In vitro activity of tigecycline against ampicillin-resistant Haemophilus influenzae isolates

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Sir,

The increasing resistance in Haemophilus influenzae has complicated the choice of antibiotics for empirical treatment of community-acquired respiratory tract infection. Tigecycline, a glycylcycline, is a new semi-synthetic 9-t-butylglycylamido derivative of minocycline with potent in vitro activity against a wide variety of Gram-positive and Gram-negative organisms, including multidrug-resistant strains.1 Tigecycline overcomes the two major tetracycline resistance mechanisms, efflux and ribosomal protection. Its activity against H. influenzae is not affected by the presence of β-lactamase enzyme.2,3 The aim of this study was to evaluate the in vitro activity of tigecycline against ampicillin-resistant H. influenzae isolates.

A total of 185 non-duplicate clinical isolates of ampicillin-resistant H. influenzae were tested. These strains were obtained as part of a multicentre surveillance of antimicrobial resistance, the VIRA (Vigilancia de la Resistencia a los Antimicrobianos) study, from 40 medical centres throughout Spain (isolation dates in October 2001 and in February 2004).4 Organisms were identified in each centre using routine methods. At the coordinating laboratory (Clinical Microbiology Laboratory, Hospital Clínico San Carlos, Madrid, Spain), the identity of isolates was confirmed by the API NH system (bioMérieux, Marcy l’Étoile, France). MICs of tigecycline were determined by the broth microdilution method following the recommendations of the NCCLS.5 Microdilution trays were prepared in-house on the day of testing using fresh broth. All but 10 isolates were β-lactamase producers. Most of the isolates were also resistant to other antimicrobial agents.3,4 Twenty-two isolates were resistant to tetracycline, 11 showed intermediate resistance to this antibiotic and 23 were resistant to chloramphenicol. Of 62 isolates that were resistant to trimethoprim/sulfamethoxazole, 14 were also resistant to chloramphenicol. Twenty-two isolates were non-susceptible to both tetracycline and chloramphenicol. Serotyping was performed using a slide agglutination procedure (Phadebact Haemophilus Test; Boule Diagnostics AB, Sweden).

Six (3.2%) isolates belonged to capsular serotypes a or c–f, four (2.2%) to capsular serotype b and the 175 (94.6%) remaining isolates were non-typeable. Tigecycline inhibited all of the isolates at concentrations of between 0.06 and 2 mg/L (MIC50 1 mg/L and MIC90 2 mg/L). If the provisional susceptibility breakpoint for tigecycline of ≤ 2 mg/L was used, all isolates would be susceptible to this new antibiotic. No difference between tigecycline MICs was detected between tetracycline-susceptible and -resistant isolates.

The increasing antimicrobial resistance in H. influenzae is of clinical concern. The results of this study confirm the absence of cross-resistance between tetracycline and tigecycline and indicate that tigecycline is very active against ampicillin-resistant H. influenzae isolates, including those resistant to other antibiotics such as trimethoprim/sulfamethoxazole, chloramphenicol or tetracycline, as well as multiresistant isolates. The MIC50 and MIC90 values of tigecycline were 1 dilution lower than those reported by Zhanel et al.,2 but 1 dilution higher than those recently reported by Fritsche et al.1 among β-lactamase-positive isolates.

In vivo efficacy of tigecycline has been evaluated in several animal infection models. Pharmacodynamic and pharmacokinetic studies demonstrated a prolonged half-life (t1/2), significant post-antibiotic effect, and excellent and homogeneous tissue diffusion using the rabbit model of endocarditis.6 Preliminary pharmacokinetic studies in humans showed that the mean t1/2 was 36 h,7 making once-daily dosing possible. Its efficacy and tolerability are being investigated in humans. Tigecycline may play an important role as a new alternative for the treatment of community-acquired respiratory tract infections caused by ampicillin-resistant H. influenzae isolates. Further clinical studies are warranted to confirm the efficacy of this new agent.

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References


Panresistance in VIM-1-producing Klebsiella pneumoniae

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SIR,
The term 'panresistance' usually refers to non-fermenting bacilli, such as Pseudomonas and Acinetobacter spp., resistant to all clinically available antimicrobials, except colistin. We report here on four Klebsiella pneumoniae clinical isolates exhibiting this pattern of resistance. The isolates, derived from patients treated in intensive care units in three teaching hospitals in Athens during 2002–2004, were positive for metallo-β-lactamase (MBL) production. Determination of antibiotic susceptibility by the microdilution method showed high levels of resistance to carboxy- and ureido-penicillins, penicillin–inhibitor combinations, cefoxitin, aztreonam, and late-generation cephalosporins, including ceftime and cefpirome (all MICs were ≥128 mg/L). MICs of imipenem and meropenem were ≥32 mg/L. MIC values above the respective resistance breakpoints were also observed for aminoglycosides (AMGs) (gentamicin, tobramycin, netilmicin and amikacin), ciprofloxacin, trimethoprim, sulphonamides and chloramphenicol.

Isolates were compared by PFGE in 1% agarose, after digestion of total DNA with Xba I. The resulting fingerprints differed by three or fewer DNA fragments, indicating a possible common ancestry, according to established criteria.1 The observed PFGE patterns are also common among VIM-producing K. pneumoniae exhibiting resistance phenotypes other than the one described here. Additionally, conjugative transfer experiments, using a highly rifampicin-resistant Escherichia coli laboratory strain as recipient, followed by plasmid DNA analysis, showed that all isolates harbouried the same two plasmids, with approximate sizes of 110 and 50 kb. The plasmids were readily segregated, were both self-transmissible, and conferred distinct multiresistant phenotypes. The 110 kb plasmid was similar to the SHV-5-encoding plasmids that belong to incompatibility group L/M (IncL/M) and are widely disseminated among clinical enterobacteria in Europe, and especially in the Mediterranean region. PCR assays based on published sequences of the above mentioned IncL/M plasmids (AJ245670 and AF550679 in GenBank) and sequencing of the amplicons, showed that the 110 kb plasmid carried a blaSHV-5 gene adjacent to an integron similar to In-T3, that contained aacC1, dfrA, aadA and sulI.2 This plasmid also mediated resistance to chloramphenicol, but the respective determinant was not examined. The antibiotic resistance region of the 50 kb plasmid included an intact class 1 integron containing blaVIM-1, aacC1, dfrA, aadA and sulI, as described previously (AY339625 in GenBank).3 This plasmid was similar to a group of IncN, VIM-1-encoding plasmids, found recently in clinical enterobacteria in Greece.4,5 In addition, a mutation in the gyrA gene associated with resistance to quinolones (Ser-83 → Phe) was detected in all isolates. gyrB and parC were not examined.

Panresistant K. pneumoniae have been noticed in the intensive care units of various Athens hospitals since 2001, coinciding with the emergence of MBL-positive enterobacteria. We have shown that this phenotype can be caused by the acquisition of two multiresistant plasmids, able to co-exist within a single cell, since they belong to different incompatibility groups. Until now, VIM-1-producing K. pneumoniae were susceptible to aztreonam—a poor substrate for the VIM-1 MBL5—and gentamicin, which remains unaffected by the AMG-modifying enzymes encoded by the VIM-1 plasmids. However, in the isolates presented here, these two drugs are also rendered inactive, by expression of blaSHV-5 and aacC1, carried by the 110 kb plasmid. Another notable characteristic of these isolates was their high-level resistance to carbapenems, contrary to the majority of VIM-producing enterobacteria, where carbapenem MICs remain within the susceptible range. Carbapenemase activity of cell extracts, assessed by spectrophotometry, did not reveal significant differences in the VIM-1 amounts produced by these highly resistant isolates, compared with the less resistant ones. Therefore, it is possible that mutations affecting intracellular carbapenem accumulation contribute to the elevated MICs, but this was not examined further.

PFGE typing suggested that the isolates may be genetically related. This clonal hypothesis is not contradicted by the identical gyrA mutations. Despite the propitious and ubiquitous antibiotic selection pressure in the nosocomial environment, these panresistant strains still only account for a small fraction of all VIM-positive K. pneumoniae isolated. Nevertheless, emergence of other enterobacterial clones with a similar phenotype can be expected, given that both plasmids are endemic in this country.

The limited number of cases and the serious nature of patients’ conditions that led to frequent changes in antibiotic treatment, do not allow us at present to make any firm suggestions for an optimal therapeutic scheme. So far, colistin, various antibiotic combinations, and non-conventional dosing schemes have been proposed for the treatment of life-threatening infec-

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