Poster 1617

Mecillinam Susceptibility against Enterobacterales Isolated from Urinary Tract Infections from US Patients in 2018

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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.

Recently, the U.S. Food and Drug Administration (FDA) has 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 uncomplicated urinary tract infection (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 2018.

MATERIALS & METHODS

A total of 1,090 Enterobacterales isolates, enriched with extended-spectrum β-lactamase (ESBL) screen-positive *Escherichia coli* and *Klebsiella pneumoniae*, from urinary tract infections in the USA were tested. The vast majority of isolates (>99.4%) were from 2018 and a small number (0.6%) of ESBL isolates were from 2017.

Isolates comprised of the following:

1. *Citrobacter freundii* (n = 52)
2. *Enterobacter cloacae* (n = 103)
3. *E. coli* (n = 620), including 78 ESBL-positive isolates
4. *K. aerogenes* (n = 52)
5. *K. oxytoca* (n = 52)
6. *K. pneumoniae* (n = 107), including 53 ESBL-positive isolates
7. *Proteus mirabilis* (n = 104)

E. coli and *K. pneumoniae* isolates were screened for the presence of extended-spectrum beta-lactamases (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] with the exception of mecillinam for which EUCAST breakpoints were used (no CLSI breakpoints currently available for non E. coli) [3].

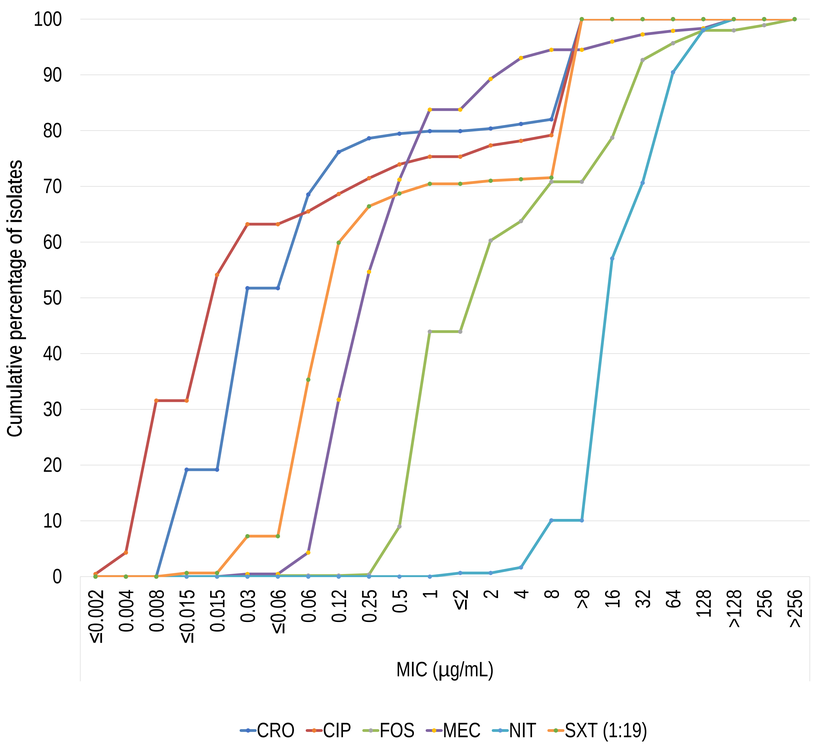
RESULTS

Table 1. Activity of Mecillinam and Comparators Against Enterobacterales

Species (n)	MIC (µg/mL)		Susceptibility			Species (n)	MIC (µg/mL)		Susceptibility		
All (1090)	MIC_{50}	MIC_{90}	%S	%I	%R	*K. aerogenes* (52)	MIC_{50}	MIC_{90}	%S	%I	%R
CRO	0.03	>8	79.9	0.5	19.6	CRO	0.12	>8	76.9	3.8	19.2
CIP	0.015	>8	71.5	2.5	26.1	CIP	0.015	0.06	96.2	0.0	3.8
FOS	2	32	95.7	2.3	2.0	FOS	16	32	96.2	3.8	0.0
MEC	**0.25**	**4**	**94.5***	**-**	**5.5**	**MEC**	**0.25**	**2**	**98.1**	**-**	**1.9**
NIT	16	64	70.6	19.8	9.5	NIT	64	128	17.3	61.5	21.2
SXT (1:19)	0.12	>8	70.5	-	29.5	SXT (1:19)	0.12	0.5	96.2	-	3.8
C. freundii (52)	MIC_{50}	MIC_{90}	%S	%I	%R	*K. oxytoca* (52)	MIC_{50}	MIC_{90}	%S	%I	%R
CRO	0.25	>8	69.2	0.0	30.8	CRO	0.06	4	86.5	1.9	11.5
CIP	0.015	1	86.5	1.9	11.5	CIP	0.015	0.5	88.5	1.9	9.6
FOS	0.5	2	98.1	0.0	1.9	FOS	8	64	94.2	5.8	0.0
MEC*	**0.25**	**1**	**96.2**	**-**	**3.8**	**MEC**	**0.25**	**2**	**90.4**	**-**	**9.6**
NIT	16	32	96.2	1.9	1.9	NIT	32	64	84.6	13.5	1.9
SXT (1:19)	0.12	>8	75.0	-	25.0	SXT (1:19)	0.12	>8	86.5	-	13.5
E. cloacae (103)	MIC_{50}	MIC_{90}	%S	%I	%R	*K. pneumoniae* (107)	MIC_{50}	MIC_{90}	%S	%I	%R
CRO	0.25	>8	58.3	0.0	41.7	CRO	0.25	>8	50.5	0.0	49.5
CIP	0.015	0.25	90.3	2.9	6.8	CIP	0.5	>8	49.5	7.5	43.0
FOS	16	64	96.1	2.9	1.0	FOS	32	256	84.1	2.8	13.1
MEC	**0.25**	**2**	**95.1**	**-**	**4.9**	**MEC**	**1**	**128**	**79.4**	**-**	**20.6**
NIT	64	128	25.2	47.6	27.2	NIT	64	>128	36.4	23.4	40.2
SXT (1:19)	0.12	>8	81.6	-	18.4	SXT (1:19)	1	>8	50.5	-	49.5
E. coli (620)	MIC_{50}	MIC_{90}	%S	%I	%R	KPN-ESBL-POS (53)	MIC_{50}	MIC_{90}	%S	%I	%R
CRO	0.03	>8	86.6	0.0	13.4	CRO	>8	>8	0.0	0.0	100.0
CIP	0.015	>8	69.2	1.9	28.9	CIP	>8	>8	5.7	9.4	84.9
FOS	1	2	98.4	1.0	0.6	FOS	32	>256	79.2	1.9	18.9
MEC	**0.25**	**2**	**97.7**	**-**	**2.3**	**MEC**	**2**	**>128**	**67.9**	**-**	**32.1**
NIT	16	32	97.1	1.5	1.5	NIT	128	>128	26.4	11.3	62.3
SXT (1:19)	0.12	>8	67.7	-	32.3	SXT (1:19)	>8	>8	15.1	-	84.9
EC-ESBL-POS (78)	MIC_{50}	MIC_{90}	%S	%I	%R	KPN-ESBL-NEG (54)	MIC_{50}	MIC_{90}	%S	%I	%R
CRO	>8	>8	0.0	0.0	100.0	CRO	0.03	0.12	100.0	0.0	0.0
CIP	>8	>8	15.4	6.4	78.2	CIP	0.015	0.06	92.6	5.6	1.9
FOS	1	2	97.4	0.0	2.6	FOS	32	128	88.9	3.7	7.4
MEC	**0.5**	**4**	**96.2**	**-**	**3.8**	**MEC**	**0.25**	**8**	**90.7**	**-**	**9.3**
NIT	16	64	87.2	6.4	6.4	NIT	64	128	46.3	35.2	18.5
SXT (1:19)	>8	>8	26.9	-	73.1	SXT (1:19)	0.12	>8	85.2	-	14.8
EC-ESBL-NEG (542)	MIC_{50}	MIC_{90}	%S	%I	%R	*P. mirabilis* (104)	MIC_{50}	MIC_{90}	%S	%I	%R
CRO	0.03	0.06	99.1	0.0	0.9	CRO	≤0.015	≤0.015	95.2	1.9	2.9
CIP	0.015	>8	76.9	1.3	21.8	CIP	0.03	>8	60.6	1.9	37.5
FOS	1	2	98.5	1.1	0.4	FOS	32	32	90.4	7.7	1.9
MEC	**0.25**	**1**	**98.0**	**-**	**2.0**	**MEC**	**0.5**	**16**	**89.4**	**-**	**10.6**
NIT	16	16	98.5	0.7	0.7	NIT	64	128	0.0	89.4	10.6
SXT (1:19)	0.06	>8	73.6	-	26.4	SXT (1:19)	0.12	>8	73.1	-	26.9

MEC, mecillinam; CRO, ceftriaxone; CIP, ciprofloxacin; FOS, Fosfomycin; NIT, nitrofurantoin; SXT (1:19), trimethoprim / sulfamethoxazole (1:19)
*EUCAST breakpoints used for mecillinam

Figure 1. Cumulative MIC Distribution for Mecillinam and Comparators Against Enterobacterales



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

RESULTS SUMMARY

- Against a selected panel of clinical isolates, mecillinam exhibited MIC_{50} and MIC_{90} values of 0.25 and 4 µg/ml, respectively and an MIC range of 0.03 - >128 µg/ml
- Mecillinam demonstrated the lowest MIC_{90} of all agents tested and a comparable susceptibility profile (94.5 % susceptible and 4.0 % resistant) to fosfomycin (95.7% and 2.0% resistant) susceptible isolates).
- Compared with other agents, mecillinam was more active than ceftriaxone (79.9% susceptible), ciprofloxacin (71.5% susceptible), nitrofurantoin (70.6% susceptible) and trimethoprim/sulfamethoxazole (70.5% susceptible), largely driven by ESBL presence
- 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 nitrofurantoin (26.4%), ceftriaxone (0%), ciprofloxacin (5.7%) and trimethoprim/sulfamethoxazole (15.1%)
- Resistance to ceftriaxone, ciprofloxacin and trimethoprim/sulfamethoxazole around or above 20% is concerning due to their extensive clinical usage to treat urinary tract infections

CONCLUSIONS

These encouraging susceptibility data, based on a selected panel of clinical isolates, support the clinical development of mecillinam/pivmecillinam for the treatment of uUTI and cUTI in the USA.

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