Activity of Nitrofurantoin Against Urinary Tract Infection (UTI) Isolates of Vancomycin-Resistant Enterococci (VRE): A Three-Year Survey in an Iranian Hospital

Mohammad Rahbar¹, Massoud Hajia¹, Mohammad Farzanehkhah¹

1. Research Center of Reference Laboratories of Iran, Tehran, Iran

ABSTRACT

Background and Objective: Vancomycin-resistant enterococci (VRE) are major causative agents of urinary tract infections (UTIs) in hospitalized patients. The aim of this study was to determine prevalence of UTI caused by VRE in an Iranian 1000-bed hospital and to assess the activity of commonly used antibiotics including nitrofurantoin against VRE isolates.

Material and Methods: This study was carried out between April 2002 and April 2006 in Milad Hospital (Tehran). Only patients who had puria and significant bacteriuria included in our study. All isolates performed identification to species level and susceptibility testing performed by disk diffusion method as recommended by Clinical Laboratory Institute Standards (CLSI).

Results: In total, 837 enterococcus species were isolated from UTIs that 668 (79.8%) and 169 (20.2%) isolates were E. faecalis and E. faecium respectively. Analysis of the collected data revealed that 9.43% of vancomycin-resistant strains were resistant to nitrofurantoin as well (6 out of 65), while 84.9% of the isolated enterococci (54 out of 65) were vancomycin-resistant and nitrofurantoin-sensitive. The obtained data also showed that both vancomycin- and nitrofurantoin-resistant isolates had higher frequency rate in admitted patients compared with out-patients.

Conclusion: It is concluded that susceptibility of approximately 85% of VRE to nitrofurantoin indicates that this antibiotic still is the suitable alternative drug for treatment of urinary tract infections caused by VRE.

Key words: Nitrofurantoin, Vancomycin, Resistance, Enterococcus, Urinary tract infection

Introduction

Urinary tract infections (UTIs) are one of the most common bacterial infections in humans both in community and hospital settings (1). In almost all cases there is a need to start treatment before the final microbiological results available (2). Area-specific monitoring studies aimed to gain knowledge about the type of pathogens responsible for UTIs and their resistance patterns may help the clinicians to choose the right empirical treatment (3). Enterococci are constitutive member of the intestinal flora of humans and animals and may also colonize the upper respiratory tract, biliary tracts and vagina of otherwise healthy persons. Enterococci have been documented to cause infection of the urinary tract and
other sites (4). Although more than one dozen species of enterococcus have been recognized, Enterococcus faecalis and Enterococcus faecium accounts for approximately 85-90% and 5-10% of human enterococcal infections respectively. Vancomycin-resistant enterococci, especially E. faecium is prevalent in the hospitalized patients. Management of VRE infections is a clinical challenge as these organisms may be resistant to several antibiotics with unique action (5). Recent studies have demonstrated that nitrofurantoin is active against urine isolates of VRE (1).

Therefore, the purpose of this study was to determine prevalence of UTI caused by VRE in a 1000-bed hospital in Tehran and to assess the activity of commonly used antibiotics, especially nitrofurantoin against urinary isolates of VRE.

Material and Methods

Study Period

This study was carried out between April 2002 and April 2006 in Milad Hospital. Milad Hospital is a 1000-bed non-teaching and the largest hospital in Tehran. Patients were from varying ethnic kinds, local patients, or referred from elsewhere.

Specimens

Only patients who had puria and significant bacteriuria obtained included in the microbiological analysis. In total, 837 enterococcal strains were isolated from patients. Only one specimen for each patient was accepted and duplicated isolates excluded.

Antibiotic susceptibility Testing

All isolates performed identification to species level and susceptibility testing performed by disk diffusion method as recommended by Clinical Laboratory Standards Institute (CLSI) (6).

Quality Control and Standard Species

For the quality control of susceptibility testes, Escherichia coli ATCC 25922, Staphylococcus aureus ATCC29213, Enterococcus faecalis ATCC 29212 and Pseudomonas aeruginosa ATCC27853 strains were used.

Applied Antibiotics for evaluating isolated specimens

All urine isolates were tested for resistance against ampicillin, penicillin, ciprofloxacin, erythromycin, tetracycline, norfloxacin, nitrofurantoin, and vancomycin.

Results

In total, 837 enterococcus species were isolated from UTI infections. Sensitivity of all of these isolates was evaluated against commonly used antibiotics (Table 1). The lowest resistance rate was for vancomycin and nitrofurantoin (Fig. 1 and Table 2).

Analysis of the collected data revealed that 9.43% of vancomycin-resistant strains were also resistant to nitrofurantoin as well (6 out of 65), while 84.9% of the isolated enterococci (54 out of 65) were vancomycin-resistant and nitrofurantoin-sensitive (Tables 2-3). In addition, 169 out of 837 isolated enterococci were E. faecium and the remaining 668 isolated organisms were identified as E. faecalis. Meanwhile, the obtained data also showed that both vancomycin- and nitrofurantoin-resistant isolates have higher frequency rate in admitted patients compared with out-patients (Table 4).

Discussion

Enterococci has been recognized as the second pathogenic agent of UTI (3,7). Vancomycin-resistant enterococci (VRE) has higher mortality rate than vancomycin-sensitive enterococci (VSE) (8). Enterococci can also cause peritonitis, pelvic abcesses, and surgical site infections. Unfortunately, the rate of VRE has increased in recent years. Therefore, early diagnosis of VRE isolates is very important among nosocomial infection, specially those VRE strains containing Van B gene. These strains show intermediate or low level of resistance causing difficulty in diagnosis (9,10).

Antibiogram sensitivity test showed vancomycin and nitrofurantoin had the lowest resistant rate in comparison with other applied antibiotics among isolated enterococci from UTI. Resistant rate was 65 (7.76%) and 58 (6.92%) out of 837 for vancomycin and nitrofurantoin in the isolated enterococci respectively.

Very few studies in our country have described the epidemiology and clinical importance of VRE in urine isolates. Previous studies in Tehran have showed that nearly 7% of urine isolates of enterococci are VRE which resembles our study (11,12).

Reported resistances rates to nitrofurantoin are lower in other studies in comparison with our research (1,13). We had 58 nitrofurantoin-resistant enterococci
that just 6 cases were resistant to vancomycin too. The rate of vancomycin- and nitrofurantoin-resistant isolated enterococci is similar to Zanel’s report (0.6%) (5), the total nitrofurantoin cases were higher in this study than other reports, meaning the lack of proper treatment strategy in the nosocomial enterococci infections therapy. Analysis of the results also revealed that the frequency of E. faecalis is similar to other reports (14). Resistance rate to vancomycin is higher in E. faecium than E. faecalis in spite of higher isolation rate of E. faecalis (79.81%) than E. faecium. Meanwhile, 12 out of 668 E. faecalis were resistant to vancomycin (1.79%) while resistance rate for E. faecium were 53 out of 169 for E. faecium (31.36%). These results are in agreement with Zhanel’ report (1,5). Resistance rate for nitrofurantoin is different than vancomycin in these two species. In this respect, 24 out of 169 (14.2%) were resistant to E. faecium while it was 34 out of 668 (5.08%) for E. faecalis.

**Conclusion**

Our study demonstrated that nitrofurantoin is more active against E. faecium and E. faecalis in comparison to other routinely-used antibiotics for treatment of UTIs caused by enterococci. More importantly, nitrofurantoin has retained its activity against VRE 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.

![Table 1. Sensitivity rate of enterococcal isolates to applied antibiotics](image)

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Ampicillin</th>
<th>Penicillin</th>
<th>Ciprofloxacin</th>
<th>Norfloxacin</th>
<th>Erytromycin</th>
<th>Tertacycline</th>
<th>Vancomycin</th>
<th>Nitrofurantoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. faecalis</td>
<td>553</td>
<td>38</td>
<td>30</td>
<td>13</td>
<td>223</td>
<td>24</td>
<td>24</td>
<td>53</td>
</tr>
<tr>
<td>E. faecium</td>
<td>24</td>
<td>212</td>
<td>214</td>
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<table>
<thead>
<tr>
<th>Grade</th>
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<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. faecalis</td>
<td>553</td>
<td>38</td>
<td>115</td>
</tr>
<tr>
<td>E. faecium</td>
<td>24</td>
<td>23</td>
<td>130</td>
</tr>
</tbody>
</table>

**Table 2. Sensitivity rate of enterococci isolates to vancomycin and nitrofurantoin**

<table>
<thead>
<tr>
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<th>Intermediate</th>
<th>Sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>65</td>
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<td>768</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>58</td>
<td>36</td>
<td>741</td>
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**Table 3. Comparison of sensitivity rate for vancomycin and nitrofurantoin**

<table>
<thead>
<tr>
<th></th>
<th>Nitrofurantoin resistant isolates</th>
<th>Nitrofurantoin intermediate isolates</th>
<th>Nitrofurantoin sensitive isolates</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin resistant isolates</td>
<td>6</td>
<td>5</td>
<td>45</td>
<td>65</td>
</tr>
<tr>
<td>Vancomycin intermediate isolates</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Vancomycin sensitive isolates</td>
<td>52</td>
<td>31</td>
<td>84</td>
<td>601</td>
</tr>
</tbody>
</table>

**Table 4. Comparison of the vancomycin- and nitrofurantoin-resistant isolates in admitted patients and out-patients**

<table>
<thead>
<tr>
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<th>Out-patient</th>
<th>In-patients</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Vancomycin-resistant</td>
<td>10</td>
<td>55</td>
<td>65</td>
</tr>
<tr>
<td>Nitrofurantoin-resistant</td>
<td>14</td>
<td>44</td>
<td>58</td>
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</tbody>
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Figure 1. Sensitivity rate of enterococcal isolates to applied antibiotics

References


