Emerging clinical role of pivmecillinam in the treatment of urinary tract infection in the context of multidrug-resistant bacteria

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The continuing spread of resistant Gram-negative bacteria is a therapeutic challenge and prudent use of antimicrobials is therefore essential. Urinary tract infections (UTIs), usually due to Gram-negative bacteria, are among the most common infections seen in the community. Moreover, bacterial strains producing extended-spectrum b-lactamases (ESBLs) that are resistant not only to cephalosporins and penicillins, but also to fluoroquinolones and trimethoprim, are becoming more prevalent in the community. This means that oral antibiotic options to treat these infections are limited. The discovery of new drugs to tackle these problems has been difficult and slow paced; it is therefore timely to 'rediscover' the current antibiotics we have available in our clinical formulary, to determine how best they can be used. Pivmecillinam is an oral antibiotic with excellent clinical efficacy in the treatment of uncomplicated UTIs. It has been used extensively in Nordic countries with few problems, but, despite this, it is not widely used in other countries. There is emerging in vitro and in vivo evidence of its activity against ESBL-producing organisms and its synergistic potential with b-lactamase inhibitors. Pivmecillinam is well tolerated with a low side-effect profile. Pivmecillinam also has a minimal effect on the intestinal and vaginal flora of the host; thus, there is a lower rate of selection of resistant bacteria, vaginal candidiasis and, of note, Clostridium difficile.

Keywords: UTIs, ESBLs, antimicrobial therapy, Gram-negative

Introduction

With the emergence of multidrug-resistant bacteria and the antibacterial drug discovery pipeline currently running dry, it is timely to re-evaluate the antibiotics we have available in our clinical formulary, to determine how best they can be used. Urinary tract infections (UTIs) are among the most common infectious diseases, both in the community and in the hospital setting. UTIs are commonly caused by Gram-negative bacteria and it is the increasing spread of resistant Gram-negative bacteria producing extended-spectrum b-lactamases (ESBLs) that is a particular therapeutic challenge. Many ESBL producers from community patients are resistant not only to cephalosporins and penicillins, but also to fluoroquinolones and trimethoprim, underscoring the need to discover new oral antimicrobial agents to combat this emerging problem.2–4 Until new agents become available, it is prudent to ‘rediscover’ agents in our current clinical formulary that have traditionally been ignored.

Pivmecillinam is an oral antibiotic, discovered in the 1970s, that has excellent clinical efficacy for the treatment of uncomplicated UTIs.5,6 It has numerous advantages when compared with other b-lactams (Figure 1), and based on long-term clinical experience from Nordic countries, it has proven bacteriological and clinical efficacy against Gram-negative organisms responsible for UTIs. Despite this, pivmecillinam is not widely used in countries outside of Scandinavia, especially in the UK, where it does not appear in any UK guidelines for the treatment of UTIs.7–9

Pivmecillinam has excellent activity against Gram-negative bacteria and there is also emerging in vitro and in vivo evidence of its activity against ‘ESBL-producing’ organisms. It also shows synergy with b-lactamase inhibitors and combination therapies are currently being evaluated.10,11 With this in mind, this review aims to ‘rediscover’ the role of pivmecillinam in the treatment of UTIs and, moreover, appraise the promising role it can play in the battle against the emergence of multidrug-resistant Gram-negative bacteria.

Chemotherapy profile

Pharmacology

Pivmecillinam is a synthetic penicillin for oral use that was first reported by Lund and Tybring12 in 1972. The molecule is a 6-amopenicillin acid derivative, in which the 6-position substituent is combined with an amidino structure (Figure 2). It is the pivaloyloxyethyl ester of mecillinam and, in contrast to the latter, is absorbed readily from the gastrointestinal tract. After absorption, pivmecillinam undergoes enzymatic hydrolysis by the action of non-specific esterases with liberation of mecillinam, which is the antimicrobially active form of the drug.13 The presence of food in the stomach does not appear to significantly affect its absorption. Peak plasma concentrations of mecillinam averaging 5 mg/L have been reached after 1 h following a dose of 10 mg/kg in children and
• Highly concentrated in the urine
• Well tolerated, can be given in impaired renal function
• β-Lactamase stability—particularly CTX-M-type ESBLs, which are increasingly prevalent community urinary pathogens
• Low risk of widespread clinical resistance developing
• Minimal effect on gut and vaginal flora

Figure 1. Clinical advantages of oral pivmecillinam.

Figure 2. Chemical structures of pivmecillinam and mecillinam.

400 mg in adults.\textsuperscript{13,14} The serum half-life is \~1 h. In animal studies, mecillinam is evenly distributed in body fluids and tissues and produces high concentrations in the kidneys, lungs and liver, but low concentrations in the fetus and breast milk.\textsuperscript{14} About 45% of the dose is excreted as mecillinam in urine within the first 6 h,\textsuperscript{13,14} resulting in urine concentrations \textgtr 200 mg/L.\textsuperscript{15} Mecillinam is also partly excreted in bile, giving rise to biliary concentrations around three times greater than serum levels.\textsuperscript{16} High biliary concentrations may indicate a therapeutic use for pivmecillinam in biliary infection, but no clinical efficacy studies have been completed to support this finding.

The key pharmacokinetic and pharmacodynamic parameters that are linked to the clinical efficacy of pivmecillinam are not known, but are likely to be time above the MIC, similar to other β-lactams. Moreover, the drug has been shown to work as a time-dependent bactericidal agent; this is evident \textit{in vitro} after prolonged incubation of the culture.\textsuperscript{17} Pivmecillinam doses range from 200 mg three times daily to 400 mg twice daily or three times daily, with duration of therapy ranging from 3 to 10 days. All regimens have been reported to have bacteriological cure rates approaching or exceeding 90%, with concomitant clinical cure.\textsuperscript{4} The current manufacturer advice is that in acute uncomplicated cystitis, the initial dose should be 400 mg orally followed by 200 mg three times daily for eight doses (3 days in total). In chronic or recurrent bacteriuria, 400 mg may be given three times daily or four times daily for longer durations.\textsuperscript{18}

\section*{Mode of action}
The precise mode of action of mecillinam has not been fully elucidated. It has been shown that mecillinam interferes with the bacterial cell wall and bacteriological and enzymatic studies have shown that its mode of action differs from that of the penicillins.\textsuperscript{19,20} Mecillinam, unique among β-lactam agents, exerts high specificity against penicillin-binding protein 2 (PBP-2) in the Gram-negative cell wall, unlike the majority of other β-lactam agents, which preferentially bind Gram-negative PBP-1A, -1B or -3.\textsuperscript{21} Synergy has been observed when mecillinam is combined with other β-lactam antibiotics, including ampicillin, amoxicillin, cefuroxime, cefadroxil, cefazolin, ceftriaxone, cefotaxime, cefotixin, ceftazidime and ceftriaxone, against selected isolates of most Enterobacteriaceae.\textsuperscript{17,22–25} Synergy is not always seen when testing \textit{in vitro} or in mouse protection studies. However, against many strains of Enterobacteriaceae, marked synergy is often found. Also, synergy has been observed in cases where the organism is resistant to one of the antibiotics used in the synergistic combination.\textsuperscript{26}

\section*{Spectrum of activity}
Mecillinam shows potent antibacterial activity against Enterobacteriaceae, whereas its activity against other Gram-negative bacteria and also Gram-positive bacteria is relatively low; \textit{Pseudomonas} spp., \textit{Enterococcus faecalis} and \textit{Staphylococcus saprophyticus} are resistant to mecillinam.\textsuperscript{25,27} Because of its low in \textit{vitro} activity against Gram-positive organisms, there were initial concerns regarding its efficacy against \textit{Staphylococcus saprophyticus}, a frequent cause of UTI in women. \textit{In vitro}, mecillinam MICs for \textit{S. saprophyticus} have been reported as 8–64 mg/L,\textsuperscript{28} however, clinical studies have shown cure rates of 73%–92%.\textsuperscript{28–30} The success of therapy likely reflects the very high urinary concentration of mecillinam (>200 mg/L).\textsuperscript{15}

Pivmecillinam does show activity against \textit{Salmonella} spp. and preliminary studies in a limited number of patients suggest that it may be a useful alternative antibiotic in the treatment of acute typhoid fever and in some carriers of \textit{Salmonella}.\textsuperscript{31,32} Efficacy data are limited due to the small number of patients and few clinical studies, so caution is recommended.

\section*{β-Lactamase stability}
Studies conducted some years ago using specific β-lactamase-producing strains reported the ability of mecillinam to resist hydrolysis by β-lactamases and its activity against β-lactamase-producing organisms.\textsuperscript{33–35} In 2000, the activity of mecillinam was assessed against ampicillin-resistant \textit{Escherichia coli} strains producing β-lactamases representing the three molecular classes A (TEM-1 and -3, SHV-3 and IRT-5), C (chromosomally encoded AmpC) and D (OXA-3).\textsuperscript{36} All strains were susceptible to mecillinam, except those producing OXA-3. More recently, \textit{in vitro} studies have also shown that mecillinam has activity against ESBL-producing Enterobacteriaceae.\textsuperscript{37–39} Two recent European studies both investigated the \textit{in vitro} activity of mecillinam against 100 ESBL-producing \textit{E. coli} isolates and found it was active against 90% and 85% of isolates, respectively.\textsuperscript{37,38} However, these studies used standard conditions for determining MICs and a more in-depth evaluation by Thomas et al.\textsuperscript{10} showed an inoculum effect for ESBL-positive organisms, with higher inocula producing higher MICs. Also, MICs for strains producing
CTX-M ESBLs were lower than for those producing TEM and SHV ESBLs, demonstrating a different susceptibility profile dependent on the mutant enzyme. It has also been noted that mecillinam is less efficacious against E. coli carrying the R1 plasmid (which encodes TEM-1 enzyme) than against its plasmid-free counterpart in a murine septicaemia model. Because of mecillinam’s relative activity, Thomas et al. concluded that pivmecillinam may potentially be used for uncomplicated UTIs caused by ESBL producers with low MICs, as high levels of mecillinam are achieved in the urine. In another study investigating the inoculum effect, Livermore et al. showed that even at higher inocula, MICs of mecillinam for CTX-M ESBL-producing organisms were \(< 1\) mg/L. However, as previously shown by Thomas et al., not all ESBL-producing isolates were susceptible to mecillinam, namely those producing SHV-2, -4 and -5. Mecillinam appears to have good activity against some ESBL-positive isolates; however, ESBL instability cannot be dismissed. What is encouraging, though, is that in this study the addition of clavulanic acid reduced the MICs for all ESBL producers to \(< 1\) mg/L, except for the transconjugant producing SHV-4.

There is a current lack of in vivo clinical data on the use of pivmecillinam for the treatment of ESBL-producing organisms. There has been a case report of the successful treatment of relapsing pyelonephritis caused by CTX-M ESBL-producing E. coli with long-term pivmecillinam. This would correlate with mecillinam having better in vitro activity against the CTX-M ESBL group. A small case-control study \((n = 17)\) showed that pivmecillinam had good clinical activity against lower UTIs caused by ESBL-producing Enterobacteriaceae, but bacteriological cure rates were low. However, half of the patients in the study had functional or structural abnormalities of the genitourinary tract and are therefore less likely to achieve bacterial eradication. This could account for the persistent bacteriuria post-treatment. All patients receiving pivmecillinam had good clinical response and none of the patients with persistent bacteriuria had a relapse of UTI symptoms within 6 months. Indeed, the lower bacteriological cure rates with \(\beta\)-lactam agents are often not considered of relevant clinical importance in complicated UTI and the advantages of using pivmecillinam in terms of lower rates of resistance developing and good clinical tolerance counterbalance this potential concern. Again, most isolates in the study belonged to the CTX-M ESBL group.

The therapeutic potential of pivmecillinam against bacteria producing CTX-M ESBLs appears promising. Before 2003, most ESBLs seen were mutants of TEM and SHV penicillinas; however, recently there has been a growing problem of CTX-M ESBLs and many of these strains occur in the community. Most CTX-M ESBL producers are not only resistant to \(\beta\)-lactam agents, but also to non-\(\beta\)-lactam agents such as gentamicin, fluoroquinolones and trimethoprim due to other coexpressed resistance mechanisms. If susceptibility testing shows concurrent resistance to trimethoprim and fluoroquinolones, oral options to treat these infections in the community are limited. An oral antibiotic option is very useful for community patients, as this may avoid hospital or outpatient parenteral antibiotic therapy referral for parenteral antibiotics. Most organisms remain susceptible to nitrofurantoin; however, nitrofurantoin has a poor side-effect profile, especially in the elderly, and cannot always be given when the patient has impaired renal function. Fosfomycin is another alternative. There are no studies that directly compare the efficacy of fosfomycin and pivmecillinam in the treatment of UTIs caused by organisms producing CTX-M ESBLs, although surveillance studies show similar low rates of resistance in urinary tract pathogens. Unfortunately, in some countries (for example the UK) fosfomycin does not hold a marketing licence. This means that it is subject to the caution and regulation of an unlicensed medicine in these areas, which may limit its use. This is compared with pivmecillinam, which is widely licensed and therefore can be used without restrictions. Pivmecillinam, therefore, is a well-tolerated available oral option to treat UTIs in the community.

Synergy in vitro and in vivo

The high affinity of pivmecillinam for PBP-2 appears to be associated with synergy when combined with \(\beta\)-lactams. Marked in vitro synergy has been found with other \(\beta\)-lactam agents against most Enterobacteriaceae isolates. Also, in animal models, mecillinam and ampicillin act synergistically against infections with most Enterobacteriaceae in vivo. Clinical studies have compared pivmecillinam with a pivmecillinam/pivampicillin combination in the treatment of complicated UTIs, with combination therapy being more successful. Pivampicillin is not available today due its adverse effect in depleting carnitine levels. Combination mecillinam and cefotixin therapy was efficacious for the treatment of complicated UTI caused by multidrug-resistant Serratia marcescens strains. Mecillinam-resistant strains of Enterobacteriaceae have been found and earlier work suggested this could be correlated with the production of \(\beta\)-lactamases. However, these organisms appear to be synergistically inhibited by addition of a \(\beta\)-lactamase inhibitor such as clavulanic acid or sulbactam. Indeed, in vitro synergy between mecillinam and clavulanic acid has been found in AmpC- and ESBL-producing Enterobacteriaceae. Resistant isolates with AmpC activity and classical TEM activity have been shown to become susceptible to mecillinam when clavulanic acid has been added. Also, the addition of clavulanic acid reduced the MICs of mecillinam for the ESBL producers tested, with the exception of those producing SHV-4.

The simultaneous administration of pivmecillinam with antibiotics that have activity against \(\beta\)-lactamases, such as co-amoxiclav, in the treatment of resistant Enterobacteriaceae appears a promising avenue for future research. Combinations of agents containing clavulanic acid with other extended-spectrum oral antibiotics that resist hydrolysis by common \(\beta\)-lactamases, such as cefixime or cefpodoxime, have been tested and reportedly used to treat UTIs caused by CTX-M ESBL-producing E. coli. These combinations are currently not licensed and reports of such use in the literature are rare. However, the combination of antimicrobials with synergistic activity against \(\beta\)-lactamases is theoretically sound. Indeed, the combination of mecillinam, a compound with moderate stability to both ESBLs and AmpC enzymes, with clavulanic acid, which is known to increase mecillinam’s activity against ESBL/AmpC producers, has ample potential to merit further evaluation.

Effect on microflora

The antibiotic treatment of UTIs should be effective and not cause major disturbances of the host’s microflora, which can lead to overgrowth of resistant bacteria and the induction of Clostridium difficile. Pivmecillinam is a prodrug that is very well absorbed intestinally and, as such, has a minimal effect on the ecological balance of the normal intestinal microflora. An early epidemiological study in the


1970s suggested that pivmecillinam does not cause any selection of resistant Enterobacteriaceae in the intestinal flora.56 More recently, Sullivan et al.56 studied the impact of pivmecillinam treatment on the intestinal microflora. Fifteen individuals were treated for 7 days with 400 mg of pivmecillinam twice daily and then again 14 and 21 days after the start of administration. There was a decrease in the numbers of E. coli, but no changes occurred in the anaerobic microflora.56 Other β-lactam antibiotics such as amoxicillin have been shown to lead to bacterial overgrowth of resistant Enterobacteriaceae, but this appears not to occur with pivmecillinam.57 What is most encouraging is that in an in vitro human gut model, meccillinam did not elicit C. difficile germination, proliferation or toxin production; therefore, pivmecillinam appears a low-risk agent for the induction of C. difficile infection.58 Of note, with technological advancement, metagenomic analysis could help determine the true effect of pivmecillinam on the microbial biodiversity of the human gut.

Pivmecillinam has been shown to have a minor ecological impact on the normal vaginal microflora.59 Maintaining healthy vaginal flora, primarily Lactobacillus spp., plays a key role in protecting women from developing UTI.60 Similar changes in the vaginal microflora have been observed in women with recurrent UTI following treatment with norfloxacin or pivmecillinam,61 however, treatment with norfloxacin has a 3-fold increased risk of developing vaginal candidiasis compared with pivmecillinam,62 suggesting that pivmecillinam has a lower incidence of symptomatic Candida infection.

Clinical guidelines and efficacy

The use of pivmecillinam as treatment for uncomplicated UTIs is recommended by the Infectious Diseases Society of America, the European Society for Clinical Microbiology and Infectious Diseases and also the European Association of Urology.63,64 Long-term clinical experience from Nordic countries supports its clinical efficacy. Between 20% and 30% of prescriptions for acute cystitis in Denmark, Sweden and Norway are for pivmecillinam. In Sweden, prescriptions of pivmecillinam for community-acquired UTIs increased significantly from 2002 (31%) to 2005 (51%), while subsequently prescriptions of trimethoprim decreased from 38% to 20%, respectively.65 Despite its widespread use, few problems in efficacy or concerns about adverse events have been reported and clinically significant resistance to pivmecillinam has not developed. This is evident from recent large epidemiological international studies. The 2003 ECO-SSENS Project in 16 European countries and Canada found resistance to range from 1.2% (E. coli) to 5.2% (Klebsiella spp.).66 The recent Antimicrobial Resistance Epidemiological Survey on Cystitis study found that pivmecillinam was one of the most active drugs (95.8%) against E. coli.67 A large Portuguese 10 year surveillance study of community-acquired UTIs calculated 16% resistance to pivmecillinam among all urinary pathogens. This ‘pondered’ resistance was based on the incidence and values of drug resistance of each bacterium in the study.68

Currently, pivmecillinam alone is the available therapeutic option to treat uncomplicated UTIs caused by ESBL producers. Pivmecillinam has been shown to have low MICs for some producers (e.g. those with CTX-M ESBLs) and high levels of meccillinam are achieved in the urine. However, in vitro data suggest that combinations with a β-lactamase inhibitor (e.g. clavulanic acid) are likely to result in a better susceptibility profile for a wider range of ESBL producers. There is a lack of both in vitro and in vivo data concerning the activity of pivmecillinam against AmpC-producing Enterobacteriaceae, but, again, combination with clavulanic acid appears promising.

To provide a more robust account of the activity of pivmecillinam against multidrug-resistant Gram-negative organisms further in vitro studies that test meccillinam against an extensive library of ESBL/AmpC-producing strains would be desirable. These studies should also include information regarding synergy with β-lactamase inhibitors. Using this in vitro data, clinical efficacy studies could be tried, not only with pivmecillinam, but also pivmecillinam with synergistic β-lactamase inhibitor combinations. As pivmecillinam is no longer protected by patent law, public funding bodies would have to support this clinical research.

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