Activity of Temocillin against KPC-Producing Klebsiella pneumoniae and Escherichia coli

Temocillin, a 6-α-methoxy derivative of ticarcillin, is currently approved for treatment of infections due to members of the Enterobacteriaceae in Belgium and the United Kingdom. It is stable against hydrolysis by most β-lactamases, including extended-spectrum β-lactamases (ESBLs) and AmpC-type β-lactamases, with studies reporting MICs at which 90% of bacteria are inhibited (MIC90s) between 16 and 32 µg/ml (3, 4, 8). Temocillin is thus drawing attention as a potential alternative to carbapenems in treatment of infections caused by the Enterobacteriaceae producing these broad-spectrum β-lactamases.

Carbapenem-resistant Klebsiella pneumoniae producing KPC-type β-lactamase has emerged in recent years and caused hospital outbreaks of serious infections in the United States and other parts of the world (7). Furthermore, KPC-type β-lactamase is increasingly identified in other species of the Enterobacteriaceae as well, including Escherichia coli. One concerning recent phenomenon is the occurrence of urinary tract infections due to KPC-producing organisms at nursing homes (10). Currently, the limited treatment options for infections due to KPC-producing organisms include colistin and tigecycline. Concern over nephrotoxicity due to colistin limits its use outside closely monitored settings, whereas tigecycline does not achieve a therapeutic urinary concentration after a 500-mg dose is approximately 500 µg/ml, with serum binding of 85% and a half-life of 4 to 5 h (9). The peak serum concentration of approximately 160 µg/ml. One gram of temocillin is known to achieve a temocillin against an E. coli isogenic clone producing KPC-3 were tested to determine the direct effect of KPC production on the temocillin MIC. E. coli ATCC 25922 was used as the control strain.

Table 1 summarizes the results. For K. pneumoniae, the MICs ranged between 16 µg/ml and 64 µg/ml (MIC at which 50% of bacteria were inhibited = 32 µg/ml; MIC90 = 32 µg/ml). The E. coli clinical isolates had MICs between 8 and 16 µg/ml. E. coli DH10B both with and without the cloning vector pBCSK+ (Stratagene, La Jolla, CA) encoding blaKPC-3 had an MIC of 8 µg/ml. An inoculum effect was not observed at 10⁵ CFU, whereas a mild inoculum effect averaging within a twofold MIC difference was seen with K. pneumoniae when 10⁴ CFU was inoculated (Table 1). This result was in line with those of a previous study documenting a modest inoculum effect of temocillin for non-KPC-producing isolates (9). The frequencies of mutants of representative clinical isolates that grew at their MICs and at 2× MICs were calculated to be approximately 1 × 10⁻¹⁰ and 0 for K. pneumoniae and 3 × 10⁻¹⁰ and 1 × 10⁻¹⁰ for E. coli, respectively.

Currently, the British Society for Antimicrobial Chemotherapy (BSAC) is the only organization that defines temocillin MIC breakpoints for the Enterobacteriaceae. The BSAC defines temocillin susceptibilities at ≤8 and ≤32 µg/ml in systemic and urinary tract infections, respectively (http://www.bsac.org.uk/). One gram of temocillin is known to achieve a peak serum concentration of approximately 160 µg/ml, with serum binding of 85% and a half-life of 4 to 5 h (9). The urinary concentration after a 500-mg dose is approximately 500 µg/ml (9). These pharmacokinetic properties of temocillin make it a potential alternative treatment option for mild to moderate urinary tract infections caused by KPC-producing members of the Enterobacteriaceae.

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**REFERENCES**


### TABLE 1. Susceptibilities of KPC-producing K. pneumoniae and E. coli isolates to temocillin

<table>
<thead>
<tr>
<th>Inoculum (CFU)</th>
<th>Species (n⁰)</th>
<th>No. of isolates inhibited at temocillin MIC (µg/ml) of:</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>32</th>
<th>64</th>
<th>128</th>
<th>256</th>
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</thead>
<tbody>
<tr>
<td>1 × 10⁴ K. pneumoniae (30)</td>
<td>E. coli (3)</td>
<td>12</td>
<td>15</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
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<tr>
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<td>1</td>
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<td>1</td>
<td>1</td>
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</tbody>
</table>

a n, no. of isolates.

b BSAC breakpoint for systemic infections.

c BSAC breakpoint for urinary tract infections.

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