CXA-101 was reduced from 4 to 1 mg/L upon the addition of tazobactam. The addition of tazobactam was of no benefit in strains producing GES, VEB and PER β-lactamases, which all had CXA-101 MICs >64 mg/L. In the only isolate producing an ESBLM-D β-lactamase (OXA-32), the MIC was reduced from >64 to 8 mg/L. The OXA-32-producing isolate was also susceptible to piperacillin/tazobactam. Susceptibility to piperacillin/tazobactam was additionally seen in one isolate (producing PER-1), which was resistant to all β-lactams except imipenem and ceftazidime plus clavulanate. The latter combination was found to have activity against four isolates (producing PER-1, BEL-1, SHV-5 and TEM-4).

In conclusion, CXA-101 was found to have good in vitro activity against 4/9 ESBLM-D-producing P. aeruginosa. The addition of tazobactam extended the activity to the one ESBLM-D-producing isolate tested. Hence, CXA-101 plus tazobactam was of no benefit in comparison, imipenem had activity against 9/10 isolates, ceftazidime plus clavulanate against 4/10 isolates, piperacillin/tazobactam against 3/10 isolates, cefepime against 2/10 isolates and ceftazidime or ceftazidime plus tazobactam against 1/10 isolates.

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References

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Clinical efficacy of temocillin
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Keywords: AmpC, ESBL, nosocomial pneumonia, sepsis, Enterobacteriaceae

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Sir, Livermore and Tulkens1 state that published clinical data on temocillin’s use in severe sepsis and nosocomial pneumonia remain scanty. This is particularly relevant when extended-spectrum β-lactam (ESBL)-producing Enterobacteriaceae are involved, as therapeutic options are limited.2 Here we present clinical data on the use of temocillin in severe sepsis related to infections of the biliary and urinary tracts, as well as nosocomial pneumonia and diverticulitis. Five patients had infections with Enterobacteriaceae producing ESBLs (three Klebsiella pneumoniae, one Escherichia coli and one dual infection with both K. pneumoniae and E. coli, both ESBL-positive). One patient had ventilator-associated pneumonia (VAP) and bacteraemia: Enterobacter aerogenes (a derepressed mutant with constitutive production of AmpC chromosomal cephalosporinase) and ESBL-negative K. pneumoniae were isolated from sputum, and a fully susceptible Proteus mirabilis from blood (Table 1). Isolates were identified using Phoenix Automated Microbiology System (BD Diagnostic Systems, Sparks, MD, USA) methodology and ESBL/AmpC production was confirmed using Phoenix and/or combination disc methodology. Temocillin MICs were determined by Etest (AB Biodisk, Solna, Sweden).

Infection completely resolved on temocillin in all but two cases, patients 4 and 5. Patient 4 developed a diverticular abscess that was drained radiologically 2 months later, and K. pneumoniae, E. coli (both ESBL-positive), Enterococcus faecium and yeasts were cultured from pus. She was initially treated with meropenem [1 g intravenously (iv) once daily] for 10 days, followed by de-escalation to temocillin (1 g iv thrice weekly with dialysis) and metronidazole (400 mg orally once daily). Definitive surgery was not possible owing to co-morbidities, and temporary withdrawal of temocillin had previously resulted in septic deterioration. She is currently stable on temocillin (1 g iv thrice weekly) and metronidazole (400 mg orally once daily) with a long-term drain in situ.

Patient 5 presented with acute cholangitis on a background of primary biliary cirrhosis, for which she was awaiting liver transplantation. Blood cultures from admission grew an ESBL-producing K. pneumoniae. Inducible AmpC was not detected on induction testing. The isolate was susceptible to
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/gender</th>
<th>Clinical indication</th>
<th>Isolate/site</th>
<th>Resistance pattern</th>
<th>MIC(^b) (mg/L)</th>
<th>dose</th>
<th>duration</th>
<th>Concurrent antibiotics</th>
<th>eGRF (mL/min) on starting temocillin</th>
<th>Clinical outcome</th>
<th>Duration (days) of temocillin before first negative culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66/male</td>
<td>severe urosepsis</td>
<td><em>K. pneumonia</em>(^c) urine and blood</td>
<td>AMP, ATM, LEX, CTX, CAZ, CXM, CIP, AMC, SXT, GEN, NOR, TZP</td>
<td>4</td>
<td>1 g once daily</td>
<td>10 days</td>
<td>AMK</td>
<td>41</td>
<td>resolution</td>
<td>blood: 4, urine: 4</td>
</tr>
<tr>
<td>2</td>
<td>98/male</td>
<td>severe urosepsis</td>
<td><em>K. pneumonia</em>(^c) urine and blood</td>
<td>AMP, ATM, LEX, CTX, CAZ, CXM, AMC, SXT</td>
<td>6</td>
<td>1 g once daily</td>
<td>10 days</td>
<td>none</td>
<td>22</td>
<td>resolution</td>
<td>blood: 4, urine: 4</td>
</tr>
<tr>
<td>3</td>
<td>34/female</td>
<td>VAP and severe sepsis</td>
<td><em>E. aerogenes</em>(^e) sputum, <em>K. pneumoniae</em> sputum, <em>P. mirabilis</em> blood</td>
<td>AMP</td>
<td>6</td>
<td>1 g twice daily</td>
<td>10 days</td>
<td>MTZ</td>
<td>81</td>
<td>resolution</td>
<td>no data</td>
</tr>
<tr>
<td>4</td>
<td>57/female</td>
<td>diverticular abscess</td>
<td><em>K. pneumoniae</em>(^c) pus</td>
<td>AMP, ATM, LEX, CTX, CAZ, CXM, CIP, AMC, SXT, GEN, TZP</td>
<td>6</td>
<td>1 g thrice weekly with dialysis</td>
<td>&gt;2 years (ongoing)</td>
<td>MTZ</td>
<td>haemodialysis</td>
<td>treatment ongoing until surgery</td>
<td>no data</td>
</tr>
<tr>
<td>5</td>
<td>23/female</td>
<td>severe biliary sepsis</td>
<td><em>K. pneumoniae</em>(^c) blood, initial isolate, <em>K. pneumoniae</em>(^c) blood, breakthrough isolate</td>
<td>AMP, ATM, LEX, CTX, CAZ, CXM, CIP, AMC, SXT, NOR, TZP</td>
<td>16</td>
<td>1 g once daily</td>
<td>4 days</td>
<td>nil</td>
<td>27</td>
<td>breakthrough bacteraemia on day 4; subsequent successful treatment with ertapenem</td>
<td>breakthrough bacteraemia on day 4</td>
</tr>
<tr>
<td>6</td>
<td>54/male</td>
<td>VAP</td>
<td><em>E. coli</em>(^e) sputum</td>
<td>AMP, ATM, LEX, CTX, CAZ, CXM, CIP, AMC, SXT, NOR</td>
<td>12</td>
<td>1 g once daily</td>
<td>7 days</td>
<td>MTZ</td>
<td>30</td>
<td>resolution</td>
<td>sputum: 4</td>
</tr>
</tbody>
</table>

\(^a\)AMK, amikacin; AMP, ampicillin; ATM, aztreonam; LEX, cefalexin; CTX, cefotaxime; CAZ, ceftazidime; CXM, cefuroxime; CIP, ciprofloxacin; AMC, co-amoxiclav; SXT, co-trimoxazole; GEN, gentamicin; MEC, mecillinam; MTZ, metronidazole; NOR, norfloxacin; TZP, piperacillin/tazobactam.

\(^b\)Temocillin breakpoints (CLSI): susceptible, ≤16 mg/L; resistant, >32 mg/L.

\(^c\)ESBL-producing isolates.

\(^d\)Derepressed mutant with constitutive production of AmpC chromosomal cephalosporinase.
Research letters

several antibiotics including temocillin (MIC 16 mg/L) and showed intermediate susceptibility to piperacillin/tazobactam (MIC 64/4 mg/L) (Table 1). She was treated with temocillin (1 g iv once daily), a lower dose regimen being applied due to renal impairment [estimated glomerular filtration rate (eGFR) 27 mL/min]. The patient rapidly improved over the next 48 h (temperature 37.2°C and C-reactive protein 75 mg/L compared with 38.7°C and 145 mg/L, respectively, on admission). During this time, her renal function improved (eGFR 103 mL/min) and her temocillin dose was increased to 1 g twice daily accordingly. On the fourth day of temocillin treatment she deteriorated and repeat blood cultures again grew an ESBL-producing K. pneumoniae. In contrast to the initial isolate, this breakthrough isolate was of only intermediate susceptibility to temocillin (MIC 32 mg/L) and resistant to mecillinam and piperacillin/tazobactam (MIC >64/4 mg/L). The patient was changed from temocillin to etrapenem (1 g iv once daily), and made a good recovery.

To our knowledge, this is the first reported case of breakthrough bacteraemia on temocillin treatment. One factor that may have predisposed to the loss of susceptibility in this patient was her renal function, which, having initially been sufficiently impaired to merit once daily dosing, rapidly improved and could therefore have resulted in temocillin levels falling and remaining below the MIC for protracted periods. In addition, biliary concentrations of temocillin would have been particularly compromised because the biliary tree was severely damaged due to primary biliary cirrhosis. The simultaneous acquisition of resistance to mecillinam and piperacillin/tazobactam is particularly worrying, and might reflect mediation by a common mechanism or genetic element.

Two other patients were treated with temocillin for infections caused by E. coli not producing ESBLs or AmpC. The first patient was a 78-year-old lady who was admitted to the Intensive Therapy Unit with severe urosepsis complicated by acute renal failure. She responded very well to a single dose of temocillin (1 g iv) and a 2 day course of gentamicin (2 mg/kg iv once daily). A fully susceptible E. coli was cultured from urine and treatment was de-escalated to co-amoxiclav (1.2 g iv thrice daily) for a further 4 days. The second patient was a 67-year-old lady with an intra-abdominal collection following biliary reconstruction, who was treated with temocillin (1 g iv twice daily) and metronidazole (500 mg iv thrice daily). She developed VAP with Pseudomonas aeruginosa on the fourth day of treatment; amikacin (15 mg/kg iv once daily) was added and temocillin switched to meropenem (1 g iv thrice daily). The patient subsequently deteriorated and died.

No side effects attributable to temocillin and no cases of Clostridium difficile infection were reported in this series of patients. These data illustrate the potential clinical usefulness of temocillin, particularly as a directed-spectrum alternative to the carbapenems in infection due to ESBL/AmpC-positive Enterobacteriaceae. Comparative clinical trials are now needed.

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Rapid selection and archiving of mutation E157Q in HIV-1 DNA during short-term low-level replication on a raltegravir-containing regimen

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Keywords: antiretroviral therapy, HIV, resistance

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Sir,

Raltegravir is the first antiretroviral agent from the integrase inhibitor class that has demonstrated virological efficacy in heavily pre-treated HIV-1-infected patients harbouring multi-resistant strains.1,2 Viral replication of >400 copies/mL upon raltegravir selective pressure has been associated with the selection of mutations associated with raltegravir resistance in the vast majority of cases, particularly when the genotypic sensitivity score (GSS) is close to zero.3 Little is known, however, regarding the impact of short-term low-level viraemia on the development of resistance to raltegravir.

A man infected with HIV-1 subtype B, diagnosed since 1995, with a history of AIDS-defining events and with prior failure to four antiretroviral classes [nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs), protease inhibitors (PIs) including tipranavir and darunavir, and fusion inhibitors (FIs)], was started on a raltegravir-containing regimen in March 2006. At that time, plasma HIV-1 RNA was 66200 copies/mL with 92 CD4 cells/mm3. A genotypic resistance test showed 9 NRTI-associated resistance mutations, 2