Effects of vancomycin, teicoplanin, linezolid, quinupristin-dalfopristin, and telithromycin on murine gut colonization by Candida albicans

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Crl:CD1(ICR) BR adult mice were fed chow containing Candida albicans or regular chow. Both groups were subsequently given either antibiotics acting mainly against Gram-positive organisms or normal saline for 10 days. Stool cultures were performed before, at the end, and one week after discontinuation of treatment to determine the effects on the stool yeast concentration. Candida colonized mice treated with vancomycin, teicoplanin, linezolid, quinupristin-dalfopristin or telithromycin had higher colony counts of yeast in their stools than control Candida fed mice treated with saline. This increase was not statistically significant. Mice fed regular chow treated with the study drugs or saline did not have any yeasts in their stools. Dissemination of Candida was not observed in the visceral organs of any mouse.

Keywords Candida albicans, vancomycin, teicoplanin, linezolid, quinupristin-dalfopristin, telithromycin, gastrointestinal tract, mice

Introduction

Disseminated candidiasis is the most frequently encountered fungal infection in immunocompromised patients and is increasing in frequency [1,2]. The gastrointestinal (GI) tract is commonly the site of origin of the disseminated infection [3–5]. Treatment with broad spectrum antimicrobial agents predisposes susceptible hosts to fungal infections [6,7]. These agents suppress the normal intestinal flora resulting in overgrowth of Candida organisms already present in the gut [3]. If the concentration of Candida increases beyond a threshold, the yeast can translocate through the intact GI mucosa into the bloodstream and spread to visceral organs leading to systemic disease [8].

We have described a mouse model of sustained GI tract colonization by Candida albicans [9], and we have successfully used it to predict the impact of antimicrobial agents on the degree of GI colonization of humans by this yeast [7].

In the present study we report the effects of vancomycin, teicoplanin, linezolid, quinupristin-dalfopristin, and telithromycin on the level of GI colonization by C. albicans in this experimental animal model.

Materials and methods

A group of 50 3-month-old Crl:CD1(ICR) BR mice 30 g each (originating from Charles River Laboratories, Wilmington, Mass.) was used in each experiment. An experiment was done with each antibiotic. All experiments were performed in triplicate. The results we
report represent the median values and ranges for all three experiments combined. Thirty mice were fed special chow containing C. albicans for two weeks, as previously described [9]. Gastrointestinal colonization by the yeast was verified one week after the end of the special diet by quantitative stool cultures [9]. The remaining 20 mice of the group were fed regular chow which did not contain C. albicans, so that the yeasts could not be recovered from their stools. Subsequently, 20 Candida-colonized mice received the study antibiotic for 10 days. The remaining 10 colonized mice that received normal saline at the same volume (300 μl) and route and for the same duration served as controls. In addition, two groups of 10 mice each derived from the uncolonized group that were given either the same antibiotic or 300 μl of saline for 10 days served as controls. The antibiotics used in the present study were vancomycin, teicoplanin, linezolid, quinupristin-dalfopristin and telithromycin in their commercial forms. Linezolid and telithromycin were administered orally through a needleless animal feeding tube (Popper and Sons Inc., New Hyde Park, NY), while vancomycin, teicoplanin, and quinupristin-dalfopristin were administered subcutaneously. The dosage schedules were equivalent to those for humans and were calculated by the method of Freireich et al. [10]. The equivalence is shown in Table 1. Quantitative stool cultures were performed on the last day of antibiotic administration and one week after discontinuation of the antibiotic. Five random mice from each group were sacrificed within hours after the last antibiotic dose. Their hearts, lungs, livers, kidneys and spleens were removed, weighed separately and homogenized in 10 ml of saline by using a stomacher Lab Blender 80 (Tekmar Co., Cincinnati, OH). A 100 μl amount of the resulting suspension was cultured onto Sabouraud agar plates with chloramphenicol. The plates were incubated at 37°C for 48 h. Histopathologic examination was performed on all organs for detection of invasion by C. albicans. Statistical analysis of the data expressed as log10 was performed by Mann-Whitney two-sample test and by Kruskal-Wallis test for several independent samples.

### Results

Prior to the administration of the drugs the median concentration of C. albicans in the stools of mice fed chow containing the yeast was 4.2 log10 CFU/g of stool (range 3.9–4.4). After treatment, colonization was increased in the stools of mice receiving antibiotics. Vancomycin increased the concentration of C. albicans to 5.4 log10 (range 4.3–6.0), teicoplanin to 5.5 (range 5.1–6.0), linezolid to 5.1 (range 4.5–5.5), quinupristin-dalfopristin to 6.0 (range 5.4–6.3) and telithromycin to 5.8 log10 (range 5.6–5.9). The increases were not statistically significant. The medians and ranges of C. albicans concentrations in the stools of mice colonized and treated with the study antibiotics on day 10 of treatment and one week later for all three experiments combined are presented in Table 2.

One week after the end of treatment, the increase in the yeast GI colonization caused by each antibiotic was not sustained. In the rest of the control animals, the yeast concentration in the stools of colonized mice receiving only saline remained unchanged, while C. albicans was not detected in the stools of mice fed regular chow and treated with the study antibiotics or saline. There was no histopathologic or microbiologic evidence of Candida infection in any of the visceral organs of the sacrificed animals.

### Discussion

Antimicrobial agents may lead to yeast overgrowth of the intestinal flora, increasing the risk of dissemination. The impact on the GI yeast flora depends on the spectrum of the agent, the dose and route of administration, and the pharmacokinetic and pharmacody-

### Table 1  Equivalence of drug dosage in humans and mice.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dosage schedule 70 kg human</th>
<th>30 g mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>1 g q12h*</td>
<td>5.1 mg q12h</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>400 mg q24h</td>
<td>2.0 mg q24h</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>800 mg q24h</td>
<td>4.1 mg q24h</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg q12h</td>
<td>3.0 mg q12h</td>
</tr>
<tr>
<td>Quinupristin+dalfopristin</td>
<td>525 mg q8h</td>
<td>2.7 mg q8h</td>
</tr>
</tbody>
</table>

*Concentration before treatment: 4.2 (range 3.9–4.4).

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namic properties of the drug [11]. Agents with broad spectrum of activity including anaerobes, and/or high intestinal concentrations cause substantial increases in the yeast gut flora. On the other hand, antibiotics with narrower spectrum or with low concentrations in the GI contents are associated with small increases [12].

Glycopeptides are active against Gram-positive aerobic bacteria and to a lesser degree against Gram-positive anaerobes. These antibiotics are eliminated mainly by the renal route and only a small amount is metabolized in the liver and appears in active form in the bile [13]. Hence, their intestinal concentration is low. These properties can explain the present results, which indicate that the administration of vancomycin and teicoplanin is associated with small increases in the GI colonization by C. albicans.

Similarly, linezolid is active mainly against Gram-positive aerobes and to a minimal degree against anaerobes [14], but the low fecal concentrations cause minimal increases in the GI flora by C. albicans.

Telithromycin is active against Gram-positive cocci, as well as H. influenzae, B. catarrhalis and atypical bacteria involved in respiratory infections [15]. The drug is mainly excreted in the feces resulting in moderate increases in the concentration of C. albicans in the gut.

Quinupristin-dalfopristin is active almost exclusively against Gram-positive cocci and to a limited number of Gram-negative bacteria, such as Neisseria [13]. Fecal excretion constitutes the main route of drug elimination [16], increasing, but not substantially, the counts of C. albicans in the gut.

Other investigators have tested some of the drugs of the present study and have reported similar findings in humans [17–19]. However, this is the first study testing and comparing directly under similar circumstances the impact of broad spectrum antibiotics on the yeast flora of the human gut. Telithromycin is active against Gram-positive cocci, as well as H. influenzae, B. catarrhalis and atypical bacteria involved in respiratory infections [15]. The drug is mainly excreted in the feces resulting in moderate increases in the concentration of C. albicans in the gut.

It has been shown that this mouse model of GI colonization by C. albicans may be useful in predicting the degree of yeast colonization of the human gut after administration of antimicrobial agents [7]. Therefore, it is likely that the administration of glycopeptides, linezolid, quinupristin-dalfopristin, and telithromycin will not increase the risk of generalized candidiasis originating in the GI tract in sensitive patients.

In conclusion, we have shown that the use of antibiotics with antimicrobial activity against Gram-positive bacteria results in small to moderate increases in the concentration of C. albicans in the GI tract of mice. Clinical studies are necessary to confirm if our findings are applicable to humans, especially for patients at risk for disseminated candidiasis originating in the GI tract.

References

17. Lode H, von der Hoh N, Ziege S, Borner K, Nord CE. Ecological effects of linezolid versus amoxicillin/clavulanic acid on the
