Background: Sulopenem is a thiopenem antibiotic with oral and IV formulations, which is stable against hydrolytic attack by many ß-lactamases, including extended spectrum ß-lactamase (ESBL) and AmpC enzymes, that is being developed for the treatment of infections associated with common hospital and community pathogens. There are currently no established susceptibility interpretive criteria for sulopenem. Anticipating the delayed introduction of sulopenem into established antimicrobial susceptibility testing devices, we evaluated the ability of ertapenem to function as a surrogate for predicting in vitro sulopenem susceptibility.

Methods: Sulopenem and ertapenem were tested for in vitro activity against 824 recent (2015-2016) Enterobacteriaceae urinary tract infection (UTI) isolates collected from patients in Europe and North America through the SENTRY Antimicrobial Surveillance Program. Reference broth microdilution susceptibility testing was conducted per CLSI guidelines using cation-adjusted Mueller-Hinton broth (CA-MHB). Antimicrobial agents tested included the following compounds and dilution ranges:

- Ertapenem (12 dilutions: 0.004-16 µg/mL)
- Sulopenem (12 dilutions: 0.004-4 µg/mL)

Conclusions: While ertapenem activity generally lies two tube dilutions lower than sulopenem at the lower end of the MIC values distribution, in vibrio activity around the breakpoint for ertapenem is similar. Once clinical breakpoints have been established for sulopenem, ertapenem in vitro testing may serve as a useful surrogate, pending inclusion of sulopenem in antimicrobial susceptibility testing devices.

Summary:

- Sulopenem is a thiopenem antibiotic with oral and IV formulations.
- Includes beta lactam and AmpC-type ß-lactamases.
- A new ß-lactamase that is not inhibited by clavulanic acid or sulbactam.
- Stability against destruction by hydrolytic enzymes.
- Proposed for use in the treatment of infections due to ß-lactamase-producing organisms.
- Similar to other new ß-lactam antibiotics, diagnostic device-to-test susceptibility to sulopenem may not be available at the time of regulatory approval.
- Evaluated the ability of ertapenem to serve as a possible surrogate test to predict sulopenem susceptibility in this analysis.

Table 1: Summary of sulopenem and ertapenem when tested against quality control reference strains (µg/mL).

<table>
<thead>
<tr>
<th>Organism / Reference Strain</th>
<th>Sulopenem (µg/mL)</th>
<th>Ertapenem (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli ATCC 35218</td>
<td>0.008</td>
<td>0.004</td>
</tr>
<tr>
<td>K. pneumoniae ATCC 70062</td>
<td>0.03</td>
<td>0.015</td>
</tr>
<tr>
<td>P. mirabilis ATCC 70062</td>
<td>0.06</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Table 2: Activity of sulopenem and ertapenem against key target pathogens.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Sulopenem MIC (µg/mL)</th>
<th>Ertapenem MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>≤0.015</td>
<td>≤0.015</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>≤0.03</td>
<td>≤0.015</td>
</tr>
<tr>
<td>P. mirabilis</td>
<td>≤0.03</td>
<td>≤0.015</td>
</tr>
</tbody>
</table>

Table 3: Comparison of sulopenem and ertapenem MIC values for Klebsiella species employing CLSI breakpoint interpretive criteria for both agents.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Sulopenem MIC (µg/mL)</th>
<th>Ertapenem MIC (µg/mL)</th>
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<tbody>
<tr>
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<tr>
<td>P. mirabilis</td>
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<td>≤0.015</td>
</tr>
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</table>

Figure 1: Scattergram of sulopenem versus ertapenem MIC values for Klebsiella species employing CLSI breakpoint interpretive criteria for both agents.

Figure 2: Scattergram of sulopenem versus ertapenem MIC values for E. coli employing CLSI breakpoint interpretive criteria for both agents.

Figure 3: Scattergram of sulopenem versus ertapenem MIC values for Klebsiella species employing CLSI breakpoint interpretive criteria for both agents.

Figure 4: Scattergram of sulopenem versus ertapenem MIC values for P. mirabilis employing CLSI breakpoint interpretive criteria for both agents.

Figure 5: Scattergram of sulopenem versus ertapenem MIC values for P. mirabilis employing CLSI breakpoint interpretive criteria for both agents.

CONCLUSIONS

- Sulopenem demonstrates potent activity for Enterobacteriaceae with MIC₉₀ results ranging from 0.06 to 0.25 µg/mL for E. coli, Klebsiella species, and P. mirabilis.
- It may be possible to use ertapenem susceptibility test results as a surrogate to predict sulopenem activity.
- E. coli: 100% correlation
- Klebsiella species: 99.7% of isolates correlated and 100% of isolates ≤2 µg/mL.
- P. mirabilis: 94% correlation.
- Establishment of breakpoints for sulopenem will help better understand the potential clinical application of these findings.

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Results

- We evaluated the ability of ertapenem to serve as a possible surrogate test to predict sulopenem susceptibility in this analysis.

- Sulopenem demonstrated potent activity for Enterobacteriaceae with MIC₉₀ results ranging from 0.06 to 0.25 µg/mL for E. coli, Klebsiella species, and P. mirabilis.
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