Clinical and bacteriological effects of pivmecillinam for ESBL-producing Escherichia coli or Klebsiella pneumoniae in urinary tract infections

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Objectives: The prevalence of urinary tract infections (UTIs) caused by extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae is increasing and the therapeutic options are limited, especially in primary care. Recent indications have suggested pivmecillinam to be a suitable option. Here, we evaluated the clinical and bacteriological effects of pivmecillinam in UTIs caused by ESBL-producing Enterobacteriaceae.

Methods: We carried out a prospective follow-up of 39 patients diagnosed with UTI caused by ESBL-producing Enterobacteriaceae, initiated on pivmecillinam. The patients were from general practice (n=29) or admitted to hospitals (n=10) in the Copenhagen area, Denmark (n=30) or Halland, Sweden (n=9). Both patients and physicians were asked to complete a questionnaire on the pretreatment signs and symptoms. Patients were asked to send in two more urine samples for culture examination, together with questionnaires for clinical effect, 2–6 and 10–20 days, respectively, after end of treatment.

Results: Of the 39 patients included, 30 received a treatment regimen of 400 mg of pivmecillinam three times a day and 9 received 200 mg three times a day. All isolates were susceptible to mecillinam. The bacteriological cure rate was 79% (31/39); 80% (24/30) and 78% (7/9) for 400 and 200 mg three times a day, respectively. Relapse, i.e. ESBL-producing bacteria in the second control urine after previous bacteriological cure, was seen in five patients. Clinical cure was evaluable in 19 patients; 16 had a clinical effect (84%).

Conclusions: Pivmecillinam was proven bacteriologically and clinically effective for treatment of lower UTIs caused by ESBL-producing Enterobacteriaceae.

Keywords: Enterobacteriaceae, mecillinam, multidrug resistance, antimicrobial therapy, community-acquired infections

Introduction

Pivmecillinam is documented to be a safe and effective agent in the treatment of urinary tract infections (UTIs)1-2 and is part of the international clinical practice recommendation for uncomplicated UTIs.3 Over recent years, there have been scant clinical indications and in vitro studies suggesting that pivmecillinam is effective against UTIs caused by extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae.4-10 However, the clinical efficacy is not as well studied. The bacteriological effect has been proven experimentally in mice in vivo.11 Titelman et al.12 indicated a good clinical effect (8/8), but with a low bacteriological cure rate (2/8).

With this background and since pivmecillinam is used as one of the first options in the treatment of UTIs in Scandinavia, we decided to study and document if pivmecillinam is a sufficient alternative in the treatment of UTIs caused by ESBL-producing Enterobacteriaceae, monitored both as clinical and bacteriological effect.

Methods

This was a clinical prospective, cross-sectional study on the bacteriological and clinical effect of pivmecillinam on UTIs caused by ESBL-producing Enterobacteriaceae, performed during August 2012 to April 2013.

Ethics approval and patient consent

The study was approved by the Danish Data Protection Agency (I –suitnr. 01755 and id.nr. HVH-2012-022). Patients were asked to participate and could withdraw from the study at any time, but without consequences for their treatments.

Patients and definitions

Patients with urine samples positive for ESBL-producing Enterobacteriaceae, initiated on pivmecillinam (i.e. 200 or 400 mg three times daily) and
with clinical suspicion of lower UTI were included consecutively through the departments of clinical microbiology; 9 patients from Hallands Hospital Halmstad, Sweden and 30 patients from Hvidovre Hospital, Denmark.

Exclusion criteria were signs of pyelonephritis (high fever with/without flank pain).

Patients were asked to complete two questionnaires (available as Supplementary data at JAC Online) regarding symptoms, before, 2 - 6 days and 10 - 20 days after treatment, respectively, adherence, current treatment (daily dose and duration), comorbidities (i.e. pathological urinary tract), urinary tract catheter use, recurrence of infection and side effects. The treating physician also completed a questionnaire (available as Supplementary data at JAC Online) regarding the patient’s signs and symptoms pretreatment as well as the recurrence of UTIs and current treatment. If patients later submitted urine samples for microbiological diagnostics, the bacteriological and clinical data were retrieved. However, many of the older patients and nursing home residents returned insufficient clinical data that could not be evaluated for clinical effect.

The three main endpoints, as decided prior to the initiation of the study, were initial bacteriological and clinical cure, and relapse within 20 days. These were measured by comparing the bacteriological results of urine culture and clinical data that were collected once pretreatment and twice post-treatment.

Bacteriological cure was defined as a significant reduction of ESBL-producing Enterobacteriaceae to \(<10^3\) cfu/mL urine (possible eradication) or, in the case of pretreatment urine being \(>10^5\) cfu/mL, a reduction to \(\leq 10^3\) cfu/mL urine. If not achieved, this was defined as bacteriological failure.

Clinical success was defined when symptom(s) (i.e. dysuria, pollakiuria, suprapubic pain and/or fever) reported prior to the treatment disappeared after the treatment. If still present, this was defined as clinical failure.

Relapse was defined when the first control urine sample(s) showed bacteriological cure, but a later sample showed significant growth of the ESBL-producing Enterobacteriaceae, in the interval 10 - 20 days after completion of antimicrobial therapy.

### Laboratory investigations

Urine samples were processed according to laboratory routine and susceptibility tested according to EUCAST guidelines;\(^1\) at each department. The criteria for UTI were for Escherichia coli and Klebsiella pneumoniae, \(>10^3\) and \(\geq 10^5\) cfu/mL, respectively. The only differences in the methods between the two laboratories were the use of cefpodoxime discs at Hvidovre and cefadroxil discs at Halland for ESBL screening, and validation of ESBLs was performed with the MAST Test (Mast Group Ltd, UK) at Hvidovre and with AST-N218 Vitek 2 Compact (bioMérieux, Marcy-l’Étoile, France) at Halland.

### Results

A total of 39 patients (32 women) were included in this study. Of these, 30 received 400 mg and 9 received 200 mg of pivmecillinam three times a day. Ten were from hospital care and 29 were from primary care. The mean age was 63 years (range 19 - 97 years) (mean of 73 years in the 400 mg group and 52 years in the 200 mg group). Twenty of 26 (77%) patients had suffered from UTIs the preceding year. Three of 33 (9%) patients were reported to have an indwelling urinary catheter; of these, two had a bacteriological failure. No patient was reported to use intermittent catheters. Ten of 25 (40%) patients were reported to have a pathological urinary tract (e.g. nephrolithiasis and benign prostate hypertrophy); of these, 4 had bacteriological failures. Sixteen of 20 (80%) patients had a positive urine dipstick for leucocyte esterase in their pretreatment urine; of these, 12 (75%) had \(\geq 10^5\) cfu/mL urine. In 31 patients, therapy was reported with full adherence, while two patients (6%) reported non-adherence (i.e. did not take all tablets); however, both demonstrated bacteriological cure. Only 3 of 24 patients (13%) reported side effects (diarrhoea, stomach pain and vaginal dryness, respectively) (see Table S1, available as Supplementary data at JAC Online).

Susceptibility testing of the pretreatment isolates of ESBL-producing Enterobacteriaceae, 34 (87%) E. coli and 5 (13%) K. pneumoniae, showed the following susceptibility frequencies: meccillinam, 39/39 (100%); ampicillin, 0/30 (0%); trimethoprim, 12/36 (33%); sulphonamide, 11/28 (39%); nitrofurantoin, 37/39 (95%); and ciprofloxacin, 6/39 (15%).

The bacteriological effect is reported in Tables 1 and 2. The cumulative bacteriological cure for pivmecillinam (i.e. 400 or 200 mg, three times a day) was 79% (31/39). The bacteriological cure for 400 and 200 mg three times a day was 80% (24/30) and 78% (7/9), respectively. Of the eight patients with bacteriological failure, five were reported to have an indwelling urinary catheter, pathological urinary tract and/or recurrent UTIs. Two who received 200 mg and one who received 400 mg three times daily, with bacteriological cure, still had a positive urine sample (i.e. \(\geq 10^5\) cfu/mL), but with a significant reduction (i.e. pretreatment urine of \(\geq 10^5\) cfu/mL). If, however, these patients were considered as bacteriological failures, the bacteriological cure rate for 400 and 200 mg three times daily would be 77% (23/30) and 56% (5/9), respectively.

### Table 1. Bacteriological cure in relation to pivmecillinam treatment dose and duration

<table>
<thead>
<tr>
<th>Duration</th>
<th>Total</th>
<th>Yes</th>
<th>No</th>
<th>Cure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 days</td>
<td>2</td>
<td>2</td>
<td>—</td>
<td>100</td>
</tr>
<tr>
<td>5 days</td>
<td>12</td>
<td>11</td>
<td>1</td>
<td>92</td>
</tr>
<tr>
<td>6 days</td>
<td>11</td>
<td>7</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>7 days</td>
<td>10</td>
<td>8</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>&gt;10 days</td>
<td>3</td>
<td>3</td>
<td>—</td>
<td>100</td>
</tr>
<tr>
<td>unknown(^a)</td>
<td>1</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Dose</th>
<th>Total</th>
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<th>No</th>
<th>Cure (%)</th>
</tr>
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<tbody>
<tr>
<td>200 mg</td>
<td>9</td>
<td>7</td>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>400 mg</td>
<td>30</td>
<td>24</td>
<td>6</td>
<td>80</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>31</td>
<td>8</td>
<td>79</td>
</tr>
</tbody>
</table>

\(^a\)The duration of treatment was not recorded for one patient.

### Table 2. Bacteriological cure in relation to cfu/mL in the pretreatment urine sample

<table>
<thead>
<tr>
<th>cfu/mL</th>
<th>Total</th>
<th>Yes</th>
<th>No</th>
<th>Cure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\geq 10^3)</td>
<td>4</td>
<td>4</td>
<td>—</td>
<td>100</td>
</tr>
<tr>
<td>(\geq 10^4)</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>(\geq 10^5)</td>
<td>30</td>
<td>23</td>
<td>7</td>
<td>77</td>
</tr>
<tr>
<td>Unknown(^a)</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>31</td>
<td>8</td>
<td>79</td>
</tr>
</tbody>
</table>

\(^a\)The initial cfu/mL was not recorded for one patient.
Patients with $\geq 10^3$ cfu/mL ($n=4$) and $\geq 10^4$ cfu/mL ($n=4$) in pretreatment urine experienced a 100% and 75% bacteriological cure rate, respectively, with no reports of clinical failure. In patients with $\geq 10^5$ cfu/mL in pretreatment urine, 77% had bacteriological cure (23/30), including the three reports of clinical failure (Table 2).

The cumulative clinical success rate of pivmecillinam after 400 or 200 mg three times daily was 84%; however, it could only be evaluated in 19 patients. Of the eight patients with missing bacteriological cure, four reported clinical success and none reported clinical failure. Of the patients with bacteriological cure, 12 reported clinical success and 3 reported clinical failure.

For 23 of the 31 patients with previous bacteriological cure, it was possible to evaluate for relapse, demonstrating a relapse rate of 22% (5/23).

The five patients with ESBL-producing K. pneumoniae demonstrated complete bacteriological cure and all three with evaluable clinical effect reported successful treatment. However, two demonstrated later bacteriological relapse (Table S1).

**Discussion**

In the present study, we demonstrated that treatment with pivmecillinam (i.e. 400 or 200 mg three times a day) leads to a bacteriological cure rate of 79% (31/39) with a clinical effect of 84% (16/19), when the pathogens show in vitro susceptibility (100%). We could not detect any difference in outcome between 200 and 400 mg three times a day, but the low number of patients in the former group precludes a sound conclusion. In the eight patients with bacteriological failure, five patients had risk factors for failing treatment. The bacteriological cure in 31 of 39 cases in our study was substantially higher than that reported by Titelman et al. 5.2% (i.e. two of eight cases). This may indicate that the 400 mg dose three times a day is a more effective.

The availability and use of pivmecillinam have been limited to only a few countries. However, the widespread and long-term use of pivmecillinam for UTIs in Scandinavian countries is well documented, with no indication of any significant increase in mecillinam resistance in these countries and, to our present knowledge, there are no indications that the use of pivmecillinam as monotherapy has given rise to mecillinam resistance.

Two cases with failed monotherapy of pivmecillinam were successfully treated with pivmecillinam combined with amoxicillin/ clavulanate. This option should be tested in clinical studies of complicated UTI caused by ESBL-producing E. coli.

Newer studies have documented good in vitro activity8–7 as well as a good bacteriological and clinical effect of fosfomycin and nitrofurantoin against uncomplicated UTIs caused by ESBL-producing Enterobacteriaceae.16–17 However, nitrofurantoin can cause serious adverse effects, notably in elderly patients,18 and has been shown to be less effective against Proteus mirabilis and K. pneumoniae.19,20

In conclusion, this is, to our knowledge, the first study of pivmecillinam treatment in a reasonably large cohort of patients with lower UTI caused by ESBL-producing E. coli or K. pneumoniae. We propose a dose of 400 mg three times a day, which seems to be effective and safe, and proves the beneficial effectiveness of pivmecillinam against these pathogens in concordance with the high in vitro activity.

**Acknowledgements**

The data were presented at the Fifty-third Interscience Conference on Antimicrobial Agents and Chemotherapy, Denver, CO, USA, 2013 (Abstract L-1332).

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**Transparency declarations**

None to declare.

**Author contributions**

F. J. helped to develop the study design, wrote the questionnaires, conducted the acquisition of data and drafted the article with analysis and interpretation of data. N. F.-M. proposed the original idea of the study, helped to develop the study design and acted as mentor throughout the process of the study, revising the analysis, interpretation of data and manuscript. I. S. helped with acquisition of data in Sweden and drafting the diagnostic methods used in Sweden. J. D. K. helped to develop the study design, drafting the diagnostic methods used in Denmark and acted as supervisor for F. J. throughout the process of the study, revising the analysis, interpretation of data and manuscript.

**Supplementary data**

The three questionnaires and Table S1 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

**References**


