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LB11058, a Novel Cephalosporin, Tested Against *Neisseria gonorrhoeae* Including Drug-Resistant Pathogens

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AMENDED ABSTRACT

Background: Resistance among *N. gonorrhoeae* (GC) isolates to various antimicrobial classes such as penicillins (PEN), tetracyclines (TET) and quinolones (ciprofloxacin [CIP]), continues to evolve limiting chemotherapy worldwide. LB11058 is a novel cephalosporin with activity against methicillin-resistant (R) staphylococci via high affinity for altered PBP targets. This agent was tested against a collection of multi-resistant GC.

Methods: LB11058 was tested against GC strains isolated from clinical infections in Europe, Japan and North America. Documented resistance among these 61 strains included PEN-, TET- and CIP-susceptibility (S) patterns in the R, S and intermediate (I) ranges of MIC values. MIC results were determined on GC agar base with the NCCLS defined supplement (M7-A6).

Results: LB11058 was very active (all MICs ≤ 0.06 μg/ml) against all GC subsets listed below:

	LB11058 MIC (μg/ml)			
GC subsets (no.)	50%	90%	Range	% ≤ 0.06[a]
PEN-S (2)	≤0.008	-	≤0.008	100
-I (21)	≤0.008	0.03	≤0.008-0.03	100
-R (38)	≤0.008	0.03	≤0.008-0.06	100
TET-S (42)	≤0.008	≤0.008	≤0.008	100
-I (4)	0.03	-	0.03	100
-R (15)	≤0.008	0.03	≤0.008-0.06	100
CIP-S (43)	≤0.008	0.015	≤0.008-0.03	100
-I (15)	0.03	0.06	≤0.008-0.06	100
-R (3)	0.03	-	0.03	100
All strains (61)	≤0.008	0.03	≤0.008-0.06	100

a. Breakpoint for PEN (NCCLS, M100-S13, 2003). Twenty-one ß-lactamase-producing isolates among PEN-R strains had LB11058 MICs at ≤ 0.008 μg/ml. Resistance patterns among three different drug classes had little influence on LB11058 activity, although I or R isolates generally had slightly elevated LB11058 MIC_{90} results (0.03 μg/ml) when compared to S strains (≤ 0.008 - 0.015 μg/ml).

Conclusions: LB11058 appears to retain potent activity against GC isolates with varying resistances to other ß-lactams, quinolones and tetracyclines. This level of activity could provide an alternative therapy for GC infections in geographic areas of high endemic resistances.

BACKGROUND

LB11058 is a novel parenteral cephalosporin which has excellent in vitro activity against Gram-positive bacteria, including oxacillin-resistant *Staphylococcus aureus* (MIC_{90}, 1 μg/ml) and penicillin-resistant *Streptococcus pneumoniae* (MIC_{90}, 0.12 μg/ml). This compound has also shown well-balanced activity against many Gram-negative bacteria implicated in respiratory tract infections, such as *Haemophilus influenzae* (MIC_{90}, 0.5 μg/ml) and *Moraxella catarrhalis* (MIC_{90}, 0.25 μg/ml).

Infections caused by multi-drug-resistant *Neisseria gonorrhoeae* are an increasing global problem. Although the quinolones have become an attractive alternative for one-dose therapy of uncomplicated cases, isolates resistant to these compounds have emerged in some geographic regions and the parenteral or oral third-generation cephalosporins remain the primary therapy for gonorrhoeae. In the present study we tested LB11058 against a worldwide collection of *N. gonorrhoeae* with various resistance phenotypes.

MATERIALS & METHODS

The LB11058 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. The isolates were susceptibility tested by agar dilution in accordance with National Committee for Clinical Laboratory Standards (NCCLS) methods found in M7-A6 [2003]. Supplemented GC agar was made at PML Micrologicals (Wilsonville, OR). The tests were validated using the following quality control strains: *N. gonorrhoeae* (ATCC 49226), *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (ATCC 25922), and *Staphylococcus aureus* (ATCC 29213).

A total of 61 well-characterized strains obtained from clinical infections in Europe, Japan and North America were evaluated. The collection included isolated with various degrees of resistance to ciprofloxacin (33 strains), penicillin (42 strains), and/or tetracycline (19 strains). All isolates were banked in rabbit blood and stored at -70 ºC or below until used. They were subcultured twice before testing.

COMMENTS

- LB11058 was highly active overall against *Neisseria gonorrhoeae* (MIC_{50}, ≤0.008 μg/ml and MIC_{90}, 0.03 μg/ml). All isolates were inhibited at ≤0.06 μg/ml (Tables 1 and 2).
- LB11058 (MIC_{90}, 0.03 μg/ml) was the most active compound tested against this worldwide collection of *Neisseria gonorrhoeae* (Table 1) and was two to four-fold more active than ceftriaxone (MIC_{90}, 0.12 μg/ml), especially against the subsets of resistant organisms (Table 2).
- Penicillin-resistant strains (MIC ≥ 2 μg/ml) showed higher MIC values to ceftriaxone (MIC_{90}, 0.12 μg/ml) when compared to LB11058 (MIC_{90}, 0.03 μg/ml). Twenty-one ß-lactamase producing isolates had LB11058 MICs at ≤0.008 μg/ml.
- Fluoroquinolone resistances (ciprofloxacin) did not significantly affect the potency of LB11058 (Table 2).
- Tetracycline-non-susceptible isolates were generally less susceptible to both tested cephalosporins.
- If the breakpoint for ceftriaxone (≤ 0.25 μg/ml) or penicillin (≤ 0.06 μg/ml) were applied to tests of LB11058 against *Neisseria gonorrhoeae*, all strains in this collection would appear susceptible (Table 2).

RESULTS

Table 1. In vitro activity of LB11058 and comparators against a worldwide collection of *N. gonorrhoeae*.

	MIC (μg/ml)			Category	
Antimicrobial agent	50%	90%	Range	% susceptible	% resistant
LB11058	≤0.008	0.03	≤0.008-0.06	-[a]	-[a]
Ceftriaxone	≤0.008	0.12	≤0.008-0.12	100.0	-[a]
Penicillin	2	4	0.06->4	3.3	63.9
Ciprofloxacin	≤0.03	0.25	≤0.03-1	70.5	4.9

a. No breakpoints have been established by the NCCLS.

Table 2. In vitro activity of LB11058 according to the resistance phenotype of *Neisseria gonorrhoeae* strains.

	LB11058 MIC (μg/ml)			
Neisseria gonorrhoeae subsets (no.)	50%	90%	Range	% ≤ 0.06[a]
Penicillin-susceptible (2)	≤0.008	-	≤0.008	100
Penicillin-intermediate (21)	≤0.008	0.03	≤0.008-0.03	100
Penicillin-resistant (38)	≤0.008	0.03	≤0.008-0.06	100
Tetracycline-susceptible (42)	≤0.008	≤0.008	≤0.008	100
Tetracycline-intermediate (4)	0.03	-	0.03	100
Tetracycline-resistant (15)	≤0.008	0.03	≤0.008-0.06	100
Ciprofloxacin-susceptible (43)	≤0.008	0.015	≤0.008-0.03	100
Ciprofloxacin-intermediate (15)	0.03	0.06	≤0.008-0.06	100
Ciprofloxacin-resistant (3)	0.03	-	0.03	100
All strains (61)	≤0.008	0.03	≤0.008-0.06	100

a. Breakpoint for penicillin [NCCLS, 2003].

Table 3. In vitro activity of LB11058 and ceftriaxone against subsets of antimicrobial resistant *Neisseria gonorrhoeae* strains.

	No. of isolates (cumulative %) inhibited at μg/ml				
Resistant phenotype (no.)	≤0.008	0.015	0.03	0.06	0.12
Penicillin-intermediate (21)					
LB11058	16(76.2)	2(85.7)	3(100.0)	0(100.0)	0(100.0)
Ceftriaxone	15(71.4)	4(90.5)	0(90.5)	2(100.0)	0(100.0)
Penicillin-resistant (38)					
LB11058	23(60.5)	3(68.4)	10(94.7)	2(100.0)	0(100.0)
Ceftriaxone	17(44.7)	6(60.5)	5(73.7)	4(84.2)	6(100.0)
Ciprofloxacin-non-susceptible[a] (18)					
LB11058	3(16.7)	1(22.2)	12(88.9)	2(100.0)	0(100.0)
Ceftriaxone	0(0.0)	4(22.2)	2(44.4)	4(66.7)	6(100.0)
Tetracycline-non-susceptible[b] (19)					
LB11058	8(42.1)	2(52.6)	8(94.7)	1(100.0)	0(100.0)
Ceftriaxone	3(15.8)	7(55.6)	3(68.4)	3(89.5)	2(100.0)
All strains (61)					
LB11058	41(67.2)	5(75.4)	13(96.7)	2(100.0)	0(100.0)
Ceftriaxone	33(54.1)	11(72.1)	5(80.3)	6(90.2)	6(100.0)

a. Includes three ciprofloxacin-resistant (MIC, ≥ 1 μg/ml) and 15 ciprofloxacin-intermediate (MIC, 0.12 - 0.5 μg/ml) strains.
b. Includes 14 tetracycline-resistant (MIC, ≥ 2 μg/ml) and five tetracycline-intermediate (MIC, 0.5 - 1 μg/ml) isolates.

CONCLUSIONS

- LB11058 is a potent new cephalosporin that demonstrated excellent in vitro activity against a wide variety of *Neisseria gonorrhoeae* strains that were resistant to alternative agents.
- LB11058 appears to be a promising antimicrobial agent that could potentially be used for the treatment of drug-resistant gonorrhea.

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