Quinolones Susceptibility of norA-Disrupted Staphylococcus aureus

HISASHI YAMADA,* SUMIKO KUROSE-HAMADA, YOSHIKO FUKUDA, JUNICHI MITSUYAMA, MASASHIRO TAKAHATA, SHIZABURO MINAMI, YASUO WATANABE, AND HIROKAZU NARITA

Research Laboratories, Toyama Chemical Co. Ltd., 2-4-1 Shimookui, Toyama City, Toyama 930, Japan

Received 19 March 1997/Returned for modification 21 April 1997/Accepted 30 July 1997

The MIC of norfloxacin for the norA-disrupted mutant termed RDN1, obtained from quinolone-susceptible Staphylococcus aureus RN4220, was eightfold lower than that for RN4220. The increase in susceptibility was related to an increase of drug accumulation by RDN1. These results indicate that NorA plays an important role in the susceptibility of quinolone-susceptible S. aureus to selected quinolones.

Quinolones demonstrate a potent antimicrobial effect against gram-positive and gram-negative bacteria (5). These drugs have been widely used as effective antimicrobial agents, but quinolone-resistant strains have emerged in many pathogens including methicillin-resistant Staphylococcus aureus (1, 11). NorA is considered to be one factor relating to quinolone resistance in S. aureus, besides mutational alterations in gyrA (8) and grlA (4) which produce the target proteins for quinolones. NorA has been reported to act as an active efflux pump for some quinolones and is classified as a member of the efflux protein superfamily along with Bmr and Tet (3, 9, 14). Several reports have shown that overproduction of this efflux protein results in quinolone resistance (7, 12). However, because studies suggest that overproduction of this efflux protein re-

norA coding region (for-
TABLE 1. Relationship between the MICs for RN4220 and RDN1 and the relative hydrophobicities of the quinolones

<table>
<thead>
<tr>
<th>Compound</th>
<th>MIC (µg/ml) for:</th>
<th>Hydrophobicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RN4220</td>
<td>RDN1</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>1.56</td>
<td>0.2</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.39</td>
<td>0.1</td>
</tr>
<tr>
<td>Enoxacin</td>
<td>1.56</td>
<td>0.39</td>
</tr>
<tr>
<td>Pazufloxacin</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.39</td>
<td>0.39</td>
</tr>
<tr>
<td>Tosufloxacin</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

for RN4220. Takenouchi et al. (10) reported that the properties of the C-7 and the C-8 substituents of quinolones were important for efflux-mediated resistance. Actually, the quinolones whose susceptibilities were influenced by norA disruption have piperazinyl residues at the C-7 position. However, we have not clarified whether this residue makes the compound hydrophilic or relates to recognition by NorA.

These results indicate that NorA plays an important role in the susceptibility to selected quinolones of quinolone-susceptible S. aureus. Therefore it may be useful to clarify the substrate specificity of NorA and what mutations result in the resistance, as well as to determine other mechanisms of resistance, in order to develop novel quinolones effective against quinolone-resistant strains.

We are grateful to Matsuhisa Inoue (Department of Microbiology, Kitasato University) for providing S. aureus RN4220.

REFERENCES