Contrasting Effect of Acidic pH on the Bactericidal Activities of CEM-102 (Fusidic Acid) vs. Linezolid and Clindamycin Towards Staphylococcus aureus.

P. M. TULKENS, S. LEMAIRE, F. VAN BAMBEKE
'Univ. catholique de Louvain, Bruxelles, Belgium.

Background:
S. aureus shows high tolerance to acidic pH. Acidity, however, may affect antibiotic activity. We have compared the influence of acidic pH on the activity of CEM-102 (a steroid-like antibiotic carrying a free carboxyl function) vs. LNZ and CLI against S. aureus.

Methods:
S. aureus ATCC 25923 was grown in Mueller-Hinton broth (MHB). MICs were determined in MHB adjusted to pH 7.4 or pH 5.5. Dose-effect relationships at 24 h were examined for concentrations from 0.01 to 100 x the MIC. Results, expressed as the change in the intracellular inoculum at 24 h compared to time 0 h, were used to fit a Hill equation to allow determination of the values of two key pharmacological descriptors of antibiotic activity (relative potency [EC50 or 50% effective concentration] and maximal relative efficacy [E_max]; see Barcia-Macay et al, AAC 50(3):841-51).

Results:
All dose-effect relationships could be modeled using a sigmoidal function (Hill equation; R² > 0.950). MICs and pharmacological descriptors at both pH values are shown in the Table.

<table>
<thead>
<tr>
<th></th>
<th>pH7.4</th>
<th></th>
<th></th>
<th></th>
<th>pH5.5</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC</td>
<td>E0</td>
<td>EC50</td>
<td>E_max</td>
<td>MIC</td>
<td>E0</td>
<td>EC50</td>
<td>E_max</td>
</tr>
<tr>
<td>CEM-102</td>
<td>0.5</td>
<td>2.6 ± 0.2</td>
<td>2.0 ± 1.3</td>
<td>-1.9 ± 0.2</td>
<td>0.005</td>
<td>2.5 ± 0.2</td>
<td>0.3 ± 1.4</td>
<td>-1.6 ± 0.2</td>
</tr>
<tr>
<td>LNZ</td>
<td>2</td>
<td>2.4 ± 0.2</td>
<td>3.0 ± 1.4</td>
<td>-1.7 ± 0.3</td>
<td>2</td>
<td>2.3 ± 0.1</td>
<td>3.7 ± 1.3</td>
<td>-1.9 ± 0.2</td>
</tr>
<tr>
<td>CLI</td>
<td>0.125</td>
<td>2.2 ± 0.3</td>
<td>0.4 ± 1.5</td>
<td>-3.0 ± 0.4</td>
<td>1-2</td>
<td>2.2 ± 0.1</td>
<td>4.9 ± 1.5</td>
<td>-2.8 ± 0.2</td>
</tr>
</tbody>
</table>

a increase in log CFU compared to time 0 for an infinitely low concentration in antibiotic (bact. growth)
b concentration (mg/L) causing a reduction of the inoculum halfway between E0 and E_max, as obtained by graphical interpolation using the corresponding Hill equation
c decrease in log CFU compared to time 0 for an infinitely high concentration in antibiotic (bact. killing)
Statistical analysis: figures with different letters are significantly different from each other (p < 0.05)
- upper case letters: analysis per column (one-way ANOVA with Tukey test for multiple comparisons between each parameter for all drugs);
- lower case letters: analysis per row (unpaired, two-tailed t-test between corresponding parameters of extracellular and intracellular activities)
Acidic pH did not affect bacterial growth (in the absence of antibiotic (Eo)) but (i) markedly decreased the MIC and the EC50 of CEM-102; (ii) had no effect on linezolid; (iii) had opposite effects on clindamycin. Maximal relative efficacies (E_{max}) remained unchanged, with absolute values for CEM-102 similar to those of linezolid but lower than those of clindamycin.

**Conclusions:**

While maximal achievable efficacy is not modified, CEM-102 shows an increased potency at acidic pH. This may confer an advantage to this molecule for infections localized in low pH environments, such as skin, urine, vagina, or phagolysosomes of infected cells.