F-546

ICAAC 2003

Antimicrobial Activity of LB11058, A Novel Cephalosporin, Tested Against Staphylococci, Streptococci and Enterococci

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AMENDED ABSTRACT

Background: LB11058 (LB) is a parenteral cephalosporin with broad-spectrum activity which includes oxacillin (OXA)-resistant (R) staphylococci and penicillin (PEN)-R streptococci. This study extends initial reports in 2002 to a wider sample of R Gram-positive cocci.

Methods: A total of 639 recent strains of staphylococci (264), streptococci (208) and enterococci (131), including a subset of multidrug-R strains (36), were tested. In addition to LB, 31 antimicrobials were evaluated, including ß-lactams, fluoroquinolones, aminoglycosides, trimethoprim/sulfamethoxazole, macrolide-lincosamide-streptogramins, glycopeptides and an oxazolidinone. LB susceptibility (S) tests were performed by procedures recommended by the NCCLS (M7-A6).

Results: LB was highly active against staphylococci, including OXA-R strains (MIC range, 0.25 - 1 µg/ml for *S. aureus*; and 0.06 - 1 µg/ml for coagulase-negative species). OXA-R strains showed LB MICs 4- to 8-fold higher than OXA-S strains. Viridans gr streptococci were very S to LB with MIC_{90} results ranging from 0.03 to 0.5 µg/ml for the PEN- S and -R strains. ß-haemolytic streptococci showed the lowest LB MIC values (≤0.008 - 0.015 µg/ml). *E. faecalis* had low LB MICs for vancomycin (VAN)-R strains (MIC_{90}, 4 µg/ml), but these were 4-fold higher than VAN-S strains. Only linezolid (LIN; MIC_{90} 2 µg/ml) was more potent than LB against VAN-R *E. faecalis*. LB was also active against VAN-intermediate *S. aureus* (MICs, ≤ 1 µg/ml), LIN-R staphylococci and streptococci (MICs, ≤0.5 µg/ml) and quinupristin/dalfopristin-R staphylococci (MICs, ≤ 2 µg/ml). The highest LB MIC results were recorded for *E. faecium* and other *Enterococcus* spp. (MIC_{90}, >64 µg/ml).

Conclusions: The results of this study demonstrate the excellent activity of LB against staphylococci and streptococci, including contemporary multi-drug R strains. Further evaluations should be performed to establish the clinical role of this cephalosporin.

INTRODUCTION

Oxacillin- and glycopeptide-resistant staphylococci, glycopeptide-resistant enterococci, and penicillin-resistant streptococci have forced clinicians to seek alternative treatments for patients with serious Gram-positive infections. Data from the global SENTRY Antimicrobial Surveillance Program revealed a high and increasing prevalence of these pathogens in the United States (USA), Latin America and several regions of Europe.

LB11058 is a novel parenteral cephalosporin with a C-3 pyrimidinyl-substituted vinyl sulfide group and a C-7 2-amino-5-chloro-1, 3-thiazole group (Figure 1). Preliminary studies have indicated that this compound has excellent in vitro activity against Gram-positive bacteria, including multi-drug resistant staphylococci and streptococci. This study was designed to confirm and extend the earlier studies on the evaluation of the potency and spectrum of LB 11058.

MATERIALS & METHODS

Antimicrobials tested. The LB11058 reagent grade compound was provided by LG Life Science, Ltd. (Taejon, South Korea). Comparator agents were purchased from Sigma Chemical Co. (St Louis, MO) or obtained from their respective manufacturers in the USA. A total of 31 comparators were evaluated depending upon the species tested.

Organisms tested. A total of 639 well characterized strains were processed, each derived from numerous laboratories worldwide, including a subset of Gram-positive strains with specific resistant phenotypes. Only non-duplicate isolates judged to be clinically significant by local criteria were included in the study. All isolates were collected in 2002, except some isolates of the multi-drug resistant subset. The multi-drug resistant Gram-positive strains included six staphylococci with elevated vancomycin MIC values (VISA/VRSA), 10 linezolid-non-susceptible strains and 20 quinupristin-dalfopristin (Synercid®) non-susceptible strains.

Susceptibility testing methods. LB11058 minimum inhibitory concentrations (MICs) were determined by the reference methods according to procedures recommended by the NCCLS. On each day of testing, a fresh stock solution (1,280 µg/ml) of LB11058 was prepared and then serial diluted for a testing concentration range of 0.008 to 64 µg/ml. Supplemented 5% lysed horse blood was added for testing *Streptococcus* spp. The MIC values were interpreted according to NCCLS criteria. Quality control (QC) was monitored using the following organisms: *S. pneumoniae* ATCC 49619, *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213, *E. coli* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853.

RESULTS

- LB11058 was very potent against ß-haemolytic streptococci with all strains being inhibited at ≤0.015 µg/ml (MIC_{90}, ≤0.008 µg/ml).
- LB11058 was the most potent compound tested against viridans group streptococci being 16-fold more potent than ceftriaxone or cefepime against this pathogen (Table 1). LB11058 MIC values ranged from ≤0.008 to 0.12 µg/ml (MIC_{90}, 0.03 µg/ml) among penicillin-susceptible isolates, and from 0.03 to 1 µg/ml (MIC_{90}, 0.5 µg/ml) among penicillin-resistant strains.
- LB11058 was very active against *S. aureus*, including oxacillin-resistant strains (ORSA). Among oxacillin-susceptible (OSSA) strains, LB11058 MIC results varied from 0.06 to 0.25 µg/ml (MIC_{90}, 0.25 µg/ml). LB11058 (MIC_{50}, 0.12 µg/ml) was 32-fold more active than ceftriaxone (MIC_{50}, 4 µg/ml), 16-fold more active than cefepime (MIC_{50}, 2 µg/ml) and four-fold more active than oxacillin (MIC_{50}, 0.5 µg/ml) against OSSA isolates. All ORSA strains were inhibited at ≤ 1 µg/ml of LB11058.
- Only LB11058 (MIC_{90}, 1 µg/ml), trimethoprim/sulfamethoxazole (MIC_{90}, 1 µg/ml), vancomycin (MIC_{90}, 2 µg/ml), quinupristin-dalfopristin (MIC_{90}, 0.5 µg/ml) and linezolid (MIC_{90}, 2 µg/ml) showed acceptable in vitro activity against ORSA strains.
- CoNS showed LB11058 susceptibility patterns similar to that showed by *S. aureus*, with all isolates being inhibited at ≤ 1 µg/ml. LB11058 was also very active against oxacillin-resistant strains (MIC_{50}, 0.25 µg/ml and MIC_{90}, 1 µg/ml).
- LB11058 and ampicillin were the most active ß-lactams evaluated against *E. faecalis*. Most *E. faecalis* isolates had LB11058 MIC ≤ 4 µg/ml, except for one isolate, which was also resistant to linezolid and had LB11058 MIC of >64 µg/ml.
- In general, vancomycin-resistant *E. faecalis* showed LB11058 MIC results approximately four-fold higher than vancomycin-susceptible *E. faecalis* (MIC_{50}, 0.25 and 1 µg/ml, respectively).
- The activity of LB11058 was greater against *E. faecalis* (MIC_{90}, 2 µg/ml) than against *E. faecium* (MIC_{50}, >64 µg/ml). Most *E. faecium* strains showed high MIC results for LB11058, ampicillin and most antimicrobial agents evaluated.
- All vancomycin-non-susceptible staphylococcal strains (MIC, ≥4 µg/ml) were inhibited at ≤ 1 µg/ml of LB11058 (Table 1).
- Linezolid resistance did not affect LB11058 activity among staphylococci and streptococci. All linezolid-resistant staphylococcal isolates had a LB11058 MIC of 0.5 µg/ml, while the linezolid-resistant *Streptococcus oralis* had a very low LB11058 MIC (≤ 0.008 µg/ml).
- All quinupristin/dalfopristin non-susceptible staphylococci showed LB11058 MIC results at ≤ 2 µg/ml.

RESULTS

Table 1. Antimicrobial activity of LB11058 and selected comparison drugs tested against Gram-positive species.

Organism/antimicrobial agent (no. tested)	MIC (µg/ml) 50%	90%	Range	% Susceptible
ß-haemolytic streptococci (102)				
LB11058	≤0.008	≤0.008	≤0.008-0.015	-[a]
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0
Cefepime	≤0.12	≤0.12	≤0.12-1	99.0
Erythromycin	≤0.06	2	≤0.06->8	82.4
Clindamycin	≤0.06	≤0.06	≤0.06->8	94.1
Levofloxacin	0.5	1	0.12-2	100.0
Vancomycin	0.25	0.5	≤0.12-1	100.0
Quinupristin/Dalfopristin	0.25	0.5	≤0.06-0.5	100.0
Linezolid	1	1	0.25-2	100.0
viridans group streptococci				
penicillin-susceptible (52)				
LB11058	0.016	0.03	≤0.008-0.12	-
Ceftriaxone	≤0.25	0.5	≤0.25-2	98.1
Cefepime	≤0.12	2	≤0.12-2	98.1
Erythromycin	≤0.06	4	≤0.06->8	71.2
Clindamycin	≤0.06	≤0.06	≤0.06->8	96.2
Levofloxacin	1	2	0.25->4	94.2
Vancomycin	0.5	1	≤0.12-1	100.0
Quinupristin/Dalfopristin	1	1	≤0.06-1	100.0
Linezolid	1	1	0.12-8	98.1
penicillin-intermediate (27)				
LB11058	0.03	0.06	0.015-0.5	-
Ceftriaxone	0.5	2	≤0.25-2	70.4
Cefepime	0.5	2	≤0.12-4	81.5
Erythromycin	1	4	≤0.06->8	33.3
Clindamycin	≤0.06	1	≤0.06->8	85.2
Levofloxacin	1	4	0.12->4	81.5
Vancomycin	0.5	0.5	0.25-1	100.0
Quinupristin/Dalfopristin	0.5	1	0.25-2	96.3
Linezolid	1	1	≤0.25-2	100.0
penicillin-resistant (27)				
LB11058	0.25	0.5	0.03-1	-
Ceftriaxone	4	32	1->32	3.7
Cefepime	4	>16	4->16	18.5
Erythromycin	2	>8	≤0.06->8	11.1
Clindamycin	≤0.06	>8	≤0.06->8	77.8
Levofloxacin	1	2	0.5->4	96.3
Vancomycin	0.5	1	0.25-1	100.0
Quinupristin/Dalfopristin	0.5	2	0.25-4	88.9
Linezolid	1	1	0.5-2	100.0
Staphylococcus aureus				
oxacillin-susceptible (53)				
LB11058	0.12	0.25	0.06-0.25	-
Ceftriaxone	4	4	0.5->32	98.1
Cefepime	2	4	0.5-16	98.1
Erythromycin	0.5	>8	0.25->8	69.8
Clindamycin	0.12	>8	≤0.06->8	86.8
Levofloxacin	0.12	4	0.06->4	86.8
Vancomycin	1	1	0.5-2	100.0
Quinupristin/Dalfopristin	0.25	0.5	0.12-1	100.0
Linezolid	2	2	1-2	100.0
oxacillin-resistant (110)				
LB11058	1	1	0.25-1	-
Ceftriaxone	>32	>32	0.5->32	4.5
Cefepime	>16	>16	4->16	20.0
Erythromycin	>8	>8	0.25->8	3.6
Clindamycin	>8	>8	0.12->8	19.1
Levofloxacin	>4	>4	0.12->4	7.3
Vancomycin	1	2	0.5-2	100.0
Quinupristin/Dalfopristin	0.5	0.5	0.12-1	100.0
Linezolid	2	2	0.5-2	100.0
Coagulase-negative staphylococci				
oxacillin-susceptible (25)				
LB11058	0.06	0.12	0.03-0.25	-
Ceftriaxone	2	4	1-8	100.0
Cefepime	0.5	2	0.25-4	100.0
Erythromycin	0.25	>8	0.12->8	64.0
Clindamycin	≤0.06	0.5	≤0.06->8	96.0
Levofloxacin	0.25	>4	0.06->4	84.0
Vancomycin	1	2	0.5-2	100.0
Quinupristin/Dalfopristin	0.12	0.5	≤0.06-0.5	100.0
Linezolid	1	1	≤0.25-2	100.0

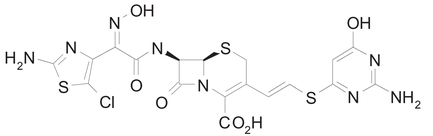
Organism/antimicrobial agent (no. tested)	MIC (µg/ml) 50%	90%	Range	% Susceptible
Coagulase-negative staphylococci				
oxacillin-resistant (76)				
LB11058	1	1	0.06-1	-
Ceftriaxone	16	>32	≤0.25->32	27.6
Cefepime	8	>16	≤0.12->16	71.1
Erythromycin	>8	>8	0.06->8	9.2
Clindamycin	4	>8	≤0.06->8	48.7
Levofloxacin	2	>4	0.12->4	50.0
Vancomycin	2	2	0.5-2	100.0
Quinupristin/Dalfopristin	0.25	0.5	≤0.06-1	100.0
Linezolid	1	1	0.5-2	100.0
Vancomycin-non-susc. staphylococci (6)[b]				
LB11058	0.5	1	0.25-1	-
Enterococcus faecalis				
vancomycin-susceptible (44)				
LB11058	0.25	1	0.12-4	-
Ampicillin	≤2	≤2	≤2-4	100.0
Chloramphenicol	8	8	4->16	88.6
Levofloxacin	1	>4	0.5->4	61.4
Gentamicin (HL)[c]	≤500	>1000	≤500->1000	79.5
Streptomycin (HL)[c]	≤1000	>2000	≤1000->2000	79.5
Vancomycin	1	2	0.5-4	100.0
Quinupristin/Dalfopristin	>8	>8	0.5->8	2.3
Linezolid	1	2	1-2	100.0
vancomycin-resistant (20)				
LB11058	1	4	0.25-4	-
Ampicillin	≤2	8	≤2-16	90.0
Chloramphenicol	8	>16	4->16	55.0
Levofloxacin	>4	>4	1->4	5.0
Gentamicin (HL)[c]	>1000	>1000	≤500->1000	20.0
Streptomycin (HL)[c]	>2000	>2000	≤1000->2000	20.0
Vancomycin	>16	>16	>16	0.0
Quinupristin/Dalfopristin	8	>8	4->8	0.0
Linezolid	1	2	1-2	100.0
Enterococcus faecium				
vancomycin-susceptible (24)				
LB11058	>64	>64	1->64	-
Ampicillin	>16	>16	≤2->16	20.8
Chloramphenicol	8	8	4->16	91.7
Levofloxacin	>4	>4	2->4	20.8
Gentamicin (HL)[c]	≤500	>1000	≤500->1000	79.2
Streptomycin (HL)[c]	≤1000	>2000	≤1000->2000	52.2
Vancomycin	1	2	1-4	100.0
Quinupristin/Dalfopristin	0.5	2	0.25-4	87.5
Linezolid	2	2	1-2	100.0
vancomycin-resistant (26)				
LB11058	>64	>64	16->64	-
Ampicillin	>16	>16	>16	0.0
Chloramphenicol	8	8	4-8	100.0
Levofloxacin	>4	>4	>4	0.0
Gentamicin (HL)[c]	≤500	>1000	≤500->1000	65.4
Streptomycin (HL)[c]	>2000	>2000	≤1000->2000	15.4
Vancomycin	>16	>16	>16	0.0
Quinupristin/Dalfopristin	0.5	1	0.25-2	96.2
Linezolid	2	2	1-4	96.2
Linezolid-resistant strains (10)[d]				
LB11058	0.5	>64	≤0.008->64	-
Ceftriaxone	>32	>32	≤0.25->32	12.5
Cefepime	>16	>16	≤0.12->16	37.5
Ciprofloxacin	>4	>4	1->4	12.5
Vancomycin	2	>16	0.5->16	62.5
Trimethoprim/Sulfamethoxazole	>2	>2	≤0.5->2	37.5
Quinupristin/Dalfopristin	0.5	8	0.25-8	87.5
Quinupristin/Dalfopristin resistant strains (20)[e]				
LB11058	1	64	0.12->64	-
Ceftriaxone	>32	>32	8->32	15.0
Cefepime	>16	>16	2->16	15.0
Ciprofloxacin	>4	>4	1->4	15.0
Vancomycin	1	>16	0.5->16	85.0
Trimethoprim/Sulfamethoxazole	≤0.5	>2	≤0.5->2	55.0

a. - = No interpretive criteria has been established by the NCCLS.
b. Vancomycin-intermediate or -resistant staphylococci; include *S. aureus* (four strains), *S. epidermidis* (one strain), and *S. haemolyticus* (one strain).
c. High-level (HL) resistance.
d. Includes *Enterococcus faecium* (four strains), *E. faecalis* (one strain), *S. aureus* (three strains), *S. epidermidis* (one strain), and *Streptococcus oralis* (one strain).
e. Quinupristin/dalfopristin-resistant strains include: *E. faecium* (nine strains), *S. aureus* (seven strains), *S. epidermidis* (two strains), and *Staphylococcus* spp. (two strains).

CONCLUSIONS

- LB11058 was very active against many clinically important Gram-positive bacterial pathogens, including streptococci (ß-haemolytic and viridans group), staphylococci (*S. aureus* and coagulase-negative), and *E. faecalis*.
- Resistance to linezolid or quinupristin/dalfopristin did not affect LB11058 activity.
- LB11058 was highly active against multidrug-resistant Gram-positive pathogens that may cause both community-acquired and hospital-acquired infections, especially ORSA and other oxacillin-resistant species.

Figure 1: Chemical structure of LB11058.



LB11058

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