In Vitro Activity of the Quinolone WCK 771 against Recent U.S. Hospital and Community-Acquired Staphylococcus aureus Pathogens with Various Resistance Types

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WCK 771 demonstrated MIC50 and MIC90 of 0.03 and 1 μg/ml, respectively, against 297 recent U.S. community-acquired and hospital strains of Staphylococcus aureus, irrespective of quinolone or glycopeptide resistance. Against quinolone-resistant strains, MIC90 of WCK 771 and moxifloxacin were 1 and 16 μg/ml, respectively.

Methicillin-resistant Staphylococcus aureus (MRSA) accounts for approximately 48 to 60% of the staphylococcal strains isolated from inpatients and outpatients in the United States, with >50% being multidrug resistant (17). Recently, the epidemiology of MRSA has changed, with emergence of quinolone-resistant community-acquired and multidrug-resistant hospital-acquired MRSA strains. Additionally, recognition of heteroresistant vancomycin-intermediate S. aureus (hVISA), vancomycin-intermediate S. aureus (VISA), and vancomycin-resistant S. aureus (VRSA) has caused concern; hVISA and VISA strains have been associated with vancomycin clinical failures (1, 7, 16). Compromised activity against VISA (10) and lack of broad-spectrum activity and bacteriostatic action are limitations of the currently employed anti-MRSA agents and point toward the need for new alternatives from other antibacterial classes.

The increase in quinolone resistance among methicillin-susceptible S. aureus (MSSA) and lack of sufficient activity against MRSA have compromised the therapeutic utility of all clinically available quinolones for the treatment of staphylococcal infections (5, 13). WCK 771 is a broad-spectrum intravenous quinolone active against MRSA and quinolone-resistant S. aureus and is currently being studied in phase 2 clinical trials (2, 8, 14). Its oral form is under development in phase 1 clinical studies. The present study was undertaken to establish the in vitro activity of WCK 771 against recent (2005 to 2007) U.S. clinical isolates of S. aureus with various resistance phenotypes, including vancomycin nonsusceptibility, originating from community and hospital settings and to determine its activity relative to currently utilized anti-MRSA agents, such as vancomycin. Moxifloxacin was included as a comparator quinolone, since among approved quinolones it shows significantly improved activity against S. aureus and possesses a superior pharmacokinetic-pharmacodynamic profile compared to other available quinolones.

(Portions of this work were previously presented at the 47th Interscience Conference on Antimicrobial Agents and Chemistry, Chicago, IL, 2007 [12].)

A total of 101 methicillin-susceptible and 196 methicillin-resistant strains were tested: 110 isolates were hospital acquired. Among 86 community-acquired MRSA strains, 73 produced Panton-Valentin leukocidin as identified by PCR using methods described previously (11); 2 hVISA, 25 VISA, and 7 VRSA strains were also included in the study. Vancomycin-susceptible strains were isolated in Pennsylvania, Texas, and Ohio, and a few strains were from western Europe. Both hVISA isolates were obtained from sputum of patients at Hershey Medical Center (HMC) who had received prior vancomycin therapy. Five of the VISA strains were isolated from blood of patients at HMC, and the rest were obtained from the Network on Antimicrobial Resistance in S. aureus (NARSA). Reference VISA strains MU3 and MU50 were obtained from ATCC. One of the seven VRSA strains was an HMC isolate, and the balance were from NARSA. MICs were determined as per CLSI recommendations on Mueller-Hinton agar containing serial twofold dilutions of the drugs (3). Vancomycin MICs were read after a full 24-h incubation. Genomic DNA isolation, PCR amplification (of the quinolone resistance-determining region [QRDR]) of vancomycin-susceptible MRSA, VISA, and VRSAs, and sequencing were performed as described previously (2, 4, 6).

Table 1 provides MIC ranges, MIC50, and MIC90 of WCK 771 against all groups of S. aureus strains. Against all S. aureus strains, WCK 771 demonstrated MIC50 and MIC90 values of 0.03 μg/ml and 1 μg/ml, respectively. Except for one isolate with an MIC of 8 μg/ml, the MIC range of WCK 771 was 0.015 to 2 μg/ml. The range, MIC50, and MIC90 of moxifloxacin were 0.06 to >32 μg/ml, 0.25 μg/ml, and 16 μg/ml, respectively. Thus, WCK 771 was 8 to 16 times superior in potency compared to moxifloxacin. The MIC range of vancomycin was 0.125 to 8 μg/ml. Higher MIC50 and MIC90 values of moxifloxacin for hospital-acquired MRSA strains (4 and 16 μg/ml, respectively) indicated elevated quinolone resistance in the...
hospital environment. For community-acquired and hospital-acquired MRSA strains, the WCK 771 MIC<sub>50</sub> and MIC<sub>90</sub> were 0.03 and 0.5 g/ml and 0.5 and 1 g/ml, respectively. Against hVISA/VISA strains, WCK 771 was 32 times more active than moxifloxacin. Vancomycin showed decreased susceptibility for hVISA/VISA strains, with MIC<sub>50</sub> and MIC<sub>90</sub> values of 4 and 4 g/ml and 2 and 4 g/ml, respectively. Higher values in the WCK 771 MIC range indicate some degree of cross-resistance; however, WCK 771 was consistently more potent than moxifloxacin (MIC range, 2 to 32 g/ml; MIC<sub>50</sub>, 4 g/ml; MIC<sub>90</sub>, 16 g/ml).

Figure 1 shows the MIC distribution data for the MRSA strains. The number of MRSA strains that were inhibited by WCK 771, moxifloxacin, and vancomycin at ≤2 μg/ml were 195, 108, and 178, respectively. Similarly, the numbers of strains inhibited at >2 μg/ml were 1 for WCK 771, 88 for moxifloxacin, and 18 for vancomycin.

Since the activities of WCK 771 and moxifloxacin are expected to be modulated by the number and variety of QRDR mutations, we chose two vancomycin-susceptible MRSA strains, two VISA strains, and seven VRSA strains (all quinolone resistant; ciprofloxacin MICs of ≤16 μg/ml) to analyze QRDRs. Table 2 shows the mutations in QRDR and corresponding MICs of WCK 771, moxifloxacin, and other agents. MRSA strains, VISA (Mu3 and Mu50) strains, and one VRSA strain (VRS2) showed double mutations, one each in gyrA and grlA. VRS3, VRS4, and VRS6 showed triple mutations, one in gyrA and two in grlA. WCK 771 demonstrated an MIC of 0.5 μg/ml against all these strains possessing two or three mutations. VRS5 (a recent VRSA isolate from Michigan) revealed four mutations, two each in gyrA (Ser84Leu and Glu88Lys) and grlA (Ser80Tyr and Glu84Gly). WCK 771 and moxifloxacin MICs for VRS5 were 8 and 32 g/ml, respectively.

The activity of WCK 771 reported in this study shows that recent community-acquired and hospital-acquired S. aureus strains continue to be susceptible to WCK 771 in the face of evolving quinolone resistance, particularly in hospital settings. The MIC<sub>90</sub> of vancomycin against MRSA was usually two times higher than against MSSA, probably indicating the steady

<table>
<thead>
<tr>
<th>Organism, resistance type or source (no. of isolates)</th>
<th>WCK 771</th>
<th>Moxifloxacin</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>All S. aureus (297)</td>
<td>0.015–8</td>
<td>0.03–1</td>
<td>0.03 to &gt;32</td>
</tr>
<tr>
<td>MSSA (101)</td>
<td>0.015–2</td>
<td>0.03–0.25</td>
<td>0.03–16</td>
</tr>
<tr>
<td>MRSA, community acquired (86)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.015–1</td>
<td>0.03–0.5</td>
<td>0.06–8</td>
</tr>
<tr>
<td>MRSA, hospital acquired (110)</td>
<td>0.015–8</td>
<td>0.5–1</td>
<td>0.06 to &gt;32</td>
</tr>
<tr>
<td>hVISA + VISA (27)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.03–1</td>
<td>0.25–0.5</td>
<td>0.125–16</td>
</tr>
<tr>
<td>Quinolone-resistant S. aureus (117)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.03–8</td>
<td>0.5–1</td>
<td>2 to &gt;32</td>
</tr>
</tbody>
</table>

<sup>a</sup> Seventy-three isolates produced Panton-Valentin leukocidin.
<sup>b</sup> Includes 2 hVISA and 25 VISA.
<sup>c</sup> Moxifloxacin MICs were ≥2 μg/ml.

**FIG. 1.** MIC distribution of 196 MRSA strains (86 community-acquired and 110 hospital-acquired strains). Values indicated at the tops of bars show the number of strains exhibiting an MIC at that concentration for each of the drugs.
gyrB showed a D432V mutation. None of the strains showed a mutation in QRDR of studies and our present observations with VRS5 suggest that mutations in quinolone target genes. Taken together the earlier findings of technical problems in their detection, but it might be higher nonsusceptible strains from clinical isolates is unknown because of quinolone-resistant strains not including commu-

accumulation of a nonsusceptible population within MRSA. Previous reports regarding suboptimal clinical responses of vanco-


REFERENCES


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