ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 1993, p. 2033–2036
0066-4804/93/092033-04$02.00/0

Vol. 37, No. 9

Activity of a Nitrofurazone Matrix Urinary Catheter against Catheter-Associated Uropathogens

JAMES R. JOHNSON,[1]* TERRIEL BERGGREN,[1] AND ANTHONY J. CONWAY[2]

Department of Medicine, University of Minnesota, Minneapolis, Minnesota 55455,[1] and Rochester Medical Corp., Stewartville, Minnesota 55976[2]

Received 22 January 1993/Returned for modification 12 April 1993/Accepted 5 July 1993

Nitrofurazone-coated urinary catheter segments inhibited 51 (75%) of 70 urinary bacterial isolates from patients with indwelling catheters. Inhibition zones correlated significantly with the nitrofurazone MIC (r^2 = 0.79, P = 0.0001). All strains except the *Pseudomonas* spp. were inhibited by ≤64 μg of nitrofurazone per ml. MICs of nitrofurazone and nitrofurantoin correlated significantly (r^2 = 0.93, P = 0.0001).

Over 900,000 episodes of catheter-associated urinary tract infections (UTIs) occur annually in acute care hospitals in the United States, accounting for 40% of all nosocomial infections and involving between 10 and 30% of patients with indwelling urinary catheters (33). Catheter-associated UTIs prolong the hospital stay by an estimated 2.4 to 4.5 days, with resultant increased costs (9, 10). Nosocomial UTIs confer a threefold increase in mortality (26), possibly due to the associated 1 to 3% likelihood of gram-negative bacteremia (16, 30).

Since the implementation of closed and sealed urinary drainage systems (17, 27), few of the additional measures introduced to prevent catheter-associated UTIs have proven beneficial. Because with closed drainage systems the most common route for acquisition of infection is along the outside of the catheter (5, 8), the most promising preventive measures have been those designed to block microbial migration along this pathway. However, aggressive meatal disinfection regimens have proved unhelpful or actually harmful (2, 13), catheters coated with hydrophilic gels (18, 21, 32) or antimicrobial compounds (3, 6, 12, 18, 29) have not convincingly succeeded in blocking infection, and catheters coated with silver oxide have given encouraging results in some (15, 20, 31) but not all (4) clinical trials.

A recently developed urinary catheter designed to block bacterial entry along the catheter-urethral interface incorporates the antimicrobial agent nitrofurazone in a silicone matrix on the catheter's outer surface (14). Nitrofurazone, a nitrofuran derivative chemically related to nitrofurantoin, is broadly active against many gram-positive and gram-negative bacteria and is used topically in burn wound care (Furacin) and veterinary medicine (7, 11, 25). Its chemical properties permit combination with silicone to form a stable matrix (14). The nitrofurazone-matrix catheter provides sustained release of nitrofurazone for at least 30 days in in vitro tests (14).

We undertook this study to determine the activity of nitrofurazone and of the nitrofurazone-matrix catheter against bacteria causing catheter-associated UTIs and to correlate nitrofurazone susceptibility with susceptibility to inhibition by the nitrofurazone-matrix catheter. We also sought to determine the validity of using the nitrofurantoin MIC as a surrogate for the nitrofurazone MIC and to evaluate the effect of autoclaving on the antibacterial activity of the nitrofurazone-matrix catheter.

Bacterial strains. Seventy urinary bacterial strains (Table 1) initially isolated from the urinary catheters or urine collection bags of 70 different hospitalized patients with indwelling urethral catheters (15) were selected to represent the typical distribution of bacterial types causing catheter-associated UTIs (2, 13, 15, 28, 31). The strains included 8 coagulase-negative staphylococci (1 *S. cohnii*, 4 *S. epidermidis*, 1 *S. hominis*, and 2 *S. warnerii*), 4 *Staphylococcus aureus* isolates, 8 *Enterococcus* spp. (7 *E. faecalis*, 1 *E. gallinarum*), 2 diphtheroids (both *Corynebacterium minutissimum*), 11 *E. coli* isolates, 7 *Enterobacter* spp. (3 *E. aerogenes*, 4 *E. cloacae*), 8 *Klebsiella* spp. (1 *K. oxytoca*, 7 *K. pneumoniae*), 6 *Proteus mirabilis* isolates, 3 *Serratia* spp. (2 *S. liquifaciens*, 1 *S. marcescens*), 3 *Citrobacter* spp. (1 *C. diversus*, 2 *C. freundii*), and 10 *Pseudomonas* and *Xanthomonas* spp. (referred to hereafter as *Pseudomonas* spp. [2 *P. aeruginosa*, 1 *P. flourescens*, 6 *P. putida*, and 1 *X. maltophilia*]). Strains were identified by standard methods (19) and were stored at −70°C until subcultured for susceptibility testing.

MIC determinations. Nitrofurazone and nitrofurantoin MICs were determined in parallel by a standard agar dilution method (22) with the use of a Steers replicator (Craft Machine, Inc., Chester, Pa.). With each day's assays, strains were tested in duplicate; duplicate results were required to be within one twofold dilution to be considered valid. Each strain was tested on at least two occasions, with the median value of two or more duplicate determinations used as the final result. *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, and *P. aeruginosa* ATCC 27853 were used daily as controls.

Catheter segment inhibition studies. Nitrofurazone-matrix catheters and identical all-silicone catheters lacking the nitrofurazone-matrix coating were provided by the manufacturer (Rochester Medical Corp., Stewartville, Minn.). Catheters were sectioned transversely to give 3-mm-thick rings (diameter, 6 mm), and catheter segments 1.5 cm long were sectioned longitudinally in fourths to give 4-mm-wide rectangular strips. Catheter segments were sterilized by autoclaving or by exposure to ethylene oxide by standard methods.

The inhibitory activity of catheter segments was studied with a modification of a standard disk diffusion antimicrobial susceptibility testing method (1, 23). The only deviation from the published National Committee for Clinical Laboratory

* Corresponding author.

TABLE 1. Susceptibility of catheter-associated uropathogens and control strains to nitrofurazone, nitrofurantoin, and the nitrofurazone-matrix catheter

Organism (no.)	MIC range (μg/ml)		Nitrofurazone catheter segment inhibition zone[a] [median (range) (mm)]
	Nitrofurazone	Nitrofurantoin	
Clinical isolates			
Coagulase-negative staphylococci (8)	2–8	2–16	19 (17–21)
S. aureus (4)	8–8	4–32	15 (14–19)
Enterococcus spp. (8)	8–32	4–16	11.5 (7–13)
C. minutissimum (2)	64–64	8–8	—[b]
E. coli (11)	4–16	8–32	14 (11–17)
Enterobacter spp. (7)	32–64	32–64	8 (4–10)
Klebsiella spp. (8)	4–64	4–64	10 (7–16)
Proteus mirabilis (6)	32–64	64–128	4 (4–5)
Serratia spp. (3)	64–64	128–128	4 (4–5)
Citrobacter spp. (3)	16–32	32–64	11 (10–13)
Pseudomonas spp. (10)	All >128	All >128	4 (4–4)
Control strains			
S. aureus (ATCC 29213)	8	16	15
E. faecalis (ATCC 29212)	8	8	7
E. coli (ATCC 25922)	8	8	15
P. aeruginosa (ATCC 27853)	>128	>128	4

[a] Width of inhibition zone around autoclaved longitudinal catheter segments. For all strains, control catheter segments showed no zone of inhibition beyond the border of the catheter (4 mm, longitudinal sections).
[b] —, insufficient growth for zone size determination.

Standards disk diffusion protocol (23) was the use of catheter segments instead of antimicrobic disks. After inoculation of a Mueller-Hinton agar plate with a defined bacterial inoculum, sterilized catheter segments were placed onto the surface of the plate with the use of sterilized forceps. On each plate, both transverse sections (rings) and longitudinal sections (strips) of both the nitrofurazone-matrix catheter and the control catheter were placed in duplicate. Zones of inhibition were read after incubation overnight for 16 to 18 h at 35°C, with the zone diameter used for transverse sections and the zone width used for longitudinal sections. The median of at least two duplicate determinations was used as the final result. Inhibition by catheter segments was defined as a zone size greater than the width or diameter of the corresponding catheter segment (4 mm for longitudinal segments, 6 mm for transverse segments).

Statistical methods. Linear correlations were evaluated with simple regression, and comparisons between groups were evaluated with a paired two-tailed *t* test. For statistical analyses, a MIC of 256 μg/ml was used for strains not inhibited at 128 μg/ml, the highest antimicrobial agent concentration tested.

Susceptibility to nitrofurazone and nitrofurantoin. All strains except the *Pseudomonas* spp. were inhibited by ≤64 μg of nitrofurazone per ml, corresponding to National Committee for Clinical Laboratory standards criteria for nitrofurantoin of susceptible or intermediately susceptible (24), whereas none of the *Pseudomonas* isolates were inhibited even at 128 μg/ml. MICs of nitrofurantoin were generally similar to those of nitrofurazone (Table 1). However, five strains (three *Serratia* spp., two *Proteus* spp.) that were inhibited by ≤64 μg of nitrofurazone per ml were resistant to nitrofurantoin (MIC = 128); in contrast, no nitrofurantoin-susceptible strains were resistant to nitrofurazone. Although MICs of nitrofurazone and nitrofurantoin correlated significantly (r^2 = 0.93, P = 0.0001), nitrofurazone MICs were significantly lower than nitrofurantoin MICs, both overall (mean MIC difference of 8 μg/ml, P = 0.02) and specifically among gram-negative bacilli other than *Pseudomonas* spp. (mean MIC difference of 17 μg/ml, P = 0.0004).

Antibacterial activity of catheter segments. The modified disk diffusion assay for inhibition by catheter segments gave interpretable results for all organisms except the two diphtheroid strains, which grew poorly on the Mueller-Hinton plates. Control silicone catheter segments failed to inhibit the growth of any organism (data not shown). In contrast, the nitrofurazone-matrix catheter measurably inhibited the growth of 51 (75%) of the clinical strains, as determined on the basis of inhibition zones from longitudinal catheter segments (Table 1). Strains not inhibited by catheter segments included *Serratia* spp. (2 of 3), *Proteus* spp. (4 of 6), *Enterobacter* spp. (1 of 7), and *Pseudomonas* spp. (all 10). Inhibition zone sizes differed significantly between the different types of bacteria but were fairly uniform within each group (Table 1).

Despite the greater width of transverse catheter segments, zones were generally larger around longitudinal catheter segments, where the entire antibiotic-coated surface of the catheter segment rather than only the cut edge of the coated surface was in contact with the agar plate (data not shown). Some strains that were not inhibited by transverse catheter segments were inhibited by longitudinal segments, whereas the reverse was not observed.

Correlation of catheter activity and nitrofurazone MIC. The sizes of the inhibition zones around nitrofurazone-matrix catheter segments correlated significantly with the log 10 of the nitrofurazone MIC. This correlation was better for inhibition zones from longitudinal catheter segments (r^2 = 0.79, P = 0.0001) than for zones from transverse segments (r^2 = 0.41, P = 0.0001).

Sterilization method. Inhibition zone sizes from autoclaved and gas-sterilized catheter segments corresponded closely (r^2 = 0.88, P = 0.0001). There was no evidence of reduced antibacterial activity with heat sterilization (data not shown).

Thus, the nitrofurazone-matrix catheter inhibited the in vitro growth of most bacterial types implicated in catheter-associated UTIs, including many gram-negative bacilli. These results suggest that the study catheter may be able to prevent such bacteria from migrating inward along the external surface of the catheter into the bladder, thereby

preventing or delaying the development of UTIs in acutely catheterized patients.

Previous investigators of antibacterial urinary catheters have demonstrated release of kanamycin (12), dibekacin (27), or cephalothin (18) from coated catheters in vivo, as well as in vitro inhibition of one or two test strains (*E. coli* [3, 18] or *S. aureus* [18]) by coated catheters. We determined susceptibility to both the active agent and the coated catheter for a large number of strains reflecting the diversity of bacterial types implicated in catheter-associated UTIs (2, 14, 15, 28, 31). Furthermore, the organisms we studied were actual clinical isolates from patients with indwelling urinary catheters (15) and thus represent an authentic sample of the typical flora of nosocomial UTIs.

It is likely that for successful prophylaxis against bacterial entry into the catheterized urinary tract, growth inhibition immediately at the catheter surface would suffice, since bacteria presumably must maintain intimate contact with the catheter in their ascent up the urethra (5, 8). Thus, the nitrofurazone-matrix catheter might be expected to block the ascent in vivo of even those organisms showing small but measurable zones of inhibition in the modified disk diffusion assay described here. Certain gram-negative bacilli, notably *Serratia* spp., *Proteus* spp., and *Pseudomonas* spp., demonstrated reduced susceptibility to nitrofurazone (as anticipated on the basis of previous studies [6, 25]), and were not inhibited by the nitrofurazone-matrix catheter. Such organisms account for approximately 30% of bacteria causing catheter-associated UTIs (2, 13, 15, 28, 31). Consequently, even if the nitrofurazone-matrix catheter were 100% protective against susceptible organisms, it could not be expected to prevent all catheter-associated UTIs.

The correlation we identified between the nitrofurazone MIC and susceptibility to inhibition by the nitrofurazone-matrix catheter indicates that the nitrofurazone MIC can be used to predict the activity of the catheter against specific bacterial strains. This may be clinically useful in assessing the appropriateness of the nitrofurazone-matrix catheter for use in specific hospital or nursing home environments, each with a distinctive spectrum of organisms causing nosocomial UTIs (2, 13, 15, 28, 31). The close correspondence of MICs of nitrofurazone and nitrofurantoin suggests that susceptibility results for nitrofurantoin, which are likely to be readily available from most clinical microbiology laboratories, could be used to estimate the susceptibility of different organisms to nitrofurazone. However, the significantly lower MICs of nitrofurazone compared with nitrofurantoin for most gram-negative bacilli indicate that such organisms are actually more susceptible to nitrofurazone than suggested by the nitrofurantoin MIC.

The similarity of inhibition zone sizes around autoclaved versus gas-sterilized catheter segments indicates that the nitrofurazone-matrix tolerates heat sterilization without any loss of antibacterial activity. This finding provides reassurance that autoclaving, which is widely available and inexpensive, should be an acceptable method for sterilizing the nitrofurazone-matrix catheter.

We thank Cynthia Fennell, Cheryl Wobbe, and the late Dolores Zeleznick for help in the microbiology laboratory; Leon D. Sabath for guidance with the MIC determinations; and Jodi A. Aasmundrud and Beth Wetak for manuscript preparation.

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