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Review Article

Tigecycline: pharmacological concerns and resistance

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ABSTRACT

Tigecycline, a semisynthetic derivative of minocycline, has a broad spectrum of activity against both gram positive and gram negative multidrug resistant bacteria. The drug acts on 30S ribosomal subunit and inhibits protein synthesis. Since the drug has excellent tissue distribution, it is very useful for treatment of skin infections, intra-abdominal infections and pneumonia. Side effects of the drug are usually mild. The common side effects include nausea and vomiting. The exact mechanism of resistance remains unclear. However, resistance mediated by enhanced expression of resistance nodulation cell division (RND) type efflux pumps is one of the most frequently reported mechanisms. Resistance has been observed worldwide. However, the rate of resistance is low.

Keywords: Tigecycline, Multidrug resistant bacteria, Resistance

INTRODUCTION

Tigecycline is the first drug in the glycylcycline class of antibiotics to be approved.[1] It is semisynthetic derivative of minocycline, a tetracycline antibiotic.[1] It overcomes the two major mechanisms of tetracycline resistance: tetracycline specific efflux pump acquisition and ribosomal protection.[2] It exhibits broad-spectrum activity against both gram positive and gram-negative bacteria, including many multidrug resistant pathogens.[3,4] Tigecycline is considered as a drug of last resort against infections caused carbapenem-resistant gram-negative bacteria.[5]

Tigecycline was approved by the US food and drug administration (FDA) in 2005 and by the European Medicines Agency (EMEA) in 2006 for the treatment of complicated skin structure infections (cSSSIs) and complicated intra-abdominal infections (cIAIs) in adults.[6] The drug further received an approval in March 2009 from FDA for the treatment of community acquired pneumonia (CAP) caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta lactamase negative isolates) and *Legionella pneumophila*.[7]

The purpose of this article is to review important pharmacological characteristics of tigecycline and its resistance.

A search of the literature was made using medline database, google database and online journals. The search was limited to publications in the English language. The search terms 'tigecycline', 'pharmacology of tigecycline' or 'tigecycline resistance' were used. Additional information was obtained from standard book and the website of Medscape.

MECHANISM OF ACTION

Tigecycline enters the bacterial cell by active transport or passive diffusion and, similar to tetracyclines, binds reversibly to the 30S ribosomal subunit preventing

peptide elongation and inhibiting synthesis of bacterial proteins.[8]

The enhanced binding affinity and antibacterial potency of this drug compared to other tetracycline antibiotics is attributable to stacking interactions between the unique 9-t-butylglycylamido group of tigecycline and the 16S rRNA of the 30S ribosomal subunit.[9] The bulkiness of this moiety also contributes to circumvent the common mechanisms of tetracycline resistance.[9]

PHARMACOKINETIC EFFECT

Tigecycline has poor gastrointestinal absorption.[1] Therefore, it must be administered intravenously.[1] The drug is given as a 100 mg loading dose, then 50 mg every 12 hours.[1] Tissue and intracellular penetration of this drug, similar to all tetracyclines, is excellent and the volume of distribution is quite large.[1] Therefore, it will be most useful as empirical therapy for polymicrobial infections, especially in cases in which deep tissue penetration is needed or in which multidrug-resistant pathogens are suspected.[2]

However, it has low peak plasma concentrations of 0.8-1 mg/l, which is discouraging for treatment of bacteremia due to micro-organisms with an MIC ≥1 mg/l and may be associated with possible poor clinical outcome and the emergence of tigecycline-resistant organisms.[10]

Tigecycline does not interfere with common cytochrome P450 enzymes, thus, pharmacokinetic drug interactions are uncommon.[2]

The drug is eliminated primarily via biliary excretion. No dosage adjustment is required for patients with renal insufficiencies.[1]

About 15% of tigecycline is excreted unchanged in the urine under standard dosing, which is not encouraging for successful treatment of urinary tract infection (UTI).[11] A previous study has indicated that administration of this drug for UTIs was associated with low microbiological treatment rate and a high rate of isolation of tigecycline non-susceptible isolates.[12] However, various studies have reported successful outcomes with tigecycline therapy in patients with a UTI.[13,14]

INDICATIONS

The following are the recommended indications of tigecycline.[15] Complicated skin infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible only), *Staphylococcus aureus* (MRSA and methicillin-susceptible), *Streptococcus pyogenes*, *Streptococcus anginosus* group, *Streptococcus agalactiae*, or *Bacteroides fragilis*. Complicated intra-abdominal infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible only), *S. aureus* (methicillin-susceptible only), *Citrobacter freundii*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *K. oxytoca*, *B. thetaiotaomicron*, *B. uniformis*, *B. vulgatus*, *Clostridium perfringens*, *Peptostreptococcus micros*. Community-acquired pneumonia caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Legionella pneumophila*.

PROMISING RESULTS IN OTHER CONDITIONS

The drug is also showing promising results in treatment of other conditions such as cancers and malaria.[16,17] In cancer, it has been found to induce cell cycle arrest, apoptosis, autophagy and oxidative stress and inhibit mitochondrial oxidative phosphorylation, cell proliferation, migration, invasion and angiogenesis.[16]

An in-vitro evaluation study highlighted that the antimalarial activity of tigecycline was significantly higher against chloroquine resistant than against chloroquine susceptible *P. falciparum* strain. This drug also selectively potentiated the anti-malarial action of chloroquine against chloroquine resistant *P. falciparum* strain.[17]

ADVERSE DRUG EFFECTS

The common side effects of tigecycline include nausea and vomiting. Cumulative incidences of nausea and vomiting in over 13 trials were about 26% and 18% respectively.[11] The exact mechanism for these adverse gastrointestinal events remains unknown. However, they were manageable with the use of standard antiemetic therapies and did not require discontinuation of the drug.[11]

The other side effects reported in 1-15% the people include diarrhea, infections, fever, abdominal pain, headache, hypertension, hypotension, anemia, dizziness, dyspnea, pruritus, rash and insomnia.[15]

BOXED WARNING

Based on meta-analyses of 10 clinical trials, a boxed warning was issued by FDA in 2010 since the drug was found to be associated with an increased risk of death.[18] Higher mortality associated with this drug was also reported by other studies.[19,20]

RESISTANCE

Resistance against tigecycline has emerged worldwide since its approval.[21]

Mechanism of resistance

The exact mechanism of resistance to tigecycline has not yet been clearly elucidated.[21] Enhanced expression of resistance nodulation cell division (RND) type efflux pumps in gram-negative bacteria was associated with decreased tigecycline susceptibility.[22] Over-expression of

the RND efflux pumps, AcrAB and OqxAB, is one of most frequently reported mechanisms in the *Enterobacteriaceae* members. Several global transcriptional regulators of the AraC family, namely, RamA, MarA, SoxS, and RarA have been found to contribute to tigecycline resistance via efflux pump activation.[23-26] A new efflux pump operon, kpgABC mediated resistance was reported by Nielsen et al in *K. pneumoniae*.[27] Alteration of ribosomal binding site via mutation has also been described for its ability to cause decreased tigecycline susceptibility in both gram negative and gram positive bacteria.[28,29]

Epidemiology of resistance

Variable rates of resistance have been observed worldwide in various bacterial pathogens including *Acinetobacter spp., Pseudomonas spp.* and *Enterobacteriaceae* family members such as *Escherichia coli, Enterobacter spp., Klebsiella spp.* and *Serratia spp.*[8,11] The drug is found to retain low non-susceptibility rates of <10% among *Enterobacteriaceae* members worldwide in most large-scale surveillance studies.[30-33] However, higher rate of resistance has been observed among extended-spectrum β-lactamase (ESBL) producing, multidrug resistant (MDR), extensively drug-resistant and carbapenem resistant (CR) isolates.[8] In the Americas, many studies have reported resistance rate of <10%.[34-37] However, few studies have reported higher rate of resistance.[38,39]

In the Asia-Pacific countries, resistance rate exhibited by the bacterial pathogens including ESBL-producing isolates and ertapenem-resistant *E. coli, K. pneumoniae* and *E. cloacae* was <10%.[40,41] However, ertapenem-resistant isolates of *E. aerogenes* and *S. marcescens* had exhibited 31% and 20% resistance, respectively.[42] In Africa and the Middle East, multiple studies have reported non-susceptibility rates of <10%.[43-45] In Europe, large number of studies reported a tigecycline non-susceptibility rate of 10% or less among ESBL-producing, carbapenem resistant and multidrug resistant strains.[46-48]

CONCLUSION

In the era of limited available antimicrobial options, tigecycline is a valuable drug for treatment of serious infections such as complicated skin infections, complicated intra-abdominal infections and community-acquired pneumonia.

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