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Tigecycline : First Member of the Novel Glycylcycline Class of Extended-Spectrum Antibiotics

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ABSTRACT

Tigecycline is the first member of a synthetic analogue of tetracycline, known as a glycylcycline. Like other tetracyclines, tigecycline is a broad spectrum bacteriostatic agent. It inhibits protein synthesis by binding to the bacterial 30S ribosomes. Tigecycline has activity against both gram-positive and gram-negative bacteria. It also has activity against many multidrug resistant organisms including methicillin-resistant *Staphylococcus aureus* (MRSA), Penicillin-resistant *Streptococcus pneumoniae* (PRSP) Vancomycin resistant *Enterococcus* species (VRE) and extended-spectrum β -lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*. Tigecycline was approved for use in the United States in 2005. It is currently indicated in patients 18 years of age and older for the treatment of complicated skin and skin structure infections and intra-abdominal infections due to sensitive organisms. Tigecycline is available in vials of 50 mg for parenteral use under the brand name Tygacil. The recommended dose is 100 mg intravenously initially, followed by 50 mg every 12 hours for 5 to 14 days depending on the severity and site of the infection. The Food and Drug Administration had issued a black box warning due to increased risk for death in patients who received tigecycline with certain severe infections. The increased mortality rate is associated with patients who were treated for hospital-acquired pneumonia, particularly ventilator-associated pneumonia. The cause of excess deaths is uncertain, but it is likely that most deaths related to the progression of the infection. A reduced dosage is recommended for patients with severe underlying liver disease.

Keywords: Tigecycline, Broad spectrum antibiotic; multi-resistant pathogens, Black box warning.

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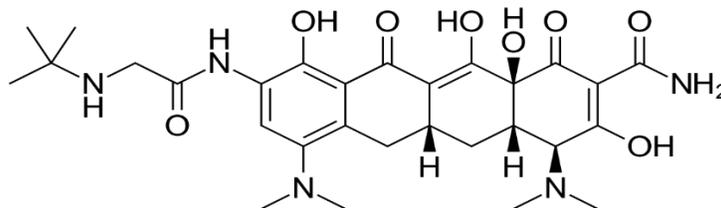
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INTRODUCTION

Tigecycline is a Tetra cycline-class antibacterial used for a number of infections. It is the first drug in the glycylycline class of antibiotics. It is administered intravenously. It was developed in response to the growing rate of antibiotic resistant bacteria such as *Staphylococcus aureus*, *Acinetobacterbaumanni*, and *Escherichia coli*. As a synthetic tetracyclin analogues, its structural modifications has expanded and its therapeutic activity towards Gram-positive and Gram-negative organisms, including those of multi-drug resistance. Thus they have the broad spectrum of activity. Tigecycline is a derivative of minocycline that was introduced in 2005.^[1]It show activity against gram-positive and negative cocci and anaerobes, including tetracycline resistant strains of *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Staphylococcus auerus*, MRSA, VRSA as well as tetracycline sensitive organisms like *Rickettsiae*, *chlamydia*, *Mycoplasma* etc. However *Pseudomonas* and *Proteus* are inherently nonresponsive to Tigecycline.^[1]

CHEMISTRY

Tigecycline is a noval classes of glycylycline have the central four-ring carbocyclic skeleton similar to tetracyclines which is necessary for the antibacterial activity. In tigecycline, substitution of an N-alkyl-glycylylamido group on the D ring at the 9th position facilitates the broader spectrum of activity, and additionally, this creates the ability to overcome most tetracycline resistance mechanisms. Tigecycline has a 9-t-butyl-glycylylamido side chain on the central skeleton, and it is an analogue of minocycline tigecycline's molecular weight is 585.65 Da and chemical formula is C₂₉H₃₉N₅O₈.^[4]



MECHANISM AND RESISTANCE

Tigecycline have a mechanism of action similar to that of tetracycline with some notable improvement. Tigecycline inhibit bacterial protein synthesis by binding to bacterial 30s ribosomal subunit with subsequent blockade of entry of amino acylt RNA molecule into A site of the ribosome thereby preventing the incorporation of amino acids into elongating peptide chains. Even though tetracycline and glycylycline share a common binding site tigecycline's in vitro activity is more due its stronger ribosome binding affinity, which is fivefold greater than tetracycline and minocycline.^[14, 5]Tigecycline is not affected by most of the common mechanisms of antibiotic resistance used by bacteria, due to steric hindrance afforded by the large D-ring substituent.

Tigecycline binds to the 30S ribosomal subunit even in the presence of ribosomal protection mechanisms, while it is also excluded from efflux pumps that serve to expel drug molecules from the cell. In addition to efflux and ribosomal protection mechanisms, there are other common antibiotic resistance mechanisms that affect other classes of antimicrobial agents but do not affect tigecycline. These include target site modifications, enzymatic degradation of the drug molecule, and DNA gyrase mutations.^[5]

Pharmacokinetics

Absorption-Tigecycline is poorly absorbed from the g.i.t. Tigecycline is available as parenteral agent due to its poor oral bioavailability. Only route of administration is as slow IV infusion.

Distribution – Tigecycline is widely distributed in the tissue and its volume of distribution ranges from 7-10L/kg. Tigecycline is moderately bound to plasma proteins.

Elimination- Tigecycline is metabolized in the liver by glucoronidation, and its major route of elimination is through feces, likely via biliary excretion. Elimination half-life is 36-60hrs.^[1,6]

Dosing and administration

Tigecycline is given as 100mg loading dose followed by 50mg 12hourly by slow iv infusion over 30-60min. The powder for injection should be reconstituted with 5.3-ml sodium chloride 0.9% or dextrose 5% to give 10-mg/ml tigecycline. Thereafter, 5 ml should be withdrawn and added to 100-ml sodium chloride 0.9% or dextrose 5% infusion bag. The drug is not available as an oral preparation which limits its use. Tigecycline has been shown to be incompatible with the following drugs: amphotericin B, chlorpromazine, diazepam, methylprednisolone and voriconazole. No dosage adjustment is required in patients with mild to moderate hepatic impairment or patients with renal impairment or receiving haemo dialysis. In severe hepatic impairment the tigecycline dose should be reduced to 25 mg bd following the 100 mg loading dose. Patients with severe hepatic impairment should be treated with caution and monitored for treatment response.^[3]

INTERACTIONS

Tigecycline has been shown to decrease clearance of warfarin. It may prolong prothrombin time (PT) and activated partial thromboplast in time (aPTT), regular anticoagulation tests should be carried out when warfarin and tigecycline are administered concomitantly. Antibiotics administered with oral contraceptives may reduce contraceptive effect so additional precautions are recommended.

WARNINGS AND PRECAUTIONS^[2]

All-Cause Mortality

An increase in all-cause mortality has been observed in a meta-analysis of Phase 3 and 4 clinical trials in Tigecycline-treated patients versus comparator-treated patients². The deaths were the result of worsening or complications of infection or in co-morbidity conditions. Tigecycline use should be reserved in situations when alternative treatments are not suitable.

Mortality Imbalance and Lower Cure Rates in Hospital-Acquired Pneumonia

Patients with hospital acquired, including ventilator-associated, pneumonia failed to demonstrate the efficacy of Tigecycline. Greater mortality was seen in patients with ventilator-associated pneumonia who received Tigecycline.

Anaphylaxis/Anaphylactoid Reactions

Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including Tigecycline, and may be life-threatening. Tigecycline is structurally similar to tetracycline-class antibiotics and should be administered in patients with caution in those who have known hypersensitivity to tetracycline-class antibiotics.

Hepatic Effects²

Increases in total bilirubin concentration, prothrombin time and transaminases have been seen in patients treated with tigecycline. Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing tigecycline therapy. Adverse events may occur after the drug has been discontinued.

Pancreatitis

Acute pancreatitis, including fatal cases, had occurred in association with tigecycline treatment. On diagnosing, acute pancreatitis should be considered in patients taking tigecycline who develop clinical symptoms, signs, or laboratory abnormalities suggestive of acute pancreatitis. Patients usually improved after the discontinuation of tigecycline, so that consideration should be given to the cessation of the treatment with tigecycline in cases suspected of having developed pancreatitis.

Use During Pregnancy

Tigecycline may cause fetal harm on administration to a pregnant woman. If the patient becomes pregnant while taking tigecycline, the patient should be aware of the potential hazard to the fetus. Animal studies indicate that tigecycline crosses the placenta and its presence was found in fetal tissues.

Tooth Development

The use of Tigecycline during tooth development can cause permanent discoloration of the teeth. There for Tigecycline should not be used during tooth development unless other drugs are not likely to be effective or are contra indicated.

Clostridium difficile Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been developed with use of nearly all antibacterial agents, including Tigecycline, and severity ranges from mild diarrhea to fatal colitis. Overgrowth of Clostridium difficile in colon occurs as a result of treatment with antibacterial agents because of the alterations in normal flora. Clostridium difficile produces toxins A and B which contribute to the development of CDAD. Hyper toxin producing strains of Clostridium difficile cause increased morbidity and mortality, as these infections may become refractory to antimicrobial therapy and may require colectomy. In case of CDAD is suspected or confirmed, ongoing antibiotic use not directed against Clostridium difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of Clostridium difficile, and surgical evaluation should be initiated as per the clinical opinion.

Patients with Intestinal Perforation

Caution should be required when considering Tigecycline monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation.

Tetracycline-Class Effects

Tigecycline is structurally similar to tetracycline-class of antibiotics and may have similar adverse effects. Such effects are the following; photosensitivity, pseudo umorcerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of Tigecycline too.

Super infection

As with other antibacterial drugs, use of Tigecycline may result in overgrowth of non-susceptible organisms, including fungi, so that patients should be carefully monitored during the therapy. If super infection occurs, appropriate measures should be taken.

Development of Drug-Resistant Bacteria

On prescribing Tigecycline in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

Use^[2]

Complicated intra-abdominal infections

The guidelines published by Infectious Diseases Society of America recommend treating mild to moderate community-acquired intra-abdominal infections with ampicillin/sulbactam, cefazolin plus metronidazole. If patients can take oral therapy, use of a fluoroquinolone, such as levofloxacin, plus metronidazole or amoxicillin/clavulanate alone is acceptable treatment. High-risk patients, defined as patients with other medical conditions or immune suppression, are recommended to receive treatment with carbapenems and piperacillin/tazobactam, or a fluoroquinolone plus metronidazole. Hospital acquired intra-abdominal infections are more likely to be caused by resistant organisms due to length of hospital stay. In such case tigecycline is recommended. Patients receiving tigecycline 100-mg loading dose followed by 50 mg every 12 hours given intravenously with imipenem/cilastatin 500 mg intravenously every 6 hours, cure rates were higher for imipenem/cilastatin group. The drug shows the non inferiority however, infection and postoperative wound infection rates were significantly higher in the tigecycline group.^[10]

Complicated Skin and Skin Structure

Infections Complicated skin and skin structure infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus*grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiellapneumoniae*, and *Bacteroidesfragilis*.

Limitations of Use

Tigecycline is not indicated for the treatment of diabetic foot infections. It is not indicated for the treatment of hospital-acquired or ventilator-associated pneumonia. In a comparative clinical trial, greater mortality and decreased efficacy were reported in Tigecycline treated patients. To reduce the development of drug-resistant bacteria and maintain the effectiveness of Tigecycline and other antibacterial drugs, Tigecycline should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to tigecycline. Tigecycline may be initiated as empiric monotherapy before results of these tests are known.

Patients with Hepatic Impairment

In patients with severe hepatic impairment, the initial dose should be 100 mg followed by a reduced

maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment should be treated with caution and monitored for treatment response and Use in Specific Populations.

Pediatric Patients

The safety and efficacy of the proposed pediatric dosing regimens have not been evaluated due to the observed increase in mortality associated with tigecycline in adult patients. Tigecycline should not be used in pediatric patients unless no alternative antibacterial drugs are available. Under these circumstances, the following doses are suggested for Pediatric patients aged 8 to 11 years should receive 1.2 mg/kg of tigecycline every 12 hours intravenously to a maximum dose of 50 mg of tigecycline every 12 hours. Pediatric patients aged 12 to 17 years should receive 50 mg of tigecycline every 12 hours. The proposed pediatric doses of tigecycline were chosen based on exposures observed in pharmacokinetic trials, which included small numbers of pediatric patients.

ADVERSE REACTIONS^[2]

In clinical trials, 2514 patients were treated with TYGACIL. TYGACIL was discontinued due to adverse reactions in 7% of patients compared to 6% for all comparators.

Table 1. Incidence (%) of Adverse Reactions Through Test of Cure Reported in $\geq 2\%$ of Patients Treated in Clinical Studies

Body System Adverse reaction	Tigecycline (N=2514)	Comparators (N=2307)
Body as a Whole		
Abdominal pain	6	4
Abscess	2	2
Asthenia	3	2
Headache	6	7
Infection	7	5
Cardiovascular System		
Phlebitis	3	4
Digestive System		
Diarrhea	12	11
Dyspepsia	2	2
Cardiovascular System		
Phlebitis	3	4
Digestive System		
Nausea	26	13
Vomiting	18	9
Hemic and Lymphatic System		
Anemia	5	6
Metabolic and Nutritional		
Alkaline Phosphatase Increased	3	3
Amylase Increased	3	2
Bilirubinemia	2	1

BUN Increased	3	1
Healing Abnormal	3	2
Hyponatremia	2	1
Hypoproteinemia	5	3
SGOT Increased	4	5
SGPT Increased	5	5

Table 2. Incidence (%) of Adverse Reactions Through Test of Cure Reported in $\geq 2\%$ of Patients Treated in Clinical Studies^[2]

Body System Adverse Reaction	Tigecycline (N=2514)	Comparators (N=2307)
Respiratory System		
Pneumonia	2	2
Nervous System		
Dizziness	3	3
Skin and Appendages		
Rash	3	4

[a Vancomycin/Aztreonam, Imipenem/Cilastatin, Levofloxacin, Linezolid].

[b LFT abnormalities in TYGACIL-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy]

BROAD-SPECTRUM COVERAGE[†]

Tigecycline has in vitro activity against a wide range of range of pathogens

+

TYGACIL[®] has broad *in vitro*^{*} activity, including many resistant pathogens²

	TYGACIL [®] (tigecycline)	Carbapenem (imipenem, meropenem)	β -lactam/ β -lactamase inhibitor (piperacillin/ tazobactam)	Third-generation cephalosporin (ceftazidime/ cefepime)	Fluoroquinolone (ciprofloxacin)
Gram-positives	✓	✓	✓	✓	✓
Gram-negatives	✓ [†]	✓	✓	✓	✓
Anaerobes	✓	✓	✓		
Resistant Gram-positives [‡]	✓				
Resistant Gram-negatives [§]	✓	✓			
<i>P aeruginosa</i>		✓	✓	✓	✓

Adapted from Wilcox 2006.²

****In vitro* activity does not necessarily correlate with clinical results.**

[†]Except *Proteus* spp. and *Providencia* spp.
[‡]Includes MRSA and glycopeptide-resistant enterococci (GRE).
[§]Includes ESBL-producing bacteria and *Acinetobacter* spp.
Please refer to SmPCs of individual antibiotics for specific coverage.

Except *Proteus* and *Providencia* spp.

Includes MRSA and glycopeptide –resistant enterococci (GRE).

Includes ESBL-producing bacteria and *Acinetobacter* spp.

- Tigecycline is indicated in adults and in children from the age of 8 years for the treatment of complicated intra-abdominal infections and complicated skin and soft tissue infections excluding diabetic foot infections
- Tigecycline should be used only in situations where other alternative antibiotics are not suitable

CONCLUSION

Tigecycline is the first in a new class of antibiotics, the glycylycyclines. Tigecycline inhibits protein synthesis and is generally considered a bacteriostatic agent. It has broad-spectrum antibacterial activity against gram-positive and gram-negative aerobes and anaerobes, including MRSA and multidrug-resistant gram-negative bacteria. It is not effective against *Pseudomonas*, *Providentia*, and *Proteus* species. Tigecycline is approved for use in adult patients with complicated skin and SSIs, complicated intra abdominal infection. It is not approved for the treatment on hospital-acquired pneumonia, having increased mortality rate in patients who receiving the drug.^[1] Tigecycline is mainly excreted unchanged into bile, with only 10% to 15% excreted unchanged in the urine. Dose adjustment is necessary for patients with severe hepatic impairment. Tigecycline therapy is sometimes accompanied by minor aminotransferase elevations, but has not been definitely associated with clinically apparent liver injury with jaundice. The most frequent side effects of tigecycline are diarrhea, nausea and vomiting.

Tigecycline was more active than clindamycin, minocycline, and cefoxitin and less active than imipenem or piperacillin-tazobactam against all isolates of the bacteria. The ultimate clinical role of tigecycline has yet to be defined in the treatment of nosocomial infections caused by multidrug-resistant gram-negative and gram-positive organisms that remain susceptible to tigecycline.

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