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ScienceDirect
Diagnostic Microbiology and Infectious Disease xx (2007) xxx–xxx
DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE
www.elsevier.com/locate/diagmicrobio

A comparison of the activity of tigecycline against multiresistant clinical isolates of *Staphylococcus aureus* and *Streptococcus agalactiae*

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Received 9 January 2007; accepted 12 February 2007

Abstract

We evaluated the activity of several antibiotics against 225 clinical isolates of *Staphylococcus aureus* and 252 isolates of *Streptococcus agalactiae*. Only tigecycline, glycopeptides, and linezolid were active against all the isolates of *S. aureus*, whereas the β-lactams were also active against *S. agalactiae*. Tigecycline could be a good alternative to ampicillin in the treatment of group B *Streptococcus* infections in patients allergic to β-lactam.

Keywords: Tigecycline; Multiresistant; *Staphylococcus aureus*; *Streptococcus agalactiae*

The tetracyclines have always been considered as important antibiotics in the treatment of infections (Chopra et al., 1992), although the appearance of resistance and the inclusion of antibiotics with fewer side effects have reduced the number of possible indications.

Tigecycline is active against Gram-positive cocci and Gram-positive rods, including *Staphylococcus aureus* (methicillin-sensitive *S. aureus* [MSSA], methicillin-resistant *S. aureus* [MRSA], vancomycin-intermediate *S. aureus*, and vancomycin-resistant *S. aureus*), *Enterococcus* spp. (vancomycin susceptible and vancomycin resistant), *Streptococcus pneumoniae*, including penicillin-resistant or macrolide-resistant strains, *Streptococcus agalactiae*, *Streptococcus pyogenes*, and the group formed by *Streptococcus anginosus*, extended-spectrum β-lactamase–producing Enterobacteriaceae, or *Acinetobacter* spp. that are resistant to carbapenems. It is also active against anaerobic bacteria (*Bacteroides* spp., *Clostridium perfringens*, or *Peptostreptococcus* spp.), intracellular microorganisms, and nontuberculous mycobacteria (Zinner, 2005). Furthermore, tigecycline is active against tetracycline-resistant microorganisms and does not present cross-resistance with other antibiotics such as the β-lactams or fluoroquinolones (Noskin, 2005). However, in vitro studies show that tigecycline is less active against *Proteus mirabilis*, *Morganella morganii*, and *Providencia* spp., although it is not active against *Pseudomonas aeruginosa* (Bradford et al., 2005; Gales et al., 2000).

It was approved for commercialization by the Food and Drug Administration in June 2005 and by the European Medicines Agency in April 2006 for empiric and directed monotherapy for nosocomial and community-acquired skin, soft tissue, and intra-abdominal infections: complicated appendicitis, intra-abdominal and perforated abscesses, deep soft tissue infections, burns, infected ulcers, and surgical wounds with suspected or confirmed resistant microorganisms. It would also be indicated in patients with suspected polymicrobial infections, abnormal renal function, or hepatic insufficiency, or in patients whose antibiotics have failed. Finally, it could be a useful alternative against multiresistant Gram-positive bacteria or in specific cases of allergy to other antibiotics such as β-lactams (Gobernado, 2006). Therefore, its activity must be studied in these new clinical situations.

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0732-8893/$ – see front matter © 2007 Published by Elsevier Inc.
doi:10.1016/j.diagmicrobio.2007.02.009

The objective of this study was to compare the in vitro activity of tigecycline with that of other commonly used antibiotics against multiresistant *S. aureus* and *S. agalactiae*.

We studied 225 clinical isolates of *S. aureus* and 252 of *S. agalactiae* obtained between January and November 2005 and identified in the clinical microbiology laboratory of Hospital Clinico "San Cecilio" in Granada, Spain, using the WIDER system (Francisco Soria Melguizo, Spain) (Canton et al., 2000). The *S. aureus* isolates came mainly from skin and soft tissue infections (74.2%), respiratory infections (19.6%), bacteremia (3.1%), and other infections (3.1%). The *S. agalactiae* isolates came from the urinary tract (2%), soft tissue infections (2%), and vaginal and rectal samples of pregnant women undergoing screening for colonization by group B *Streptococcus* to avoid neonatal infection by this microorganism (96%).

All 477 isolates underwent broth microdilution in Mueller–Hinton agar following the guidelines of the Clinical and Laboratory Standards Institute (CLSI, 2006). The ranges of concentrations (in μg/mL) assayed for *S. aureus* for each antibiotic were the following: penicillin (0.002–4), oxacillin (0.015–32), gentamicin (0.125–256), kanamycin (0.25–512), tobramycin (0.125–256), vancomycin (0.03–64), teicoplanin (0.03–64), levofloxacin (0.03–64), telithromycin (0.03–64), erythromycin (0.03–64), josamycin (0.015–32), clindamycin (0.03–64), linezolid (0.004–8), and trimethoprim–sulfamethoxazole (0.03/0.6–64/1216). The ranges of concentrations (in μg/mL) assayed for *S. agalactiae* for each antibiotic were the following: ampicillin (0.002–4), cefotaxime (0.002–4), gentamicin (0.125–256), vancomycin (0.004–8), teicoplanin (0.004–8), levofloxacin (0.03–64), erythromycin (0.03–64), josamycin (0.015–32), clindamycin (0.03–64), and linezolid (0.004–8).

The MIC of tigecycline was also determined in using the E-test (AB Biodisk, Solna, Sweden) only in those isolates that were resistant to at least one of the antibiotics assayed by microdilution. For this purpose, we prepared a 0.5-McFarland suspension of each microorganism, which was inoculated onto Mueller–Hinton agar (bioMérieux, Marcy-l'Etoile, France) supplemented with 5% sheep blood for *S. agalactiae*. The plates were incubated overnight at 35 °C in ambient air. *S. aureus* ATCC 29213 was used as control strain for all the procedures.

After the microdilution assay, 141 (62.7%) of the 225 *S. aureus* isolates and 63 (25%) of the 252 *S. agalactiae* isolates presented some degree of resistance (resistant or intermediate clinical category according to the CLSI) to one or more antibiotics. Table 1 shows the range, MIC_{50} and MIC_{90} (in μg/mL), and the percentage of isolates sensitive to each of the antibiotics assayed against both species.

After determining the MIC of tigecycline using the E-test in the 204 isolates, the values (in μg/mL) were as follows: range = 0.047 to 0.38, MIC_{50} = 0.125, MIC_{90} = 0.25, and 100% for the tigecycline-susceptible *S. aureus* isolates; and range = 0.032 to 0.25, MIC_{50} = 0.125, MIC_{90} = 0.25, and 100% for the tigecycline-susceptible *S. agalactiae* isolates.

We observed that tigecycline shows excellent activity against both microorganisms, regardless of their resistance

Table 1
In vitro activity of antibiotics assayed by microdilution against 141 clinical isolates of *S. aureus* and the 63 isolates of *S. agalactiae*

Microorganism	Antibiotic assayed	Range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	Susceptible (%)
S. aureus	Penicillin	0.015 to >4	>4	>4	6.4
	Oxacillin	≤0.015 to >32	8	>32	48.9
	Gentamicin	≤0.125 to >256	0.5	128	66.7
	Kanamycin	≤0.25 to >512	64	>512	48.2
	Tobramycin	≤0.125 to >256	16	>256	48.2
	Vancomycin	≤0.03 to 4	0.25	1	100
	Teicoplanin	≤0.03 to 4	0.125	1	100
	Levofloxacin	≤0.03 to >64	8	32	36.2
	Telithromycin	≤0.03 to >64	0.125	>64	61.7
	Erythromycin	≤0.03 to >64	>64	>64	19.1
	Josamycin	0.03 to >32	>32	>32	ND
	Clindamycin	≤0.03 to >64	32	>64	46.1
	Linezolid	0.125 to 4	2	4	100
	Trimethoprim–sulfamethoxazole	≤0.03/0.6 to >64/1216	0,06/1,19	1/19	91.5
S. agalactiae	Ampicillin	0.015 to 0.125	0.06	0.125	100
	Cefotaxime	0.008 to 0.125	0.03	0.06	100
	Gentamicin	1 to 128	4	16	ND
	Vancomycin	0.5 to 1	1	1	100
	Teicoplanin	≤.004 to 0.06	≤0.004	≤0.004	ND
	Levofloxacin	0.25 to 8	0.5	2	93.7
	Erythromycin	≤0.03 to >64	>64	>64	7.9
	Josamycin	0.06 to >32	16	>32	23.8
	Clindamycin	≤0.03 to >64	>64	>64	11.1
	Linezolid	0.5 to 2	1	2	100

The CLSI have not defined the susceptibility cutoffs of this antibiotic for this species. ND = not defined.

to other groups of antibiotic such as the β-lactams, aminoglycosides, fluoroquinolones, macrolides, or lincosamides. Only tigecycline, glycopeptides, and linezolid remained active against all the isolates of *S. aureus*, although tigecycline did present lower MIC_{50} and MIC_{90} values. In the case of *S. agalactiae*, tigecycline, glycopeptides, linezolid, and β-lactams were active against all the isolates, with β-lactams being slightly superior in vitro. This idea is supported in a previous study by our group (Sorlozano et al., 2006) in which we observed that the activity of tigecycline does not present significant differences against isolates of MSSA or MRSA.

The results of the present study are similar to those published by other authors who have evaluated the activity of tigecycline against various multiresistant Gram-positive bacteria from different geographic areas. Against *S. aureus*, for example, the MIC_{50} and MIC_{90} values range from 0.12 to 0.25 μg/mL depending on the study, whereas for *S. agalactiae*, they range from 0.06 to 0.25 μg/mL (Betriu et al., 2006; Fritsche et al., 2005; Gales et al., 2000; Hoban et al., 2005; Milatovic et al., 2003; Sader et al., 2005).

Furthermore, intravenous administration of antibiotics intrapartum to *S. agalactiae* carriers is the only currently accepted efficacious measure of preventing vertical transmission of this microorganism. To prevent infection of the neonate by this microorganism, intrapartum penicillin G or ampicillin is recommended for all women identified as vaginal or rectal carriers of *S. agalactiae* during pregnancy (The Spanish Society of Obstetrics and Gynecology et al., 2003). As we can see from our study, in which 96% of the *S. agalactiae* samples came from vaginal and rectal colonization in pregnant women, ampicillin conserves excellent activity against this microorganism. However, alternatives must be sought in patients allergic to β-lactams. In these cases, erythromycin or clindamycin is indicated (The Spanish Society of Obstetrics and Gynecology et al., 2003). Nevertheless, there are increasingly few therapeutic options available for patients allergic to β-lactams because current rates of resistance to erythromycin for *S. agalactiae* in Spain stand at approximately 18% (Betriu et al., 2003). Given its activity, tigecycline could be an alternative to the β-lactams in infections caused by erythromycin-resistant *S. agalactiae* in allergic patients.

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