Can interchangeability of lincosamides be assumed in clinical practice? Comparative MICs of clindamycin and lincomycin for Streptococcus pyogenes, Streptococcus agalactiae and Staphylococcus aureus

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Sir,

Recently in Australia, prescribing patterns for lincosamides have changed. Parenteral lincomycin use now exceeds parenteral clindamycin use in hospitals, including intensive care units. The reasons pertain to availability, cost and the recommendations of the national antibiotic guidelines. The Australian therapeutic guidelines present lincomycin and clindamycin as equivalent treatments for serious infections due to Streptococcus pyogenes, Streptococcus agalactiae and Staphylococcus aureus.

As there are no CLSI or EUCAST breakpoints for lincomycin, Australian clinicians infer lincomycin susceptibility from clindamycin susceptibility. Challenging the validity of this approach are reports of ‘L-phenotype’ staphylococci and β-haemolytic streptococci that test clindamycin susceptible but lincomycin resistant. L-phenotype staphylococci and streptococci of both animal and human origin have been identified, mediated by Inu(A), Inu(B), Inu(C), Inu(D) and Inu(F). The frequency of L-phenotype isolates occurring in Australia is unknown.

We compared the MICs of lincomycin and clindamycin for local clinical isolates of S. pyogenes, S. agalactiae and S. aureus to determine whether L-type susceptibility patterns were present, and to compare MIC values. The data will be used as an evidence base for local policies regarding lincosamide choice.

Ninety S. pyogenes, 45 S. agalactiae and 100 S. aureus isolates (50 methicillin susceptible and 50 methicillin resistant) were tested for MICs of clindamycin and lincomycin by the CLSI agar dilution method. A 52-pin Steers replicator delivering a 2 μL inoculum was utilized. Erythromycin susceptibility was also determined using agar dilution. S. aureus ATCC 29213 and S. pneumoniae ATCC 29619 were included as controls. CLSI breakpoints were used for erythromycin and clindamycin susceptibility interpretation. The Comité de L’Antibiogramme de la Société Française de Microbiologie (CA-SFM) clindamycin breakpoints for Gram-positive cocci (susceptible ≤2 mg/L, resistant >8 mg/L) were utilized to define lincomycin susceptibility. Erythromycin-resistant, clindamycin-susceptible isolates were tested for inducible clindamycin resistance by ‘D-test’. MICs of clindamycin and lincomycin were compared in Stata v11 (College Station, TX, USA) using the Wilcoxon signed-rank test for matched pairs.

All S. pyogenes and S. aureus isolates tested, regardless of their macrolide–lincosamide–streptogramin B phenotype, had concordant susceptibilities for clindamycin and lincomycin (Table 1). Of interest, three of the S. agalactiae isolates had an erythromycin-resistant, low-level clindamycin-resistant pattern (clindamycin MIC=1 mg/L, CLSI breakpoint: susceptible ≤0.25 mg/L) but were susceptible to lincomycin at the CA-SFM breakpoint (lincomycin MIC=2 mg/L, CA-SFM breakpoint: susceptible ≤2 mg/L). This phenotype of macrolide-susceptible, clindamycin-resistant S. agalactiae has previously been reported. All other S. agalactiae strains had concordant lincosamide susceptibilities.

All lincosamide-susceptible isolates, of all the bacterial species tested, displayed lower MICs of clindamycin than of lincomycin (Wilcoxon signed-rank test for pairs P<0.0001). MIC50 values for local policies regarding lincosamide choice.

<table>
<thead>
<tr>
<th>Organism</th>
<th>ERY S, CLI S, LNC S</th>
<th>ERY S, CLI R, LNC S</th>
<th>ERY R, CLI R, LNC R</th>
<th>D-test for inducible CL1 resistance (+)</th>
<th>D-test for inducible CL1 resistance (−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pyogenes n = 45</td>
<td>28 62.2% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>39 6.7% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>5 11.1% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>5 11.1% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>4 8.9% 0% 0% 0% 0% 0% 0% 0% 0%</td>
</tr>
<tr>
<td>S. pyogenes n = 90</td>
<td>86 95.6% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>0% 0% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>4 4.4% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>0% 0% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>0 0% 0% 0% 0% 0% 0% 0% 0% 0%</td>
</tr>
<tr>
<td>S. aureus methicillin S n = 50</td>
<td>25 50.0% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>0% 0% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>5 10.0% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>20 4.0% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>0 0% 0% 0% 0% 0% 0% 0% 0% 0%</td>
</tr>
<tr>
<td>S. aureus methicillin R n = 50</td>
<td>23 46.0% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>0% 0% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>12 24.0% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>13 26.0% 0% 0% 0% 0% 0% 0% 0% 0%</td>
<td>2 4.0% 0% 0% 0% 0% 0% 0% 0% 0%</td>
</tr>
</tbody>
</table>

ERY, erythromycin; CLI, clindamycin; LNC, lincomycin; S, susceptible; R, resistant.

*Clindamycin MIC=1 mg/L (resistant at CLSI breakpoint); lincomycin MIC=2 mg/L (susceptible at CA-SFM breakpoint).
were 3-fold higher for lincomycin compared with clindamycin for S. agalactiae (0.12 mg/L compared with 0.03 mg/L), 2-fold higher for S. pyogenes (0.12 mg/L compared with 0.06 mg/L) and 4-fold higher for S. aureus (0.5 mg/L compared with 0.03 mg/L), with no difference found in the MIC<sub>50</sub> for methicillin-susceptible and methicillin-resistant S. aureus.

In summary, the S. pyogenes, S. agalactiae and S. aureus isolates tested demonstrated concordant lincosamide susceptibilities, with the exception of a few S. agalactiae isolates where discrepant susceptibility was a function of breakpoint interpretation. The MICs of lincomycin were uniformly higher than those of clindamycin for the tested isolates. The MIC disparity was greater among staphylococci than streptococci.

Whether the MIC differential translates into a difference in therapeutic efficacy is unclear, as the MIC value is not the sole determinant of antimicrobial efficacy in vivo. Clinical data regarding comparative efficacy are lacking. The advantages of clindamycin in treating S. pyogenes infections are attributed to effects other than direct antimicrobial action, including inhibition of toxin production and avoidance of the ‘Eagle effect’<sup>10</sup>. Clindamycin and lincomycin have the same mode of antimicrobial action but, to our knowledge, assumptions of equivalent activity with respect to toxin inhibition and the Eagle effect have not been examined.

In conclusion, based on data from a limited number of isolates, L-type staphylococci and β-haemolytic streptococci appear to be uncommon. Lincosamide-discrepant phenotypes are, however, described, raising questions regarding the appropriateness of inferring lincomycin susceptibilities from those of clindamycin. Higher MIC values of lincomycin for staphylococci and β-haemolytic streptococci should be considered by antimicrobial stewardship committees formulating a lincosamide prescribing policy. This is particularly the case given the current lack of evidence regarding the therapeutic equivalence of lincomycin and clindamycin in the therapy of infections due to S. pyogenes, S. agalactiae and S. aureus.

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Successful treatment of post-neurosurgical multidrug-resistant Pseudomonas aeruginosa meningoencephalitis with combination therapy of colistin, rifampicin and doripenem

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