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Review Article

Clinical Pharmacology of Tigecycline in Children

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Abstract

The currently available glycylcycline is tigecycline which is administered to children but not to infants. Tigecycline enters gram-negative bacteria by passive diffusion through channels formed by porins in the outer membrane and by active transport that pumps tigecycline across the cytoplasmic membrane. Tigecycline is more active against gram-positive than gram-negative organisms. Tigecycline is active against *Streptococcus pneumoniae*, methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, *Bacillus anthracis, Listeria monocytogenes, Haemophilus influenzae, Burkholderia pseudomallei* (the cause of melodies), *Brucella, Haemophilus ducreyi* (cancroid), *Vibrio cholera, Vibrio vulnificus, Campylobacter jejuni, Helicobacter pylori, Yersinia pestis, Yersinia enterocolitis, Francisella tularensis, Pasteurella multocida, Rickettsia, Coxiella burnetii, Mycoplasma pneumoniae, Chlamydia* species. *Legionella* species, *Ureaplasma*, *Plasmodium* species, *Borrelia recurrentis*, *Borrelia burgdorferi* (Lyme disease), *Treponema pallidum* (syphilis), *Treponema pertenue*, *Enterobacteriaceae, Acinetobacter, Bacteroides fragilis,* and *Stenotrophomonas*. Tigecycline elimination half-life is dose dependent and increases with the dose. Tigecycline has been found efficacy and safe in children but may induce adverse-effects. The metabolic pathways of tigecycline are the glucuronidation, amide hydrolysis, and N-acetylation. Tigecycline interacts with drugs and the treatment of children with tigecycline has been extensively studied. This antibiotic penetrates into the cerebrospinal fluid in limited amounts but when is co-administered with other drugs successfully cured bacterial meningitis. The aim of this study in the review of the published data on tigecycline dosing, efficacy, safety, effects, adverse-effects, metabolism, pharmacokinetics, drug interactions, treatment, penetration into the cerebrospinal fluid, and meningitis in children.

Keywords: Dosing; Drug-interaction; Meningitis; Pharmacokinetics; Tigecycline; Treatment

Introduction

Glycylcyclines are tetracycline congeners with substituents that confer broad-spectrum activity and activity against tetracycline-resistant bacteria; the currently available glycylcycline is tigecycline. This antibiotic is used in children but not in infants [1]. In children, aged <8 years, tigecycline causes deposition in growing bone and teeth, by binding to calcium, staining and occasionally dental hypoplasia, and diabetic foot infections [2].

Mechanism of action of tigecycline

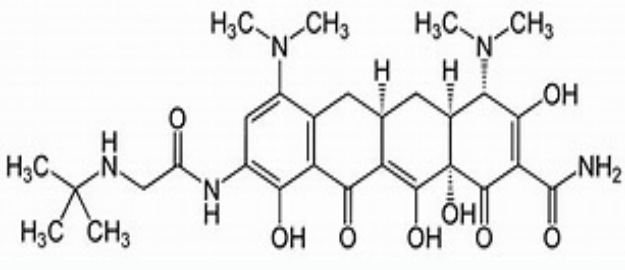
Tigecycline inhibits bacterial protein synthesis by binding to the 30S bacterial ribosome and preventing access of aminoacyl tRNA to the acceptor (A) site on the mRNA-ribosome complex. Tigecycline enters gram-negative bacteria by passive diffusion through channels formed by porins in the outer cell membrane and by active transport that pumps tigecycline across the cytoplasmic membrane [1].

Antimicrobial activity of tigecycline

Tigecycline is a bacteriostatic antibiotic with activity against a wide range of bacteria. Tigecycline intrinsically is more active against gram-positive than gram-negative microorganisms. Tigecycline is active against *Streptococcus pneumoniae*, methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, *Bacillus anthracis, Listeria monocytogenes, Haemophilus influenzae, Burkholderia pseudomallei* (the cause of melodies), Brucella, *Haemophilus ducreyi* (cancroid), *Vibrio cholera, Vibrio vulnificus, Campylobacter jejuni, Helicobacter pylori, Yersinia pestis, Yersinia enterocolitis, Francisella tularensis, Pasteurella multocida, Rickettsia, Coxiella burnetii, Mycoplasma pneumoniae, Chlamydia* species. *Legionella* species, *Ureaplasma*, Plasmodium species, *Borrelia recurrentis, Borrelia burgdorferi* (Lyme disease), *Treponema pallidum* (syphilis), *Treponema pertenue, Enterobacteriaceae, Acinetobacter, Bacteroides fragilis,* and *Stenotrophomonas.*

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "tigecycline dosing children", "tigecycline efficacy, safety children", "tigecycline effects children", "tigecycline adverse-effects children", "tigecycline metabolism and excretion", "tigecycline pharmacokinetics children", "tigecycline drug interactions", "tigecycline treatment children", "tigecycline penetration into cerebrospinal fluid" and "treatment of meningitis". In addition the books: The Pharmacological Basis of Therapeutics [1] and the British National Formulary for Children [2] were consulted.



Molecular structure of tigecycline (molecular weight = 586 grams/mole)

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Results

Administration schedule of tigecycline to children [2]

Intravenous administration for (1) complicate skin and soft-tissue infection (when other antibiotics are not suitable) and (2) complicated intraabdominal infections (when other antibiotic are not suitable).

Children aged 8 to 11 years. Give: 1.2 mg/kg twice-daily (maximum per dose=50 mg) for 5 to 14 days and the treatment is given under expert supervision.

Children aged 12 to 17 years. Give: 50 mg twice-daily for 5 to 14 days and the treatment is given under expert supervision.

Efficacy and safety of tigecycline in children

An infant, aged 5 months, with bronchiolitis caused by multidrug-resistant *Pseudomonas aeruginosa* was treated with tigecycline co-administered with other antibiotics and the treatment was efficacy and safe [3]. A child, aged 12 months, with extensively drug-resistant *Acinetobacter baumannii* was treated with tigecycline and the treatment was found effective and safe [4]. Twenty-four children, aged 8 months (range, 27 days to 6.9 years), suffered from bacterial pneumonia and were treated with tigecycline; the median duration of treatment was 10.7 days and this disease was cured in children thus tigecycline is effective in the treatment of bacterial pneumonia [5]. Children, aged 8 to 11 years, suffering from infection caused my multidrug-resistant organisms and were treated with tigecycline at a dose of 50 mg twice-daily and tigecycline was found efficacy and safe and eradicated these organisms [6]. One-hundred-ten children were infected by multidrug-resistant *Acinetobacter baumannii* or by multidrug-resistant *Acinetobacter baumannii* strains. Tigecycline was administered for 10 days (range, 2 to 47), the total improvement-rate was 47.3% in children with infection caused by multidrug-resistant *Acinetobacter baumannii* and 50.0% in children with infection caused by multidrug-resistant *Acinetobacter* strains thus tigecycline is efficacy and safe in these children [7]. Thirteen children, aged 8 years (range, 2.5 months to 14 years), had an infection caused by extensively drug-resistant bacteria and were treated with tigecycline and the treatment was well tolerated and effectively cured the infection [8]. Sixteen children, aged 4.4 years, had an infection due to multidrug-resistant bacteria and were treated with tigecycline at the recommended dose and favourable clinical response was achieved in 74.2% children [9].

Effects of tigecycline in children

Tigecycline is highly active against *Candida albicans in-vitro* particularly when combined with amphotericin B and echinocandins [10]. Thirteen subjects, aged 20 to 31 years, had and infection in the oropharyngeal and intestine caused by gram-negative aerobic and anaerobic bacteria and received 100 mg of tigecycline intravenously on day 1 followed by a maintenance dose of 50 mg twice-daily. The number of enterococci and *Escherichia coli* was reduced at day 8 of treatment (P-value <0.05) [11]. The increasing antimicrobial-resistance in important species of bacteria causes serious and life-threatening diseases and represents a difficult challenge for clinicians and tigecycline was found an effective antibiotic for treating these diseases [12]. Tigecycline has been found efficacious and well tolerated in complicated skin, skin-structure, intraabdominal, and respiratory-tract infections [13].

Adverse-effects caused by tigecycline in children

Common or very common adverse-effects caused by tigecycline are: abscesses, appetite decreased diarrhoea, dizziness, gastrointestinal discomfort, headache, healing impaired, hyperbilirubinemia, hypoglycaemia, hypoproteinaemia, increased risk of infection, nausea, sepsis, skin reaction, and vomiting. Uncommon adverse-effects are: hepatic disorders, pancreatitis, thrombocytopenia, and thrombophlebitis. Adverse-effects whose frequency is not known are: acidosis, azotaemia, hyperphosphatemia, hyperfibrinogenaemia, idiopathic intracranial hypertension, photosensitivity reaction, *pseudomembranous enterocolitis*, severe cutaneous adverse-reactions, and tooth discoloration [2]. Tigecycline was given for ≥ 1 month for treating infections caused by *Mycobacterium abscessus* and *Mycobacterium chelonae* and the adverse-effects were reported in >90% of children and the most common adverse-effects were nausea and vomiting [14]. Two boys underwent allogenic bone marrow transplantation for acute myeloid leukaemia and were treated with tigecycline. Erythrocyte and platelet engraftment followed a normal course, but the neutrophil count remained low despite the increase in leukocyte count. After the interruption of tigecycline treatment the neutrophil count rapidly raised in both boys. Neutropenia is the adverse-effect caused by tigecycline [15]. Tigecycline was effective in the treatment of complicated skin, skin-structure and intraabdominal infections but gastrointestinal adverse-effects were observed [16].

Metabolism and excretion of tigecycline in humans

The major route of tigecycline elimination is faeces, containing 59% of the radioactive dose, whereas urine contained 32% of radioactivity. Unchanged tigecycline is the predominant drug-related compound in serum, urine, and faeces. The major metabolic pathways were glucuronidation of tigecycline and amide hydrolysis followed by N-acetylation to form N-acetyl-9-aminominocycline. The glucuronide metabolite accounted for 5% to 20% of serum radioactivity, and approximately 9% of the dose is excreted as glucuronide conjugate within 48 hours. Concentrations of N-acetyl-9-aminominocycline were approximately 6.5% and 11% of the tigecycline concentrations in serum and urine, respectively. Excretion of unchanged tigecycline into faeces is the primary route of elimination, and the secondary elimination pathways are renal excretion of unchanged drug, glucuronide conjugate and N-acetyl-9-aminominocycline [17].

Pharmacokinetics of tigecycline in children

Meagher et al. [18] studied the pharmacokinetics of tigecycline in 5 children. A single intravenous administration of tigecycline was infused for 1 hour at the following doses: 12.5 mg, 25 mg, 50 mg, 75 mg, 100 mg, 200 mg, and 300 mg. Multiple administrations were given at the following doses: 25, 50, and 100, and the results are shown in Table 1.

This table shows that the distribution volume is greater than the water volume. The elimination half-life, distribution volume, and AUC are dose dependent and increase with tigecycline dose. The elimination half-life is longer following multiple doses than after single dose.

Interactions of tigecycline with drugs

Using standard coagulation tests, the activated thromboplastin time in plasma was prolonged with increasing concentrations of tigecycline. Furthermore, it was demonstrated a rapid loss of mitochondrial activity in hepatic cells with supra-therapeutic tigecycline dosages [19]. The doripenem-tigecycline combination showed a higher antagonistic activity (5.8%) than colistin-tigecycline combination (1.4%) against extensively drug-resistant and multidrug-resistant *Acinetobacter baumannii* [20]. Tigecycline co-

Table 1: Pharmacokinetic parameters of tigecycline were investigated in 5 children. Figures are the mean ± SD, by Meagher et al. [18].

	Tigecycline dose (mg)						
Parameters	12.5	25	50	75	100	200	300
Single dose							
Peak conc. (µg/ml)	0.11 ± 0.01	0.25 ± 0.06	0.38 ± 0.06	0.57 ± 0.08	0.93 ± 0.22	1.79 ± 0.53	2.82 ± 0.48
DVss (L/kg)	2.8 ± 0.95	6.4 ± 1.3	6.5 ± 2.0	4.5 ± 0.77	6.8 ± 2.5	13 ± 3.3	12 ± 2.4
$AUC_{0-\infty(\mu g.h/ml)}$	0.75 ± 0.52	2.26 ± 1.02	2.26 ± 0.53	3.66 ± 1.00	4.87 ± 1.41	13.2 ± 2.80	17.3 ± 2.18
TBC (L/h/kg)	0.29 ± 0.20	0.20 ± 0.10	0.28 ± 0.04	0.29 ± 0.04	0.30 ± 0.08	0.23 ± 0.04	0.25 ± 0.03
Elimination half-life (h)	11 ± 10	32 ± 20	18 ± 3.6	22 ± 5.3	22 ± 10		44 ± 7.8
Multiple doses							
Peak conc.(µg/ml)	---	0.32 ± 0.05	0.62 ± 0.09	---	1.17 ± 0.18	---	---
DVss (L/kg)	---	8.6 ± 1.98	7.2 ± 0.50	---	9.1 ± 2.91	---	---
$AUC_{0-\infty(\mu g.h/ml)}$	---	1.48 ± 0.26	3.07 ± 0.38	---	4.87 ± 0.93	---	---
TBC (L/h/kg)	---	0.20 ± 0.04	0.20 ± 0.02	---	0.24 ± 0.05	---	---
Elimination half-life (h)	---	49 ± 35	37 ± 12	---	66 ± 23	---	---

DVss: Distribution Volume at steady-state; TBC: Total Body Clearance

administered with colistin displayed synergistic activity in 24.3% of multidrug-resistant *Acinetobacter baumannii* isolates and tigecycline combined with sulbactam had synergistic activity in 64.3% of these isolates. These results suggest that both combination therapies are good options for treating infection caused by multidrug-resistant *Acinetobacter baumannii* [21]. Tigecycline showed synergism when is co-administered with levofloxacin, amikacin, imipenem or colistin, and antagonism was observed for the tigecycline combined with piperacillin-tazobactam [22].

Treatment of children with tigecycline

Thirteen children received tigecycline at a dose of 2 mg/kg twice-daily for 10 ± 5 days for the treatment of ventilator-associated pneumonia, bloodstream and complicated intraabdominal infections caused by carbapenem-resistant organisms. The isolates included *Klebsiella pneumoniae* and *Acinetobacter baumannii*; the clinical efficacy was achieved in 84.6% of children and pathogens were eradicated in 69.2% of subjects. The overall mortality-rate was only 15.4% and no serious adverse-effects were reported and tigecycline is effective in the treatment of these infections [23]. Children had bacteraemia and urinary-tract infection caused by *Leptospira* and tigecycline cured these infections [24]. Gong et al. [25] performed a systematic review and a meta-analysis about tigecycline treatment in children. Of 951 publications retrieved, 17 studies were included in the meta-analysis. The primary outcome was the cure of the infections, the mortality-rate which was low, and the adverse-effects did not differ between high and low dose of tigecycline. High tigecycline dose reduced the mortality-rate meanwhile improved the clinical efficacy and should be considered in serious infections caused by multidrug-resistant and extensively drug-resistant bacteria [26]. Twenty-two children, aged 7.5 months (range, 6 months to 4 years), had a median body-weight of 7.3 kg. Tigecycline was prescribed as culture-directed therapy in 91% of infected children and as empirical therapy in 9% of infected children. The median intensive care unit stay was 56 days and median hospital stay was 78 days. Clinical success was reported in 86% of children, the all-cause mortality-rate was only 18% and no serious adverse-effects were observed. Tigecycline therapy is successful in most critically ill children with infections due to multidrug-resistant and extensively drug-resistant organisms [27]. Twenty-four children, aged 4 years (range, 50 days to 12 years), had an infection caused by *Acinetobacter baumannii* in the tracheal aspirate fluid and in the ventilator-associated pneumonia. Tigecycline was administered at a loading dose of 1.5 or 2.0 mg/kg followed by a maintenance dose of 1.0 mg/kg twice-daily and the average duration of treatment was 11.6 ± 5.8 days. The clinical response and microbiological eradication-rate were 37.5% and 29.2%, respectively. Six children (25.0%) died, and three of these deaths were related to the infection. Adverse-effects were identified in only 4 children (16.7%) and included abnormal liver function, prolonged prothrombin time and diarrhoea. These findings suggest that tigecycline may be an option for children with severe infections [28]. A total of 9,422 gram-positive isolates were obtained in 1,255 centers, predominantly from Europe and North America. One-third of *Staphylococcus aureus* isolates were methicillin-resistant and all organisms were susceptible to tigecycline and the susceptibility-rate was >92%. In addition, all *Streptococcus pneumoniae*, *Streptococcus agalactiae, Enterococcus faecalis,* and *Enterococcus faecium* isolates were highly susceptible to tigecycline and the overall susceptible-rate was >97%. Thus tigecycline is active against different bacteria [29]. Children received tigecycline or ceftriaxone-metronidazole to treat intraabdominal infections and the clinical responses were 81.8% for tigecycline and 79.4% for ceftriaxone-metronidazole. Common adverse-effects were nausea (21.6% tigecycline *vesrus* 21.3% ceftriaxone-metronidazole) and vomiting (17.7% tigecycline *vesrus* 13.2% ceftriaxone-metronidazole). Discontinuation-rates due to the adverse-effects were 7.8% for tigecycline and 6.4% for ceftriaxone-metronidazole. Tigecycline is effective in the treatment of intraabdominal infections and is non-inferior to ceftriaxone-metronidazole [30]. Tigecycline is active in the treatment complicated skin, skin-structure and intraabdominal infections caused by gram-positive and gram-negative organisms, including methicillin-resistant *Staphylococcus aureus*, multidrug-resistant *enterococci*, extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. Tigecycline is also active against many anaerobic bacteria, as well as atypical pathogens, including rapidly growing nontuberculous mycobacteria. Tigecycline was found effective in the treatment of all these infections [31].

Penetration of tigecycline into the Cerebrospinal Fluid (CSF)

The entry of antibiotics into the central nervous system compartments is determined by the physicochemical properties of the drug and by conditions of the host. The most important drug properties are lipophilicity at a neutral pH, molecular mass and drug binding to serum proteins [32]. Patients with meningitis received tigecycline at a dose of 1 mg intraventricularly and 49 mg intravenously. The $AUC_{0-12\ hours}$ in plasma and CSF were 23.0 and 4.7 µg*h/ml, respectively, and the CSF to serum ratio was 20.4%. These findings reveal that tigecycline penetrate into the CSF in significant amounts and may be used to treat meningitis caused by multidrug-resistant gram-negative bacteria [33]. When tigecycline is administered intravenously may achieve low concentration in the CSF and clinicians should administrate tigecycline intrathecally [34]. A patient had meningitis

caused by extensively drug-resistant *Acinetobacter baumannii* and was treated with tigecycline intraventricularly. The culture in the CSF became negative thus intraventricular tigecycline therapy is an effective antibiotic for the treatment of intracranial infection caused by this organism [35]. Tigecycline weakly penetrates into the CSF, the CSF-to-serum concentration ratio was 0.079 and CSF-to-serum $AUC_{0\text{-}12\ hours}$ ratio was 0.067 [36]. A patient received tigecycline intravenously for treating bacterial meningitis and never obtained tigecycline concentrations in excess of the MIC of *Acinetobacter baumannii* in either the serum or the CSF. The patient experienced low CSF tigecycline concentrations and failed to achieve a clinical response while on therapy. Low tigecycline CSF concentrations suggest that a standard intravenous dose of tigecycline is inadequate to treat meningitis [37]. A single 100 mg dose of tigecycline given intravenously produced therapeutic concentrations in the CSF and the CSF to serum ratio was 11% [38].

Treatment of meningitis with tigecycline in adult and paediatric patients

A 68-year-old male patient had severe brain injury caused by extensively drug-resistant *Acinetobacter baumannii* and developed pyogenic ventriculitis on the 24th postoperative day and this organism was susceptible only to tigecycline. Successful treatment was achieved with intravenous tigecycline combined with continuous ventricular irrigation plus intraventricular tigecycline. The pus was cleared on the 3rd day of post-irrigation, and cerebrospinal fluid cultures became negative after 12 days of tigecycline treatment. Multi-route administration of tigecycline cured pyogenic ventriculitis caused by extensively drug-resistant *Acinetobacter baumannii* [39]. A newborn infant with purulent meningitis due to carbapenem-resistant *Klebsiella pneumoniae* was treated with tigecycline and this microorganism was eradicated from the central nervous system [40]. A child had the meningitis caused by *Klebsiella pneumoniae* and the treatment consisted in a combination of intravenous (1.2 mg/kg daily) and intraventricular (4 mg daily) tigecycline and was co-administered with meropenem at a dose of 120 mg/kg daily. On the 7th day of the combined therapy, the CSF culture became sterile. Because tigecycline distribution into the CSF is not sufficient following intravenous administration a combination of intraventricular and intravenous tigecycline infusion is necessary [41]. Twenty-six isolates of Carbapenem-resistant *Acinetobacter baumannii* were identified in the CSF of 23 patients and the mortality-rate due to the infection was 73.9%. This organism was susceptible to tigecycline (MIC_{50}, MIC_{90}=1 μg/ml, 1 μg/ml). Although the mortality-rate was high, tigecycline cured the meningitis caused by this organism in some patients [42]. A total of 25 patients underwent neurosurgery and the CSF became infected by *Acinetobacter baumannii* after surgery. This organism had extensive resistance to all tested antibiotics except for tigecycline and colistin, and tigecycline was administered for 13.4 ± 2.8 days. The time required to obtain a negative CSF culture was 8.9 ± 4.0 days and tigecycline cured the meningitis caused by this organism [43]. Extended spectrum β-lactamase-producing *Klebsiella pneumoniae* grew in the CSF of an infant. At the end of the fourth week of treatment with meropenem plus gentamicin therapy this organism was not eradicated from the CSF. Intravenous tigecycline (1.2 mg/kg twice-daily) and intrathecal amikacin were administered. On the 6th day of tigecycline treatment the CSF became sterilized. Tigecycline co-administered with other antibiotics may be a salvage therapy of meningitis [44]. Two isolates of *Acinetobacter baumannii* were cultured from the CSF in a 20-year-old man with a gunshot trauma in the abdomen. E-test showed that the isolates were sensitive to colistin and tigecycline with MIC of 0.25 μg/ml and 1.5 μg/ml, respectively. The isolates became resistant to colistin with MIC >256 μg/ml but remained sensitive to tigecycline with MIC=1.5 μg/ml and tigecycline cured the meningitis caused by *Acinetobacter baumannii* [45].

Discussion

Glycylcyclines are tetracycline congeners with substituent's that confer broad-spectrum activity and activity against tetracycline-resistant bacteria; the currently available glycylcycline is tigecycline. This antibiotic is used in children but not in infants. Tigecycline inhibits bacterial protein synthesis by binding to the 30S bacterial ribosome and preventing access of aminoacyl tRNA to the acceptor (A) site on the mRNA-ribosome complex. Tigecycline enters gram-negative bacteria by passive diffusion through channels formed by porins in the outer cell membrane and by active transport that pumps tigecycline across the cytoplasmic membrane. Tigecycline is a bacteriostatic antibiotic with activity against a wide range of bacteria. Tigecycline intrinsically is more active against gram-positive than gram-negative microorganisms. Tigecycline is active against *Streptococcus pneumoniae*, methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, *Bacillus anthracis, Listeria monocytogenes*, *Haemophilus influenzae, Burkholderia pseudomallei* (the cause of melodies), *Brucella, Haemophilus ducreyi* (cancroid), *Vibrio cholera, Vibrio vulnificus, Campylobacter jejuni, Helicobacter pylori, Yersinia pestis, Yersinia enterocolitis, Francisella tularensis, Pasteurella multocida, Rickettsia, Coxiella burnetii, Mycoplasma pneumoniae, Chlamydia* species, *Legionella* species, *Ureaplasma, Plasmodium* species, *Borrelia recurrentis, Borrelia burgdorferi* (Lyme disease), *Treponema pallidum* (syphilis), *Treponema pertenue, Enterobacteriaceae, Acinetobacter, Stenotrophomonas,* and *Ureaplasma* [1]. Tigecycline is found efficacy and safe in children [3-9]. Tigecycline is effective in the treatment of extensively drug-resistant and multidrug-resistant bacteria [3,4,6,8,9], bacterial pneumoniae [5], and sepsis caused by *Acinetobacter baumannii* [7]. Tigecycline produced different effects in children [10-13] it is efficacy in the treatment of *Candida albicans* [10], of aerobic and anaerobic gram-negative organisms [11], of serious and life-threatening infections [12] and in complicated skin, skin-structure, intraabdominal and lower respiratory-tract infections [13]. For the treatment of *Candida albicans*, tigecycline is co-administered with amphotericin B and echinocandins [10] but for the treatment of the other infections tigecycline is the only administered antibiotic [11-13]. Tigecycline may induce adverse-effects [2,14-16]. Common or very common adverse-effects caused by tigecycline are: abscesses, appetite decreased diarrhoea, dizziness, gastrointestinal discomfort, headache, healing impaired, hyperbilirubinemia, hypoglycaemia, hypoproteinaemia, increased risk of infection, nausea, sepsis, skin reaction, and vomiting. Uncommon adverse-effects are: hepatic disorders, pancreatitis, thrombocytopenia, and thrombophlebitis. Adverse-effects whose frequency is not known are: acidosis, azotaemia, hyperphosphatemia, hyperfibrinogenaemia, idiopathic intracranial hypertension, photosensitivity reaction, *pseudomembranous enterocolitis*, severe cutaneous adverse-reactions, and tooth discoloration [2], nausea and vomiting [14], neutropenia [15] and gastrointestinal adverse-effects [16]. Tigecycline is metabolized and the metabolic pathways are the glucuronidation, amide hydrolysis, and N-acetylation [17]. The pharmacokinetics of tigecycline has been studied in children following single and multiple doses [18]. The distribution volume, AUC, and the elimination half-life of tigecycline are dose dependent and increase

with the dose, whereas the total body clearance is independent by the dose. Tigecycline interacts with drugs [19-22]. Tigecycline causes a rapid loss of mitochondrial activity in hepatic cells [19]. The doripenem-tigecycline combination shows a higher antagonistic activity than colistin-tigecycline combination against extended drug-resistant and multidrug resistant *Acinetobacter baumannii* [20]. Synergistic effect was observed with the combination of tigecycline with colistin or sulbactam [21] and with the combination of tigecycline with levofloxacin, amikacin, imipenem, whereas an antagonistic effect was observed for tigecycline co-administered with piperacillin-tazobactam against multidrug resistant *Acinetobacter baumannii* [22]. Treatment of children with tigecycline has been extensively explored [23-31]. Tigecycline is effective in the treatment of intraabdominal, ventilator-associated pneumonia and bloodstream infections caused by *Klebsiella pneumoniae* and *Acinetobacter baumannii* [23] and in the treatment of bacteraemia and urinary-tract infection due to *Leptospira* [24]. Gong et al. [25] reviewed the treatment of tigecycline in children; tigecycline cured different infections and reduced the mortality-rate. High dose of tigecycline reduced the mortality-rate caused by multidrug-resistant and extensively drug-resistant organisms and improved the clinical efficacy in infections caused by these organisms [26]. Tigecycline successfully treated infections due to multidrug-resistant and extensively drug-resistant bacteria [27], produced a high rate of microbiological-rate and clinical response [28], eradicated *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus agalactiae, Enterococcus faecalis,* and *Enterococcus faecium* in children [29] cured intraabdominal infections [30], and infections caused by methicillin-resistant *Staphylococcus aureus*, multidrug-resistant enterococci, extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* [31]. Tigecycline penetrates into the cerebrospinal fluid [32-38] and the penetration-rate depends on the lipophilicity at a neutral pH and by the molecular mass [32]. Tigecycline penetrates into the cerebrospinal fluid in significant amounts [3], whereas other authors observed that tigecycline administered systemically may not achieve therapeutic concentration in the cerebrospinal fluid [36,37] in such a case tigecycline should be administered intrathecally or intraventricularly [35]. Following an intravenous dose of 100 mg of tigecycline administration the corresponding concentrations in the cerebrospinal fluid is 11% of that in serum [38]. Tigecycline cured meningitis caused by extensively drug-resistant *Acinetobacter baumannii* following intravenous and intraventricular administrations [39]. Tigecycline eradicated carbapenem-resistant *Klebsiella pneumoniae* from the central nervous system [40] but the eradication of carbapenem-resistant *Acinetobacter baumannii* and β-lactamase-producing *Klebsiella pneumoniae* from the central nervous system requires a combination of tigecycline with other antibiotics [42,43], and the eradication of carbapenem-resistant *Klebsiella pneumoniae* required a combination therapy of tigecycline with amikacin and meropenem [44]. Two isolates of *Acinetobacter baumannii* were sensitive to colistin and tigecycline but during treatment the isolates became resistant to colistin but sensitive to tigecycline which cured the meningitis [45].

In conclusion, Glycylcyclines are tetracycline congeners with substituents that confer broad-spectrum activity and activity against tetracycline-resistant bacteria; the currently available glycylcycline is tigecycline. This antibiotic is used in children but not in infants. Tigecycline inhibits bacterial protein synthesis by binding to the 30S bacterial ribosome and preventing access of aminoacyl tRNA to the acceptor (A) site on the mRNA-ribosome complex. Tigecycline enters gram-negative bacteria by passive diffusion through channels formed by porins in the outer cell membrane and by active transport that pumps tigecycline across the cytoplasmic membrane. Tigecycline is a bacteriostatic antibiotic with activity against a wide range of bacteria and is more active against gram-positive than gram-negative microorganisms. Tigecycline has been found efficacy and safe but may induce adverse-effects. This antibiotic is metabolized and the metabolic pathways are glucuronidation, amide hydrolysis, and N-acetylation. Elimination half-life of tigecycline is dose dependent and increase with the dose. Tigecycline interacts with drugs and the treatment of children with tigecycline has been extensively described. Tigecycline weakly penetrates into the cerebrospinal fluid and when it is administered with other antibiotic cure the meningitis. The study reviews the clinical pharmacology of tigecycline in children.

Conflict of Interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria. This article is a review and drugs have not been administered to men or animals.

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