Poster 1678

Activity of Mecillinam Against Urinary Tract Clinical Isolates from the United States During 2017-2020 Including Isolates Resistant to Comparator Antibiotics and Multi-Drug Resistant Isolates

S. Hawser[1], I. N. Kothari[1], F. Monti[1], A. Santerre Henriksen[2,3]

[1]IHMA, Monthey, Switzerland, [2]Maxel Consulting ApS, Jyllinge, Denmark, [3]UTILITY Therapeutics Ltd., Altrincham, United Kingdom

IHMA
Rte. de l'Ile-au-Bois 1A,
Monthey 1870 Switzerland
www.ihma.com

INTRODUCTION

Mecillinam is a unique amidinopenicillin antibiotic, being the first and the only compound in its class. In contrast to other beta-lactams, it has a unique mechanism of action whereby it exerts its antibacterial activity through binding to penicillin binding protein 2. Pivmecillinam is the oral-prodrug of mecillinam and recommended as a first line therapy in the Infectious Disease Society of America (IDSA) guidelines for uncomplicated urinary tract infections (uUTI). It is approved for use in Europe and included as a first line therapy in multiple guidelines.

In 2018, the U.S. Food and Drug Administration (FDA) designated both mecillinam (injectable) and pivmecillinam (oral prodrug) as Qualified Infectious Disease Products (QIDP) for the indication of complicated urinary tract infections (cUTI) and designated pivmecillinam as a QIDP for the indication of uUTI.

To support the clinical development of mecillinam and pivmecillinam in the USA for the treatment of both cUTI and uUTI this study investigated the activity of mecillinam against Enterobacterales isolates from the USA during 2017-2020.

MATERIALS & METHODS

A total of 3,303 Enterobacterales isolates, enriched with extended-spectrum beta-lactamase (ESBL) screen-positive *Escherichia coli* and *Klebsiella pneumoniae*, from urinary tract infections in the USA were tested. Isolates comprised of the following:

1. Enterobacterales (n = 3,303)
2. Ceftriaxone-resistant Enterobacterales (n = 634)
3. Ciprofloxacin-resistant Enterobacterales (n = 636)
4. Fosfomycin-resistant Enterobacterales (n = 51)
5. Nitrofurantoin-resistant Enterobacterales (n = 399)
6. Trimethoprim/Sulfamethoxazole-resistant Enterobacterales (n = 895)
7. Multi-drug resistant (MDR) Enterobacterales (n = 288)
8. MDR *Escherichia coli* (n = 128)
9. MDR *Klebsiella pneumoniae* (n = 103)

E. coli and *K. pneumoniae* isolates were screened for the presence of ESBLs in using cefotaxime and ceftazidime +/- clavulanic acid in line with CLSI susceptibility testing standards [1].

Agar dilution MIC determinations were performed against all isolates in line with CLSI susceptibility testing methodology [2] and susceptibility interpreted according to CLSI guidelines [1]. For all isolates tested, the mecillinam CLSI *E. coli* breakpoint was used as a surrogate breakpoint for mecillinam susceptibility testing for all Enterobacterales.

RESULTS

Table 1. Activity of Mecillinam and Comparators Against All Enterobacterales

All Isolates (n = 3303)							
Drug	MIC $_{50}$	MIC $_{90}$	MIN	MAX	%S	%I	%R
MEC	0.25	4	≤0.015	> 128	94.9	1.3	3.8
CRO	0.06	> 8	≤0.015	> 8	80.2	0.6	19.2
CIP	0.015	> 8	≤0.002	> 8	78.8	1.9	19.3
FOS	2	32	≤0.06	> 256	97.1	1.4	1.5
NIT	16	128	≤2	> 128	70.3	17.7	12.1
SXT (1:19)	0.12	> 8	≤0.015	> 8	72.9	--	27.1

MEC, mecillinam; CRO, ceftriaxone; CIP, ciprofloxacin; FOS, fosfomycin; NIT, nitrofurantoin; SXT (1:19), trimethoprim / sulfamethoxazole (1:19)

Table 2. Activity of Mecillinam and Comparators Against Resistant Enterobacterales

CIP-R (n = 636)							
Drug	MIC$_{50}$	MIC$_{90}$	MIN	MAX	%S	%I	%R
MEC	0.5	8	≤0.015	> 128	90.9	1.6	7.5
CRO	0.06	> 8	≤0.015	> 8	57.4	0.6	42.0
CIP	> 8	> 8	4	> 8	0.0	0.0	100.0
FOS	1	32	0.25	> 256	95.1	0.9	3.9
NIT	16	128	≤2	> 128	70.6	13.5	15.9
SXT (1:19)	> 8	> 8	≤0.015	> 8	42.7	--	57.3

CRO-R (n = 634)							
Drug	MIC $_{50}$	MIC $_{90}$	MIN	MAX	%S	%I	%R
MEC	0.5	16	0.06	> 128	89.7	1.0	9.3
CRO	> 8	> 8	4	> 8	0.0	0.0	100.0
CIP	1	> 8	0.004	> 8	51.1	6.8	42.1
FOS	4	64	≤0.06	> 256	93.7	1.9	4.4
NIT	32	128	≤2	> 128	54.9	23.6	21.5
SXT (1:19)	> 8	> 8	≤0.015	> 8	45.4	--	54.6

FOS-R (n = 51)							
Drug	MIC $_{50}$	MIC $_{90}$	MIN	MAX	%S	%I	%R
MEC	1	> 128	0.06	> 128	82.4	3.9	13.7
CRO	8	> 8	≤0.015	> 8	45.1	0.0	54.9
CIP	2	> 8	0.004	> 8	43.1	7.8	49.0
FOS	> 256	> 256	256	> 256	0.0	0.0	100.0
NIT	64	> 128	8	> 128	31.4	23.5	45.1
SXT (1:19)	4	> 8	0.03	> 8	49.0	--	51.0

NIT-R (n = 398)							
Drug	MIC $_{50}$	MIC $_{90}$	MIN	MAX	%S	%I	%R
MEC	0.5	32	0.06	> 128	86.7	2.3	11.0
CRO	0.12	> 8	≤0.015	> 8	64.3	1.5	34.1
CIP	0.06	> 8	0.004	> 8	68.6	6.0	25.4
FOS	16	64	≤0.06	> 256	90.5	3.8	5.8
NIT	128	> 128	128	> 128	0.0	0.0	100.0
SXT (1:19)	0.25	> 8	0.03	> 8	67.0	--	32.0

SXT-R (n = 893)							
Drug	MIC$_{50}$	MIC$_{90}$	MIN	MAX	%S	%I	%R
MEC	1	4	≤0.015	> 128	93.7	1.0	5.3
CRO	0.06	> 8	≤0.015	> 8	60.7	0.6	38.8
CIP	1	> 8	0.004	> 8	53.8	5.4	40.8
FOS	2	32	0.25	> 256	95.8	1.3	2.9
NIT	16	128	≤2	> 128	70.5	15.2	14.3
SXT (1:19)	> 8	> 8	4	> 8	0.0	--	100.0

MDR Enterobacterales (n = 288)							
Drug	MIC $_{50}$	MIC $_{90}$	MIN	MAX	%S	%I	%R
MEC	1	> 128	0.12	> 128	79.2	1.0	19.8
CRO	> 8	> 8	<= 0.015	> 8	10.4	0.7	88.9
CIP	> 8	> 8	0.008	> 8	11.1	5.5	83.4
FOS	8	256	0.25	> 256	86.9	2.8	10.3
NIT	64	> 128	<= 2	> 128	42.9	11.8	45.3
SXT	> 8	> 8	0.06	> 8	10.4	0.00	89.6

MDR *E. coli* (n = 128)							
Drug	MIC $_{50}$	MIC $_{90}$	MIN	MAX	%S	%I	%R
MEC	0.5	8	0.12	> 128	92.2	0.8	7.0
CRO	> 8	> 8	0.06	> 8	7.0	0.0	93.0
CIP	> 8	> 8	0.12	> 8	3.1	0.0	96.9
FOS	1	2	0.5	> 256	93.8	1.6	4.6
NIT	16	64	<= 2	> 128	83.6	8.6	7.8
SXT	> 8	> 8	0.06	> 8	3.1	0.0	96.9

MDR *K. pneumoniae* (n = 103)							
Drug	MIC $_{50}$	MIC $_{90}$	MIN	MAX	%S	%I	%R
MEC	2	> 128	0.25	> 128	72.8	1.0	26.2
CRO	> 8	> 8	0.06	> 8	2.9	1.0	96.1
CIP	> 8	> 8	0.015	> 8	12.6	12.6	74.8
FOS	32	> 256	1	> 256	79.6	3.9	16.5
NIT	128	> 128	8	> 128	9.7	12.6	77.7
SXT	> 8	> 8	0.06	> 8	16.5	0.0	83.5

Figure 1. Cumulative MIC Distribution for Mecillinam and Comparators Against MDR Populations

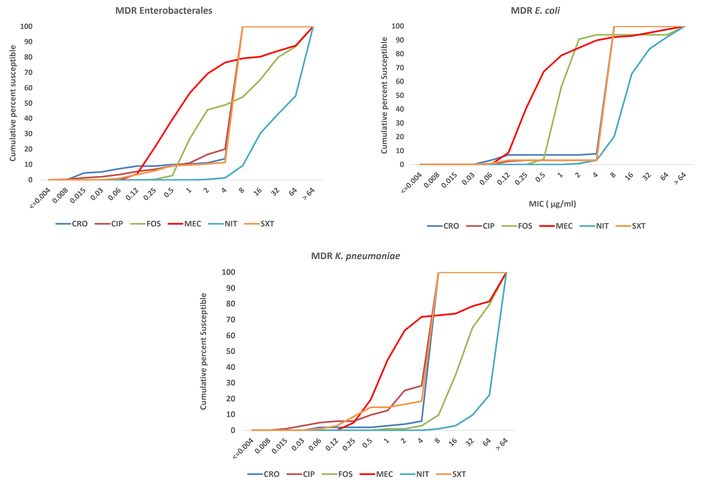
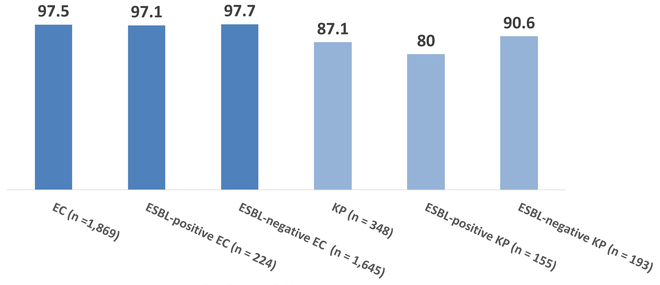


Figure 2. Percent susceptibility of ESBL populations to mecillinam



EC, *E. coli*; KP, *K. pneumoniae*

RESULTS SUMMARY

- Against a selected panel of clinical isolates, mecillinam susceptibility ranged from 72.8% (MDR *K. pneumoniae*) to 94.9% (all Enterobacterales grouped).
- Mecillinam was active against the majority of isolates that were resistant to comparator antibiotics and had percent susceptible values similar to fosfomycin and improved compared with others.
- Mecillinam retained good activity against ESBL-positive *E. coli* unlike ceftriaxone, ciprofloxacin and trimethoprim/sulfamethoxazole. Mecillinam was less active against the ESBL-positive *K. pneumoniae* but maintained ~70% susceptibility, notably greater than other comparators.
- Resistance phenotype had little influence on mecillinam susceptibility which was high even against MDR populations.

CONCLUSIONS

Mecillinam exhibited promising activity against the majority of Enterobacterales tested. The drug was notably active against isolates resistant to antibiotics in routine clinical use and was similarly active against many MDR isolates. The data from our study strongly support the clinical utility of mecillinam and pivmecillinam in the USA for the treatment of cUTI and uUTI.

REFERENCES

1. CLSI, 2022. *Performance Standards for Antimicrobial Susceptibility Testing. 30th ed.* CLSI supplement M100. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA 19087-1898 USA.
2. CLSI, 2018. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. 11th ed.* CLSI Standard - M07. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA 19087-1898 USA.

ACKNOWLEDGMENTS

Funding for this research was supported by a grant from UTILITY Therapeutics Ltd.

Presented at IDWeek 2022, Washington DC, 20-23 October 2022