**Antistaphylococcal Activity of CB-181963 (CAB-175), an Experimental Parenteral Cephalosporin**

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Among 265 methicillin-susceptible and -resistant staphylococci, CB-181963 (CAB-175) had a 50% minimum inhibitory concentration of 2 μg/ml and a 90% minimum inhibitory concentration of 4 μg/ml. All strains except two vancomycin-resistant *S. aureus* and 5 vancomycin-intermediate *S. aureus* strains were also susceptible to vancomycin and teicoplanin, and all were susceptible to linezolid, ranbezolid, tigecycline, and quinupristin-dalfopristin. Most methicillin-resistant strains were levofloxacin resistant. CB-181963 was bactericidal against all six methicillin-resistant strains at four times the MIC after 24 h.

Emergence of methicillin-, quinolone-, and, recently, vancomycin-intermediate and -resistant staphylococci, as well as the propensity of these organisms to cause serious systemic infections in immunocompromised hosts, necessitates other therapeutic modalities (1, 7, 8, 10, 13, 15, 18). During 2002, two clinical strains of vancomycin-resistant *Staphylococcus aureus* (VRSA) carrying the *vanA* gene, one from Detroit, Mich., and one from our hospital (Hershey, Pa.), have been isolated (2, 17). Most methicillin-resistant staphylococci are also resistant to available quinolones, such as ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin (1, 7, 10, 15). Thus, the latter compounds may not be safely used in empirical therapy of patients with methicillin-resistant staphylococcal infections.

CAB-175 (CB-181963) (Fig. 1) is a novel parenteral investigational cephalosporin belonging to the azomethine subclass that exhibits a broad antibacterial spectrum, including against gram-positive organisms. CB-181963 activity was tested by agar dilution as described previously (9, 14). Colony counts were performed on plates yielding 30 to 300 bacterial colonies. The upper limit of sensitivity of colony counts was 300 CFU/ml (9, 14).

Time-kill assays were analyzed by determining the number of strains which yielded 1, 2, and 3 log₁₀ CFU/ml decrease at 0, 3, 6, 12, and 24 h compared to counts at time 0 h. Antimicrobials were considered bactericidal at the lowest concentration that reduced the original inoculum by greater than 3 log₁₀ CFU/ml (99.9%) at each of the time periods and was considered bacteriostatic if the inoculum was reduced by less than 3 log₁₀ CFU/ml. The problem of bacterial carryover was addressed by dilution as described previously (9, 14).

Staphylococcal MICs are listed in Table 1. As can be seen, CB-18963 had MICs of ≤4 μg/ml against all staphylococci tested, with slightly higher MICs (0.5 to 4 μg/ml) in methicillin-resistant compared to methicillin-susceptible strains (≤0.12 to 1 μg/ml). CAB-18963 was equally active against VRSA and VISA strains. Vancomycin and teicoplanin were active against all strains except those with raised glycopeptide MICs, while linezolid, ranbezolid, tigecycline, and quinupristin-dalfopristin were potent (MICs of ≤0.06 to 8 μg/ml) against all organisms irrespective of their β-lactam or glycopeptide susceptibility. Levofloxacin resistance occurred frequently among methicillin-
lin-resistant \textit{S. aureus} strains. NARSA repository identifiers as well as relevant MICs of active compounds against the two VRSA and five VISA strains are listed in Table 2.

MICs of strains tested by time kill are listed in Table 3. CAB-18963 gave the best kill kinetics of the tested compounds, with bactericidal activity against five of the six strains tested at two times the MIC and against all six strains at four times the MIC after 24 h. Bactericidal activity against the Hershey VRSA strain occurred at two times the MIC after 24 h. By comparison, vancomycin and levofloxacin were bactericidal against three strains and teicoplanin was bactericidal against one strain at two times the MIC after 24 h. Both oxazolidinones, tigecycline and quinupristin/dalfopristin, were bacteriostatic.


Results of these studies indicate a potential place for CB-18963 in therapy of staphylococcal infections, including those

\begin{table}[h]
\centering
\caption{ MICs (in micrograms per milliliter) for 265 \textit{S. aureus} strains} \\
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
\textbf{MIC} & \textbf{Methicillin susceptible} & \textbf{Methicillin resistant} \\
& \textbf{\textit{(n = 66)}} & \textbf{\textit{(n = 199)}} \\
\hline
\text{Range} & \text{MIC}_{50} & \text{MIC}_{90} & \text{Range} & \text{MIC}_{50} & \text{MIC}_{90} \\
\hline
\text{CB-18963} & \leq 0.12 & 0.5 & 1 & 0.5–4 & 2 & 4 \\
\text{Vancomycin} & 0.5–4 & 1 & 2 & 0.5–256 & 1 & 2 \\
\text{Teicoplanin} & 0.25–16 & 1 & 2 & \leq 0.12–128 & 0.5 & 1 \\
\text{Linezolid} & \leq 0.25 & 2 & 2 & 0.25 & 2 & 2 \\
\text{Ranbezolid} & \leq 0.25 & 2 & 4 & 0.5–8 & 2 & 4 \\
\text{Tigecycline} & \leq 0.06 & 0.25 & 0.5 & \leq 0.06–1 & 0.25 & 0.25 \\
\text{Quinupristin-} & 0.12 & 0.25 & 0.5 & \leq 0.06–1 & 0.5 & 0.5 \\
\text{dalfopristin} & & & & & & \\
\text{Levofloxacin} & 0.12–>32 & 8 & 32 & 0.12–>32 & 8 & >32 \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{ Time-kill results of six \textit{S. aureus} strains} \\
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
\textbf{Drug} & \textbf{MIC (\mu g/ml) for strain\textsuperscript{a}:} & \textbf{No. of strains killed at time point\textsuperscript{b}:} & \textbf{3 h} & \textbf{6 h} & \textbf{12 h} & \textbf{24 h} & \textbf{24 h} \\
\hline
\text{CB-18963} & & & \text{-1} & \text{-2} & \text{-3} & \text{-1} & \text{-2} \\
\text{Vancomycin} & & & 1 & 0 & 0 & 0 & 0 \\
\text{Teicoplanin} & & & 1 & 0 & 0 & 0 & 0 \\
\text{Linezolid} & & & 1 & 0 & 0 & 0 & 0 \\
\text{Ranbezolid} & & & 0 & 0 & 0 & 0 & 0 \\
\text{Tigecycline} & & & 0 & 0 & 0 & 0 & 0 \\
\text{Levofloxacin} & & & 0 & 0 & 0 & 0 & 0 \\
\hline
\text{Quinupristin-} & & & 0 & 0 & 0 & 0 & 0 \\
\text{dalfopristin} & & & 0 & 0 & 0 & 0 & 0 \\
\text{Linezolid} & & & 0 & 0 & 0 & 0 & 0 \\
\text{Quinupristin-} & & & 0 & 0 & 0 & 0 & 0 \\
\text{dalfopristin} & & & 0 & 0 & 0 & 0 & 0 \\
\text{Levofloxacin} & & & 0 & 0 & 0 & 0 & 0 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a} Methicillin resistant.
\textsuperscript{b} Vancomycin intermediate.
\textsuperscript{c} Vancomycin resistant.
caused by methicillin- and vancomycin-resistant strains. Toxicity and pharmacokinetic/pharmacodynamic studies (which are not available at this time) are necessary before results of in vitro tests can be tested in humans.

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REFERENCES