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Antimicrobial Activity of the Novel Cephalosporin LB 11058 Tested Against Pathogens Commonly Associated with Bacterial Meningitis

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ABSTRACT

Background: The increasing prevalence of multi-drug resistant (MDR) pathogens has jeopardized the use of extended-spectrum cephalosporins for empiric treatment of community-acquired bacterial meningitis. LB 11058 is a novel cephalosporin which has shown broad-spectrum activity and high potency against penicillin (PEN)-R streptococci. Additionally, the activity of LB 11058 against isolates from bacterial species most frequently associated with bacterial meningitis was further assessed.

Methods: A total of 573 organisms were tested, including 63 *N. menigitidis* (NM), 205 *S. pneumoniae* (SPN; 103 penicillin [PEN]-non-susceptible), 203 *H. influenzae* (HI; 100 ß-lactamase [BL] producers). LB 11058 MIC values were determined by methods recommended by NCCLS (M7-A6).

Results: LB 11058 was highly active against NM with all isolates being inhibited at ≤0.008 mg/L (see Table).

Antimicrobial	MIC_{50}	MIC_{90}	Range
LB 11058	≤0.008	≤0.008	≤0.008
Ceftriaxone	≤0.25	≤0.25	≤0.25
Penicillin	≤0.016	0.25	≤0.016-0.25
Gatifloxacin	≤0.03	≤0.03	≤0.03
Rifampin	≤0.25	≤0.25	≤0.25

All PEN-R SPN (MIC ≥2 mg/L) were very susceptible to LB 11058 (MIC_{90}, 0.12 mg/L; range 0.06 - 0.25 mg/L). LB 11058 was 8- to 16-fold more potent than ceftriaxone (CRO) or cefepime (CPM) against PEN-I and -R strains. LB 11058 activity against HI (MIC_{90}, 0.25-0.5 mg/L) was not affected by BL production, and it was similar to that of CPM (MIC_{90}, 0.12-0.25 mg/L), but inferior to CRO (MIC_{90}, ≤0.008-0.016 mg/L).

Conclusions: LB 11058 showed excellent activity against the most significant pathogens causing community-acquired bacterial meningitis. This compound may represent an excellent option for empiric therapy of this infection, especially in areas with high rates of ß-lactam resistance among SPN.

BACKGROUND

Bacterial meningitis remains a very important disease worldwide. The three most common meningeal pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*. Third-generation cephalosporins are the most common antimicrobial used for empiric therapy; however, pneumococcal strains resistant to these compounds have been reported and vancomycin may be used in association to third-generation cephalosporins for initial antimicrobial therapy.

Penicillin G and ampicillin are the antimicrobial agents of choice for meningitis caused by *N. menigitidis*. However, these recommendations may need to be modified in the future because of trends in the antimicrobial susceptibility of meningococci.

LB 11058 is a novel parenteral cephalosporin which has shown excellent in vitro activity against penicillin-resistant streptococci. The compound has also shown well-balanced activity against *Haemophilus influenzae*, another important cause of community-acquired meningitis. In this study we evaluated the in vitro activity and potency of LB 11058 against clinical isolates of pathogens commonly associated with bacterial meningitis.

MATERIAL AND METHODS

Bacterial strains: A total of 573 well-characterized strains obtained from clinical infections in Europe, Japan and North America were evaluated. The collection included 205 *S. pneumoniae* (103 penicillin non-susceptible), 102 ß-haemolytic streptococci, 203 *Haemophilus influenzae* (101 ß-lactamase-positive), and 63 *N. menigitidis* strains.

Susceptibility Testing: The LB 11058 reagent grade compound was provided by LG Life Science, Ltd. (South Korea). Comparator agents were purchased from Sigma Chemical Co. (St Louis, MO, USA) or obtained from their respective manufacturers in the USA. Susceptibility testing was performed by agar dilution or broth microdilution in accordance with National Committee for Clinical Laboratory Standards (NCCLS) methods. On each day of testing, a fresh stock solution (1,280 mg/L) of LB 11058 was prepared and then serially diluted, producing a concentration range of 0.008 to 64 mg/L. Supplemental 5% lysed horse blood was added for testing *S. pneumoniae* and *N. menigitidis* whereas Haemophilus Test Medium (HTM) was utilized for testing *H. influenzae*. The MIC values of comparator agents were interpreted according to NCCLS criteria [22]. Quality control (QC) was monitored using the following organisms: *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 29213, *E. coli* ATCC 25923, *Pseudomonas aeruginosa* ATCC 27853, and *N. gonorrhoeae* (ATCC 49226).

RESULTS

- LB 11058 was the most potent compound tested against *S. pneumoniae*, but activity varied according to the organism's susceptibility to penicillin. Penicillin-susceptible *S. pneumoniae* were highly susceptible to LB 11058 (MIC_{90}, ≤0.008 mg/L), while penicillin-intermediate (LB 11058 MIC_{90}, 0.06 mg/L) strains and penicillin-resistant strains (LB 11058 MIC_{90}, 0.12 mg/L) showed slightly higher LB 11058 MIC results (range 0.06 - 0.25 mg/L).
- The novel cephalosporin was eight to 16-fold more potent than ceftriaxone, cefepime or penicillin against both penicillin-intermediate and –resistant pneumococcal strains.
- ß-haemolytic streptococci were very susceptible to LB 11058 (MIC_{90}, ≤0.008 mg/L), ceftriaxone (MIC_{90}, ≤0.25 mg/L), penicillin (MIC_{90}, ≤0.016 mg/L), and most of the antimicrobial agents evaluated.
- LB 11058 activity against *H. influenzae* (MIC_{90}, 0.25 – 0.5 mg/L) was not significantly affected by the production of ß-lactamase, and it was similar to that of cefepime (MIC_{90}, 0.12 - 0.25 mg/L) and cefuroxime (MIC_{90}, 0.12 – 0.25 mg/L), but inferior to that of ceftriaxone (MIC_{90}, ≤0.008 – 0.016 mg/L).
- *N. meningitidis* was very susceptible to LB 11058 with all strains tested being inhibited at ≤0.008 mg/L.

Table 1. Antimicrobial activity of LB 11058 and selected comparison drugs tested against pathogens commonly associated with bacterial meningitis.

Organsim/antimicrobial agent (no. tested)	MIC (mg/L) 50%	90%	Range	Category: % susceptible	% resistant
Streptococcus pneumoniae					
penicillin-susceptible (102)					
LB 11058	≤0.008	≤0.008	≤0.008-0.06	-	-
Ceftriaxone	0.016	0.03	≤0.008-0.12	100.0	0.0
Cefepime	≤0.06	≤0.06	≤0.06-0.5	100.0	0.0
Cefpodoxime	≤0.03	0.06	≤0.03-0.25	100.0	0.0
Cefuroxime	≤0.06	0.12	≤0.06-0.5	100.0	0.0
Penicillin	≤0.06	≤0.06	≤0.06-0.12	100.0	0.0
Chloramphenicol	≤2	4	≤2-16	99.0	1.0
Levofloxacin	1	1	≤0.03->4	99.0	1.0
Vancomycin	0.25	0.5	≤0.06-1	100.0	0.0
penicillin-intermediate (52)					
LB 11058	0.03	0.06	≤0.008-0.12	-	-
Ceftriaxone	0.25	0.5	0.016-2	92.3	1.9
Cefepime	0.25	1	≤0.06-4	82.7	1.9
Cefpodoxime	0.25	1	0.06-4	73.1	5.8
Cefuroxime	0.5	4	0.12-4	73.1	13.5
Penicillin	0.25	1	0.12-1	0.0	0.0
Chloramphenicol	4	4	≤2->16	92.3	7.6
Levofloxacin	1	1	0.25->4	98.1	1.9
Vancomycin	0.25	0.5	≤0.06-1	100.0	0.0
penicillin-resistant (51)					
LB 11058	0.12	0.12	0.06-0.25	-	-
Ceftriaxone	1	1	0.03-8	29.4	7.8
Cefepime	1	2	0.5-2	13.7	15.7
Cefpodoxime	2	4	1->4	0.0	88.2
Cefuroxime	4	8	2->8	0.0	96.1
Penicillin	2	4	2->4	0.0	100.0
Chloramphenicol	4	16	≤2-16	82.7	17.3
Levofloxacin	1	1	0.5->4	94.2	5.8
Vancomycin	0.25	0.5	0.25-0.5	100.0	0.0
ß-haemolytic streptococci (102)					
LB 11058	≤0.008	≤0.008	≤0.008-0.016	-[a]	-
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0	0.0
Cefepime	≤0.12	≤0.12	≤0.12-1	99.0	-
Ceftazidime	≤1	≤1	≤1-8	-	-
Penicillin	≤0.016	0.06	≤0.016-0.12	100.0	0.0
Chloramphenicol	≤2	4	≤2-4	100.0	0.0
Levofloxacin	0.5	1	0.12-2	100.0	0.0
Vancomycin	0.25	0.5	≤0.12-1	100.0	0.0
Haemophilus influenzae					
ß-lactamase negative (102)					
LB 11058	0.12	0.5	0.016-0.5	-	-
Ceftriaxone	≤0.06	0.016	≤0.008-0.03	100.0	0.0
Cefepime	≤0.06	0.12	≤0.06-0.5	100.0	0.0
Ampicillin	≤0.5	1	≤0.5-1	100.0	0.0
Chloramphenicol	≤2	≤2	≤2	100.0	0.0
Levofloxacin	≤0.03	≤0.03	≤0.03	100.0	0.0

Table 1. Continued.

Organsim/antimicrobial agent (no. tested)	MIC (mg/L) 50%	90%	Range	Category: % susceptible	% resistant
ß-lactamase-positive (101)					
LB 11058	0.12	0.25	0.03-0.5	-	-
Ceftriaxone	≤0.008	≤0.008	≤0.008-0.016	100.0	0.0
Cefepime	≤0.06	0.25	≤0.06-0.25	100.0	0.0
Ampicillin	>4	>4	2->4	0.0	100.0
Chloramphenicol	≤2	≤2	≤2->16	96.0	4.0
Levofloxacin	≤0.03	≤0.03	≤0.03	100.0	0.0
N. meningitidis (63)					
LB 11058	≤0.008	≤0.008	≤0.008	-	-
Ceftriaxone	≤0.25	≤0.25	≤0.25	-	-
Penicillin	≤0.016	0.25	≤0.016-0.25	-	-
Gatifloxacin	≤0.03	≤0.03	≤0.03	-	-
Rifampin	≤0.25	≤0.25	≤0.25	-	-

a. - = No interpretive criteria has been established by the NCCLS.

CONCLUSIONS

- LB 11058 was highly active in vitro against the most common causes of bacterial meningitis.
- Because LB 11058 showed higher potency than the commonly prescribed third-generation cephalosporin (ceftriaxone) against *S. pneumoniae*, and retains potent activity against *H. influenzae* and *N. menigitidis*, this compound may represent an excellent therapeutic candidate for empiric therapy of bacterial meningitis.

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