

In Vitro Activity of Fusidic Acid (CEM-102) Against Resistant Strains of *Staphylococcus aureus*

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Abstract

Background: CEM-102 (fusidic acid) is being developed for the treatment of acute bacterial skin and skin structure infections (ABSSSI). The activity against a variety of resistant strains of *Staphylococcus aureus* was investigated.

Methods: The *in vitro* activity of CEM-102 was compared with that of telithromycin, azithromycin, erythromycin, levofloxacin, linezolid and doxycycline against a total of 272 resistant *S. aureus* by agar dilution procedures (CLSI, M7-A7, M100-S18). The tested strains included *S. aureus* MRSA (*mecA* genotype; 176 isolates), macrolide-resistant (*ermA, B, C* genotype or MLSb-resistant; 58) and ciprofloxacin-resistant (*gyrA* and *parC* genotype; 38).

Results: Against *S. aureus* MRSA (*mecA*), CEM-102 (MIC₉₀ 0.25 mg/L) and telithromycin (MIC₉₀ 0.06 mg/L) were more active than doxycycline (MIC₉₀ 1 mg/L), linezolid (MIC₉₀ 2 mg/L), levofloxacin (MIC₉₀ 16 mg/L), azithromycin (MIC₉₀ >32 mg/L) and erythromycin (MIC₉₀ >32 mg/L). CEM-102 (MIC₉₀ 0.25 mg/L) was significantly superior to linezolid (MIC₉₀ 2 mg/L), levofloxacin (MIC₉₀ 4 mg/L), telithromycin (MIC₉₀ 4 mg/L), azithromycin (MIC₉₀ >32 mg/L), and erythromycin (MIC₉₀ >32 mg/L) against macrolide-resistant *S. aureus* (*ermA, B, C* genotype or MLSb-resistant). Against ciprofloxacin-resistant *S. aureus* (*gyrA* and *parC* genotype), CEM-102 (MIC₉₀ 0.25 mg/L) and telithromycin (MIC₉₀ 0.06 mg/L) were more active than doxycycline (MIC₉₀ 1 mg/L), linezolid (MIC₉₀ 2 mg/L), azithromycin (MIC₉₀ 16 mg/L), levofloxacin (MIC₉₀ >32 mg/L), and erythromycin (MIC₉₀ >32 mg/L).

Conclusions: These data confirm the interesting activity of CEM-102 against resistant *S. aureus*. Being the only member of a class of antibiotics called fusidanes, CEM-102 is active against methicillin resistant and susceptible *S. aureus*, including CA- and HA-MRSA, showing no cross-resistance with any other class of antibiotic.

Introduction

CEM-102 (fusidic acid) is being developed for the treatment of acute bacterial skin and skin structure infections. CEM-102 inhibits protein synthesis by interference with elongation factor G (translocase) present in Gram-positive microorganisms.

In susceptibility studies, CEM-102 is appreciably more potent than most macrolides and quinolones against many Gram-positive organisms, including resistant *Streptococcus*, *Bacillus*, *Corynebacterium* and *Staphylococcus* sp.

Objective

In this study, we determined the minimum inhibitory concentration (MIC₅₀ and MIC₉₀) of CEM-102, telithromycin, azithromycin, erythromycin, levofloxacin, linezolid and doxycycline against a variety of *S. aureus* strains isolated from patients.

Materials and Methods

Strains

- A variety of recently isolated (1995-2008) *S. aureus* strains represented clinical isolates, mostly from upper or lower respiratory tract infections, blood cultures or wound cultures.
- The *S. aureus* strains represented both CA- and HA-MRSA isolates.
- Multiple cultures from the same patient or source were excluded unless a change in organism or antibiogram was noted.
- Organisms were identified by standard methods as described by Murray *et al* (1).

<i>Staphylococcus aureus</i> strains	No. tested
-Methicillin-resistant (<i>mecA</i> genotype)	176
-Macrolide-resistant (<i>ermA, B, C</i> genotype)	58
-Ciprofloxacin-resistant (<i>gyrA</i> and <i>parC</i> genotype)	38
TOTAL	272

Determination of MICs

- MICs were determined using the CLSI agar dilution method (2, 3), with replicate plating of the organisms onto a series of agar plates of increasing concentrations from 0.004 mg/L to 64 mg/L.
- Mueller-Hinton agar was used as the testing medium for the *S. aureus* strains.
- Staphylococcus aureus* ATCC 29213 and *Escherichia coli* ATCC 25922 were included as controls.

Determinations of genotypes *mecA*; *ermA, B, C*; *mefE*; *gyrA* and *parC*

- Genomic DNA was isolated as described by Smith *et al* (4).
- Multiplex PCR was performed with primers specific for *mecA*, *ermA*, *ermB*, *ermC* and *mefE* as described by Sutcliffe *et al* (5).
- Multiplex PCR was performed with primers specific for *gyrA* and *parC* as described by Gonzalez *et al* (6).

Results

- CEM-102 was significantly superior ($p < 0.05$) to antimicrobial agents tested, such as macrolides (with the exception of telithromycin), some common quinolone compounds tested such as levofloxacin, linezolid and doxycycline.
- Against *S. aureus* macrolide-resistant group (*ermA, B, C* genotype), CEM-102 (MIC₉₀ 0.25 mg/L) was the most active compound tested.
- Against *S. aureus* ciprofloxacin-resistant (*gyrA* and *parC* genotype) and methicillin-resistant (*mecA* genotype) strains, telithromycin (MIC₉₀ 0.06 mg/L) and CEM-102 (MIC₉₀ 0.25 mg/L) were the most active compounds tested.

TABLE 1. Susceptibility of *Staphylococcus aureus*

Organism (No. tested)	Antibiotic	MIC (mg/L)		
		Range	50%	90%
<i>S. aureus</i> Methicillin-R <i>mecA</i> (176)	CEM-102	0.12-0.5	0.25	0.25
	Telithromycin	0.016-32	0.06	0.06
	Azithromycin	0.12-264	2	≥64
	Erythromycin	0.016-≥64	1	≥64
	Levofloxacin	1-16	4	16
	Linezolid	0.5-4	1	2
<i>S. aureus</i> Macrolide-R <i>erm A,B,C</i> (58)	CEM-102	0.12-0.5	0.25	0.25
	Telithromycin	0.12-16	2	4
	Azithromycin	4-≥64	32	≥64
	Erythromycin	8-≥64	≥64	≥64
	Levofloxacin	0.5-4	1	4
	Linezolid	1-4	1	2
<i>S. aureus</i> Ciprofloxacin-R <i>gyrA, parC</i> (38)	CEM-102	0.06	0.25	0.25
	Telithromycin	0.016-0.25	0.03	0.06
	Azithromycin	0.016-≥64	0.12	32
	Erythromycin	0.06-≥64	1	≥64
	Levofloxacin	8-≥64	≥64	≥64
	Linezolid	1-4	2	2
	Doxycycline	0.5-1	1	1

Discussion

- CEM-102 showed significant activity (MIC₉₀ 0.25 mg/L) against categorized *S. aureus* strains, including strains that were resistant to β-lactams, macrolides or quinolones.
- Activity of CEM-102 was significantly superior ($p < 0.05$) to the macrolides tested, azithromycin and erythromycin, and was much more potent than linezolid and doxycycline.
- Activity of CEM-102 against *S. aureus* was also significantly superior to levofloxacin, the quinolone tested.
- Against methicillin-resistant (*mecA* genotype group) *S. aureus* the activity of CEM-102 (MIC₉₀ 0.25 mg/L) was greater than doxycycline (MIC₉₀ 1mg/L), linezolid (MIC₉₀ 2 mg/L), levofloxacin (MIC₉₀ 16 mg/L).
- Against macrolide-resistant (*ermA, B, C* genotype) *S. aureus* strains, CEM-102 (MIC₉₀ 0.06 mg/L) was the most active agent tested and was significantly more active than all other macrolides tested (telithromycin, azithromycin and erythromycin (MIC₉₀ >4 mg/L).

Conclusions

CEM-102 shows broad spectrum antimicrobial activity against the most usual strains of *S. aureus* isolated from upper or lower respiratory tract, blood culture or wound infections.

CEM-102 is active against methicillin, macrolide or ciprofloxacin-resistant *S. aureus*.

CEM-102 is active against resistant *S. aureus* strains represented by both CA- and HA-MRSA isolates.

References

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