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AN IMPORTANT DRUG OF LAST RESORT FOR MULTIDRUG-RESISTANT (MDR) PATHOGENS AND THE FIRST GLYCYLCYCLINE ANTIBIOTIC -TIGECYCLINE

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Abstract: Tigecycline is an antibiotic of glycylcycline class used a reserve drug for infections resistant to most other antibacterial classes. It is recommended to be used for the treatment of complicated skin & intra-abdominal infections and community-acquired pneumonia as well. It has emerged as a promising drug that was initially developed to overcome the resistance issues to earlier tetracyclines use. Due to difference in structure over other tetracyclines, this glycylcycline antibiotic has increased structure activity and resistance becomes minimum. Thus, this antibiotic can be used as a drug of last choice when other drugs are not showing any effect on the bacterial infection. It covers both gram positive and gram negative classes. There are no serious drug-drug interactions known where tigecycline is contraindicated. Hence, it can be used in most of the conditions but care must be taken not to use it often and only reserve it for most severe strains of bacteria, as improper use may result in resistance. This review will help to highlight the usefulness of tigecycline and at the same time make the clinicians aware that it is not a drug that should be used very frequently and should be used as a high-end antibiotic only for resistant bacterial infections.

Keywords: Tigecycline, glycylcycline, antibacterial, antibiotic, resistant strain

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INTRODUCTION

Tigecycline is an injectable anti-bacterial antibiotic[1]. It belongs to drug class glycylcycline. It was approved by FDA in June 2005[1, 2]. The ATC code of the drug is J01AA12[2]. The molecular formula of the drug is $C_{29}H_{39}N_5O_8$ and it has molecular mass of 585.658 g/mol. The chemical name of tigecycline is (4S,4aS,5aR,12aS)-9-[2-(tert-butylamino)acetamido]-4,7bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a tetrahydroxy-1,11-dioxo-2naphthacenecarboxamide. The chemical structure is shown in fig. 1[1, 3].

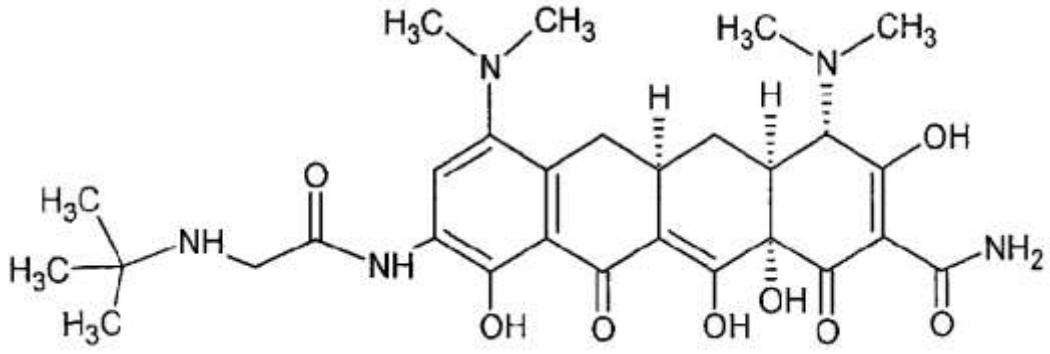

Figure 1: Chemical Structure of Tigecycline

Glycylcycline is comparatively a newer class among antibiotics and was derived from tetracycline. Similar to the tetracyclines, it has central four-rings carbocyclic skeleton with a substitution at the D-9 (dimethylglycylamido) position of the structure. This substitution results in broad-spectrum activity, defense against the antimicrobial efflux pumps which otherwise would have decreased the activity of tigecycline and ribosomal protection mechanisms as well, over other antibiotics of similar class[1, 3, 4]. Tigecycline has been found to be useful in the treatment of a broad spectrum of multi-drug resistant gram-positive along with gram-negative pathogens, including extended-spectrum ß-lactamase producing organisms and anaerobic pathogens as well. The clinical usefulness of this glycylcycline has been well established in complicated skin & skin structure and intraabdominal infections[1, 5]. Increased disease misdiagnosis and use of different antibiotics as prophylaxis without proper rationale are an emerging concern along with the increased resistance of antibiotics to various organisms[6, 7]. Though tigecycline acts upon most of the bacterial infections but does not exhibit any activity against *Pseudomonas aeruginosa* and *Proteus* species[1, 5].

MECHANISM OF ACTION

This first glycylcycline: tigecycline acts by inhibiting the bacterial protein translation by binding with the 30S ribosomal subunit and blocking of the entry of amino-acyl tRNA molecules to the A-site of the ribosomes. The desired antibacterial action of the tigecycline antibiotic is achieved

due to the same. This is a unique characteristic apart from the unique structure changes from tetracycline ring which makes tigecycline tremendously useful in various resistant strains of bacteria[3, 4].

DOSING

The available powder for injection of tigecycline is 50 mg per vial. This is the standard formulation available worldwide and it needs to be used as per infection and severity. The powdered drug needs to be mixed to saline or dextrose Solution and then could be injected as a bolus or can be given as intravenous infusion as per clinician's choice and requirement of the treatment[3, 8]. Types of infections where the glycylcycline: tigecycline is a preferred choice and its dosing has been shown in Table 1.

Table 1: Types of infections and dosing of tigecycline

Type of Infection	Dosing	
Complicated Intra-Abdominal Infections	Starting dose: 100 mg intravenous infusion; Maintenance dose: 50 mg IV infusion every 12 hourly	5-14 days
Complicated Skin Infections		
Community-acquired Pneumonia		7-14 days
An oral formulation of this drug does not exist. Only available as intravenous (IV).		

The duration of therapy is generally as per the severity and site of the infection and the patient's clinical and bacterial infection progress[3, 4, 8].

SUSCEPTIBLE ORGANISMS FOR TIGECYCLINE

The susceptible organisms[3, 8] are listed as per infections in table 2 below.

Table 2: Susceptible organisms for tigecycline

S. No.	TYPE	SUSCEPTIBLE ORGANISMS
I.	Complicated skin infections	It is useful in complicated skin infections caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible only), *Staphylococcus aureus* (MRSA and methicillin-susceptible), *Streptococcus pyogenes*, *Streptococcus anginosus grp, Streptococcus agalactiae* and *Bacteroides fragilis*.
II.	Complicated intra-abdominal infections	It has been recommended to be used in intra-abdominal infections caused by *E 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* and *Peptostreptococcus micros*.
III.	Community-acquired pneumonia	It is useful in treating community-acquired pneumonia caused by *Streptococcus pneumoniae, Haemophilus influenza* and *Legionella pneumophila*.

RENAL AND HEPATIC REQUIREMENTS FOR DOSAGE MODIFICATIONS

The renal and hepatic dose adjustments[3, 8] required for tigecycline has been listed in table 3.

Table 3: Renal and Hepatic adjustments for Tigecycline

PATIENT TYPE	DOSE ADJUSTMENT
RENAL IMPAIRMENT	Not required
HEPATIC IMPAIRMENT	• Mild (Child Pugh A) to moderate (Child Pugh B) hepatic impairment: Not required, • Severe hepatic impairment (Child Pugh C): Starting dose=100 mg and maintenance dose=25 mg, every 12 hourly.

PREGNANCY AND LACTATION

Tigecycline is a drug listed under pregnancy category D. Hence, it is only advised to be used in life-threatening emergencies, when no other safer drugs are available. Positive evidences of human fetal risk have been reported and the drug may be used for short-term while breastfeeding if no other alternative drugs are available. Though risk of infant harm is not expected based on drug properties but limited human data is available with other tetracyclines and there is no human data available to assess effects on the excretion of tigecycline in the human-breast milk. Hence, choosing tigecycline in pregnancy and lactation must be based upon clinician's judgement after benefit-to-risk evaluation[3, 8].

ADVERSE DRUG REACTIONS (ADRs)

ADRs are the one of the major concerns for clinicians when choosing any drugs as use may result in serious ADRs ranging from severe reactions like Stevens-Johnson Syndrome[9] to drug-induced gastrointestinal bleeding and anaemia[10]. Some of the ADRs of Tigecycline[3, 8, 11] are shown in Table 4.

Table 4: Adverse Drug Reactions of Tigecycline

Severe Reactions	Mild and Moderate Reactions
• **hypersensitivity reaction**	• Nausea and vomiting
• **anaphylaxis/anaphylactoid reaction**	• diarrhea
• **severe skin reaction**	• abdominal pain
• ***C. difficile*-associated diarrhea**	• anemia
• **cholestasis**	• hypoproteinemia
• **pancreatitis**	• asthenia
• **hyponatremia**	• BUN increase
• **photosensitivity anabolic effects**	• dizziness
	• hyperamylasemia
	• LFTs elevated

DRUG-DRUG INTERACTIONS

Tigecycline is generally not contraindicated to be used with other drugs but there are some serious drug interactions with use of some drugs along with tigecycline[3, 8, 11].

a) Some of the serious interactions that require use of alternative drugs are as follows[8, 11]:

i. **Tigecycline-BCG Vaccine:** Tigecycline decreases effects of BCG vaccine live by pharmacodynamic antagonism. Hence, is contraindicated to use with it.

ii. Tigecycline-cholera vaccine: Pharmacodynamic antagonism. Either should be avoided or alternate agents should be used. Should not administer cholera vaccine to patients who had received oral or parenteral antibiotics within 14 days prior to vaccination tigecycline decreases effects of typhoid vaccine live by pharmacodynamic antagonism. Hence, is contraindicated.

b) Monitor Closely[8, 11]

i. **Dichlorphenamide-tigecycline**

Either increases toxicity of the other by pharmacodynamic synergism. Modify Therapy/Monitor Closely. Both drugs can cause metabolic acidosis.

ii. **Warfarin- tigecycline**

Tigecycline increases levels of warfarin by decreasing elimination. Use Caution/Monitor. Minimal effect on INR; monitor.

CONCLUSIONS

Overall, it can be concluded that the first glycylcycline- tigecycline, is an effective agent available for the treatment of multi-drug resistant gram-negative and gram-positive infections as well. It can especially be recommended to be safe in the patients with a history of a penicillin allergy or antimicrobial agents-related toxicities, but ADRs associated with the drug use cannot be ruled out completely. Caution must be taken when using this drug, as its frequent use or using it as the drug of first choice may lead to unnecessary drug-resistance. It must be used as a reserve drug and clinicians must be made aware of its usefulness as well as its toxicities and the risk-to-benefit must be considered when choosing tigecycline for the treatment in pregnant and at-risk populations like hepatic impairment.

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