Diagnostic Microbiology and Infectious Disease 88 (2017) 177–183

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Antimicrobial activity of tigecycline and cefoperazone/sulbactam tested against 18,386 Gram-negative organisms from Europe and the Asia-Pacific region (2013–2014)

M.A. Pfaller [a,b], R.K. Flamm [a], L.R. Duncan [a], R.E. Mendes [a], R.N. Jones [a], H.S. Sader [a,*]

[a] JMI Laboratories, North Liberty, IA, USA
[b] University of Iowa, Iowa City, IA, USA

ARTICLE INFO

Article history:
Received 8 December 2016
Received in revised form 23 February 2017
Accepted 26 February 2017
Available online 6 March 2017

Keywords:
Cefoperazone/sulbactam
tigecycline
antimicrobial resistance
Enterobacteriaceae
Acinetobacter spp.
Stenotrophomonas maltophilia
China

ABSTRACT

A total of 18,386 organisms, including 13,224 Enterobacteriaceae, 3536 *Pseudomonas aeruginosa*, 1254 *Acinetobacter* spp., and 372 *Stenotrophomonas maltophilia* were collected from Western Europe (WEU; $n = 10{,}021$), Eastern Europe (EEU; $n = 4957$), and the Asia-Pacific region (APAC; $n = 3408$ [1052 from China]) in 2013–2014 as part of the SENTRY Antimicrobial Surveillance Program and tested by a reference broth microdilution method for susceptibility against tigecycline, cefoperazone/sulbactam, and comparator agents. Overall, 95.3% of Enterobacteriaceae were susceptible (≤1 μg/mL; EUCAST) to tigecycline ($MIC_{50/90}$, 0.12/1 μg/mL) with regional EUCAST susceptibility rates of 94.8–97.8% (98.9–99.6% inhibited at ≤2 μg/mL [US FDA]). Among *Acinetobacter* spp., 66.1% (EEU) and 79.5% (WEU) were inhibited at ≤1 μg/mL of tigecycline (94.9% and 97.3% inhibited at ≤2 μg/mL; pan-European $MIC_{50/90}$, 1/2 μg/mL). For *S. maltophilia*, 65.4% (China) to 88.9% (EEU) of the isolates were inhibited at ≤1 μg/mL of tigecycline. Cefoperazone/sulbactam inhibited 94.6/83.5/91.5% of Enterobacteriaceae at ≤16 μg/mL in WEU/EEU/APAC, respectively.

1. Introduction

Healthcare-associated infections are important causes of morbidity, mortality, and excess medical costs worldwide (Magill et al., 2014). Population-based surveillance of antibiotic resistance in both Europe (ECDC, 2013) and the United States (US) (CDC, 2013) has documented increasing resistance among Gram-negative bacilli (GNBs) in a large proportion of facilities. Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae (CRE), and multidrug-resistant (MDR; resistant to at least three antimicrobial classes) non-fermenters such as *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* are prominent among the resistant species (Boucher et al., 2009; Kollef et al., 2011; Walsh and Toleman, 2012). Notably, this increase in resistance among GNBs reduces the likelihood of appropriate empiric therapy (Zhang et al., 2015). A delay in initial appropriate therapy is well established as being associated with an increased morbidity and mortality in patients with severe infections, particularly those caused by ESBL-producing Enterobacteriaceae (Tumbarello et al., 2007) and *A. baumannii* (Micek et al., 2005; Zhang et al., 2015).

These findings underscore the continued importance of antibiotic resistance surveillance and the need to assess the potential impact of newly introduced and novel antibacterial agents targeting specific resistance phenotypes (Perez and Villegas, 2015; van Duin and Bonomo, 2016). Systematic and comprehensive antibiotic resistance surveillance is essential to document the extent of the resistance problem and to inform local, regional, national, and global efforts to combat the challenge of resistance (Perez and Villegas, 2015).

Tigecycline is a semisynthetic derivative of minocycline and the first member of the novel class of glycylcyclines (Draper et al., 2014; Honeyman et al., 2015; Macone et al., 2014). Similar to the older tetracyclines (doxycycline, minocycline, and tetracycline), tigecycline binds to the 30S ribosomal subunit of target Gram-positive and Gram-negative bacteria with resultant inhibition of protein synthesis (Draper et al., 2014; Honeyman et al., 2015; Roberts, 2003). Notably, tigecycline remains active in the face of both ribosomal protection and efflux tetracycline resistance genes (Hawkey and Finch, 2007). Tigecycline also maintains its activity against difficult-to-treat pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and Enterobacteriaceae isolates that produce a wide array of ESBLs and carbapenemases in addition to MDR strains of *Acinetobacter* spp. and *S. maltophilia* (DiPersio and Dowzicky, 2007; Hawkey and Finch, 2007; Karageorgopoulos et al., 2008; Kelesidis et al., 2008; Livermore, 2005; Sader et al., 2014).

Tigecycline received approvals from the US Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) to treat complicated acute bacterial skin and skin structure infections (ABSSSI)

* Corresponding author. Tel.: +1-319-665-3370; fax: +1-319-665-3371.
E-mail address: helio-sader@jmilabs.com (H.S. Sader).

http://dx.doi.org/10.1016/j.diagmicrobio.2017.02.020
0732-8893/

and complicated intraabdominal infections (cIAI) in 2005 (US FDA) and 2006 (EMA). In 2008 the US FDA also approved tigecycline to treat community acquired bacterial pneumonia (CABP). Sentinel monitoring through surveillance programs, including the global SENTRY Antimicrobial Surveillance Program, has provided information on the continuing activity of tigecycline against antimicrobial-resistant Gram-positive and Gram-negative bacteria since the initial approval of tigecycline for clinical use (Chen et al., 2012; DiPersio and Dowzicky, 2007; Sader et al., 2014).

Cefoperazone is a broad-spectrum third-generation cephalosporin with activity against Gram-positive and Gram-negative organisms, including *Pseudomonas aeruginosa* (Fass et al., 1990; Jones et al., 1985; Klastersky, 1988; McLaughlin et al., 1994). Its pharmacologic properties include a long elimination half-life of approximately 2 hours, which allows for twice-daily administration. Cefoperazone was widely used in the 1980s to treat infections in neutropenic patients and in immunocompetent individuals (Klastersky, 1988). Due to its lability to β-lactamases, cefoperazone was combined with the β-lactamase inhibitor sulbactam, and this combination has been used in many geographic regions to treat several types of infections, including nosocomial pneumonia, intraabdominal infections, gynecological infections, sepsis, and infections in febrile neutropenic patients (Bin et al., 2006).

In the present study, we evaluated the antimicrobial activities of tigecycline, cefoperazone/sulbactam, and comparator agents tested against 18,386 isolates of Gram-negative organisms collected in 2013 and 2014 from individual medical centers in Europe (EU) and the Asia-Pacific region (APAC; including China, Australia and New Zealand) as part of the SENTRY Antimicrobial Surveillance Program.

2. Materials and methods

2.1. Organism collection

A total of 18,386 organisms were collected from Western Europe (WEU; $n = 10{,}021$), Eastern Europe (EEU; $n = 4957$), and the Asia-Pacific region (APAC; $n = 3408$ [1052 from China and 478 from Australia/New Zealand]) in 2013–2014 as part of the SENTRY Antimicrobial Surveillance Program. The number of medical centers and collected isolates per country were as follows (number of medical centers; number of isolates): 1) WEU – Belgium (1; 131), France (4; 1354), Germany (7; 1974), Ireland (2; 920), Italy (5; 1602), Portugal (1; 549), Spain (3; 1584), Sweden (2; 624), and UK (3; 1019); 2) EEU – Bulgaria (2; 96), Croatia (1; 92), Czech Republic (2; 284), Greece (1; 638), Hungary (1; 201), Israel (1; 488), Poland (3; 512), Russia (3; 393), Slovakia (1; 97), Slovenia (1; 156), Turkey (6; 1499), and Ukraine (1; 150); 3) Australia (6; 551) and New Zealand (2; 147); 4) China (10; 1052); and 5) Asia excluding China – Hong Kong (1; 229), Indonesia (1; 119), Malaysia (1; 204), Philippines (1; 95), Singapore (1; 242), South Korea (2; 355), Taiwan (1; 79), and Thailand (3; 333). The isolates were collected from patients hospitalized with pneumonia (5475 isolates; 29.8%), bloodstream infections (4402; 23.9%), skin and soft tissue infections (4039; 22.0%); urinary tract infections (2925; 15.9%), intra-abdominal infections (1090; 5.9% and other infection types (455; 2.5%). The participant center identified the organisms, and JMI Laboratories (North Liberty, IA, USA) confirmed the species, when necessary, by Vitek 2 or by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) using the Bruker Daltonics MALDI Biotyper (Billerica, MA, USA) and following manufacturer instructions.

2.2. Susceptibility testing

The central reference laboratory used reference broth microdilution methods to test isolates for susceptibility to multiple antimicrobial agents using validated broth microdilution panels produced by ThermoFisher Scientific Inc. (Cleveland, OH, USA). The methods used are described by the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document (CLSI, 2015). Cefoperazone/sulbactam was tested at a 1:1 ratio. Minimal inhibitory concentration (MIC) results were interpreted according to CLSI criteria in M100-S26 (CLSI, 2016) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables (version 6.0, January 2016) (EUCAST, 2016; Reitberg et al., 1988). Tigecycline MIC breakpoints used for Enterobacteriaceae were found in the US FDA approved package insert (MIC, ≤2 μg/mL) (Tygacil, 2016) and in EUCAST 6.0 (MIC, ≤1 μg/mL). Cefoperazone/sulbactam MIC breakpoints used were found in the Sulperazone® package insert (Sulperazone®, 2009) as well as the Cefobid® package insert (CEFOBID®, 2006) (≤16 μg/mL for susceptible and ≥64 μg/mL for resistance). It is important to note that cefoperazone-sulbactam breakpoint criteria was established in the early 1980s when the compound was approved for clinical use in Europe and has not been reviewed by EUCAST, CLSI or the US FDA (cefoperazone-sulbactam was not submitted for US FDA approval). CLSI has established breakpoints for cefoperazone (≤16 μg/mL for susceptible and ≥64 μg/mL for resistance CLSI, 2016) but these breakpoints have not been revaluated by the CLSI in 2010 when certain cephalosporin breakpoints were re-assessed.

2.3. Resistant subsets

Escherichia coli and *Klebsiella* spp. isolates were grouped as "ESBL phenotype" based on the CLSI screening criteria for potential ESBL production: i.e., MIC of ≥2 μg/mL for ceftazidime and/or ceftriaxone and/or aztreonam. Carbapenem-resistant Enterobacteriaceae (CRE) were defined as isolates displaying MIC values at ≥4 μg/mL (CLSI, 2016) for imipenem (*P. mirabilis* and indole-positive Proteeae were not included due to the intrinsically elevated MIC values) and/or meropenem and/or doripenem. MDR, extensively drug-resistant (XDR), and pan-drug-resistant (PDR) Enterobacteriaceae strains were classified according to recently recommended guidelines (Magiorakos et al., 2012) and the antimicrobial classes and drug representatives used in the analysis were: broad-spectrum cephalosporins (ceftriaxone, ceftazidime, and cefepime), carbapenems (imipenem, meropenem, and doripenem), broad-spectrum penicillin combined with β-lactamase-inhibitor (piperacillin-tazobactam), fluoroquinolone (ciprofloxacin and levofloxacin), aminoglycosides (gentamicin, tobramycin, and amikacin), glycylcyclines (tigecycline) and the polymyxins (colistin; EUCAST criteria) for Enterobacteriaceae; and antipseudomonal cephalosporins (ceftazidime and cefepime), carbapenems (imipenem, meropenem, and doripenem), broad-spectrum penicillins combined with β-lactamase-inhibitor (piperacillin-tazobactam), fluoroquinolones (ciprofloxacin and levofloxacin), aminoglycosides (gentamicin, tobramycin, and amikacin) and the polymyxins (colistin) for *P. aeruginosa*. Classifications were based on the following recommended parameters: MDR = non-susceptible (NS; CLSI/EUCAST breakpoints) to at least 3 antimicrobial classes; XDR = susceptible (S) to 2 or fewer antimicrobial classes; and PDR = NS to all antimicrobial classes (Magiorakos et al., 2012). Quality control (QC) followed CLSI methods and used *E. coli* ATCC 25922 and 35,218, *S. aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, and *Enterococcus faecalis* ATCC 29212.

3. Results and discussion

The 18,386 isolates tested were composed of 13,224 Enterobacteriaceae isolates, 3536 *Pseudomonas aeruginosa*, 1254 *Acinetobacter* spp. isolates, and 372 *S. maltophilia* isolates (Table 1). Among the Enterobacteriaceae isolates, the following antimicrobial-resistant phenotypes were detected: ESBL (2694; 20.4%), MDR (2347; 17.7%), XDR (419; 3.2%), and CRE (378; 2.9%). PDR strains were not detected in the survey. There were 1021 (81.4%) MDR *Acinetobacter* spp. isolates, and all 372 isolates of *S. maltophilia* were considered MDR (data not shown).