24). The fact that less adsorption was detected with ciprofloxacin at a 0.1-μg/ml concentration, in comparison with the significant degree of adsorption and leaching detected with the drug at 0.5 μg/ml, might explain why the latter concentration killed *P. aeruginosa* at higher rates. The concentration of 0.1 μg/ml is a sub-MIC of the drug and the 0.5-μg/ml concentration is greater than the MIC, and these concentrations per se should have affected killing of the bacteria.

The present results not only illustrate the potency of ciprofloxacin, a drug with a low incidence of side effects (29), but suggest that administration of this drug could lead to drug adsorption onto a prosthetic device, thereby reducing the risk of biomaterial-related infections (27). There was up to a 99% reduction in the number of viable adherent bacteria on catheters preexposed to 100 μg of ciprofloxacin per ml. The fact that low, sub-MIC doses of the drug were also effective at reducing adherence suggests that perhaps any potential problems of resistance could be minimized by using shorter, lower-dosage therapy. In one study, ciprofloxacin was used successfully as a prophylactic agent to prevent infections in surgical patients (28). It seems unlikely, on the basis of the present in vitro data and the results of other clinical studies (22, 23), that ciprofloxacin could be less effective than trimethoprim-sulfamethoxazole, which is used most frequently against uropathogens. Other in vitro studies have shown that doses significantly greater than the MIC of tobramycin were required to kill *P. aeruginosa* in biofilms (3).

The finding by Phaneuf and colleagues (18) that ciprofloxacin could resist adhesion by staphylococci to dacron led to the suggestion that sustained infection resistance would depend on the chemical interaction of the substrate. The role of the silicone latex used in the present study was not compared with the roles of other catheter surfaces (studies in progress), but adsorption of drug was high (up to 88%). The fact that up to 56% of the ciprofloxacin leached out within 24 h is not surprising, because it was not covalently or otherwise specifically chemically bonded to the device. The amount which bound had a dramatic effect not only in killing *P. aeruginosa* AK1 but also in damaging the morphological structure of the bacteria which adhered. Because there was as much as 87% (100% − 12.62%) of adsorbed drug still on the surface 24 h after a simple 1-h reaction time, it could be argued that this treatment could provide several days of protection against infection.

It was hypothesized that the ciprofloxacin might affect a surface adhesin, such as fimbriae, on *P. aeruginosa*, in part because studies have shown that sub-MICs of antibiotics can impair bacterial adhesins (4). However, an examination by transmission electron microscopy did not detect obvious differences in the extent of fimbriation after exposure to the antibiotic.

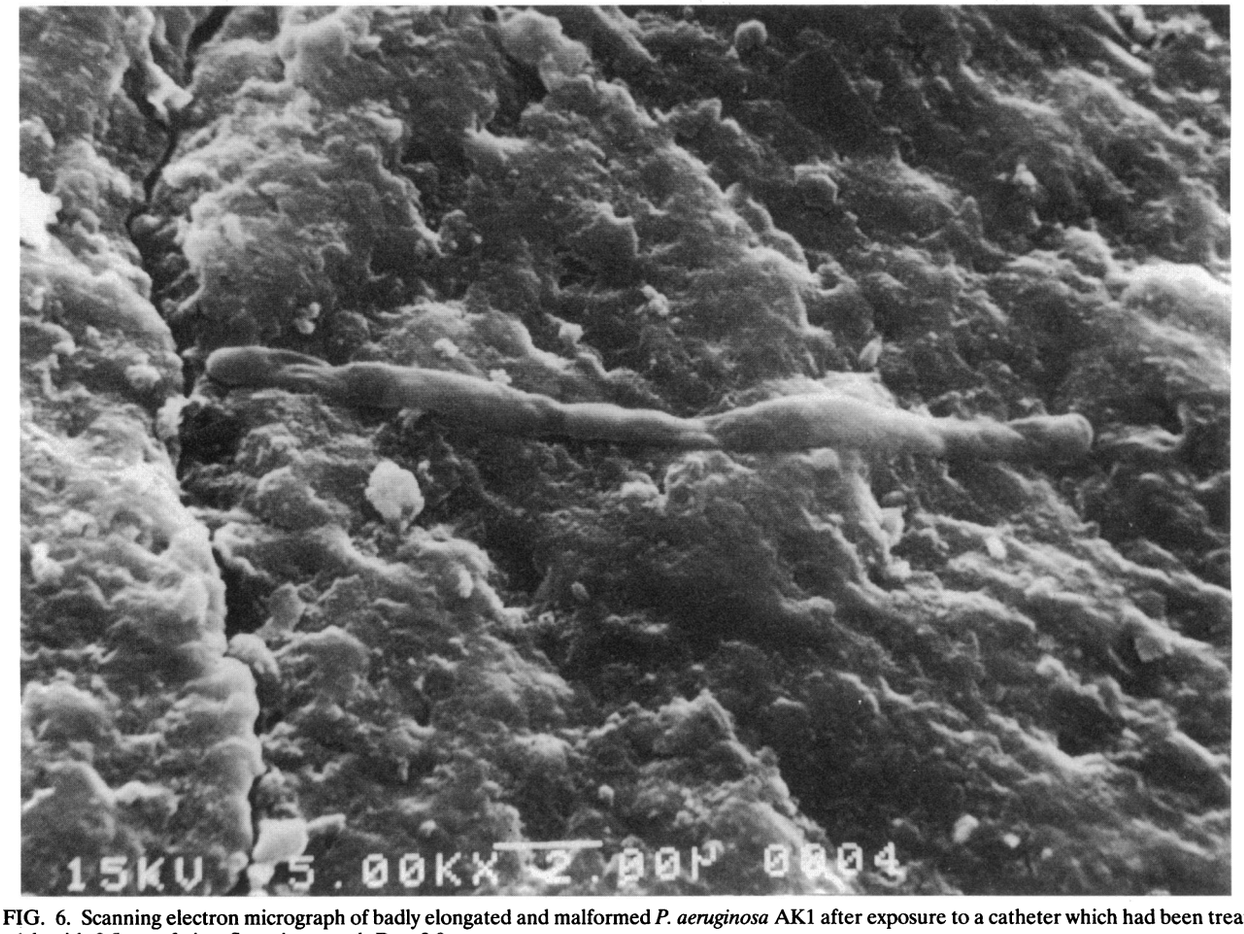

FIG. 6. Scanning electron micrograph of badly elongated and malformed *P. aeruginosa* AK1 after exposure to a catheter which had been treated for 1 h with 0.5 μg of ciprofloxacin per ml. Bar, 2.0 μm.

The fluoroquinolones are particularly potent in the urinary tract (25), even after 1 and 3 days of therapy (17, 20), making them an attractive choice for prophylaxis and treatment when prostheses are used. In the present study, three fluoroquinolones, ciprofloxacin, ofloxacin, and norfloxacin, proved extremely effective at penetrating young *P. aeruginosa* AK1 biofilms, especially at concentrations greater than the MIC. When applied at concentrations which can be found in the urinary bladder (50 and 100 μg/ml at pH 5.5 and 7.1), ciprofloxacin completely eradicated the adherent *P. aeruginosa* AK1.

ACKNOWLEDGMENTS

This work was supported by a grant from Miles Canada and in part by The Rick Hanson Man in Motion Foundation and The National Sciences and Engineering Research Council of Canada. Sunaina Sharma is a recipient of an NSERC Women's Faculty Award.

We appreciate the assistance of Dominique Lam, supported by the Medical Research Council of Canada, Ron Smith, Eddy Brecevic, Cindy Wong, Deborah L. Reid, and Surface Science Western. We are grateful to Miles, Ortho-McNeil, and Merck Frosst Canada for providing the pure antibiotic preparations.

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