Poster No.

EV0561

In vitro activity of mecillinam against urine isolates of *Escherichia coli* from outpatient departments in Germany

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27th ECCMID
Vienna, Austria
22.–25. April 2017

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Background

Escherichia coli is the leading pathogen of community-acquired urinary tract infections (UTI), (1). The management of UTI in the community is empirically in most cases, but acquired antimicrobial resistance in *E. coli* is a growing serious problem that complicates effective treatment of UTI (2-4). In this context, pivmecillinam, a prodrug of the penicillin derivative mecillinam, has become an attractive drug for oral first-line treatment of acute uncomplicated UTI (5, 6). The purpose of this study was to evaluate the *in vitro* activity of mecillinam against a German collection of *E. coli* urine isolates prior to its introduction. Pivmecillinam has become available in Germany in May 2016.

Material/methods

Bacterial strains were obtained from patients in outpatient departments and collected during a laboratory surveillance study conducted by the Paul-Ehrlich-Society between October and December 2013. Twenty-five laboratories across Germany were requested each to collect 20 consecutive non-duplicate urine isolates. Organisms were shipped to a coordinating laboratory for species confirmation and susceptibility testing. Species identification was confirmed by MALDI-TOF. Minimal inhibitory concentrations (MICs) of mecillinam were determined using the agar dilution method according to the CLSI standard M07-A10 (7), while MICs of other antibacterial agents were determined using the microdilution method according to the standard ISO 20776-1 (8). Results were interpreted according to EUCAST criteria (version 6.0) (9). Breakpoints of mecillinam for susceptibility and resistance were ≤8 mg/l (susceptible) and >8 mg/l (resistant). Extended-spectrum beta-lactamase (ESBL) screening and confirmatory tests were performed according to the guideline of the CLSI (10).

Results

A total of 494 isolates were tested. An ESBL phenotype was confirmed for 23 (4.7%) isolates and 22 (95.7%) of these isolates expressed a CTX-M type ESBL (CTX-M-15 [n=9], CTX-M-1 [n=6], CTX-M-14 [n=4], CTX-M-27 [n=3]. One isolate did not possess a CTX-M, SHV or TEM ESBL. Of the 22 isolates producing a CTX-M type ESBL 10 isolates additionally expressed a TEM-1 β-lactamase.

484 (98%) of all isolates were mecillinam-susceptible and 10 (2%) were mecillinam-resistant (**Table 1**). In comparison, rates of resistance to fosfomycin, nitrofurantoin, 2nd- and 3rd-generation cephalosporins, amoxicillin-clavulanic acid, ciprofloxacin and trimethoprim-sulfamethoxazole were 0.8%, 1%, app. 6%, 9.3%, 16% and 23.7%, respectively (**Table 2**). All but three isolates were intermediate or resistant to amoxicillin. Applying the EUCAST epidemiological cut-off value of mecillinam (1 mg/L), 121 (24.5%) isolates showed acquired resistance mechanisms (non-wild type) to the agent, but were classified as mecillinam-susceptible (i. e. MICs 2-8 mg/L).

$MIC_{50/90}$ values of mecillinam for isolates with an ESBL phenotype were 1/4 mg/L, as compared to 0.25/4 mg/L for non-ESBL isolates. All isolates producing a CTX-M ESBL plus a TEM-1 β-lactamase were susceptible to mecillinam, but $MIC_{50/90}$ values for these isolates tended to be slightly higher (2/4 mg/L) than those for isolates that possess a CTX-M ESBL but no TEM-1 β-lactamase (1/2 mg/L), (**Table 2**).

Conclusions

This study demonstrated that the susceptibility of *E. coli* to mecillinam is high and at the same level as fosfomycin and nitrofurantoin in Germany. Pivmecillinam may thus (still) be a first-line oral therapeutic option in the treatment of acute uncomplicated UTI caused by *E. coli*, as recommended by international and national guidelines.

Table 1: Distribution of mecillinam MICs and cumulative % of *E. coli* isolates inhibited at 8 mg/L

Group of isolates (no. tested)	MIC [mg/L]												Cum. % inhibited at 8 mg/L
	≤0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	>32	
All isolates (494)		5	99	164	45	50	58	38	25	5	1	4	98.0
Non-ESBL phenotype (471)		5	98	161	43	43	53	34	25	5		4	98.1
ESBL phenotype (23)*			1	3	2	7	5	4			1		95.7
CTX-M type ESBL solely (12)			1	3	1	5	1				1		91.7
CTX-M type ESBL plus TEM-1 (10)					1	2	4	3					100

Abbreviation: cum. %, cumulative %
* Of the 23 isolates with an ESBL phenotype 12 isolates express a CTX-M type ESBL solely and 10 isolates additionally a TEM-1 β-lactamase. One isolate did not possess a CTX-M, SHV or TEM ESBL.

§Members of the Working Party

The list of members is shown on the website of the Paul-Ehrlich-Society for Chemotherapy (http://www.p-e-g.org/econtext/resistenzdaten).

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Disclosures

MK is a partner and CEO of Antiinfectives Intelligence GmbH, a research organization providing services to pharmaceutical companies. BK-I is head of laboratory of Antiinfectives Intelligence GmbH.

Acknowledgements

The authors are grateful to Leo Pharma GmbH for supporting the study by a grant.

Table 2: *In vitro* activity of mecillinam in comparison to other drugs used for the treatment of uncomplicated UTI against *E. coli* urine isolates

Group of isolates (no. tested)	Drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Percent of isolates		
				S	I	R
All isolates (494)	AMX**	4	>32	0.6	56.7	42.7
	A/C	4	32	90.7	–	9.3
	CFI	0.25	0.5	93.9	–	6.1
	CPP	0.25	0.5	94.1	–	5.9
	CXM	4	8	93.3	–	6.7
	CIP	≤0.063	>8	83.6	0.4	16.0
	T/S***	≤0.25	>16	75.3	1.0	23.7
	FOS	≤1	4	99.2	–	0.8
	NFT	≤16	32	99.0	–	1.0
	MEC	0.25	4	98.0	–	2.0
Non-ESBL phenotype (471)	AMX**	4	>32	0.6	59.4	39.9
	A/C	4	32	91.5	–	8.5
	CFI	0.25	0.5	98.5	–	1.5
	CPP	0.25	0.5	98.7	–	1.3
	CXM	4	8	97.9	–	2.1
	CIP	≤0.063	8	87.0	0.2	12.7
	T/S***	≤0.25	>16	77.9	1.1	21.0
	FOS	≤1	4	99.6	–	0.4
	NFT	≤16	32	98.9	–	1.1
	MEC	0.25	4	98.1	–	1.9
ESBL phenotype (23)*	AMX**	>32	>32	0	0	100
	A/C	32	128	73.9	–	26.1
	CFI	>8	>8	0	–	100
	CPP	>8	>8	0	–	100
	CXM	>32	>32	0	–	100
	CIP	>8	>8	13.0	4.3	82.6
	T/S***	>16	>16	21.7	0.0	78.3
	FOS	2	8	91.3	–	8.7
	NFT	≤16	32	100	–	0
	MEC	1	4	95.7	–	4.3
CTX-M-type ESBL solely (12)	A/C	8	>128	66.7	–	33.3
	CIP	>8	>8	8.3	0.0	91.7
	T/S***	>16	>16	25.0	0.0	75.0
	FOS	2	64	83.3	–	16.7
	NFT	≤16	32	100	–	0
	MEC	1	2	91.7	–	8.3
CTX-M-type ESBL plus TEM-1 (10)	A/C	32	64	80.0	–	20.0
	CIP	>8	>8	20.0	10.0	70.0
	T/S***	>16	>16	20.0	0.0	80.0
	FOS	≤1	2	100	–	0
	NFT	≤16	32	100	–	0
	MEC	2	4	100	–	0

Abbreviations: S, susceptible; I, intermediate; R, resistant; AMX, amoxicillin; A/C, amoxicillin-clavulanic acid; CFI, cefixime; CPP, cefpodoxime; CXM, cefuroxime; CIP, ciprofloxacin; T/S, trimethoprim-sulfamethoxazole; FOS, fosfomycin; NFT, nitrofurantoin; MEC, mecillinam
* Of the 23 isolates with an ESBL phenotype 12 isolates express a CTX-M type ESBL solely and 10 isolates additionally a TEM-1 β-lactamase. One isolate did not possess a CTX-M, SHV or TEM ESBL.
** Breakpoints approved by the German breakpoint committee NAK were applied.
*** T/S concentrations were in the ratio 1:19. Breakpoint are expressed as the trimethoprim concentration.