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Antimicrobial Activity of Flomoxef against *Enterobacteriaceae* Including Extended Spectrum Beta-Lactamases-Producing Strains Isolated at Ramathibodi Hospital: A 1000-bed Tertiary Care Hospital in Bangkok, Thailand

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Abstract

Background: The spreading of antimicrobial resistance among Gram-negative bacteria is a global issue. To explore a treatment option for Gram-negative bacilli infection, we investigated the *in vitro* activity of flomoxef and comparators against clinically isolated *Enterobacteriaceae* from a tertiary care hospital in Bangkok, Thailand.

Methods: A total of 359 isolates of extended spectrum beta-lactamases- (ESBL-) and non-ESBL-producing *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* were analyzed for minimum inhibitory concentration (MIC) using standard broth microdilution procedure.

Results: The susceptibility rates of non-ESBL-producing *E. coli*, *K. pneumoniae* and *P. mirabilis* to flomoxef were 98.3%, 98.3% and 100%, respectively and the isolates with ESBL-production were susceptible to flomoxef except one *K. pneumoniae* isolate. Intriguingly, flomoxef showed a unique antimicrobial profile among cephems, the MIC required to inhibit the growth of 90% of organisms (MIC90) was 0.25 μg/mL against ESBL-producing strains. However, seventeen isolates with lower susceptibility to flomoxef were found in this study and thirteen were phenotypically confirmed producing AmpC beta-lactamase.

Conclusions: Compared to other beta-lactams widely used in Thailand, flomoxef was the most active except meropenem. Therefore, Flomoxef could be considered as a new alternative and appropriate treatment option for hospitalized patients with various localized infections caused by *Enterobacteriaceae* including ESBL-producing strains.

Keywords: Cepharosporin; Cephamycin; Oxacephem; Carbapenem; Flomoxef; ESBL; AmpC beta-lactamase

Introduction

Recently, emerging antimicrobial resistant bacteria is one of the most serious problems in various geographical regions including South East Asia [1,2]. In Thailand, antimicrobial resistance among Gram-negative bacteria has been spreading, which limits the therapeutic options for bacterial infections [3]. Carbapenem is one of the commonly available treatment options for the ESBL-producing bacterial infections. However, because of the broad spectrum of carbapenem, excessive use of the drug has led to the emergence of carbapenem resistant Gram-negative bacteria that include not only *Enterobacteriaceae* but also non-fermenting Gram-negative bacteria such as *Pseudomonas aeruginosa* or *Acinetobacter baumannii*. To overcome this conundrum regarding antimicrobial resistance and prevent carbapenem resistant bacteria from spreading, an effective treatment alternative for ESBL infection is required.

Flomoxef is an intravenous beta-lactam antibiotic, which is classified under the oxacephem group. It has better *in vitro* activity among beta-lactams against *Enterobacteriaceae* including ESBL-producing bacteria but is not active against non-fermenting bacteria such as *P. aeruginosa* or *A. baumannii* [4]. However, the activity of flomoxef has not yet been reported against clinical isolates in Thailand.

Hence, we assessed *in vitro* susceptibility of clinically isolated major strains of *Enterobacteriaceae* to flomoxef in comparison with antibiotics that are widely used in clinical settings. The introduction of intravenous flomoxef will enrich the treatment armamentarium for ESBL infections in Thailand.

Material and Methods

Clinical isolates

Clinical isolates of three common *Enterobacteriaceae* pathogens; *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* used in this study were collected from Ramathibodi Hospital, a 1000-bed tertiary care hospital in Bangkok, Thailand. These isolates included both ESBL- and non-ESBL-producing strains which were isolated mainly during 2015-2016 (some ESBL-producing *P. mirabilis* were isolated during 2013-2014).

2. Susceptibility test

The following antibiotics were tested with designated concentration ranges: cefotaxime (CTX) and ceftazidime (CAZ), 1 - 32 μg/mL; cefoxitin (CFX), ceftriaxone (CRO), piperacillin/tazobactam (PIP/TAZ), and flomoxef (FMOX), 0.06 - 64 μg/mL; and imipenem (IPM) and meropenem (MEM), 0.5 - 16 μg/mL. Flomoxef was provided from Shionogi Co., Ltd. (Osaka, Japan) and the other antibiotics were obtained from Sigma-Aldrich (USA). Susceptibility of the isolates to the antimicrobial agents was determined by serial microdilution in cation-adjusted Mueller-Hinton broth (BBL, USA) in accordance with Clinical and Laboratory Standards Institute (CLSI) recommendation [5]. The interpretation of susceptibility was based on CLSI M100 S27 (2017) criteria [6]. The quality of the test was monitored using standard strains of E. coli ATCC25922 and ATCC35218. Since there was no available breakpoint (BP) for flomoxef in the CLSI guideline, the BP for moxalactam (8 μg/mL) that also belonged to oxacephem was applied.

3. Phenotypic ESBL and AmpC beta-lactamase detection

ESBL screening and confirmation tests were performed as recommended by CLSI [6]. For detection of AmpC beta-lactamase production, phenotypic test using cloxacillin-containing agar was applied [7] to strains with flomoxef MIC equal to or higher than 0.5 μg/mL. For non-ESBL-producing strains, the inhibition zone diameter of CTX and CAZ discs on 200 μg/mL cloxacillin (Sigma-Aldrich, USA) containing agar was compared with that on the plate without cloxacillin. For ESBL-producing strains, 4 μg/mL clavulanic acid was added in both the cloxacillin containing and non-containing agar plates. If more than 5 mm diameter increase was observed in either CTX or CAZ disc on the plates with beta-lactamase inhibitors (cloxacillin and/or clavulanic acid), we defined it AmpC beta-lactamase producing strain.

Results

1. *In vitro* activity of antimicrobial agents against *Enterobacteriaceae*

For this study, major three Enterobacteriaceae pathogens isolated in Ramathibodi Hospital during 2015-16 were separately collected based on ESBL-production and their susceptibilities were determined against each antimicrobial agent.

	Breakpoints μg/mL		**Total (n=180)**			*E. coli* **(n=60)**					*K. pneumoniae* **(n=60)**					*P. mirabilis* **(n = 60)**			
Antimicrobial agents	S	R	MIC50	MIC90		%S	%R	MIC50	MIC90		%S	%R	MIC50	MIC90		%S	%R	MIC50	MIC90
Cefotaxime	≤ 1	≥ 4	≤ 1	≤ 1		90.0	10.0	≤1	≤ 1		95.0	3.3	≤1	≤1		96.7	3.3	≤ 1	≤ 1
Ceftazidime	≤ 4	≥ 16	≤ 1	≤ 1		91.7	3.3	≤1	≤1		96.7	1.7	≤1	≤1		100	0	≤ 1	≤ 1
Ceftriaxone	≤ 1	≥ 4	≤ 0.06	≤ 0.06		90.0	8.3	≤ 0.06	0.13		96.7	1.7	≤ 0.06	≤ 0.06		96.7	1.7	≤ 0.06	≤ 0.06
Cefoxitin	≤ 8	≥32	2	8		88.3	6.7	4	16		93.3	5.0	2	4		100	0	2	4
Flomoxef	≤ 8	≥ 64	≤ 0.06	0.13		98.3	1.7	≤ 0.06	0.13		98.3	0.0	≤ 0.06	≤0.06		100	0	0.13	0.13
PIP/TAZ*	≤ 16	≥ 128	1	4		100	0	1	2		100	0.0	4	8		100	0	1	2
Imipenem	≤ 1	≥ 4	≤ 0.5	1		100	0	≤ 0.5	≤0.5		100	0.0	≤ 0.5	≤ 0.5		73.3	3.3	≤ 0.5	2
Meropenem	≤ 1	≥ 4	≤ 0.5	≤0.5		100	0	≤ 0.5	≤0.5		100	0.0	≤ 0.5	≤ 0.5		100	0	≤ 0.5	≤ 0.5

Table 1A: *In vitro* activity of antimicrobial agents against non-ESBL-producing *E. coli*, *K. pneumoniae* and *P. mirabilis*
*Piperacillin/Tazobactam (Breakpoints except flomoxef: 2017 CLSI M100 S27, Breakpoint for flomoxef: Breakpoint for moxalactam is applied)

	Breakpoints μg/mL		**Total (n=179)**			*E. coli* **(n=60)**					*K. pneumoniae* **(n=60)**					*P. mirabil***is (n = 59)**			
Antimicrobial agents	S	R	MIC50	MIC90		%S	%R	MIC50	MIC90		%S	%R	MIC50	MIC90		%S	%R	MIC50	MIC90
Cefotaxime	≤ 1	≥ 4	32	>32		0	100	32	>32		0	100.0	>32	>32		0.0	94.9	8	32
Ceftazidime	≤ 4	≥ 16	8	>32		43.3	35.0	8	32		11.7	58.3	16	>32		59.3	37.3	≤ 1	>32
Ceftriaxone	≤ 1	≥ 4	64	>64		0	100	>64	>64		0	100.0	>64	>64		11.9	62.7	4	16
Cefoxitin	≤ 8	≥ 32	4	16		78.3	16.7	8	32		90.0	1.7	8	8		100	0	2	4
Flomoxef	≤ 8	≥ 64	0.13	0.25		100	0	≤ 0.06	0.25		98.3	0.0	0.13	0.13		100	0	0.13	0.13
PIP/TAZ*	≤ 16	≥ 128	2	8		100	0	2	4		90.0	3.3	8	16		100	0	2	8

Imipenem	≤ 1	≥ 4	≤ 0.5	2		100	0	≤ 0.5	≤ 0.5		100	0.0	≤ 0.5	≤ 0.5		69.5	3.4	1	2
Meropenem	≤ 1	≥ 4	≤ 0.5	≤ 0.5		100	0	≤ 0.5	≤ 0.5		100	0.0	≤ 0.5	≤ 0.5		100	0	≤ 0.5	≤ 0.5

Table 1B: *In vitro* activity of antimicrobial agents against ESBL-producing *E. coli*, *K. pneumoniae* and *P. mirabilis*
*Piperacillin/Tazobactam (Breakpoints except flomoxef: 2017 CLSI M100 S27, Breakpoint for flomoxef: Breakpoint for moxalactam is applied)

In non-ESBL-producing group, all three species were shown to be highly susceptible to nearly all tested antibiotics. The susceptibility rates of piperacillin/tazobactam and meropenem were 100% in all three species. The susceptibility rates of *E. coli* and *K. pneumoniae* to flomoxef were equally at 98.3%, which were higher comparing with other four cephalosporins.

The MIC90 of flomoxef against *E. coli* and *K. pneumoniae* were 0.13 μg/mL and ≤ 0.06 μg/mL, respectively. A 100% susceptibility was demonstrated to flomoxef, cefoxitin and ceftazidime in *P. mirabilis* (Table 1A). The overall MIC90 of flomoxef against 180 isolates of non-ESBL-producing strains was 0.13 μg/mL. of flomoxef against 180 isolates of non-ESBL-producing strains was 0.13 μg/mL.

In the ESBL-producing group, all of the isolates were resistant to cefotaxime, and all of the isolates were resistant to ceftriaxone except *P. mirabilis*. On the other hand, susceptibility rate of *E. coli* and *P. mirabilis* to ceftazidime was 43.3% and 59.3%, respectively, while it remained at 11.7% in *K. pneumoniae*. Meropenem achieved 100% susceptibility in all tested isolates while *E. coli* and *K. pneumoniae* isolates solely were susceptible to imipenem. Although only 69.5% of *P. mirabilis* isolates were susceptible to imipenem, it is a common feature of the drug which is not attributable to beta-lactamase production, such as ESBL, AmpC, and carbapenemase. On the other hand, piperacillin/tazobactam showed 100% susceptibility rate in *E. coli* and *P. mirabilis*. Similar to piperacillin/tazobactam, flomoxef was 100% effective against these two species. Additionally, flomoxef achieved higher susceptibility rate comparing with piperacillin/tazobactam (98.3 versus 90.0%) in ESBL-producing *K. pneumoniae*. The overall MIC90 of flomoxef against 179 isolates of ESBL-producing strains was 0.25 μg/mL (Table 1B).

Effect of AmpC production on flomoxef activity

		MIC (μg/mL)												
	n	≤ 0.06	0.13	0.25	0.5	1	2	4	8	16	32	64	MIC50	MIC90
Total	359	164	162	16	5	2	3	2	2	2	0	1	0.13	0.13
to non-ESBL	180	104	61	6	0	1	3	2	1	1	0	1	≤ 0.06	0.13
to ESBL	179	60	101	10	5	1	0	0	1	1	0	0	0.13	0.13

Table 2A: MIC distribution of Flomoxef.

						MIC	μg/mL				
Organism	**Strain**	**ESBL**	**FMOX**	**CTX**	**CAZ**	**CRO**	**CFX**	**PIP/TAZ**	**IMP**	**MEM**	**AmpC**
E. coli	EC-P24	Negative	64	32	32	64	>64	4	≤ 0.5	≤ 0.5	Positive
K. pneumoniae	KP-P18	Negative	16	4	16	2	>64	8	≤ 0.5	≤ 0.5	Positive
E. coli	EC-P12	Negative	8	8	8	16	64	2	≤ 0.5	≤ 0.5	Positive
E. coli	EC-P10	Negative	4	4	4	4	32	2	≤ 0.5	≤ 0.5	Positive
K. pneumoniae	KP-P37	Negative	4	8	8	8	>64	8	≤ 0.5	≤ 0.5	Positive
E. coli	EC-P01	Negative	2	4	8	2	64	4	≤ 0.5	≤ 0.5	Positive
K. pneumoniae	KP-P54	Negative	2	≤ 1	≤ 1	0.13	>64	8	≤ 0.5	≤ 0.5	Positive
P. mirabilis	PM-P43	Negative	2	4	2	2	8	8	≤ 0.5	≤ 0.5	Positive
E. coli	EC-P49	Negative	1	4	8	4	16	2	≤ 0.5	≤ 0.5	Positive
K. pneumoniae	KPE-P31	Positive	16	>32	32	>64	64	32	≤ 0.5	≤ 0.5	Positive
E. coli	ECE-P50	Positive	8	>32	16	>64	16	4	≤ 0.5	≤ 0.5	Positive
P. mirabilis	PME-P28	Positive	1	16	>32	4	2	2	≤ 0.5	≤ 0.5	Positive

E. coli	ECE-P45	Positive	0.5	16	≤ 1	16	32	2	≤ 0.5	≤ 0.5	Positive
E. coli	ECE-P08	Positive	0.5	>32	32	>64	32	4	≤ 0.5	≤ 0.5	Negative
E. coli	ECE-P19	Positive	0.5	>32	> 32	>64	32	4	≤ 0.5	≤ 0.5	Negative
E. coli	ECE-P52	Positive	0.5	>32	> 32	>64	32	8	≤ 0.5	≤ 0.5	Negative
K. pneumoniae	KPE-P38	Positive	0.5	>32	16	>64	8	4	≤ 0.5	≤ 0.5	Negative

Table 2B: AmpC beta-lactamase detection. CTX: Cefotaxime; CAZ: Ceftazidime; CFX: Cefoxitin; CRO: Ceftriaxone; PIP/TAZ: Piperacillin/tazobactam; FMOX: Flomoxef; IPM: Imipenem; MEM: Meropenem

The MIC distribution of flomoxef against ESBL- and non-ESBL-producing isolates is shown in Table 2A. The MIC90 of flomoxef against 359 isolates of ESBL- and non-ESBL-producing strains from three species were 0.13 μg/mL. Although only a single isolate of non-ESBL-producing *E. coli* was resistant to flomoxef with the MIC of 64 μg/mL, there were some isolates which showed higher MICs than most of the strains. This phenotype is likely to be attributable to AmpC production. The hypothesis is reflected from high MIC of cefoxitin in these isolates' combination with data from previous study among Enterobacteriaceae [8]. In order to assess the production of AmpC beta-lactamases, 17 isolates with the MIC of flomoxef equal to or higher than 0.5 μg/mL were tested for AmpC production. Among these isolates, nine were non-ESBL-producing strains which consisted of five E. coli, three K. pneumoniae and one P. mirabilis. In addition, eight ESBL-producing strains included five E. coli, two K. pneumoniae and one P. mirabilis. The result from the phenotypic test of AmpC beta-lactamase production depicted in Table 2B showed that all strains with flomoxef MIC of higher than or equal to 1 μg/mL and one of five strains with MIC of 0.5 μg/mL had AmpC beta-lactamase

Discussion

Antimicrobial resistance represents an emerging threat to our community. The spread of antimicrobial resistant bacteria, especially ESBL-producing bacteria is a growing concern in Thailand as is a global issue. According to an earlier study and the data from National Antimicrobial Resistance Surveillance Center, Thailand (NARST) [http://narst.dmsc.moph.go.th], recent ESBL-producing rate in *E. coli* and *K. pneumoniae* was approximately 40% [9].

Flomoxef is classified as oxacephem antibiotic as its chemical structure is based on the oxygen atom being substituted for the sulfur of cephem nucleus. It also has a 7-α-methoxy group in the beta-lactam core, which provides the stability against various beta-lactamases [10]. In the circumstance with high prevalence of ESBL-producing bacteria in Thailand, flomoxef was shown to retain its antimicrobial activity against major *Enterobacteriaceae* strains, which coincide with the outcomes reported in other Northeastern Asian regions [11-13]. The detection of AmpC beta-lactamase in *Enterobacteriaceae* suggested that production of AmpC beta-lactamase conferred the resistance to flomoxef. This finding was consistent with the previous study result [8], and additionally we found that even one of the strains with flomoxef MIC of 0.5 μg/mL produced AmpC beta-lactamase. Although 4 of 5 isolates with flomoxef MIC of 0.5 μg/mL had a negative phenotype for AmpC production, these isolates were resistant to cefoxitin with MIC ranged between 8-32 μg/mL. This could be the limitation of the detection method [14]. Since only a small number of isolates were tested in this study, further study on the correlation of AmpC and the MIC distribution of flomoxef would provide useful information on this matter. However, these data suggest that any isolates with MIC of flomoxef between 1-8 μg/mL may require close monitoring, as this can be inferred as resistance acquisition. A recent Monte-Carlo simulation suggests that the flomoxef dosing regimen of 1 g every 8 h is effective against *Enterobacteriaceae* strains with MIC90 0.5 μg/mL to achieve the target attainment of 80% for 70% of time above MIC [15]. Considering these observations, the BP of flomoxef, 8 μg/mL applied in this study might be higher than the optimal BP. These AmpC-producing strains are not as common in Thailand when compared to Taiwan and South Korea [16,17]. Although in this study, only a few isolates were AmpC-producing with high MICs of flomoxef, which implied that the success rate of using flomoxef for empirical therapy would rely on the prevalence of AmpC in the region. Therefore, regular susceptibility monitoring to flomoxef is recommended for optimal clinical outcome.

Based on this study, flomoxef might be a carbapenem-sparing option for an infection presumably caused by ESBL-producing strains and a de-escalation option in mild to moderate urinary tract infection, intra-abdominal infection, and biliary tract infection. Flomoxef holds a potential to alleviate the overuse of carbapenem.

Flomoxef has activity against most of the *Enterobacteriaceae* isolates in Thailand. Given the favorable antimicrobial profiles, flomoxef represents one of the appropriate treatment options for hospitalized patients with infections caused by *Enterobacteriaceae*.

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SK and TY are employee of Shionogi & Co., Ltd. PS, KW, ST and SC declare that they have no competing interests.

Authors' contributions to the work

PS and TY designed this study and made the protocol of this study. PS, SK and KW modified the protocol. PS, SK and TY made the concept of manuscript. PS, KW, ST and SC analyzed and interpreted

the data of MIC and AmpC test. PS and SK were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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