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ORIGINAL ARTICLE

Antimicrobial Activities of Cefoperazone-sulbactam in Comparison to Cefoperazone against Clinical Organisms from Medical Centers in Taiwan

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Background: The multidrug-resistant Gram-negative bacteria (MDRGNBs) have emerged as important pathogens recently. Cefoperazone-sulbactam is active against a great proportion of those MDRGNBs. However, the susceptibilities data of cefoperazone-sulbactam are lacking in Taiwan. **Object:** This study was conducted to evaluate the susceptibilities data of cefoperazone-sulbactam aganist commonly encountered clinical pathogens in Taiwan. **Materials and Methods:** 2272 isolates were collected from various clinical specimens from five centers in Taiwan in 2012. The agar dilution method was used to evaluate the susceptibility of the isolated pathogens to cefoperazone and cefoperazone-sulbactam. **Result:** cefoperazone-sulbactam showed better activity against various GNBs, including MDRGNBs and part of carbapenem-resistant isolates tested compared to cefoperazone alone. **Conclusion:** Cefoperazone-sulbactam is active against most commonly encountered clinical pathogens, including MDRGNBs and part of carbapenem-esistant A. baumannii complex. It can be a potentially therapeutic agent for treating infections caused by these pathogens in Taiwan.

Key words: Antibiotic, cefoperazone, resistance, susceptibility, sulbactam

INTRODUCTION

Cefoperazone has a broad-spectrum activity against both Gram-positive cocci (GPCs) and Gram-negative bacteria (GNBs).[1,2] However, antimicrobial resistance developed through various mechanisms, including β-lactamases produced by GNBs in recent decades.[3,4] Sulbactam has been shown to enhance the *in vitro* spectrum of cefoperazone,[5,6] and the combination is active against a great proportion of many clinical pathogens including multidrug-resistant GNBs (MDRGNBs).[7] These include extended-spectrum beta-lactamases (ESBLs) producing *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.[8] Of noted, the sulbactam contained in this drug is also potentially active against *A. baumannii*,[5] which has become an emerging clinical pathogen.[9]

The antimicrobial susceptibilities of the microorganisms are crucial for the selection of appropriate antimicrobial therapy. Unfortunately, there were fewer data of the susceptibility of cefoperazone-sulbactam against commonly encountered clinical pathogens and the above-mentioned MDRGNBs in Taiwan recently. The most updated data were collected about 5 years ago.[3] Therefore, this study is conducted to evaluate the susceptibilities of cefoperazone-sulbactam in comparison

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to cefoperazone against various clinical isolates collected from medical centers in Taiwan.

METHODS

Hospital settings

The clinical isolates were collected from five medical centers in Taiwan, including Lin Kou Chang Gung Memorial Hospital and Taipei Veterans General Hospital in the north; China Medical University Hospital in the middle region; and Chi Mei Hospital and Kaohsiung Chang Gung Memorial Hospital in the south [Table 1].

Bacterial isolates

Isolates were collected from various clinical specimens from five centers in 2012, which included Group A and B *Streptococcus, Streptococcus pneumoniae,* methicillin-susceptible *Staphylococcus aureus* (MSSA), *Escherichia coli, Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *P. aeruginosa*, and *A. baumannii* [Table 1].

Antimicrobial susceptibility tests

The agar dilution method was performed in accordance with the guidance of Clinical and Laboratory Standards Institute (CLSI).[10] The combination ratio of cefoperazone and sulbactam for tests was 1:1.[11] Sulbactam combined with cefoperazone in a 1:1 ratio was purchased from TTY Biopharm, Taiwan.

Table 1: Clinical isolates collected in medical centers in Taiwan

Pathogens	Northern Taiwan	Middle Taiwan	Southern Taiwan	Total
Gram-positive bacteria				
Group A *Streptococcus*	34	0	5	39
Group B *Streptococcus*	34	0	68	102
MSSA	100	50	92	242
Streptococcus pneumoniae	30	0	63	93
Gram-negative bacteria				
Salmonella spp.	85	0	64	149
Acinetobacter baumannii	259	47	69	375
Pseudomonas aeruginosa	34	46	98	178
Stenotrophomonas maltophilia	17	0	70	87
Escherichia coli	100	50	100	250
Klebsiella pneumoniae	100	50	81	231
Proteus mirabilis	100	20	54	174
Serratia marcescens	54	15	53	122
Enterobacter cloacae	75	46	57	178
Other *Enterobacteriaceae*	50	2	0	52
Total	1072	326	874	2272

MSSA=Methicillin-susceptible *Staphylococcus aureus*

The susceptibility breakpoints for cefoperazone-sulbactam are not elucidated in the current CLSI guidelines; hence, the CLSI breakpoint criteria[10] for cefoperazone alone were applied for cefoperazone-sulbactam for comparison purpose only. *E. coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853 were used as control strains.

Statistical analysis

To assess differences, the Chi-square test with Yate's correction or Fisher's exact test was used. A $P < 0.05$ was considered statistically significant. All the analyses were processed with Statistical Package for the Social Sciences software version 18.0 (SPSS, Chicago, IL, USA).

RESULTS

A total of 476 GPC and 1796 GNB clinical isolates were collected. These included Group A *Streptococcus* (1.71%), Group B *Streptococcus* (4.48%), *S. pneumoniae* (3.82%), MSSA (10.65%), *E. coli* (11.00%), *K. pneumoniae* (10.17%), *E. cloacae* (7.83%), *S. marcescens* (5.37%), *P. mirabilis* (7.66%), *P. aeruginosa* (7.83%), *Stenotrophomonas maltophilia* (3.83%), *Salmonella* spp. (6.56%), and *A. baumannii* (16.51%). Antimicrobial susceptibilities of cefoperazone alone and in combination with sulbactam against GPCs are shown in Table 2 and those against GNBs are shown in Table 3. Cefoperazone exhibited potent activity against most *Streptococcus* spp. and MSSA. In GNBs, cefoperazone had limited activity against most *Enterobacteriaceae* and nonfermenting GNBs. The overall susceptibilities of cefoperazone against important GNBs, including *E. coli, K. pneumoniae*, *E. cloacae*, *P. mirabilis*, *P. aeruginosa*, and other *Enterobacteriaceae*, were ranging from 5.8% to 76.4%. However, the susceptibilities against *A. baumannii* and *S. maltophilia* were low: 0.27% and 5.8%, respectively.

The combination of sulbactam and cefoperazone showed better activity against various GNBs tested compared to cefoperazone alone [Table 3]. In addition, the combination also exhibited better activity against *A. baumannii* than cefoperazone alone (71.2% vs. 0.27%).

The susceptibilities of cefoperazone-sulbactam against MDRGNBs are shown in Table 4. In ESBL-producing *E. coli* and ESBL-producing *K. pneumoniae*, the susceptibilities were 65.9% and 60.7%. And those against carbapenem-resistant *A. baumannii* and *P. aeruginosa* were 62.2% and 0%.

Table 2: Antimicrobial susceptibilities of cefoperazone and cefoperazone-sulbactam against Gram-positive bacteria

Pathogens	*n*	Cefoperazone					Cefoperazone-sulbactam				
		MIC_{50}	MIC_{90}	*S* (%)	*I* (%)	*R* (%)	MIC_{50}	MIC_{90}	*S* (%)	*I* (%)	*R* (%)
Group A *Streptococcus*	39	0.125	0.25	100	0	0	0.25	0.5	100	0	0
Group B *Streptococcus*	102	0.25	0.5	100	0	0	0.25	0.5	100	0	0
MSSA	242	4	4	100	0	0	2	4	100	0	0
Streptococcus pneumoniae	93	2	8	100	0	0	2	8	100	0	0

MSSA=Methicillin-susceptible *Staphylococcus aureus*; MIC=Minimum inhibitory concentration

Table 3: Antimicrobial susceptibilities of cefoperazone and cefoperazone-sulbactam against Gram-negative bacteria

Pathogens	*n*	Cefoperazone					Cefoperazone-sulbactam				
		MIC_{50}	MIC_{90}	*S* (%)	*I* (%)	*R* (%)	MIC_{50}	MIC_{90}	*S* (%)	*I* (%)	*R* (%)
Escherichia coli	250	16	128	46.4	24.8	28.8	2	16	88	9.2	2.8
Klebsiella pneumoniae	231	2	128	64.9	7.4	27.7	0.5	32	84.8	9.1	6.1
Proteus mirabilis	174	2	128	76.2	10.8	13.1	1	8	95.4	3.5	0
Serratia marcescens	122	4	64	70.7	13.8	15.3	2	8	90	9.2	0.8
Enterobacter cloacae	178	2	128	76.4	7.3	16.3	1	16	84.8	14.6	0.6
Other *Enterobacteriaceae*	52	16	128	34.6	44.2	21.2	4	16	84.6	15.4	0
Acinetobacter baumannii	375	>128	>128	0.27	5.1	94.7	8	64	71.2	17.6	11.2
Pseudomonas aeruginosa	178	8	128	75.8	6.7	17.4	8	32	81.5	12.1	6.2
Stenotrophomonas maltophilia	87	128	>128	5.8	4.6	89.7	64	128	20.7	12.6	66.7
Salmonella spp.	149	4	64	75.2	6.0	18.8	2	8	99.3	0.7	0

MSSA=Methicillin-susceptible *Staphylococcus aureus*; MIC=Minimum inhibitory concentration

Table 4: Antimicrobial susceptibilities of cefoperazone and cefoperazone-sulbactam against multidrug-resistant Gram-negative bacteria

Pathogens	*n*	Cefoperazone			Cefoperazone-sulbactam		
		S (%)	*I* (%)	*R* (%)	*S* (%)	*I* (%)	*R* (%)
ESBL-producing							
Escherichia coli	88	30.8	1.1	68.1	65.9	26.1	8
Klebsiella pneumoniae	89	13.5	16.9	69.7	60.7	23.6	15.7
Carbapenem-resistant							
Acinetobacter baumannii	270	0	0	100	62.2	23.7	14.1
Pseudomonas aeruginosa	23	0	0	100	0	56.5	43.5

ESBL=Extended-spectrum beta-lactamase

DISCUSSION

This study demonstrated the antimicrobial susceptibilities of cefoperazone alone and in combination of sulbactam against various clinical pathogens. Cefoperazone-sulbactam showed great activities against those commonly encountered clinical pathogens. In MDRGNBs, especially *Enterobacteriaceae*, *P. aeruginosa*, and *A. baumannii* isolates, cefoperazone-sulbactam demonstrated good antimicrobial activities, except those were carbapenem resistant and which may provide another therapeutic option for treating MDRGNBs.

In recent years, the emergence of antimicrobial resistance has become a worldwide problem. ESBL-producing *Enterobacteriaceae*, *P. aeruginosa*, and *A. baumannii* are frequently encountered MDRGNBs. In Taiwan, the annual prevalence rate of ESBL-producing *E. coli* and *K. pneumoniae* isolates doubled from 2008 to 2010 (5.2%–11.5%, and 4.5%–12.1%, respectively).[12,13] This significantly limited the choice of antimicrobial agents. Carbapenems were regarded as one of very limited choices for treating ESBL-producing *Enterobacteriaceae* infection.[14,15] In the current result, cefoperazone-sulbactam exhibited good activity against most *Enterobacteriaceae*, including those ESBL-producing strains. In addition, *P. aeruginosa* and *Acinetobacter* spp. are common pathogens of hospital-acquired infections, which are frequently resistant to multiple antibiotics. Recently, the antimicrobial resistance of *P. aeruginosa* was increasing including carbapenems.[11] The overall susceptibility of *P. aeruginosa* to cefepime, piperacillin-tazobactam, and imipenem was 71%, 83.9%,

and 74.7%, respectively.[11] Furthermore, *A. baumannii* complex even exhibited higher resistances to cefepime, piperacillin-tazobactam, and imipenem, ranging from 58% to 68% (60.9%, 68.4%, and 58.7%, respectively).[4] In the current study, cefoperazone-sulbactam demonstrated good activity against *P. aeruginosa* and *A. baumannii* complex. By the irreversibly block the effects of several β-lactamases, cefoperazone-sulbactam also showed good activities against ESBLs such as TEM, SHV, and CTX-M.[5] The addition of sulbactam makes the full potential of cefoperazone to against *Pseudomonas* species and *Enterobacteriaceae*, even encountered those harboring plasmid-mediated transferable enzymes and extended-spectrum enzymes.[5]

In comparison to other countries of Asia-pacific region, cefoperazone-sulbactam exhibited better activities against those MDRGNBs in Taiwan, except for carbapenem-resistant *P. aeruginosa* and *A. baumannii* complex.[16-18] In recent published data, the antimicrobial resistances of cefoperazone-sulbactam to *E. coli* and *K. pneumoniae* ranged from 2% to 35% and 4% to 17% in Asian countries other than Taiwan.[16,17,19] The ESBL producers ranged 9.7%–59.9% and 9.6%–61.3% among *E. coli* and *K. pneumoniae* isolates in Asia-pacific region.[16,20,21] The resistances of cefoperazone-sulbactam to those ESBL-producing *E. coli* and *K. pneumoniae* ranged 3.3%–71% and 8.6%–28.8%.[16,17,19,21] The resistances of cefoperazone-sulbactam to *P. aeruginosa* and *A. baumannii* complex ranged 11.7%–24.2% and 26.3%–50%, respectively.[16,18,19,22] As the emerging prevalence of carbapenem-resistant *P. aeruginosa* and *A. baumannii* complex ranging 10.4%–56.9% and 22.2%–86.7% among all those isolates,[16,23-25] the resistances of cefoperazone-sulbactam to those carbapenem-resistant isolates mentioned above were even higher: 55.3%–69.8%.[16,22,26,27]

CONCLUSION

Cefoperazone-sulbactam is active against most commonly encountered clinical pathogens in Taiwan. Moreover, it is active against MDR pathogens, such as ESBL-producing *E. coli* and *K. pneumoniae* and part of carbapenem-resistant *A. baumannii* complex, which can be a potentially therapeutic agent for treating infections caused by these pathogens.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Brogden RN, Carmine A, Heel RC, Morley PA, Speight TM, Avery GS. Cefoperazone: A review of its *in vitro* antimicrobial activity, pharmacological properties and therapeutic efficacy. Drugs 1981;22:423-60.
2. Matsubara N, Minami S, Muraoka T, Saikawa I, Mitsuhashi S. *In vitro* antibacterial activity of cefoperazone (T-1551), a new semisynthetic cephalosporin. Antimicrob Agents Chemother 1979;16:731-5.
3. Kuo HY, Wang FD, Yen YF, Lin ML, Liu CY. *In vitro* activities of piperacillin or cefoperazone alone and in combination with beta-lactamase inhibitors against gram-negative bacilli. New Microbiol 2009;32:49-55.
4. Kuo SC, Chang SC, Wang HY, Lai JF, Chen PC, Shiau YR, *et al.* Emergence of extensively drug-resistant *Acinetobacter baumannii* complex over 10 years: Nationwide data from the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program. BMC Infect Dis 2012;12:200.
5. Williams JD. Beta-Lactamase inhibition and *in vitro* activity of sulbactam and sulbactam/cefoperazone. Clin Infect Dis 1997;24:494-7.
6. Akova M. Sulbactam-containing beta-lactamase inhibitor combinations. Clin Microbiol Infect 2008;14 Suppl 1:185-8.
7. Wang FD, Lin ML, Lee WS, Liu CY. *In vitro* activities of beta-lactam antibiotics alone and in combination with sulbactam against Gram-negative bacteria. Int J Antimicrob Agents 2004;23:590-5.
8. Tseng SH, Lee CM, Lin TY, Chang SC, Chang FY. Emergence and spread of multi-drug resistant organisms: Think globally and act locally. J Microbiol Immunol Infect 2011;44:157-65.
9. Sheng WH, Wang JT, Li SY, Lin YC, Cheng A, Chen YC, *et al.* Comparative *in vitro* antimicrobial susceptibilities and synergistic activities of antimicrobial combinations against carbapenem-resistant *Acinetobacter* species: *Acinetobacter baumannii* versus *Acinetobacter* genospecies 3 and 13TU. Diagn Microbiol Infect Dis 2011;70:380-6.
10. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing: Twenty-First Informational Supplement: CLSI Document M100-S21. Wayne: Clinical and Laboratory Standards Institute; 2011.
11. Liu YM, Chen YS, Toh HS, Huang CC, Lee YL, Ho CM,

et al. *In vitro* susceptibilities of non-*Enterobacteriaceae* isolates from patients with intra-abdominal infections in the Asia-Pacific region from 2003 to 2010: Results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). Int J Antimicrob Agents 2012;40 Suppl 1:S11-7.
12. Hsueh PR, Badal RE, Hawser SP, Hoban DJ, Bouchillon SK, Ni Y, *et al.* Epidemiology and antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region: 2008 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). Int J Antimicrob Agents 2010;36:408-14.
13. Huang CC, Chen YS, Toh HS, Lee YL, Liu YM, Ho CM, *et al.* Impact of revised CLSI breakpoints for susceptibility to third-generation cephalosporins and carbapenems among *Enterobacteriaceae* isolates in the Asia-Pacific region: Results from the Study for Monitoring Antimicrobial Resistance Trends (SMART), 2002-2010. Int J Antimicrob Agents 2012;40 Suppl 1:S4-10.
14. Paterson DL. Recommendation for treatment of severe infections caused by *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBLs). Clin Microbiol Infect 2000;6:460-3.
15. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing *Enterobacteriaceae*: An emerging public-health concern. Lancet Infect Dis 2008;8:159-66.
16. Hu FP, Guo Y, Zhu DM, Wang F, Jiang XF, Xu YC, *et al*. Resistance trends among clinical isolates in China reported from CHINET surveillance of bacterial resistance, 2005-2014. Clin Microbiol Infect 2016;22 Suppl 1:S9-14.
17. Yamamoto A, Yamasaki K. Evaluation of antibiotic treatments for urinary tract infections in the elderly, especially regarding the effect on extended spectrum ß-lactamase producing (ESBL-) *Escherichia coli*: A comparison between meropenem and alternatives. Nihon Ronen Igakkai Zasshi 2015;52:153-61.
18. Dhanoa A, Rajasekaram G, Lean SS, Cheong YM, Thong KL. Endemicity of *Acinetobacter calcoaceticus*-baumannii complex in an intensive care unit in Malaysia. J Pathog 2015;2015:789265.
19. Mendes RE, Mendoza M, Banga Singh KK, Castanheira M, Bell JM, Turnidge JD, *et al.* Regional resistance surveillance program results for 12 Asia-Pacific nations (2011). Antimicrob Agents Chemother 2013;57:5721-6.
20. Jean SS, Coombs G, Ling T, Balaji V, Rodrigues C, Mikamo H, *et al.* Epidemiology and antimicrobial susceptibility profiles of pathogens causing urinary tract infections in the Asia-Pacific region: Results from the Study for Monitoring Antimicrobial Resistance Trends (SMART), 2010-2013. Int J Antimicrob Agents 2016;47:328-34.
21. Karagöz A, Sunnetcioglu M, Ceylan MR, Bayram Y, Yalcin G, Kocak N, *et al.* Characterisation of drug resistance of nosocomial ESBL-producing *E. coli* isolates obtained from a Turkish university hospital between 2009 and 2012 by pulsed field gel electrophoresis and antibiotic resistance tests. Infez Med 2016;24:24-31.
22. Mohanty S, Maurya V, Gaind R, Deb M. Phenotypic characterization and colistin susceptibilities of carbapenem-resistant of *Pseudomonas aeruginosa* and *Acinetobacter* spp. J Infect Dev Ctries 2013;7:880-7.
23. Chung DR, Song JH, Kim SH, Thamlikitkul V, Huang SG, Wang H, *et al.* High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. Am J Respir Crit Care Med 2011;184:1409-17.
24. Huh K, Kim J, Cho SY, Ha YE, Joo EJ, Kang CI, *et al.* Continuous increase of the antimicrobial resistance among gram-negative pathogens causing bacteremia: A nationwide surveillance study by the Korean Network for Study on Infectious Diseases (KONSID). Diagn Microbiol Infect Dis 2013;76:477-82.
25. Lai CC, Lee K, Xiao Y, Ahmad N, Veeraraghavan B, Thamlikitkul V, *et al*. High burden of antimicrobial drug resistance in Asia. J Glob Antimicrob Resist 2014;2:141-7.
26. Pei G, Mao Y, Sun Y. *In vitro* activity of minocycline alone and in combination with cefoperazone-sulbactam against carbapenem-resistant *Acinetobacter baumannii*. Microb Drug Resist 2012;18:574-7.
27. Shamaeva SK, Portnyagina US, Edelstein MV, Kuzmina AA, Maloguloval S, Varfolomeeva NA. Results of monitoring metallo-beta-lactamase-producing strains of *Pseudomonas aeruginosa* in a multi-profile hospital. Wiad Lek 2015;68:546-8.