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Research Article

Pivmecillinam Treatment of Community-Acquired Uncomplicated Pyelonephritis Based on Sparse Data

Abstract

Background: Pivmecillinam has good pharmacokinetic properties for treatment of infections in the urinary tract, and the mecillinam resistance rate in Enterobacteriaceae is very low. In a European guideline pivmecillinam is recommended as a first-line drug for treatment of lower urinary tract infections. In Danish and Norwegian guidelines pivmecillinam is also recommended for acute uncomplicated pyelonephritis, although with very sparse documentation of effect.

Objectives: We intended to investigate the therapeutic outcome of pivmecillinam treatment of uncomplicated pyelonephritis caused by Enterobacteriaceae treated by general practitioners (GP's) in primary care.

Material and methods: We included patients clinically diagnosed with pyelonephritis at the GP, urine samples positive for Enterobacteriaceae and empirical treatment with pivmecillinam. We intended to include patients prospectively, but due to slow inclusion we also included patients retrospectively. The prospectively included patients were asked to fill out a questionnaire and submit control urine samples. The retrospectively included patients were followed by available urine samples and the text on the requisition only. The patients were followed by their urine samples for three months.

Results: We identified 22 patients (*i.e.* six patients prospectively and found another 16 patients retrospectively). Bacterial and clinical cure rate was 77% (95%c.i.: 60-95%), respectively. In seven (32%) of the patients, we observed a recurrent or new infection within three months.

Conclusion: There is indication for safe oral treatment with pivmecillinam in uncomplicated pyelonephritis caused by a mecillinam susceptible *E. coli*. More studies and especially prospective and randomized clinical studies are needed before pivmecillinam can be recommended as first line option for treatment of pyelonephritis.

Introduction

Pivmecillinam is one of the first-line options in a European guideline for treatment of lower urinary tract infections (LUTI) [1]. In Denmark and Norway it is also recommended for 7-14 days as an oral treatment for acute pyelonephritis without signs of urosepsis [2-4]. *Escherichia coli* (*E. coli*) is the major pathogen in both LUTIs and pyelonephritis [5]. Pivmecillinam has especially good in-vitro activity against uropathogenic *E. coli* with or without production of extended-spectrum beta-lactamase (ESBL) [6-8]. Recent studies have shown that pivmecillinam in 400 mg three times daily for five days have clinical and bacteriological effect in LUTIs caused by ESBL producing *E. coli* [9,10]. The long-term use of pivmecillinam in the Nordic countries has shown it to be safe and effective in the treatment of LUTI, with continuously low rates of mecillinam resistance [11-13]. Danish physicians have for several years adapted the regular use of pivmecillinam in treatment of acute pyelonephritis, as 400 mg three times daily for 14 days [2,4].

To our knowledge there are only few small clinical studies published on the effect of mono- or concomitant therapy with pivmecillinam for pyelonephritis [14,15]. Randomized clinical controlled studies are much needed before pivmecillinam can be widely recommended in everyday clinical practice. Prior to any larger comparison studies, we performed an observational study in order to investigate the prevalence of acute uncomplicated pyelonephritis (AUP) treated in Danish primary care and the clinical and microbiological outcome of such infections treated with pivmecillinam.

Material and Methods

The Department of Clinical Microbiology (DCM), Hvidovre Hospital, serves five hospitals and more than 700 General Practitioners (GPs) based on a population of app. 900,000 inhabitants. The DCM receives urine samples both from hospital departments and GP´s. All urine samples are processed according to laboratory routine and susceptibility tested according to EUCAST guidelines [16]. Significant bacteriuria is defined as growth of > 10^3 bacteria/ml urine for *E. coli*, and as > 10^4 bacteria/ml urine for other Enterobacteriaceae.

A prospective observational study was planned for 30 patients. During a nine months' time period (September 2014 to May 2015) we asked the GP's in the catchments area of the DCM to report, by an electronic prompt on the electronic requisition for analyses,

when an urine sample was collected from an adult patient with AUP, and to state the antibiotic therapy initiated after the urine sample was collected. These patients received two self-urine sample kits for control samples and questionnaires for the clinical effect.

As patient-inclusion was slow, we decided to supplement with a retrospective study. In the retrospective analysis we used the laboratory database to identify the patients, and to analyze the bacteriological effect, *i.e.* further urine samples were scrutinized for growth of relevant bacteria. However, we could not, in all cases, see if the new or a second urine sample were collected as a control of treatment or because of new symptoms. If no urine samples were sent for analyses after the initial AUP sample from a surviving patient, it was considered as satisfactorily clinical outcome.

Bacteriological cure in the prospectively included patients was defined as urine samples with no, non-significant growth (5), or significant reduction of growth by a factor 100 of Enterobacteriaceae. Bacteriological failure or recurrent infection was defined as significant growth of uropathogenic bacteria in the control urine samples within 28 days, or between 28 days and 3 months, respectively. Probable bacteriological cure was defined as no urine samples or negative urine sample less than seven days after the antibiotic therapy was initiated.

Clinical cure was defined as resolution of AUP symptoms reported by patients or by the GP (retrospectively, by requisition form on new urine sample). Clinical failure was defined as a non-reduction of symptoms reported by patient or GP (retrospective, by requisition form on new urine sample). Clinical relapse was defined as symptoms of AUP reported by the patient, or new urine sample with symptoms of AUP (retrospectively, reported on by GP on requisition form). Probable clinical cure or relapse was defined as non-availability or negative control urine sample, or significant growth in new urine sample, respectively.

The patient with an *E. coli* resistant to mecillinam, with relapse, was considered probable clinical and bacteriological failure.

The study was approved by the local Ethical Committee (H-4-2014-071), and the Danish Data Protection Agency (2012-58-0004).

Results and Discussion

Over a period of nine months, we could identify 22 patients empirically treated with pivmecillinam for AUP, with urine samples positive for Enterobacteriaceae (Table 1). Six patients were followed prospectively and 16 patients were analysed retrospectively. Three patients were male, 19 were females. The median age was 46 years (range 21-83).

Table 1: Urine samples - Species CFU/ml (MEC-S/R) Comments.

Patient nr.	Age[1]-Sex	Pre-treatment – Species CFU/ml (MEC-S/R)	Control urine 1 ($\leq$28 days)	Bacterial cure[2]	Control urine 2 28-90 days	Re-/New- infection	Clinical cure (i.e. no failure or relapse)
Prospective							
1	33-F	*E. coli* 10^5 (S)	0	Yes	*E. coli* 10^3 (S)	Reinfection (ABU[5])	Clinical cure (*i.e.* patient diary)
2	51-F	*E. coli* 10^5 (S)	0	Yes	0x2	No	Clinical cure (*i.e.* patient diary)
3	25-F	*E. coli* 10^5 (S)	0x2	Yes	0	No	Clinical cure (*i.e.* patient diary)
4	69-F	*K. pneumiae* 10^5 (S)	0 (2 days)	Probably yes	No data	Probably no	Probably clinical cure[5]
5	23-F	*E. coli* 10^3 (S)	0	Yes	No data	Probably no	Probably clinical cure[5]
6	78-F	*E. coli* 10^5 (S)	0x2	Yes	0	No	Probably clinical cure[5]
Retrospective							
7	46-F	*E. coli* 10^5 (R)	No data	Probably no	*E. coli* 10^5 (R)	Recurrent	Probably no clinical cure[5]
8	39-F	*E. coli* 10^4 (S)	No data	Probably yes	*S. agalactiae* 10^3	New infection	Probably clinical cure[5]
9	28-F	*E. coli* 10^4 (R)	*E. coli* 10^3 (S)	No (ABU[5])	ND	Probably no	Clinical cure according to general practitioner
10	55-F	*E. coli* – 10^4 (S)	No data	Probably yes	No data	Probably no	Probably clinical cure[5]
11	20-F	*E. coli* 10^5 (S)	No data	Probably yes	*E. coli* 10^5 (R)	Recurrent	Clinical relapse according to treating physician
12	33-F	*E. coli* 10^5 (S)	No data	Probably yes	No data	Probably no	Probably clinical cure[5]
13	46-F[3]	*E. coli* 10^5 (S)	*E. coli* 10^5 (S)	No	*E. coli* 10^5 (S)	Recurrent	Probably no clinical cure[5]
14	32-F	*E. coli* 10^5 (S)	0 (2 days)	Probably yes	No data	Probably no	Probably clinical cure[5]
15	83-F[3]	*E. coli* 10^5 (S)	*E. coli* 10^5 (S)	No	*E. coli* 10^5 (S)	Recurrent	Probably no clinical cure[5]
16	60-F	*E. coli* 10^5 (S)	No data	Probably yes	No data	Probably no	Probably clinical cure[5]
17	58-M[3]	*E. coli* 10^5 (S)	*E. coli* 10^5 (S)	No	Several	Recurrent	Probably no clinical cure[5]
18	44-F	*E. coli* 10^4 (S)	No data	Probably yes	No data	Probably no	Probably clinical cure
19	61-M	*E. coli* 10^4 (S)	0	Yes	No data	Probably no	Probably clinical cure[5]
20	76-M	*E. coli* 10^5 (S)	No data	Probably yes	No data	Probably no	Probably clinical cure[5]
21	21-F	*E. coli* 10^4 (S)	No data	Probably yes	No data	Probably no	Probably clinical cure[5]
22	61-F	*E. coli* (ESBL) 10^5 (S)	0	Yes	No data	Probably no	Probably clinical cure[5]

[1]Median age: 46;
[2]Only yes if the urine sample was taken > 7 days from the pre-treatment urine sample.
[3]Mulitple urine samples both prior and after this episode of pyelonephritis.
[4]Asymptomatic bacteriuria
[5]No clinical data
"Probably" is used when we do not have data but have drawn a theoretical conclusion on the outcome (see article for more detailed description).

In the prospective observational study, six patients with diagnosed pyelonephritis caused in five cases by *E. coli*, and in one by *Klebsiella pneumoniae*. All six bacterial isolates were susceptible to mecillinam. All six patients experienced bacteriological and clinical cure, and no relapses were seen in these cases.

In the retrospective analysis, 16 patients were included with AUP all caused by *E. coli*. In two cases the *E. coli* isolate was mecillinam resistant and one of these experienced bacteriological re-infection and feasible clinical relapse. In the other case we found bacteriological failure, but the GP reported clinical cure.

Five patients were either men (N=3) or older than 70 years (N=3). Arguably, by definition [5] these patients should probably not have been considered to be uncomplicated pyelonephritis, but were nonetheless treated with oral pivmecillinam by their GP. Two of these cases (one man) experienced treatment failure and both had several positive urine samples both before and after the investigated episode.

Two patients were admitted to hospital after the urine sample was collected, however, with no indication of treatment failure. In two cases the *E.coli* were resistant to mecillinam, with unsuccessful bacteriological outcome in both, but one with reported clinical cure. One patient had an ESBL producing *E. coli* (susceptible to mecillinam), and had a negative control urine sample. This is also in accordance with a report from Nicolle et al. who reported a patient, successfully treated with mecillinam for relapsing pyelonephritis caused by ESBL producing *E. coli* [15].

Cumulatively, the indicated bacteriological and clinical cure was 77 % (95%c.i.: 60-95%), respectively, Table 2. In seven of the patients, we observed a relapse or new infection, 32% (95%c.i.: 12-51%).

We are unable from the present study to calculate an actual prevalence-rate of AUP in primary care, since we have little information on how many of such patients were seen by GP´s and not reported to us. And some patients with AUP may not be recognized as such by the GP. Anyway, with 22 cases only found over a 9-month period in our catchment area, the prevalence of AUP treated in primary care seems to be low.

Although pivmecillinam in Europe only is recommended as a first line choice against LUTI, Danish physicians have for several years used pivmecillinam in treatment of acute pyelonephritis [2,4]. There are only few publications on the outcome of treatment of pyelonephritis with pivmecillinam; In one study, 600 mg mecillinam intravenously followed by 400 mg pivmecillinam orally twice daily, concomitant with ampicillin treatment, demonstrated a 63% cure rate for pyelonephritis, which was similar to the comparative cephalosporin [14].

Of other oral antibiotics tried for treatment of AUP, cephalosporines, trimethoprim/sulphamethoxazole and fluoroquinolones have shown more or less the same clinical and bacteriological effect as pivmecillinam in this study [17-20]. For all these antibiotics bacterial resistance is becoming a problem in many parts of the world [7] and since no new antibiotics are appearing especially with activity against Enterobacteriaceae, it is crucial to re-vitalize old effective antibiotics such as pivmecillinam.

Table 2: The cumulative outcome for 22 patients with acute uncomplicated pyelonephritis.

	Yes	No	Probable Yes	Probable No	Outcome
Clinical cure total	**4**	**1**	**13**	**4**	**77% (95%c.i.: 60-95%) clinical cure**
Women	4	1	11	3	79% (95%c.i.: 61-97%) clinical cure
Men	0	0	2	1	67% (95%c.i.: 13-120%) clinical cure
Bacteriological cure total	**7**	**4**	**10**	**1**	**77 % (95%c.i.: 60-95%) bacteriological cure**
Women	6	3	9	1	79% (95%c.i.: 61-97%) bacteriological cure
Men	1	1	1	0	67% (95%c.i.: 13-120%) bacteriological cure
Recurrent infection total	**7**	**3**	**0**	**12**	**32% (95%c.i.: 12-51%) re/new infection**
Women	6	3	0	10	32% (95%c.i.: 11-52%) re/new infection
Men	1	0	0	2	33% (95%c.i.: -20-87%) re/new infection

There are many limitations in our study (only six patients were included in the initial prospective study and further 16 patients in the retrospective study). However, since there (to our knowledge) are no clinical studies on the effect of pivmecillinam as mono-therapy for AUP, we believe that our results can be of interest as a possible supplementary oral treatment option for outpatients with AUP in times with increasing resistance against common urinary antibiotics. Still, we believe a randomized comparative clinical study is needed before a general recommendation can be made.

Acknowledgments

Contribution

FJ came up with the idea of the study, developed the study design, conducted the acquisition of data and drafted the article. FBH helped with the above mentioned processes. JDK is the primary mentor in the study, helped with the above mentioned processes, revised the analysis and interpretation of the data and manuscript. NFM helped develop the idea, revised the analysis and interpretation of the data and manuscript.

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