POSTER E-277
ICAAC 2007

Activity of Ceftobiprole (BPR) Tested Against Gram-Positive and -Negative Pathogens in the Asia-Pacific Region: Report From the SENTRY Antimicrobial Surveillance Program (2006)

J.M. Bell,[1] T.R. Fritsche,[2] R.N. Jones,[2] J.D. Turnidge[1]

[1]Women's and Children's Hospital, Adelaide, Australia; [2]JMI Laboratories, North Liberty, Iowa, USA

Jan M. Bell
Microbiology and Infectious Diseases
Women's & Children's Hospital
72 King William Road
North Adelaide SA 5006
Australia
Tel: (61-8) 8161 6359
Fax: (61-8) 8161 6051
e-mail: JBell@wcharl.net

Updated Abstract

Background: Ceftobiprole, an investigational, parenteral cephalosporin with broad activity against Gram-negative and -positive pathogens including oxacillin-resistant staphylococci, is currently in clinical trials for skin and skin structure infections and pneumonia. We evaluated the activity of ceftobiprole against pathogens, including resistant subsets, originating from the Asia-Pacific region (SENTRY Program, 2006).

Methods: Clinically significant patient isolates (N=7531) of staphylococci, streptococci, enterococci, Enterobacteriaceae, and nonfermentative Gram-negative bacilli except *Pseudomonas* spp. were submitted from 42 medical centres in 10 countries. Identifications were confirmed by the regional monitor and tested using validated broth microdilution panels according to CLSI methods.

Results: Ceftobiprole showed high-level activity against staphylococci regardless of oxacillin resistance, streptococci, *Enterococcus faecalis*, and extended-spectrum β-lactamase (ESBL)-negative *Escherichia coli*, and *Klebsiella* spp. Its activity was affected by ESBLs and some carbapenemases. Like other cephalosporins, ceftobiprole MICs were elevated in strains of *Streptococcus pneumoniae* with altered PBPs, but retained useful activity.

Conclusions: Ceftobiprole displayed potent activity against major pathogens from 10 countries in the Asia-Pacific region, including those countries with high resistance rates among key pathogens. Ceftobiprole would particularly be a welcome addition for therapy of MRSA infections in this region.

Introduction

Ceftobiprole is a novel investigational, broad-spectrum cephalosporin, especially noted for its activity against Gram-positive species with altered penicillin-binding proteins, particularly methicillin-resistant *Staphylococcus aureus* (MRSA). The rates of MRSA and related resistances in the Asia-Pacific region are known to be high in many of its countries. We evaluated the activity of ceftobiprole against recognized Gram-negative and Gram-positive pathogens, including resistant subsets, originating from the Asia-Pacific region (SENTRY Program, 2006).

Methods

Bacterial Isolates

- Nonduplicate clinically significant patient isolates were submitted from 42 medical centres in 10 countries (Australia, 5 sites; China 11; Thailand 2; Korea 3; Taiwan 2; Hong Kong 1; Singapore 1; Philippines 2; India 11; Indonesia 4)
- Gram-positive isolates included *S. aureus* (n=1678); coagulase-negative staphylococci (CoNS) (n=396); *Streptococcus pneumoniae* (n=256); *Enterococcus faecalis* (n=379), and *E. faecium* (n=264)
- Gram-negative isolates included *Escherichia coli* (n=918); *Klebsiella* species (n=906); *Pseudomonas* species (n=754); *Acinetobacter* species (n=546); and *Enterobacter* species (n=360).
- Identification of all isolates was confirmed in a central laboratory (Women's and Children's Hospital, Adelaide, Australia) using reference methodologies (1, 2).

Susceptibility Tests

- Isolates were tested against ceftobiprole using validated dry-form broth microdilution MIC panels (TREK Diagnostic Systems) according to reference Clinical and Laboratory Standards Institute (CLSI) methods (2006) and interpretive criteria (2006).
- MIC tests were performed in cation-adjusted Mueller-Hinton broth (with the addition of 2–5% lysed horse blood for testing of streptococci).
- Quality control strains utilized included *E. coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, and *S. pneumoniae* ATCC 49619; all MIC results were within CLSI specified ranges.

Analysis

- Data were analysed for MIC_{50} and MIC_{90}.
- Analyses were performed by species and specific subsets.
- Enterobacteriaceae with elevated MIC values (≥2 µg/ml) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as extended-spectrum β-lactamase (ESBL)-producing phenotypes.
- *Acinetobacter* species, and *Pseudomonas* species with imipenem or meropenem MIC ≥8 µg/ml; and Enterobacteriaceae with imipenem or meropenem MIC ≥2 µg/ml, were screened for metallo-β-lactamase (MBL) enzymes and OXA-23, -24, -51, and -58 enzymes.
- Enterobacteriaceae with ertapenem MIC ≥1 µg/ml were screened for KPC-type carbapenemases.

Results

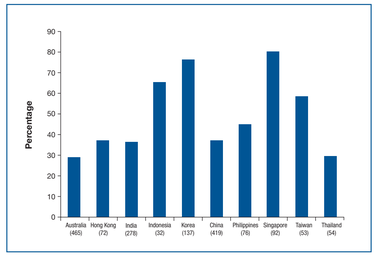
- Ceftobiprole inhibited all tested staphylococci at MICs ≤4 µg/ml, with the exception of 2 coagulase-negative staphylococci from India which had reproducible ceftobiprole MIC values of 8 µg/ml (**Table 1**).
- The MIC_{90} for oxacillin-resistant strains when compared to susceptible strains were 4- and 16-fold higher for *S. aureus* and coagulase-negative staphylococci, respectively.
- Oxacillin resistance in the Asia-Pacific region *S. aureus* was 41.8% overall. Oxacillin resistance ranged from 29% in Australia to 80% in Singapore (**Figure 1**).
- All except 5 strains (Korea n=3; China n=2) of *S. pneumoniae* were inhibited at ≤1 µg/ml of ceftobiprole despite the increased rates of penicillin and ceftriaxone nonsusceptibility (37.9 and 18.8%). Ceftobiprole and ceftriaxone were 4- to 8-fold more potent against penicillin-susceptible strains compared with penicillin-resistant strains.

Table 1. Activity of ceftobiprole against Gram-positive organisms collected as part of the Asia-Pacific SENTRY Surveillance Program (2006)

	MIC (µg/ml)		Number of isolates inhibited at each MIC (µg/ml)									
Organism (no. tested)	**50%**	**90%**	**≤0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**>8**	**% ≤4 µg/ml**
Enterococcus faecium (264)	>8	>8						7	8	1	248	5.7
Enterococcus faecalis (379)	0.5	4	3	9	38	200	54	24	23	6	22 [a]	92.6
Staphylococcus aureus												
Oxacillin-susceptible (977)	0.25	0.5	3	6	726	240	2					100.0
Oxacillin-resistant (701)	2	2				114	158	418	11			100.0
Streptococcus pneumoniae												
Penicillin-susceptible (159)	≤0.06	≤0.06	159									100.0
Penicillin-intermediate (24)	≤0.06	0.25	15	4	5							100.0
Penicillin-resistant (73)	0.5	1			7	49	12	1	3	1		98.6
Coagulase-negative staphylococci												
Oxacillin-susceptible (57)	0.25	0.25	5	21	31							100.0
Oxacillin-resistant (339)	1	4	1	11	37	70	68	27	123	2		99.4

[a] These strains were penicillin-resistant. All *E. faecalis* strains were ampicillin-susceptible.

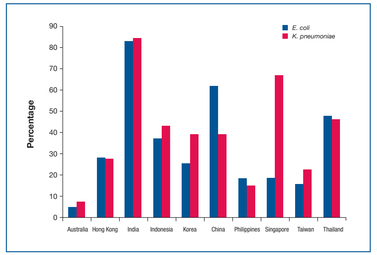
Figure 1. Oxacillin resistance among *S. aureus* (n=1678) isolates from the Asia-Pacific region.



The 4 strains with ceftobiprole MICs above 1 µg/ml all had grossly elevated penicillin and ceftriaxone MICs (≥4 and ≥8 µg/ml, respectively) compared to the ceftobiprole MICs of 2 and 4 µg/ml.

- ESBLs are quite prevalent in many countries in the Asia-Pacific region (**Figure 2**). Ceftobiprole was very active against ESBL-negative strains but was inactivated by most ESBLs in *E. coli, Klebsiella* species, and *Proteus mirabilis* (**Table 2**).
- *Salmonella* species, including the invasive Typhi and Paratyphi serovars, were generally inhibited by ceftobiprole at MICs <0.12 µg/ml (**Table 2**). One strain from Thailand with ceftobiprole MIC >8 µg/ml contained TEM- and CTX-M-group 9 ESBLs.

Figure 2. ESBL phenotypes among *E. coli* (n=918) and *K. pneumoniae* (n=850) isolates from the Asia-Pacific region.



- For *Enterobacter* species which possess chromosomal cephalosporinases, ceftobiprole resembles the extended-spectrum cephalosporins in being highly active against those strains whose enzymes are not de-repressed (**Table 2**).
- The activity of ceftobiprole in the absence of a confirmed metallo-β-lactamase *P. aeruginosa* was bimodal. About half of these strains were inhibited by concentrations ≤4 µg/ml. A similar picture was seen with *Acinetobacter baumannii* (**Table 3**).
- Ceftobiprole had no useful activity against *Stenotrophomonas maltophilia* (**Table 3**) or *Burkholderia cepacia* complex.

Table 2. Activity of ceftobiprole against Enterobacteriaceae collected as part of the Asia-Pacific SENTRY Surveillance Program (2006)

	MIC (µg/ml)		Number of isolates inhibited at each MIC (µg/ml)									
Organism (no. tested)	**50%**	**90%**	**≤0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**>8**	**% ≤4 µg/ml**
No chromosomal cephalosporinases												
E. coli												
ESBL-negative (437)	≤0.06	≤0.06	413	17	6	1						100
ESBL-positive (481)	>8	>8	7	4	5	1	2	2		3	457	4.4
Klebsiella species												
ESBL-negative (449)	≤0.06	0.12	402	31	12	4						100
ESBL-positive (457)	>8	>8	8	2	1	1	4	3	8	3	427	5.9
P. mirabilis												
ESBL-negative (92)	≤0.06	≤0.06	88	1			1	1		1		98.9
ESBL-positive (42)	8	>8	5	5	2	4		1	3	2	20	47.6
Salmonella species												
Typhi/Paratyphi (86)	≤0.06	0.12	69	17								100
Nontyphoidal (22)	≤0.06	≤0.06	21								1	95.5
Citrobacter species other than *C. freundii* (28)	≤0.06	>8	20	3							5	
Chromosomal cephalosporinases												
Enterobacter species												
Ceftriaxone MIC ≤1 (178)	≤0.06	≤0.06	163	10	2					3		98.3
Ceftriaxone MIC >1 (183)	>8	>8	3	10	6	3	5	3	4	7	142	18.6
Other *Proteus* species (19)	>8	>8	1								18	5.3
Morganella morganii (35)	≤0.06	>8	24	4	2						5	85.7
Serratia species (94)	0.12	0.25	25	50	10	1	1	2		1	4	94.7
C. freundii (52)	≤0.06	>8	32			1	1	2	2	2	12	73.1

Table 3. Activity of ceftobiprole against nonfermentative Gram-negative bacilli collected as part of the Asia-Pacific SENTRY Surveillance Program (2006)

	MIC (µg/ml)		Number of isolates inhibited at each MIC (µg/ml)									
Organism (no. tested)	**50%**	**90%**	**≤0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**>8**	**% ≤4 µg/ml**
P. aeruginosa												
MBL-negative (654)	4	>8				3	64	153	121	81	232	52.1
MBL-confirmed[a] (66)	>8	>8									66	0.0
Other *Pseudomonas* species (32)	8	>8	1		1	4		3	5	5	13	43.8
A. baumannii												
Carbapenemase-negative (365)	>8	>8	5	14	62	45	34	13	3	3	186	48.2
Carbapenemase-positive[b] (149)	>8	>8					1				148	0.7
Other *Acinetobacter* species (32)	≤0.06	>8	20	3	4		1				4	87.5
Stenotrophomonas maltophilia (127)											127	0.0

[a] class B metallo-β-lactamase detected. [b] class D/B carbapenemases detected.

Conclusions

- **Ceftobiprole displayed potent *in-vitro* activity against major Gram-positive pathogens from the Asia-Pacific region, including resistant subsets expressing altered penicillin-binding protein targets.**
- **Ceftobiprole had similar potency as the extended-spectrum cephalosporins against Gram-negative bacteria.**
- **These characteristics warrant continued development of ceftobiprole as therapy for cSSSI and pneumonia in the region.**

Acknowledgment

This study was supported by Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ.

References

1. **CLSI.** 2006. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically M7-A7. Wayne, PA: Clinical and Laboratory Standards Institute.
2. **CLSI.** 2007. Performance Standards for Antimicrobial Susceptibility Testing; 17th informational supplement M100-S17. Wayne, PA: Clinical and Laboratory Standards Institute.