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Nitrofurantoin Is Active against Vancomycin-Resistant Enterococci

GEORGE G. ZHANEL,* DARYL J. HOBAN, AND JAMES A. KARLOWSKY

Departments of Clinical Microbiology and Medicine, Health Sciences Centre and Faculties of Medicine and Pharmacy, University of Manitoba, Winnipeg, Manitoba, Canada

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The activity of nitrofurantoin was tested against 300 isolates of *Enterococcus faecium*, *Enterococcus faecalis*, and *Enterococcus gallinarum*. No isolates tested were resistant to nitrofurantoin (MIC, ≥128 μg/ml), including vancomycin-resistant *E. faecium* isolates with *vanA*- and *vanB*-positive genotypes and vancomycin-resistant *E. gallinarum* isolates. We conclude that nitrofurantoin may provide effective treatment of urinary tract infections caused by vancomycin-resistant enterococci.

Enterococci are constitutive members of the intestinal flora of humans and animals but may also colonize the upper respiratory tracts, biliary tracts, and vaginas of otherwise healthy persons. The isolation of clinical isolates of enterococci generally denotes colonization rather than infection; however, enterococci may also cause infection, most commonly, urinary tract infection, but also cholecystitis, cholangitis, peritonitis, septicemia, endocarditis, meningitis, and simple wound infections (5). Although more than a dozen species of *Enterococcus* have been identified, two species, *Enterococcus faecalis* and *Enterococcus faecium*, account for approximately 85 to 90% and 5 to 10% of human enterococcal infections, respectively. The emergence of vancomycin resistance, most commonly in *E. faecium*, has introduced additional challenges to therapy, as these isolates are frequently resistant to additional antibiotics as well. The purpose of the current study was to assess the activities of nitrofurantoin and comparative antibiotics against isolates of *E. faecium*, *E. faecalis*, and *Enterococcus gallinarum* including vancomycin-resistant isolates.

The *E. faecium*, *E. faecalis*, and *E. gallinarum* stool isolates tested in this study were taken from previous and ongoing Canadian surveillance studies of vancomycin-resistant enterococci (VRE) (8, 17). In total, 100 vancomycin-susceptible *E. faecium* isolates, 100 vancomycin-susceptible *E. faecalis* isolates, 50 vancomycin-resistant *E. faecium* isolates, 25 vancomycin-susceptible *E. gallinarum* isolates, and 25 vancomycin-resistant *E. gallinarum* isolates were tested. Each stool isolate was from a different patient (8, 17) and had been identified to the species level by a conventional algorithm (4) supplemented with methyl-α-D-glycopyranoside testing (16). The identities of all discrepant organisms were determined by 16S rRNA gene sequencing (16). The genotypes of vancomycin-resistant isolates were determined by a previously described multiplex PCR protocol for *vanA*, *vanB*, *vanC1* and *vanC2-vanC3* (3).

Antibiotics for susceptibility testing were obtained from their various manufacturers as standard powders. Prior to antibiotic susceptibility testing all isolates were subcultured twice onto blood agar. MICs were determined by the standard broth microdilution method of NCCLS (M7-A4) with Mueller-Hinton broth (11) and were interpreted by using the breakpoints suggested by NCCLS (12).

None of the 300 isolates of enterococci tested were resistant to nitrofurantoin (MICs, ≥128 μg/ml) including vancomycin-resistant isolates of *E. faecium* with the *vanA* or *vanB* genotype and vancomycin-resistant *E. gallinarum* isolates with *vanC* genotypes (Table 1). Isolates of *E. faecium* positive for *vanA* and *vanB* demonstrated uniform phenotypic resistance to ampicillin, streptomycin, and ciprofloxacin, while they retained their susceptibility to quinupristin-dalfopristin. The percent susceptibilities for isolates of vancomycin-susceptible *E. faecium*, *E. faecalis*, and *E. gallinarum* are presented in Table 1. Rates of resistance to ampicillin, gentamicin, streptomycin, and ciprofloxacin were lower among vancomycin-susceptible enterococci than among vancomycin-resistant isolates. Quinupristin-dalfopristin demonstrated less potent activity against *E. faecalis* than against *E. faecium* and *E. gallinarum*, which is consistent with previously published data (8). The distributions of MICs of nitrofurantoin for all isolates of enterococci tested are presented in Table 2. Nitrofurantoin was less active against *E. faecium* than against *E. faecalis* and *E. gallinarum*. All isolates of *E. faecalis* and *E. gallinarum* were susceptible to nitrofurantoin, while 92 and 8% of *E. faecium* isolates were nitrofurantoin susceptible and nitrofurantoin intermediate, respectively.

The prevalence of VRE has been increasing in the United States in the past 10 years (5, 10). Approximately 70% of all vancomycin-resistant isolates of *E. faecium* and *E. faecalis* in the United States exhibit the *vanA* phenotype, which is characterized by resistance to vancomycin and teicoplanin and which is frequently associated with a multidrug resistance phenotype (5, 10). However, these isolates are frequently susceptible to quinupristin-dalfopristin (6, 7). Of the remaining 30%

* Corresponding author. Mailing address: Department of Clinical Microbiology, Health Sciences Centre, MS673, 820 Sherbrook St., Winnipeg, Manitoba R3A 1R9, Canada. Phone: (204) 787-4902. Fax: (204) 787-4699. E-mail: ggzhanel@pcs.mb.ca.

TABLE 1. Antibiotic susceptibilities for isolates of *E. faecium*, *E. faecalis*, and *E. gallinarum*[a]

Organism	No. of isolates	MIC_{90} (μg/ml [% resistant])							
		Nitrofurantoin	Vancomycin	Teicoplanin	Ampicillin	Gentamicin	Streptomycin	Ciprofloxacin	Q-D
VS *E. faecium*	100	32 (0)	1 (0)	1 (0)	64 (38)	1,000 (15)	4,000 (36)	>32 (46)	1 (3)
VS *E. faecalis*	100	8 (0)	2 (0)	0.5 (0)	1 (2)	>2,000 (26)	>4,000 (11)	>32 (23)	8 (57)
VS *E. gallinarum*	25	8 (0)	2 (0)	0.5 (0)	1 (0)	≤50 (0)	≤125 (4)	2 (8)	2 (8)
VR *E. faecium*									
VanA	40	32 (0)	256 (100)	32 (100)	64 (100)	>2,000 (50)	>4,000 (100)	>32 (100)	0.5 (0)
VanB	10	32 (0)	16 (100)	1 (0)	64 (100)	2,000 (50)	>4,000 (100)	>32 (100)	0.5 (0)
VR *E. gallinarum* VanC	25	8 (0)	8 (100)	0.5 (0)	1 (0)	≤50 (4)	≤125 (0)	2 (4)	2 (8)

[a] VS, vancomycin-susceptible; VR, vancomycin-resistant; Q-D, quinupristin-dalfopristin; MIC_{90}, MIC at which 90% of isolates are inhibited.

of vancomycin-resistant isolates, most exhibit a *vanB* phenotype, which is characterized by resistance to vancomycin and susceptibility to teicoplanin (5, 10). Vancomycin-resistant enterococci not only colonize the gastrointestinal tract but also have been associated with various infections including bacteremias, surgical site infections, peritonitis, pelvic abscesses, skin and soft tissue infections, and urinary tract infections including chronic prostatitis (1, 9, 13, 15, 17). Recently, seven cases of urinary tract infection caused by VRE were characterized (9). The urinary tract infections in five of the seven patients resolved in the absence of therapy or by removal of the Foley catheter or nephrostomy tube. The remaining two patients received nitrofurantoin, the infection resolved clinically, and negative urine cultures were documented (9). More recently, Taylor and coworkers (15) reported on a case of chronic prostatitis caused by VRE in which the organism was resistant to vancomycin, ampicillin, ciprofloxacin, and doxycycline. This organism retained susceptibility to rifampin (MIC, ≤1 μg/ml), chloramphenicol (MIC, ≤4 μg/ml), and nitrofurantoin (MIC, ≤32 μg/ml). The patient was treated with oral rifampin (600 mg/day for 6 weeks) and nitrofurantoin (200 mg four times daily for 2 weeks, followed by 100 mg four times daily for 4 weeks). The patient improved clinically, and all subsequent urine cultures were negative (15). As it is known that nitrofurantoin penetrates the prostate poorly, its exact role in the cure of this patient's infection is unclear (2). As well, clinicians should be reminded that because nitrofurantoin is retained in the blood of uremic patients, it should not be used in patients with moderate to severe renal impairment (creatinine clearance, ≤50 ml/min) (14).

TABLE 2. Distribution of nitrofurantoin MICs for isolates of *E. faecium*, *E. faecalis*, and *E. gallinarum*

Organism[a]	No. of isolates	No. of isolates for which nitrofurantoin MICs (μg/ml) were as follows:				
		4	8	16	32	64
VS *E. faecium*	100	1	9	2	80	8
VS *E. faecalis*	100	1	93	3	3	0
VS *E. gallinarum*	25	3	21	1	0	0
VR *E. faecium*						
VanA	40	0	2	5	30	3
VanB	10	0	3	4	3	0
VR *E. gallinarum* VanC	25	3	21	1	0	0

[a] VS, vancomycin-susceptible; VR, vancomycin-resistant.

Our study has demonstrated that nitrofurantoin is active against *E. faecium* and *E. faecalis*. More importantly, nitrofurantoin retained its activity against *vanA*- and *vanB*-positive isolates. Our in vitro data are consistent with the very limited clinical studies that suggest that nitrofurantoin may be effective in the treatment of VRE infections associated with the urinary tract.

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REFERENCES

1. **Childs, S. J.** 1998. Enterococcal infections of the urinary tract. Antibiot. Clinicians **2:**17–22.
2. **Conklin, J. D.** 1978. The pharmacokinetics of nitrofurantoin and its related bioavailability. Antibiot. Chemother. **25:**233–252.
3. **Dutka-Malen, S., S. Evers, and P. Courvalin.** 1995. Detection of glycopeptide resistance genotypes and identification to the species level of clinically relevant enterococci by PCR. J. Clin. Microbiol. **33:**24–27.
4. **Facklam, R. R., and M. D. Collins.** 1989. Identification of *Enterococcus* species isolated from human infections by a conventional test scheme. J. Clin. Microbiol. **27:**731–734.
5. **French, G. L.** 1998. Enterococci and vancomycin resistance. Clin. Infect. Dis. **27**(Suppl 1)**:**S75–S83.
6. **Jones, R. N., C. H. Ballow, D. J. Biedenbach, J. A. Deinhart, and J. J. Schentag.** 1999. Antimicrobial activity of quinupristin-dalfopristin (RP 59500, Synercid®) tested against over 28,000 recent clinical isolates from 200 medical centers in the United States and Canada. Diagn. Microbiol. Infect. Dis. **30:**437–451.
7. **Jones, R. N., D. E. Low, and M. A. Pfaller.** 1999. Epidemiologic trends in nosocomial and community-acquired infections due to antibiotic-resistant gram-positive bacteria: the role of streptogramins and other newer compounds. Diagn. Microbiol. Infect. Dis. **33:**101–112.
8. **Karlowsky, J. A., G. G. Zhanel, The Canadian VRE Surveillance Group, and D. J. Hoban.** 1999. Vancomycin-resistant enterococci (VRE) colonization of high-risk patients in tertiary care Canadian hospitals. Diagn. Microbiol. Infect. Dis. **35:**1–8.
9. **Lai, K. K.** 1996. Treatment of vancomycin resistant *Enterococcus faecium* infections. Arch. Intern. Med. **156:**2579–2584.
10. **Moellering, R. C.** 1998. Vancomycin resistant enterococci. Clin. Infect. Dis. **26:**1196–1199.
11. **National Committee for Clinical Laboratory Standards.** 1997. Methods for dilution of antimicrobial susceptibility tests for bacteria that grow aerobically, 4th ed. Publication M7–A4. National Committee for Clinical Laboratory Standards, Wayne, Pa.
12. **National Committee for Clinical Laboratory Standards.** 1999. Performance standards for antimicrobial susceptibility testing: ninth informational supplement. Publication M100–S9. National Committee for Clinical Laboratory Standards, Wayne, Pa.
13. **Roy, P. B., B. R. Joglekur, and S. M. Sayed.** 1972. Urinary tract infection and drug response. Indian J. Med. Sci. **26:**710–717.
14. **Sachs, J., T. Geer, P. Noell, and G. M. Kunin.** 1968. Effect of renal function

on urinary recovery of orally administered nitrofurantoin. N. Engl. J. Med. **278:**1032–1035.
15. **Taylor, S. E., D. L. Patterson, and V. L. Yu.** 1998. Treatment options of chronic prostatitis due to vancomycin-resistant *Enterococcus faecium*. Eur. J. Clin. Microbiol. Infect. Dis. **17:**798–800.
16. **Turenne, C. Y., D. J. Hoban, J. A. Karlowsky, G. G. Zhanel, and A. M. Kabani.** 1998. Screening of stool samples for identification of vancomycin-resistant *Enterococcus* isolates should include the methyl-α-D-glucopyranoside test to differentiate nonmotile *Enterococcus gallinarum* from *E. faecium*. J Clin. Microbiol. **36:**2333–2335.
17. **Zhanel, G. G., G. K. M. Harding, S. Rosser, D. J. Hoban, J. A. Karlowsky, M. Alfa, A. Kabani, J. Embil, A. Gin, T. Williams, and L. E. Nicolle.** 1999. Low prevalence of VRE gastrointestinal colonization of hospitalized patients in Manitoba tertiary care and community hospitals. Can. J. Infect. Dis. **10:**340–344.