Mecillinam: A Possible Alternative Option for Non-Complicated Urinary Tract Infections Treatment Caused by Enterobacterales

Mecillinam: Uma Possível Alternativa Terapêutica para o Tratamento de Infeções Não Complicadas do Trato Urinário Causadas por Enterobacterales

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Palavras-chave: Amdinocilina/uso terapêutico; Infecções por Enterobacteriaceae/tratamento farmacológico; Infeções do Trato Urinário/tratamento farmacológico

Urinary tract infections (UTIs) are the second most common type of infections requiring antibiotics, with *Enterobacterales* being the most common agents of infection.[1] Due to the extensive use of broad-spectrum antibiotics, the prevalence of multidrug-resistant *Enterobacterales* has increased in the community, which makes therapeutic choices a great challenge.

Pivmecillinam (orally active prodrug of mecillinam) is one of the first-line drugs recommended for the treatment of uncomplicated UTIs in the European clinical practice guidelines due to its selective activity against gram-negative bacteria, its pharmacokinetic properties with high drug concentration in urine, and its low community resistance rate.[2-4]

A prospective study was performed from March to September 2021 in a Portuguese community hospital, to determine the sensitivity profiles of *Enterobacterales* isolated from urine samples of UTI patients to the following antibiotics: mecillinam, fosfomycin, nitrofurantoin, amoxicillin-clavulanate, cefuroxime, and trimethoprim-sulfamethoxazole. *Enterobacterales* isolates were recovered from urine samples of patients with clinical UTI diagnoses made by their family physician and identified using automated identification systems (VITEK®MS, bioMérieux). Susceptibility testing was performed on Vitek®2 (bioMérieux) with the AST-N355 card. Mecillinam susceptibility (10 mg) was confirmed by disc diffusion methodology. Results were interpreted according to the EUCAST breakpoints (version 13.0). For extended-spectrum beta-lactamase (ESBL) confirmation, a combination disk test was performed (Mast Group®, U.K.).

A total of 1943 organisms were isolated from the urine samples of 1865 patients. Most isolates were from female patients (n = 1494; 76.9%, median age 71 years old). *Escherichia coli* was the most frequent agent (70.2%, n = 1364), followed by *Klebsiella* (19.0%, n = 370), *Proteus* (7.2%, n = 139), *Enterobacter* (1.4%, n = 26) and *Citrobacter* (2.2%, n = 44) species.

Of all *E. coli* isolates, approximately 99%, 98%, and 90% were sensitive to nitrofurantoin, fosfomycin, and mecillinam, respectively (Table 1). When compared with the

Table 1 – Susceptibility pattern of *E. coli*, *Klebsiella* spp. and *Proteus* spp. to six different oral antibiotics and susceptibility comparison between mecillinam and the other oral antibiotics

Organisms	Missing pairs	Mecillinam sensitivity p_1 (ns)	Sensitivity of other antibiotics p_2 (ns)		*p*-value	95% CI for $p_1 - p_2$
E. coli (*n = 1364*)	36	**0.90** (1198)	NFE	**0.99** (1308)	< 0.001	(-0.10, -0.07)
	36	**0.90** (1198)	FOS	**0.98** (1301)	< 0.001	(-0.10, -0.06)
	63	**0.90** (1173)	AMC	0.71 (924)	< 0.001	(0.16, 0.22)
	36	**0.90** (1198)	CXM	0.88 (1167)	0.043	(< 0.001, 0.05)
	38	**0.90** (1197)	SXT	0.80 (1057)	< 0.001	(0.08, 0.13)
E. coli ESBL (*n = 64*)	7	**0.89** (51)	NFE	**0.96** (55)	0.157	(-0.18, 0.03)
	7	**0.89** (51)	FOS	**0.98** (56)	0.059	(-0.20, 0.001)
	9	**0.89** (49)	AMC	0.22 (18)	< 0.001	(0.51, 0.79)
	7	**0.89** (51)	CXM	0 (0)	< 0.001	(0.82, 0.97)
	7	**0.89** (51)	SXT	0.40 (23)	< 0.001	(0.33, 0.63)
Klebsiella spp. (*n = 370*)		————	NFE	————	——	————
		————	FOS	————	——	————
	68	**0.85** (256)	AMC	**0.67** (201)	< 0.001	(0.12, 0.25)
	56	**0.85** (267)	CXM	**0.81** (253)	0.045	(-0.01, 0.10)
	56	**0.85** (267)	SXT	**0.84** (265)	0.768	(-0.05, 0.06)
Proteus spp. (*n = 139*)		————	NFE	————	——	————
		————	FOS	————	——	————
	20	**0.75** (89)	AMC	**0.92** (109)	< 0.001	(-0.26, -0.08)
	12	**0.73** (93)	CXM	**0.94** (120)	< 0.001	(-0.30, -0.13)
	12	**0.73** (93)	SXT	0.67 (86)	0.223	(-0.06, 0.17)

McNemar's test was used for the difference between two paired proportions. Statistical significance level was set at 5%.
MEC: pivmecillinam; NFE: nitrofurantoin; FOS: fosfomycin; AMC: amoxixillin-clavulanate; CXM: cefuroxime; SXT: trimethoprim-sulfamethoxazole.
ns is the number of susceptibles and missings are the number of missing values in the pairwise comparison.

other oral treatment options, mecillinam has an overall higher rate of sensitivity in both *E. coli* and *Klebsiella* spp., but not in *Proteus* spp. Regarding multidrug-resistant *Enterobacterales* (n = 114), ESBL-positive *E. coli* was the most frequent organism (n = 64), reaching similar mecillinam sensitivity as non-ESBL *E. coli* (89% *versus* 90%). In ESBL-positive *E. coli*, mecillinam sensitivity was shown to be significantly higher ($p < 0.001$) compared to amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, and cefuroxime, and non-significantly lower compared to fosfomycin and nitrofurantoin ($p = 0.059$ and $p = 0.157$, respectively) (Table 1). Unfortunately, our sample was not large enough to establish the susceptibility of multidrug-resistant *Enterobacterales* to mecillinam other than ESBL-*E. coli*.

The results showed an *in vitro* mecillinam resistance rate under 20% for the most prevalent ITU species, suggesting that mecillinam could be considered an appropriate empirical antibiotic for uncomplicated UTIs in Portugal. Although nitrofurantoin and fosfomycin are equally recommended for UTI treatment, none of them is an option to treat uncomplicated UTIs other than those caused by *E. coli*.[5] In this context, mecillinam appears to be a good alternative first-line beta-lactam option since its overall *in vitro* activity is higher than that of amoxicillin-clavulanate (even in ESBL isolates). However, more studies are needed to prove its efficacy *in vivo*.

AUTHOR CONTRIBUTIONS

MF: Practical work, data analysis, writing of the manuscript.

VA: Supervision of the practical work, critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors declared that there are no competing interests and that they have no connection with any company or laboratory that produces or markets the antibiotic that is the subject of this study.

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