REVIEW ARTICLE

Drugs 2004; 64 (1): 63-88
0012-6667/04/0001-0063/$34.00/0

The Glycylcyclines
A Comparative Review with the Tetracyclines

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Abstract

The tetracycline class of antimicrobials exhibit a broad-spectrum of activity against numerous pathogens, including Gram-positive and Gram-negative bacteria, as well as atypical organisms. These compounds are bacteriostatic, and act by binding to the bacterial 30S ribosomal subunit and inhibiting protein synthesis. The tetracyclines have been used successfully for the treatment of a variety of infectious diseases including community-acquired respiratory tract infections and sexually transmitted diseases, as well in the management of acne. The use of tetracyclines for treating bacterial infections has been limited in recent years because of the emergence of resistant organisms with efflux and ribosomal protection mechanisms of resistance. Research to find tetracycline analogues that circumvented these resistance mechanisms has lead to the development of the glycylcyclines.

The most developed glycylcycline is the 9-*tert*-butyl-*g*lycylamido derivative of minocycline, otherwise known as tigecycline (GAR-936). The glycylcyclines exhibit antibacterial activities typical of earlier tetracyclines, but with more potent activity against tetracycline-resistant organisms with efflux and ribosomal protection mechanisms of resistance. The glycylcyclines are active against other resistant pathogens including methicillin-resistant staphylococci, penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci.

Tigecycline is only available in an injectable formulation for clinical use unlike currently marketed tetracyclines that are available in oral dosage forms. Tigecycline has a significantly larger volume of distribution (>10 L/kg) than the other tetracyclines (range of 0.14 to 1.6 L/kg). Protein binding is approximately 68%. Presently no human data are available describing the tissue penetration of tigecycline, although studies in rats using radiolabelled tigecycline demonstrated good penetration into tissues. Tigecycline has a half-life of 36 hours in humans, less than 15% of tigecycline is excreted unchanged in the urine. On the basis of available data, it does not appear that the pharmacokinetics of tigecycline are markedly influenced by patient gender or age.

The pharmacodynamic parameter that best correlates with bacteriological eradication is time above minimum inhibitory concentration. Several animal studies have been published describing the efficacy of tigecycline. Human phase 1 and 2 clinical trials have been completed for tigecycline. Phase 2 studies have been conducted in patients with complicated skin and skin structure infections, and in patients with complicated intra-abdominal infections have been published as abstracts. Both studies concluded that tigecycline was efficacious and well tolerated. Few human data are available regarding the adverse effects or drug interactions resulting from tigecycline therapy; however, preliminary data report that tigecycline can be safely used, is well tolerated and that the adverse effects experienced were typical of the tetracyclines (i.e. nausea, vomiting and headache).

Tigecycline appears to be a promising new antibacterial based on *in vitro* and pharmacokinetic/pharmacodynamic activity; however more clinical data are needed to fully evaluate its potential.

The tetracycline class of antimicrobials exhibit a broad spectrum of activity against numerous pathogens, including Gram-positive and Gram-negative bacteria, as well as atypical organisms.[1] The first tetracyclines were discovered in the 1940s (table I).[2] Chlortetracycline, a product of *Streptomyces aureofaciens* was discovered in 1945.[2] Other tetracyclines soon followed, some naturally occurring

Table I. Year of discovery of selected tetracyclines[1-5]

Tetracycline	Year
Chlortetracycline	1945
Tetracycline	1953
Doxycycline	1967
Minocycline	1972
DMG-DMDOT	1993
DMG-MINO	1993
Tigecycline	1993

DMDOT = 6-demethyl-6-doxytetracycline; **DMG** = N,N-dimethylglycylamido; **MINO** = minocycline.

molecules such as tetracycline from *S. aureofaciens*, and others, such as doxycycline and minocycline, semisynthetic products.[1] Tetracyclines are bacteriostatic and act by binding to the bacterial 30S ribosomal subunit and inhibiting protein synthesis.[3]

The tetracyclines have been used successfully for the treatment of a variety of infectious diseases since their discovery. Clinically, tetracyclines have been used for the treatment of community acquired respiratory tract infections and sexually transmitted diseases, as well in the management of acne; however more recent applications include using tetracyclines as part of triple therapy for the management of gastritis and peptic ulcer disease associated with *Helicobacter pylori*, as well as prophylactic use against malaria.[1] Tetracyclines have been used in veterinary medicine to treat infections as well as to enhance growth rate and feed conversion efficiency in poultry, cattle, sheep and swine.[1] In addition, tetracyclines have been used to treat infections in fish, trees and insects of commercial value.[1]

The use of tetracyclines for treating bacterial infections has been limited because of the emergence of resistant organisms.[6] The two major mechanisms of resistance include tetracycline efflux and ribosomal protection, where tetracycline is prevented from binding to the ribosome.[7] In order to overcome the resistance occurring with tetracycline antimicrobials, the development of newer and more effective agents that are active against tetracycline-resistant strains was clinically important.[8] This area of research has lead to the development of the glycylcyclines, which are the newest agents of this class since the development of minocycline in the 1970s.[2]

The glycylcyclines are synthetic analogues of the tetracyclines, with the most promising compound being the 9-*tert*-*b*utyl-*g*lycylamido derivative of *mino*cycline, TBG-MINO or GAR-936, which has recently been named tigecycline.[3] The glycylcyclines exhibit antibacterial activities typical of earlier tetracyclines, and also display activity against tetracycline-resistant organisms containing genes responsible for efflux mechanisms or ribosomal protection.[4] The glycylcyclines are also active against other resistant pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) and *S. epidermidis* (MRSE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant enterococci (VRE).[8]

This review compares the glycylcyclines to the earlier tetracyclines, namely tetracycline, doxycycline and minocycline, with respect to their chemistry, mechanisms of action and resistance, *in vitro* and *in vivo* activity, pharmacokinetics, pharmacodynamics, clinical trials, adverse effects and drug interactions. Tigecycline or GAR-936 is evaluated as the representative glycylcycline. All information currently available was included in this review and was obtained by searching PubMed and Medline, other journals and abstracts, with some references obtained directly from Wyeth Research (Pearl River, NY, USA). The search terms included tetracycline, glycylcycline, tigecycline, GAR-936, new antibiotics, and the years searched were 1990 to 2002.

1. Chemistry

The tetracycline nucleus consists of four linear fused tetracyclic rings, with a variety of functional groups attached at different positions (figure 1).[1] The most basic molecule to display activity is 6-deoxy-6-demethyltetracycline, which can be considered the minimum pharmacophore (figure 2).[1] Several structural features are important for the tetracyclines to maintain antibacterial activity, including maintenance of the linear fused ring system, naturally occurring (α) stereochemical configurations at the 4a, 12a (A-B ring junction) and 4 (dimethylamino group) positions, and conservation of the keto-enol system (positions 11, 12, and 12a) in proximity to the phenolic D ring.[1,9]

Several substitutions and modifications to the tetracycline nucleus result in a loss of activity. Derivatives comprised of less than four rings are inac-

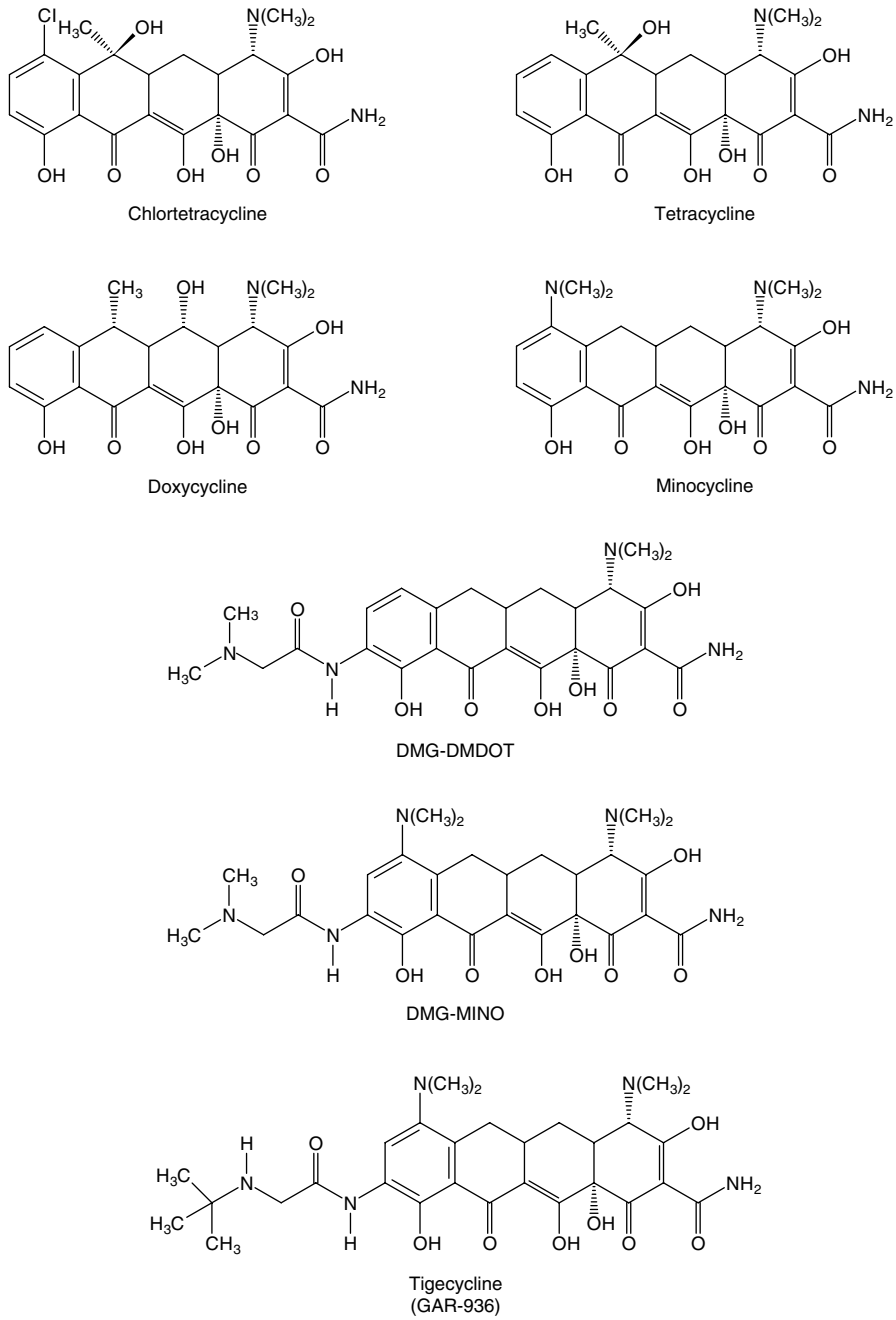

Fig. 1. Chemical structures of selected tetracyclines and glycylcyclines.

tive or nearly inactive, and each of the rings must be six membered and purely carbocyclic (figure 2).[1,5] Replacement of the carboxamide at C-2 with other groups such as aldehyde or nitrile, reduces antibacterial activity, and monoalkylation of the amide nitrogen reduces activity proportionately to the size

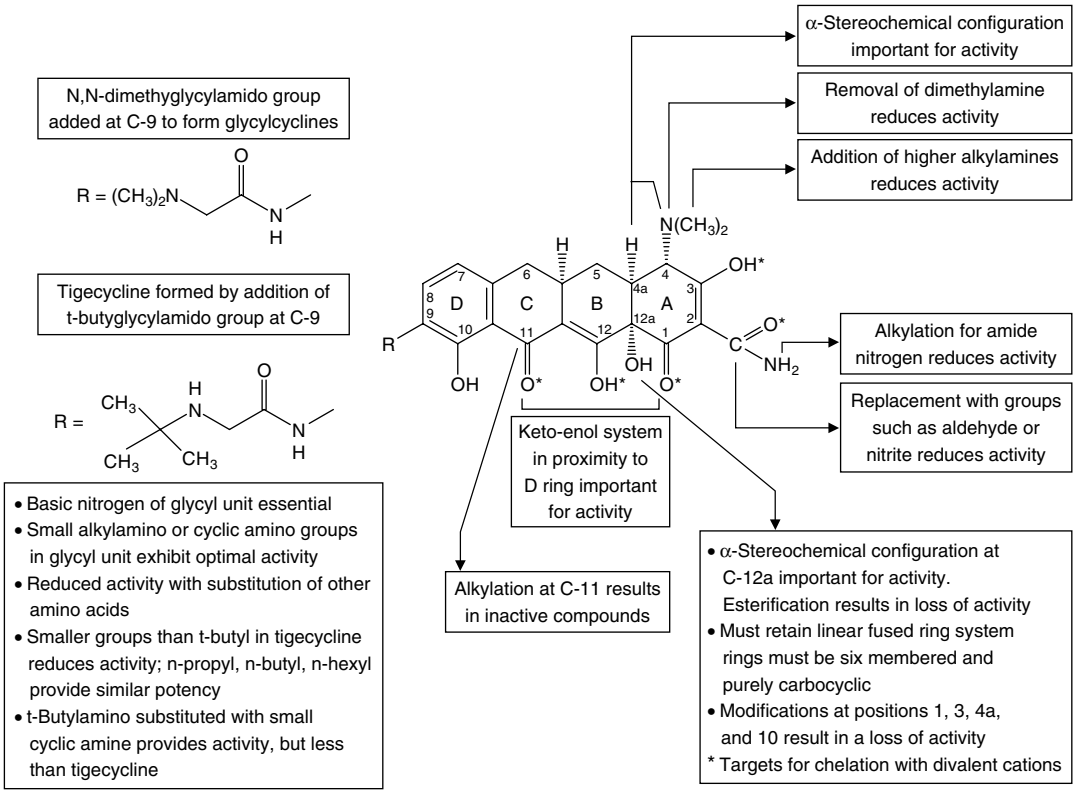

Fig. 2. Structure activity relationships of tetracyclines.

of the alkyl group.[1,5] The dimethylamino group at C-4 must have the α-orientation and removal of this group results in an even greater loss of activity.[5] The primary and *N*-methyl secondary amines retain activity at this position, but the addition of higher alkylamines reduces activity.[5] Esters of the C-12a hydroxyl group and alkylation at the C-11 position leads to inactive compounds, as do modifications at positions 1, 3, 4a, and 10.[1,5] A loss of activity results from epimerisation at C-5a, dehydrogenation to form a double bond between C-5a and C-11a, as well as aromatisation of ring C forming anhydrotetracyclines.[5]

The removal of the chlorine atom at position 7 of chlortetracycline results in the production of tetracycline, which is a 4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide.[5] Doxycycline, or α-6-deoxy-5-oxytetracycline, is formed from tetracycline through the removal of the hydroxyl group at C-6 and the addition of a hydroxyl group at C-5.[5] Further structural modification of tetracycline gives minocycline, a 7-dimethylamino-6-demethyl-6-deoxytetracycline, which has a dimethylamino group at position 7 and no substituents at position 6.[5]

A research programme was developed at Lederle Laboratories to develop a new tetracycline that would overcome the resistance seen with earlier tetracyclines.[1,9-11] Semisynthetic derivatives were developed containing the N,N-dimethylglycylamido (DMG) substituent at the 9 position of minocycline (MINO) and 6-demethyl-6-deoxytetracycline (DMDOT).[8,11] Derivatives with the 9-DMG group are referred to as the glycylcyclines, with the two compounds being specifically called DMG-MINO and DMG-DMDOT.[11] Further modification of the structure lead to the discovery of tigecycline, which is the 9-*tert*-butyl-glycylamido derivative of minocycline.[3,12,13]

Certain structural features have been observed in the glycylcyclines which are important for maintaining activity (figure 1). The basic nitrogen of the glycyl unit is essential, and derivatives with small alkylamino or cyclic amino groups in the glycyl unit exhibit optimal activity.[8] Efforts to replace the alkyl-substituted glycyl group with other amino acids, such as leucine, alanine, phenylalanine, etc., all resulted in compounds with significantly reduced activity.[8] Smaller groups than *t*-butylamino substituted in the tigecycline structure resulted in compounds with reduced potency, while n-propyl, n-butyl and n-hexyl substituted amines had similar potency.[12] The *t*-butylamino group of tigecycline can be substituted with a small cyclic amine to produce derivatives with good activity; however, these compounds remain less potent than tigecycline.[12]

It is important to note that the tetracyclines form chelation complexes with metal ions, which significantly influence their antimicrobial and pharmacokinetic properties.[1,5] Targets for chelation on the tetracycline nucleus include the β-diketone system (positions 11 and 12), and the enol (positions 1 and 3) and carboxamide (position 2) groups of the A ring (figure 2).[1] Examples of cations that will bind to tetracyclines include calcium, magnesium and iron, which form complexes that are insoluble in water, thereby inhibiting absorption.[5] The glycylcyclines also form chelation complexes with divalent cations.[1]

2. Mechanism of Action

Antibacterial agents prevent the growth of bacteria by disrupting cellular processes either within the bacterial cell or at the cell surface.[4] The tetracyclines as a class bind to a single high affinity site on the bacterial 30S ribosome within the cell.[1,3,4,12,14-16] This action blocks the entry of aminoacyl transfer RNA into the A site of the ribosome which prevents the incorporation of amino acid residues into elongating peptide chains, thereby inhibiting protein synthesis.[1,3,4,12,14] The tetracyclines, including tetracycline, chlortetracycline, minocycline, doxycycline and tigecycline, are bacteriostatic, whereas the atypical tetracyclines, including anhydrotetracyclines, are bactericidal (as a result of interactions with the cytoplasmic membrane rather than the ribosome).[8,14,17] The interaction between the tetracyclines and the ribosome is reversible, which may help explain their bacteriostatic action.[1]

In Gram-negative enteric bacteria, tetracyclines enter the cell by first passing through the porins OmpF and OmpC of the outer membrane.[1] Tetracyclines pass through porin channels as positively charged cation (probably magnesium)-tetracycline co-ordination complexes. These then dissociate to yield free tetracycline, which then diffuses through the lipid bilayer of the inner cytoplasmic membrane;[1] it is assumed that it is the lipophilic form that crosses the cytoplasmic membrane of Gram-positive bacteria.[1] Once inside the cell, the tetracylcines probably become chelated and it is likely that the active species that binds to the ribosome is a magnesium-tetracycline complex.[1,5] Tetracyclines can enter bacterial cells either by passive diffusion or active transport, which is an energy-dependent process.[1,5]

The tetracyclines and glycylcyclines share a common binding site on the ribosome.[15] The glycylcyclines have been shown to inhibit protein synthesis in wild-type ribosomes, as well as TetM-protected and tetracycline-resistant ribosomes.[6,8,15,18] It has been shown that the glycylcyclines bind 5-fold more strongly to the ribosome than tetracycline or minocycline, and it is likely this enhanced binding is responsible for overcoming the ribosomal protection mechanism of tetracycline resistance.[6,8,14,15]

3. Mechanism of Resistance

The widespread use of tetracyclines in both humans and animals has resulted in the emergence of many resistant organisms and this has consequently limited their use in therapy.[8,9,17] The problem of resistance is certainly not limited to the tetracyclines and has been reported amongst various classes of antibacterials.[2,8] There are three mechanisms responsible for tetracycline resistance – efflux, ribosomal protection and chemical modification. The first two mechanisms are the most clinically significant.[1,7,10]

Resistance occurs through the acquisition of tetracycline resistance genes, which are encoded on plasmids, conjugative transposons and integrons,

Table II. Mechanisms of resistance for specific *tet* genes and where they are found[1,4,8]

Efflux		Ribosomal protection
Gram-negative	Gram-positive	Gram-positive/negative
tet(A)	*tet*(K)	*tet*(O)
tet(B)	*tet*(L)	*tet*(S)
tet(C)	*tet*(Z)	*tet*(M) [from different genera]
tet(D)		*tet*(Q) [from Bacteroides]
tet(E)	*tet*A(P) [from Clostridia]	*tet*(T) [from *Streptococcus pyogenes*]
tet(G)		*tet*B(P) [from Clostridia]
tet(H)	*tet*(V) [from *Mycobacterium smegmatis*]	*tet*(W) [from *Butyrivibrio fibrisolens*]
tet(I)		
tet(J)		
tet(Y)		
tet(30)		**Inactivation**
tet(31)		*tet*(X) [from Bacteroides]

which allow the *tet* genes to move from species/genera to species/genera through conjugation.[4,8] Various *tet* genes have been identified and are designated with letters of the alphabet (with *tetR* being reserved for the repressor gene), in addition to numbers now being assigned to identify new genes.[1,8] Different *tet* genes code for either efflux or ribosomal protection (table II).[1,8] Some isolated strains of bacteria express both efflux and ribosomal protection genes which are organised as single, coordinately regulated operons.[14]

The products of efflux genes that pump tetracyclines out of the cell are located in the cytoplasmic membrane and belong to the major facilitator family of efflux proteins.[1,8] The efflux pumps are antiporters which exchange a monocationic magnesium-tetracycline complex for a proton, this decreases the intracellular concentration of tetracyclines and in turn protects the ribosomes within the cell.[1,8] Efflux pumps in Gram-negative bacteria are effective at pumping tetracycline and the synthetic derivatives (minocycline and doxycycline), whereas in Gram-positive bacteria, the pumps are ineffective at transporting the synthetic derivatives, including the glycylcyclines, out of the cell.[8,14] The *tet*(B) gene, which is found in Gram-negative organisms, has been shown to be effective at pumping tetracycline and minocycline out of the cell, but was ineffective at pumping out glycylcyclines.[1,10]

The exact mechanisms through which *tet* gene products protect ribosomes from the action of tetracyclines have not been clearly identified but it is likely that the products of the genes associate with the ribosome cause a conformational change, which either prevents the binding of the tetracyclines or causes their dissociation from the ribosome, without affecting protein synthesis.[1,8] Tet(M) shares strong homology with elongation factor G (EF-G) and both compete for the same biding site on the ribosome.[1,6] EF-G has the ability to hydrolyse guanosine triphosphate (GTP) in the presence of ribosomes and Tet(M) has also been shown to have some ribosome-dependent GTPase activity.[1,6] Because the Tet proteins and EF-G share overlapping binding sites, the Tet proteins must dissociate from the ribosome to allow EF-G to bind so that protein synthesis can occur.[1]

The glycylcyclines have demonstrated antibacterial activity against tetracycline-resistant organisms which have Tet(M)-protected ribosomes.[6] The exact mechanism through which the glycylcyclines overcome this resistance has not been discovered, but it is suggested that they bind more avidly to the ribosomes so that the product of the *tet*(M) gene is unable to disrupt the tight bond or that the product of the *tet*(M) gene is unable to interact with the ribosome to allow protein synthesis to occur.[6,14,15] The glycylcyclines are also active against organisms that display efflux-based resistance, which may be because of the inability of the glycylcyclines to induce tetracycline efflux proteins or because the efflux protein cannot export the glycylcyclines.[14,17]

Efforts have been made to create glycylcycline-resistant isolates in the laboratory but a truly resistant isolate has not yet been created.[14] Although no naturally occurring glycylcycline-resistant organ-

Table III. *In vitro* activity of tigecycline and the tetracyclines against Gram-positive aerobes[3,8,11,12,18,19,22,25,27,31-33,39,41-45,49,53]a

Bacteria	Tigecycline		Tetracycline		Doxycycline		Minocycline	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Staphylococcus aureus (MS)	0.25	0.5	0.5	1	0.25	0.5	0.12	0.12
S. aureus (MR)	0.25	0.5	0.5	32	0.25	2	0.12	2
Staphylococcus epidermidis (MS)	0.25	0.5	0.25	2	NA	NA	0.12	0.5
S. epidermidis (MR)	0.25	0.5	2	>8	NA	NA	0.25	4
Staphylococcus saprophyticus	0.5	0.5	0.25	0.5	NA	NA	NA	NA
Streptococcus pyogenes	0.03	0.06	0.25	4	0.25	0.5	0.06	0.25
Streptococcus agalactiae	0.06	0.12	32	64	16	16	16	32
Streptococcus pneumoniae (PS)	0.06	0.125	0.25	32	0.125	8	0.06	8
S. pneumoniae (PI)	0.03	0.06	1	64	0.5	8	0.25	16
S. pneumoniae (PR)	0.06	0.125	32	64	0.5	8	2	16
Enterococcus faecalis	0.12	0.25	32	128	8	16	8	32
Enterococcus faecium	0.125	0.25	0.25	64	0.12	16	0.06	16
Listeria monocytogenes	0.25	0.5	4	4	0.25	0.25	0.25	0.25

a National Committee for Clinical Laboratory Standards Approved and Tentative Breakpoints.[54] (i) *Staphylococcus* spp: tetracycline ≥16 μg/mL is resistant, doxycycline ≥16 μg/mL is resistant, minocycline ≥16 μg/mL is resistant. (ii) *S. pneumoniae*: tetracycline ≥8 μg/mL is resistant. (iii) *Streptococcus* spp. other than *S. pneumoniae*: tetracycline ≥8 μg/mL is resistant. (iv) *Enterococcus* spp.: tetracycline ≥16 μg/mL is resistant, doxycycline ≥16 μg/mL is resistant, minocycline ≥16 μg/mL is resistant.

MIC_{50} = minimum inhibitory concentration (μg/mL) of 50% of isolates; **MIC_{90}** = minimum inhibitory concentration (μg/mL) of 90% of isolates; **MR** = methicillin resistant; **MS** = methicillin sensitive; **NA** = information not available; **PI** = penicillin intermediate (MIC 0.12–1 μg/mL); **PR** = penicillin resistant (penicillin MIC ≥2.0 μg/mL); **PS** = penicillin susceptible (MIC ≤0.06 μg/mL).

isms have been obtained from human isolates, two strains of *Salmonella* spp. (*S. typhimurium* and *S. cholerasuis*) obtained from veterinary isolates of porcine origin were documented to be resistant to DMG-DMDOT and DMG-MINO; however, tigecycline was active against these strains.[4,14] It is therefore unlikely that strains resistant to tigecycline will arise quickly.[7,10,14,17]

4. *In Vitro* Activity

The *in vitro* activities of tigecycline, tetracycline, doxycycline and minocycline against clinically relevant bacteria are summarised in table III, table IV, table V and table VI.[3,4,8,11,12,18-53] The tables indicate the minimum concentrations of each antibiotic necessary to inhibit growth in 50% (MIC_{50}) and 90% (MIC_{90}) of isolates. The MIC values listed in the table represent the most common values obtained from recently published reports. Studies were included regardless of growth conditions (including growth media) or of the method in which the study was conducted.

Table III displays the *in vitro* activity of the tetracyclines against Gram-positive aerobes.[3,8,11,12,18,19,22,25,27,31-33,39,41-45,49,53] Against methicillin-susceptible *S. aureus* (MSSA), the order of activity is minocycline > tigecycline = doxycycline > tetracycline, whereas tigecycline is more active against MRSA (based on MIC_{90} values). A similar order is observed for methicillin-susceptible *S. epidermidis* (MSSE) and MRSE, where minocycline is most active against MSSE and tigecycline is most active against MRSE. With respect to *Streptococcus* spp., tigecycline displays better activity than the other three tetracyclines against *S. pyogenes* and *S. agalactiae*. Tigecycline displays significantly better activity against penicillin-susceptible, -intermediate and -resistant strains of *S. pneumoniae*, with MIC_{90} values ranging from 0.06 to 0.125 μg/mL, compared with an MIC_{90} range of 8–64 μg/mL for the three other tetracyclines. The same also applies to *Enterococcus faecalis* and *E. faecium*, with tigecycline displaying the best activity compared with tetracycline, doxycycline and minocycline with respect to MIC_{90} values. Minocycline, doxycycline and tigecycline display better activity than tetracycline against *Listeria monocytogenes*.

The activity of tigecycline against strains of *Bacillus anthracis* was evaluated in a study conducted by Heine et al.[55] The MIC for tigecycline was found to be <0.03–0.5 μg/mL, by using the broth dilution method according to NCCLS standards.

The study showed that tigecycline compared favourably to doxycycline (<0.03–0.12 μg/mL).

The activity of tetracyclines against Gram-negative aerobes is outlined in table IV.[4,8,11,19-21,26,27,29,34,35,38,40,41,44,51-53] Against *Enterobacter aerogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Morganella morganii*, *Neisseria meningitidis* and *Yersinia enterocolitica*, the tetracyclines display equal activity based on similar MIC_{90} values for each organism. Tigecycline displays improved activity against *Citrobacter freundii*, *Escherichia coli*, *E. cloacae*, *Klebsiella pneumoniae*, *Klebsiella* spp., *Salmonella* spp., *Serratia marcescens* and *Shigella* spp. since its MIC_{90} values are several folds lower than the other tetracyclines. Tigecycline and minocycline, with MIC_{90} values of 2 and 1 μg/mL, respectively, are more active than tetracycline (MIC_{90} >32 μg/mL) against *Acinetobacter* spp., whereas tigecycline and doxycycline with MIC_{90} values of 1–2 μg/mL are more active than tetracycline and minocycline with values >32 μg/mL against *N. gonorrhoeae*. Tigecycline is less active than minocycline and tetracycline against *Burkholderia cepacia*, having an MIC_{90} value of 32 μg/mL. Minocycline is more active against *Stenotrophomonas maltophilia* with an MIC_{90} value of 1 μg/mL compared with tigecycline (4 μg/mL) and tetracycline (32 μg/mL). The tetracyclines do not have good activity against *Proteus* or *Providencia* spp., with MIC_{90} values ranging from 8 to 32 μg/mL, and *Pseudomonas aeruginosa* is resistant to all

Table IV. *In vitro* activity of tigecycline and the tetracyclines against Gram-negative aerobes[4,8,11,19-21,26,27,29,30,34,35,38,40,41,44,51-53]a

Bacteria	Tigecycline		Tetracycline		Doxycycline		Minocycline	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Acinetobacter spp.	0.5	2	4	>32	NA	NA	0.125	1
Citrobacter freudii	0.5	2	2	8	NA	NA	2	8
Enterobacter aerogenes	0.5	1	1	4	12.2–25*	NA	1	2
Enterobacter cloacae	0.5	4	2	>8	NA	NA	2	>8
Escherichia coli	0.25	0.5	1	>8	2–16*	NA	0.5	8
Haemophilus influenza	0.5	1	0.25	0.5	1–2*	3.1	0.12	0.25
H. influenza (BLP)	1	2	0.5	1	NA	NA	0.5	1
Klebsiella pneumoniae	0.25	1	1	4	8–64*	NA	1	4
Klebsiella spp.	0.5	0.5	2	128	6.3–300*	NA	3.1–500*	NA
Moraxella catarrhalis	0.02	0.12	0.12	0.25	NA	NA	0.03	0.06
Morganella morganii	1	8	2	16	NA	NA	2	4
Neisseria gonorrhoeae (PS, PR)	0.5	1	1	>32	0.1–0.5*	2	0.5	32
Neisseria meningitidis	0.03	0.12	0.25	0.25	1–2*	NA	0.12	0.12
Proteus mirabilis	4	8	16	32	64-R*	NA	8	16
Proteus vulgaris	4	8	8	32	NA	NA	8	>8
Providencia rettgeri	4	8	>8	>8	NA	NA	>8	>8
Providencia stuartii	4	8	>8	>8	NA	NA	>8	>8
Pseudomonas aeruginosa	8	16	16	>32	32–128*	NA	8	32
Burkholderia cepacia	4	32	2	4	NA	NA	0.5	2
Salmonella spp.	0.5	0.5	2	32	NA	NA	2	16
Serratia marcescens	2	2	>8	>8	64*	NA	2	8
Shigella spp.	0.25	0.5	32	32	4–128*	NA	2	4
Stenotrophomonas maltophilia	1	4	4	32	NA	NA	0.25	1
Yersinia enterocolitica	0.25	0.5	1	2	NA	NA	1	1

a National Committee for Clinical Laboratory Standards Approved and Tentative Breakpoints.[54] (i) Enterobacteriaceae: tetracycline ≥16 μg/mL is resistant, doxycycline ≥16 μg/mL is resistant, minocycline ≥16 μg/mL is resistant. (ii) *N. gonorrhoeae*: tetracycline ≥2 μg/mL is resistant. (iii) *P. aeruginosa* and other non-Enterobacteriaceae: tetracycline ≥16 μg/mL is resistant, doxycycline ≥16 μg/mL is resistant, minocycline ≥16 μg/mL is resistant. (iv) *H. influenzae*: tetracycline ≥8 μg/mL is resistant.

BLP = beta lactamase-positive; **MIC_{50}** = minimum inhibitory concentration (μg/mL) of 50% of isolates; **MIC_{90}** = minimum inhibitory concentration (μg/mL) of 90% of isolates; **NA** = information not available; **PR** = penicillin resistant; **PS** = penicillin susceptible; * indicates MIC in μg/mL, though number or range does not reflect the percentage of isolates that were inhibited (i.e. not an actual MIC_{50} or MIC_{90}).

tetracyclines including tigecycline with MIC_{90} values >16 μg/mL.

In a study conducted by Citron and Goldstein,[23] the *in vitro* activity of tigecycline was evaluated against strains of unusual aerobic and anaerobic bacteria isolated from infected bite wounds. Gram-negative strains of interest include *Pasteurella* spp. and *Eikenella corredens*. Tigecycline was very active against the Gram-negative strains tested, with MIC_{90} values of <0.25 μg/mL. Less activity was observed against *E. corrodens*, with an MIC_{50} and MIC_{90} of 0.5 and 4 μg/mL, respectively.

Tetracyclines have been used successfully in treating infections due to other Gram-negative bacteria, including *Campylobacter jejuni*, *Bartonella* spp., *Brucella* spp., *Francisella tularensis*, *Leptotrichia buccalis*, *Vibrio cholerae*, *Actinomyces israeli*, *Nocardia* spp. and *Trophenyma whippellii*.[56] However, there are no comparative data with tigecycline against these bacteria at this time.

Table V outlines the activity of the tetracyclines against anaerobic bacteria.[19,23,24,28,44,46,50,52] Compared with the tetracyclines, tigecycline displays improved activity against *Bacteroides fragilis*, with MIC_{90} values of 2 μg/mL and 8–32 μg/mL, respectively, although tigecycline, minocycline and doxycycline display similar activity against *B. fragilis* group, with MIC_{90} values of 4 μg/mL. Tigecycline displays greater activity against *Peptostreptococcus* spp. than other tetracyclines. In addition, a study conducted by Hedberg and Nord[57] evaluated the activity of tigecycline against various anaerobic bacteria, including 29 strains of *Propionibacterium acnes*. The MIC for tigecycline was in the range of 0.032–0.064 μg/mL; however, there were no comparative data with other tetracyclines.

Little data are available for the tetracyclines against atypical pathogens (table VI).[36,37,47,52,53] Tigecycline and doxycycline display comparable activity against *Chlamydia pneumoniae*. Tigecycline demonstrates improved activity against *Mycoplasma pneumoniae* compared with tetracycline and doxycycline. The tetracyclines are active against other pathogens, including *Rickettsia* spp., *Borrelia* spp., *Leptospira* spp. and *Treponema* spp.; however, no comparative data with tigecycline are currently available.[56]

In addition to the various bacteria listed in this section, the tetracyclines display activity against *Erlichia* spp., *Coxiella* spp. and *Haemophilus ducreyi*.[56] No data are available at this time to compare the activity of tigecycline against these pathogens.

5. Pharmacokinetics

The pharmacokinetic parameters of the tetracyclines after single oral or intravenous doses are summarised in table VII.[5,26,35,52,58-64] It should be mentioned that considerable variability in pharmacokinetic parameters occurs between patients with tetracyclines.

5.1 Absorption

Tigecycline is currently available as a parenteral agent, whereas the tetracyclines are available in oral dosage forms. The oral formulations of tetracycline, doxycycline and minocycline are well absorbed from the gastrointestinal tract, with bioavailability ranging from 75% to 100% for the three agents (table VII). The tetracyclines are absorbed quickly, and reach their maximum serum concentrations (C_{max}) within approximately 4 hours after oral administration. Food can decrease the bioavailability of tetracycline by as much as 50%, whereas doxycycline and minocycline can be given without regard to food. However, tetracycline (doxycycline and minocycline to a lesser extent) binds to divalent cations which further decreases its absorption; therefore, to maximise absorption administration should occur one hour before or two hours after consuming substances containing cations (e.g. dairy products, multivitamins or antacids).[26,58,60,62]

5.2 Distribution

Tigecycline has a significantly larger volume of distribution (>10 L/kg) than the other tetracyclines (range of 0.14 to 1.6 L/kg) and protein binding is approximately 68% (table VII). Presently no human data are available describing the tissue penetration of tigecycline, although studies in rats using radiolabelled tigecycline demonstrated good penetration into tissues.[65] Elimination of radio-labelled tigecycline was slower from tissues than from plasma, so the tissue to plasma ratios were high. The highest

Table V. *In vitro* activity of tigecycline and the tetracyclines against anaerobes[19,23,24,28,44,46,50,52]

Bacteria	Tigecycline		Tetracycline		Doxycycline		Minocycline	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Bacteroides fragilis	0.25	2	1	32	0.5	8	0.032	8
B. fragilis group	1	4	16	32	2	4	2	4
Clostridium difficile	0.06	0.125	0.064	0.125	0.032	0.125	0.032	0.032
Clostridium perfringens	0.032	0.25	0.064	8	0.064	0.125	0.016	0.125
Fusobacterium spp.	0.03	0.06	0.25	0.25	0.06	0.125	0.032	0.06
Peptostreptococcus spp.	0.06	0.125	0.5	16	0.125	4	0.125	8

MIC_{50} = minimum inhibitory concentration (μg/mL) of 50% of isolates; **MIC_{90}** = minimum inhibitory concentration (μg/mL) of 90% of isolates.

tissue to plasma ratios were 2046 in bone, 149 in bone marrow, 90.3 in thyroid, 45.4 in spleen and 24.1 in liver at 168 hours after a 30-minute intravenous infusion.[65] Little quantitative data are available regarding tissue penetration of the other tetracyclines, although they have been shown to penetrate 'well' into body fluids and tissues.[26,38] Minocycline and doxycycline are more lipophilic and, therefore, demonstrate greater tissue penetration than tetracycline, especially into tissues such as the brain, eye, prostate and intestinal epithelium.[26,35,38,52]

Therapeutic concentrations of doxycycline may be found in the aqueous humour and tetracyclines can be found in 'substantial' concentrations in the eye.[26,38] Penetration of minocycline into the cerebrospinal fluid (CSF) is poor, especially in the non-inflamed state; however, tetracycline concentrations in the CSF may be 10–25% of those in the blood and doxycycline concentrations may be 11–56% of those in the plasma.[26,38,59,62] Doxycycline concentrations may reach 75% of plasma concentrations in the gall bladder, while the tissue/plasma ratio for minocycline in the gall bladder is 6.5.[26] Concentrations in the bile for tetracycline and doxycycline may reach 5- to 10-fold and 8-fold the serum concentration, respectively, while the tissue/plasma ratio for minocycline is 38%.[26,35] Tetracycline is reported to penetrate well into the prostate, while doxycycline can attain 60% of the level observed in serum and minocycline can reach concentrations 40–100% of the serum concentration.[26,38,59] The mean sputum concentration of the tetracyclines is approximately 20% of that in serum, although minocycline can reach concentrations of up to 60%, and maxillary sinus secretions and bronchial mucosal tissue have concentrations comparable to those in serum.[26,38,61] The tetracyclines achieve low concentrations in the saliva, with minocycline being able to achieve slightly higher concentrations than tetracycline or doxycycline, which helps to explain its use in the treatment of the meningococcal carrier state.[26,38,52,61] The tetracyclines concentrate in the sebum and are excreted in perspiration, which makes them useful in the treatment of acne vulgaris.[1,52]

Tetracyclines can cross the placenta and enter the foetal circulation and amniotic fluid, where concentrations may be in the range of 20–60% of the maternal serum concentration, and tetracyclines may also achieve high concentrations in breast milk.[26,38,52,59-62]

Table VI. *In vitro* activity of tigecycline and the tetracyclines against other clinically important bacteria[36,37,47,48,52,53]

Bacteria	Tigecycline		Tetracycline		Doxycycline		Minocycline	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Chlamydia pneumoniae	0.125	0.125	1*	NA	0.25	0.25	NA	NA
Legionella pneumophila	NA	NA	0.5–2	1–8	NA	4	NA	4
Mycoplasma pneumoniae	0.12	0.25	0.5	1	NA	1.6	0.5	1
Ureaplasma urealyticum	4	NA	1	NA	NA	NA	0.25	NA

MIC_{50} = minimum inhibitory concentration (μg/mL) of 50% of isolates; **MIC_{90}** = minimum inhibitory concentration (μg/mL) of 90% of isolates; **NA** = information not available; * indicates MIC in μg/mL, though number or range does not reflect the percentage of isolates that were inhibited (i.e. MIC_{50} or MIC_{90}).

Table VII. Pharmacokinetic parameters of tigecycline and the tetracyclines after a single oral or intravenous dose[3,5,26,35,52,58-64]

Drug	Tigecycline		Tetracycline	Doxycycline		Minocycline	
Dose (mg)[a]	12.5 (IV)	300 (IV)	500 (oral)	200 (oral)	200 (IV)	200 (oral)	200 (IV)
F (%)	ND		75 (oral)	90–100 (oral)		90–100 (oral)	
C_{max} (μg/mL)	0.11 (IV)	2.8 (IV)	3–4 (oral)	2.5 (oral)	4 (IV)	2.5 (oral)	4 (IV)
t_{max} (h)	ND		1–4	1.5–4		2	
AUC (μg • h/mL)	0.9	17.9	ND	ND		ND	
$t_{½}$ (h)	36		10	12–22		11–26	
Vd (L/kg)	>10		1.3–1.6	0.7		0.14–0.7	
Protein binding (%)	68		20–65	60–95		55–96	
Excreted unchanged (%)	<15		60	30–42		5–12	
Dose adjustment[b]							
renal	ND		Yes	No		Yes	
hepatic	ND		Yes	ND		No	

a Dose only applies to C_{max} and AUC, the other parameters represent an average of the values available in the literature irrespective of dosage, the dosages reported are based on the dosages commonly used in clinical trials for these drugs.

b Dose adjustment refers to whether or not the tetracycline requires any dosage adjustments in patients with impaired renal or hepatic function.

AUC = area under the plasma concentration-time curve; **C_{max}** = peak concentration reached in the plasma/serum; **F** = bioavailability; **IV** = intravenous; **ND** = no data; **t_{max}** = time to reach C_{max}; **$t_{½}$** = half life; **Vd** = volume of distribution.

5.3 Elimination

Tigecycline has a half life of 36 hours, which is greater than that of tetracycline, doxycycline or minocycline, with half lives of 10, 12–22, and 11–26 hours, respectively (table VII). Less than 15% of tigecycline is excreted unchanged in the urine, which is similar to minocycline (5–12%), while 60% of tetracycline and 30–42% of doxycycline is excreted in the urine unchanged. A recent study reported a 20–40% increase in the tigecycline area under the concentration-time curve (AUC) in patients with end-stage renal disease.[66] Tigecycline was not dialysable. The investigators concluded that the tigecycline dosage should not have to be reduced in patients with renal impairment. Doxycycline does not require a dosage adjustment in renal failure, while the data for minocycline are conflicting (minor dosage adjustments may be required for patients receiving minocycline).[38] Tetracycline does require a dosage adjustment in renal failure and it should not be used in patients with a creatinine clearance less than 30 mL/min, in which case doxycycline should be used instead.[67]

Tetracycline also requires a dosage adjustment in hepatic failure, while no data is available for doxycycline. The half-life of minocycline has not been reported to be prolonged in patients with hepatic failure, although caution should be exercised when prescribing the tetracyclines to these patients.[38,60,61]

A study conducted by Muralidharan et al.[68] investigated the effects of age and gender on the pharmacokinetics of tigecycline. Healthy male and female participants were placed in one of three age groups (18–50, 65–70 and >75 years) for this open-label, single-dose study. Each participant received tigecycline 100mg as a 1-hour intravenous infusion. For each group, the mean C_{max} values were in the range of 0.85 to 1 μg/mL. The lowest AUC was reported in males <50 years (4.2 μg • h/mL) and the highest in males >75 years (5.8 μg • h/mL). In all three female groups, the mean AUC was approximately 5 μg • h/mL. Tigecycline was extensively distributed into tissues with a volume of distribution at steady state (Vss) in females and males of approximately 350L and 500L, respectively. This study concluded that the pharmacokinetics of tigecycline were not markedly different among different gender and age groups.

5.4 Pharmacodynamics

The MIC and the minimum bactericidal concentration (MBC) have both been used to assess the activity of antibacterial agents against infectious organisms.[69] While these are useful parameters for predicting the potency of a drug, they do not provide adequate information regarding the time course of

antibacterial activity.[69,70] Specifically, the MIC does not reflect events that occur after exposure to an antibacterial, and the MBC does not establish the killing rate and whether or not this is affected by increasing concentration.[69,70] Pharmacodynamics, which describes the relationship between serum concentration and the pharmacological and toxicological effects of drugs, together with pharmacokinetics better reflects the time course of antibacterial activity and, therefore, aids in establishing effective dosage regimens.[69]

Two types of bactericidal activity have been described: concentration-dependent and concentration-independent (time-dependent) killing.[69-71] Concentration-dependent killing is observed with several classes of antibacterials, including the aminoglycosides and the fluoroquinolones, whereas concentration-independent killing is observed among the β-lactams, the macrolides and the tetracyclines, as well as vancomycin and clindamycin.[69-71] Increasing drug concentrations are important with regards to the rate and extent of killing for concentration-dependent agents, as is a large plasma C_{max} to MIC ratio.[69,71] Concentration-independent killing does not rely on high drug concentrations, rather on the time of exposure of the agent or the length of time above the MIC.[69,71] Threshold concentrations (approximately 4-fold the MIC) are achieved with concentration-independent antibacterials, at which point concentrations above the threshold do not further increase the rate or extent of bactericidal activity.[69-71]

Another pharmacodynamic factor is the post-antibiotic effect (PAE), which refers to a period of time after removal of an antibacterial (or a decrease in concentration to below the MIC) where bacterial growth continues to be suppressed.[69-72] The PAE may increase with longer exposure times or higher drug concentrations, up to a maximal response.[70] Protein synthesis inhibitors have been shown to induce PAEs of moderate to long duration, with tetracyclines providing a PAE of 2.5–4 hours against *S. aureus* and streptococci, and >4 hours against Enterobacteriaceae.[69,70,72] Because tetracyclines reversibly bind to the ribosomal subunit, it is possible that the PAE for these agents represents the time required for the molecules to diffuse from the ribosomal binding site.[72] Sub-MIC concentrations of antibacterials can slow the growth of organisms, which can consequently prolong the PAE, as can the post-antibiotic leucocyte effect (PALE), where organisms are more susceptible to phagocytosis by leucocytes during the post-antibiotic period.[69,72]

Several studies[73,74] have been conducted to investigate the pharmacodynamic parameters of tigecycline. One study conducted by van Ogtrop et al.[73] tested the *in vivo* pharmacodynamic activity of tigecycline against isolates of *S. pneumoniae*, *S. aureus*, *E. coli* and *K. pneumoniae* using the neutropenic murine thigh infection model.[73] All isolates used were susceptible to tigecycline, with MICs in the range of 0.06 to 0.5 μg/mL and MBCs were typically 1 to 2 dilutions higher than the MIC.[73] The pharmacokinetics of tigecycline appeared to be non-linear in this study,[73] which differs from a study conducted by Muralidharan et al.[64] that showed the kinetics in humans were linear. The activity of tigecycline was shown to be dependent on the time above the MIC and the concentration should be maintained above the MIC at least 50% of the dose administration interval for optimal activity.[73] The AUC/MIC was also important in predicting activity.[73] The PAE of tigecycline was determined using a 3 mg/kg dose, which showed a PAE of 8.9 hours against *S. pneumoniae* and 4.9 hours against *E. coli*.[73]

Another study conducted by Lefort et al.,[74] evaluated different dose administration regimens on the activity of tigecycline against a clinical VanA-type strain of *E. faecium* HB217 (tigecycline MIC of 0.06 mg/L). Animals with aortic endocarditis received intravenous doses of tigecycline 14 mg/kg twice daily, 14 mg/kg once daily or 7 mg/kg once daily for a duration of 5 days, which showed reductions of bacterial counts ($\log_{10}$ cfu/g of vegetation [cfu = colony forming units]) at the end of therapy of 3.7 ± 0.9, 3.2 ± 1.2 and 3.1 ± 1.0 for each dose, respectively.[74] Serum concentrations were constantly above the MIC with the twice daily dose administration and below the MIC 50% of the time with once daily dose administration, and the PAE at 1- and 10-fold the MIC for tigecycline was 4 hours.[74] The study concluded that regimens that maintained the serum concentration above the MIC at all times were just as effective as those where the concentration dropped below the MIC for 50% of the time.[74]

The PAE of tigecycline has been shown to be greater than that of minocycline when tested against different strains of *S. aureus* and *E. coli*.[14] Each isolate was exposed for 2 hours to tigecycline or minocycline at concentrations of 8-fold the MIC, at which point the compound was diluted 1000-fold, lowering the concentration to well below the MIC.[14] The PAE for each strain, measured in hours, was greater for tigecycline than minocycline, with the difference ranging from 0.6 to 2 hours.[14]

The tetracyclines were introduced before the importance of pharmacodynamics was realised; therefore, there are little data regarding the optimal dosage regimens of these antibiotics, and previous dose administration guidelines were based largely on pharmacokinetic parameters.[75] One study conducted by Cunha et al.,[75] focused on the pharmacodynamic parameters of doxycycline. Results show that at low concentrations (2- to 4-fold the MIC), doxycycline displays time-dependent killing, whereas at higher concentrations (8- to 16-fold the MIC), it displays concentration-dependent killing.[75] The PAE of doxycycline is dose-dependent and is in the range of 2.1 and 4.2 hours, but it is clinically insignificant since adequate serum concentrations can be maintained for the duration of the dose administration interval if given on a 12 or 24 hourly basis.[75] Dosages of 200mg every 12 hours or 400mg once a day are sufficient for concentration-dependent killing, while lower doses of 100mg every 12 hours or 200mg once a day provide adequate levels for time-dependent killing for mild to moderate infections.[75]

6. Trials in Animals and Clinical Trials

Phase 1 and 2 clinical trials have been completed for tigecycline. Phase 1 trials have focused on dose ranging studies in patients with renal or hepatic impairment.[66] Two phase 2 clinical trials have been reported, one in patients with complicated skin and skin structure infections (SSSI) and the second in patients with complicated intra-abdominal infections.[76,77] In the first study, 164 hospitalised patients with complicated SSSI were studied in a randomised, multicentre, open-label dose comparison of intravenous tigecycline 25mg every 12 hours (initial 50mg load) and intravenous tigecycline 50mg every 12 hours (initial 100mg load).[76] Both clinical cure rates (74% vs 67%) and microbiological eradication (74% vs 62%) were higher in the 50mg dose group. In the second study, 111 hospitalised patients with complicated intra-abdominal infections were studied in a mutlicentre, open-label study using intravenous tigecycline 50mg every 12 hours (initial 100mg load).[77] Clinical cure rates at the test-of-cure visit and end of treatment were 67% and 76%, respectively. Both studies concluded that tigecycline was efficacious (safe) agent. With the limited amount of clinical data available, the focus of this section will be on preclinical *in vivo* animal studies.

Table VIII summarises the available animal data for tigecycline.[40,43,44,73,74,78-81] One study conducted by Edelstein et al.[78] assessed the activity of tigecycline against extracellular and intracellular *Legionella pneumophila* as well as the treatment of guinea pigs with *L. pneumophila* pneumonia. The MIC_{50} for tigecycline for 101 different strains of *L. pneumophila* was 4 μg/mL (0.125 μg/mL for azithromycin and 0.25 μg/mL for erythromycin). Tigecycline was as active as erythromycin against the F889 strain of *L. pneumophila* grown in alveolar macrophages (both 1 μg/mL) but was more active than erythromycin against the F2111 strain. Azithromycin (0.25 μg/mL) was more active against F889 and was as active against F2111 as tigecycline (1 μg/mL) in the macrophage model. When tigecycline was administered to guinea pigs with *L. pneumophila* pneumonia as a single subcutaneous dose of 7.5 mg/kg, mean peak serum and lung concentrations were 2.3 and 1.7 μg/mL, respectively, at 1-hour post injection, and 1.2 and 1.5 μg/mL at 2 hours post injection. The elimination half-lives from serum and lung were 3.7 and 2.6 hours, respectively, whereas the serum and lung $AUC_{0–24}$ were 13.3 and 15.8 μg • h/mL, respectively. Of the 16 guinea pigs treated with tigecycline 7.5 mg/kg subcutaneously once daily for 5 days, 13 survived for 7 days post therapy, whereas 11 of the 12 guinea pigs treated with azithromycin 15 mg/kg intraperitoneally once daily for 2 days survived 7 days after therapy (none of the guinea pigs treated with saline survived).[74] Guinea pigs treated with tigecycline had average end of therapy lung counts of 1×10^6 cfu/g (range 3.2×10^6 to 2.5×10^4 cfu/g), versus $<1 \times 10^2$ cfu/g for azithromycin. A second group of guinea pigs were studied to assess the ability of tigecycline to clear *L.*

Table VIII. Animal studies involving tigecycline

Study	Animal model	Dosage	Duration	n	Results
Edelstein et al.[78]	*Legionella pneumophila* pneumonia in guinea pigs	SC G 7.5 mg/kg od	5 days	16	13/16[a] (1×10^6 cfu/g)[b]
		IP AZ 15 mg/kg od	2 days	12	11/12[a] ($<1 \times 10^2$ cfu/g)[b]
		S ND	ND	12	0/12[a]
Nannini et al.[79]	Enterococcal mouse peritonitis model	G ND	Single SC dose given	6 mice per dosing group	PD_{50} in mg/kg: (0.6)[c]; (1.9)[d]; (1.8)[e]; (2.1)[f]; (3.6)[g]; (5.7)[h]; (5.5)[i]
		T ND			PD_{50} in mg/kg: (6)[c]; (>200)[d]; (–)[e]; (–)[f]; (>200)[g]; (–)[h]; (–)[i]
		M ND			PD_{50} in mg/kg: (–)[c]; (>200)[d]; (2.8)[e]; (3.8)[f]; (–)[g]; (>200)[h]; (9.3)[i]
		AM ND			PD_{50} in mg/kg: (11.3)[c]; (–)[d]; (35.3)[e]; (–)[f]; (–)[g]; (–)[h]; (>200)[i]
		V ND			PD_{50} in mg/kg: (29.5)[c]; (–)[d]; (–)[e]; (–)[f]; (–)[g]; (16)[h]; (>200)[i]
		QD ND			PD_{50} in mg/kg: (–)[f]; (–)[g]; (32.1)[hjk]; (10.2)[ijk]
van Ogtrop et al.[73]	Neutropenic murine thigh infection model	G bid dosing (*S. pneumoniae* 0.19–24 mg/kg, all others 0.19–192 mg/kg)	ND	ND	*Streptococcus pneumoniae* ED_{50} (BD) range 1.1–9.6 (0.8–5.9) mg/kg/d
					Staphylococcus aureus ED_{50} (BD) range 4–41 (7.2–23) mg/kg/d
					Escherichia coli ED_{50} (BD) range 5.8–11 (11–14) mg/kg/d
					Klebsiella pneumoniae ED_{50} (BD) 115 (151)
Murphy et al.[43]	Endocarditis in rats	G 0.5 mg/kg/d	ND	8	Mean log cfu/heart 7.60
	(*E. faecalis*	G 2 mg/kg/d		4	Mean log cfu/heart 6.27
	GC6181)	G 7 mg/kg/d		7	Mean log cfu/heart 5.69
		G 14 mg/kg/d		10	Mean log cfu/heart 4.58
		G 40 mg/kg/d		11	Mean log cfu/heart 4.70
		G 80 mg/kg/d		9	Mean log cfu/heart 3.69
		V 40 mg/kg/d		10	Mean log cfu/heart 5.52
		V 120 mg/kg/d		3	Mean log cfu/heart 5.54
		V 240 mg/kg/d		3	Mean log cfu/heart 5.75
		Control		30	Mean log cfu/heart 7.01
	(*E. faecalis*	G 0.5 mg/kg/d	ND	7	Mean log cfu/heart 8.59
	GC6191)	G 7 mg/kg/d		8	Mean log cfu/heart 5.79
		G 14 mg/kg/d		4	Mean log cfu/heart 5.12
		G 40 mg/kg/d		7	Mean log cfu/heart 4.94
		G 80 mg/kg/d		2	Mean log cfu/heart 4.61
		V 40 mg/kg/d		4	Mean log cfu/heart 7.66
		V 120 mg/kg/d		2	Mean log cfu/heart 7.44

Continued next page

Table VIII. Contd

Study	Animal model	Dosage	Duration	n	Results
		V 240 mg/kg/d		4	Mean log cfu/heart 7.24
		Control		19	Mean log cfu/heart 7.80
	(*E. faecalis*	G 0.5 mg/kg/d	ND	11	Mean log cfu/heart 7.22
	GC6207)	G 2 mg/kg/d		7	Mean log cfu/heart 4.89
		G 7 mg/kg/d		4	Mean log cfu/heart 3.99
		G 14 mg/kg/d		4	Mean log cfu/heart 3.01
		Control		11	Mean log cfu/heart 7.72
	(MRSA)	G 1 mg/kg/d	ND	6	Mean log cfu/heart 10.98
		G 2 mg/kg/d		4	Mean log cfu/heart 9.89
		G 10 mg/kg/d		5	Mean log cfu/heart 7.93
		G 14 mg/kg/d		5	Mean log cfu/heart 6.85
		G 40 mg/kg/d		7	Mean log cfu/heart 6.23
		V 40 mg/kg/d		3	Mean log cfu/heart 10.70
		Control		17	Mean log cfu/heart 11.40
Lefort et al.[74]	Endocarditis due to VanA-type *E. faecium* in rabbits	G 14 mg/kg bid	5 days	ND	Log cfu/g of vegetation 4.8 ± 0.9
		G 14 mg/kg od			Log cfu/g of vegetation 5.3 ± 1.2
		G 7 mg/kg od			Log cfu/g of vegetation 5.4 ± 1.0
		Control untreated			Log cfu/g of vegetation 8.5 ± 1.4
Lefort et al.[80]	Enterococcal endocarditis in rabbits	G 14 mg/kg bid	5 days	ND	Log_{10} cfu/g of vegetation 7.9 ± 0.8 (JH2-2)[l]
					Log_{10} cfu/g of vegetation 6.2 ± 1.1 (BM4316)[l]
					Log_{10} cfu/g of vegetation 4.8 ± 0.9 (HB217)[m]
		Control untreated			Log_{10} cfu/g of vegetation 9.8 ± 1.0 (JH2-2)[l]
					Log_{10} cfu/g of vegetation 8.8 ± 1.0 (BM4316)[l]
					Log_{10} cfu/g of vegetation 8.6 ± 0.8 (HB217)[m]
Petersen et al.[44]	Intraperitoneal inoculation in mice	IV G ND single dose	1 day	5 per group	*S. aureus* ED_{50} range 0.79–2.3 mg/kg/d
					S. pneumoniae ED_{50} range 0.61–1.7 mg/kg/d
					E. coli ED_{50} range 1.5–3.9 mg/kg/d
		IV M ND single dose			*S. aureus* ED_{50} range 0.31–16 mg/kg/d
					S. pneumoniae ED_{50} range 3.5–20 mg/kg/d
					E. coli ED_{50} range 3.2–>32 mg/kg/d
Mikels et al.[40]	*Pseudomonas aeruginosa* pneumonia in mice[n]	Control	2 days	23	Mean change from control (log_{10} cfu) ND
		G or GE 50 mg/kg/d		8 (12)	Mean change from control (log_{10} cfu) −2.75 (−3.16)
		G or GE 20 mg/kg/d		5 (6)	Mean change from control (log_{10} cfu) −2.80 (−3.30)
		G or GE 10 mg/kg bid		7 (8)	Mean change from control (log_{10} cfu) −2.98 (−3.36)
		G or GE 10 mg/kg/d		15 (11)	Mean change from control (log_{10} cfu) −2.49 (−2.34)

Continued next page

Table VIII. Contd

Study	Animal model	Dosage	Duration	n	Results
		G or GE 5 mg/kg/d		6 (6)	Mean change from control (log_{10} cfu) −2.05 (−1.62)
		G or GE 1 mg/kg/d		7 (8)	Mean change from control (log_{10} cfu) −1.52 (−1.30)
		G or GE 0.5 mg/kg/d		3 (3)	Mean change from control (log_{10} cfu) −1.02 (−0.78)
		P 300 mg/kg/d		5	Mean change from control (log_{10} cfu) −3.42
		P 200 mg/kg/d		8	Mean change from control (log_{10} cfu) −2.29
		P 100 mg/kg bid		8	Mean change from control (log_{10} cfu) −2.98
		P 100 mg/kg/d		8	Mean change from control (log_{10} cfu) −1.33
		P 50 mg/kg/d		4	Mean change from control (log_{10} cfu) −1.78
		P 25 mg/kg bid		5	Mean change from control (log_{10} cfu) −1.71
		G + GE 5 + 5 mg/kg/d		7	Mean change from control (log_{10} cfu) −2.66
		G + GE 1 + 1 mg/kg/d		5	Mean change from control (log_{10} cfu) −2.13
		G + GE 25 + 50 mg/kg/d		5	Mean change from control (log_{10} cfu) −4.50
		G + GE 10 + 50 mg/kg/d		8	Mean change from control (log_{10} cfu) −4.36
		G 25 mg/kg/d od		5	Mean change from control (log_{10} cfu) −3.75
		P 200 mg/kg/d od		6	Mean change from control (log_{10} cfu) −2.29
		GE 50 mg/kg/d od		12	Mean change from control (log_{10} cfu) −3.16
		G + P 25 + 200 mg/kg/d od		5	Mean change from control (log_{10} cfu) −3.87
		GE + P 50 + 200 mg/kg/d od		3	Mean change from control (log_{10} cfu) −3.12
		G 20mg/kg/d bid		7	Mean change from control (log_{10} cfu) −2.98
		P 200 mg/kg/d bid		8	Mean change from control (log_{10} cfu) −2.98
		GE 20 mg/kg/d bid		8	Mean change from control (log_{10} cfu) −3.36
		G + P 20 + 200 mg/kg/d bid		7	Mean change from control (log_{10} cfu) −3.80
		GE + P 20 + 200 mg/kg/d bid		8	Mean change from control (log_{10} cfu) −3.69
Mikels et al.[81]	PSSP and PRSP thigh and lung infections in mice	SC G od	3 days	3–5 mice per group (lung infection)	PD_{50} 0.4 (PSSP) 0.5 (PRSP)
		SC G bid			PD_{50} 0.2 (PRSP)
		SC V od			PD_{50} 1.9 (PSSP) 1.8 (PRSP)
		SC V bid			PD_{50} 1.6 (PRSP)
		Oral A od			PD_{50} 0.5 (PSSP) 13.1 (PRSP)
		Oral A bid			PD_{50} 2.8 (PRSP)
		SC M od			PD_{50} 3.3 (PSSP) – (PRSP)
		SC M bid			PD_{50} – (PRSP)
	PSSP	SC G 1mg/kg od	3 days	ND (thigh infection)	Log reduction cfu/mL 72 hours pt −4.0
		SC G 0.125 mg/kg od			Log reduction cfu/mL 72 hours pt −0.7

Continued next page

Table VIII. Contd

Study	Animal model	Dosage	Duration	n	Results
		Control			Log cfu/mL 72 hours pt 8.4
	PRSP	SC G 4 mg/kg od	3 days	ND (thigh	Log reduction cfu/mL 72 hours pt −3.2
		SC G 1 mg/kg od		infection)	Log reduction cfu/mL 72 hours pt −0.4
		SC G 0.5 mg/kg od			Log reduction cfu/mL 72 hours pt −1.7
		SC G 0.125 mg/kg od			Log reduction cfu/mL 72 hours pt +0.5
		Control			Log cfu/mL 72 hours pt 7.3
	PRSP	SC G 8 mg/kg od	2 days	ND (thigh	Log reduction cfu/mL 48h (72h) pt −2.3 (−4.9)
		SC G 4 mg/kg bid		infection)	Log reduction cfu/mL 48h (72h) pt −4.1 (>−5)
		SC G 2 mg/kg qid			Log reduction cfu/mL 48h (72h) pt −4.1 (>−5)
		Control			Log cfu/mL 48h (72h) pt 7.2 (7.4)

a Number of guinea pigs that survived 7 days post antimicrobial therapy.

b Average end of therapy lung counts.

c PD_{50} results after 1 SC dose (mg/kg) for *Enterococcus faecalis* OGIRF (ATCC 47077).

d PD_{50} results after 1 SC dose (mg/kg) for *E. faecalis* INY1200 (OGERF::Tn925).

e PD_{50} results after 1 SC dose (mg/kg) for *E. faecalis* V583 (vanB and erm[B]).

f PD_{50} results after 1 SC dose (mg/kg) for *Enterococcus faecium* TX5034 (SH16SSp) [vanA].

g PD_{50} results after 1 SC dose (mg/kg) for *E. faecium* TX5037 (TX5034::Tn925).

h PD_{50} results after 1 SC dose (mg/kg) for *E. faecium* TX0016 (Tetr).

i PD_{50} results after 1 SC dose (mg/kg) for *E. faecium* TX2465 (vanA).

j Historical values.

k Intravenous, one dose.

l Specific strain of *E. faecalis*.

m Specific strain of *E. faecium*.

n First number and result is G; number/result in brackets is for GE.

A = amoxicillin; **AM** = ampicillin; **AZ** = azithromycin; **BD** = bacteriostatic dose, in mg/kg/day; **bid** = twice a day; **cfu** = colony forming units; **ED_{50}** = dose providing one-half of the maximum effect, in mg/kg/day; **G** = tigecycline/GAR-936; **GE** = gentamicin; **IP** = intraperitoneal; **IV** = intravenous; **M** = minocycline; **MRSA** = methicillin-resistant *S. aureus*; **n** = number of animals; **ND** = no data; **od** = once a day; **P** = piperacillin; **PD_{50}** = the concentration (in mg/kg) of antibiotic required to prevent death in 50% of the population; **PRSP** = penicillin-resistant *S. pneumoniae*; **PSSP** = penicillin-susceptible *S. pneumoniae*; **pt** = post treatment; **QD** = quinupristin/dalfopristin; **qid** = four times a day; **S** = saline; **SC** = subcutaneous; **T** = tetracycline; **V** = vancomycin; – indicates not tested.

pneumophila from the lung after 5 to 9 days of therapy. Bacterial concentrations 1 day after therapy ranged from $\log_{10}$ 4.1 to 4.8 cfu/g for four different dosing regimens. This study concluded that tigecycline is about as effective as erythromycin against intracellular *L. pneumophila*, and that tigecycline was effective in a Legionnaires' disease animal model.[78]

A study conducted by Nannini et al.[79] tested the *in vivo* efficacy of tigecycline against different strains of *E. faecalis* and *E. faecium* in a mouse peritonitis model (table VIII).[79] Each dosing group consisted of six mice, and each mouse received a single subcutaneous dose of antibacterials immediately after intraperitoneal injection of the bacterial solution. Animals infected with *E. faecalis* were observed for 96 hours and mice infected with *E. faecium* were observed for 120 hours, at which point the 50% lethal dose (LD_{50}) and the 50% protective dose (PD_{50}) were determined. The PD_{50} values are listed in table VIII and show that tigecycline values were below those obtained for tetracycline and minocycline, and that tigecycline maintained a protective effect against strains with tetracycline and vancomycin resistance phenotypes.[79]

A study was conducted by van Ogtrop et al.[73] to determine the *in vivo* pharmacodynamic activity of tigecycline against various Gram-positive and Gram-negative bacteria (table VIII). Experiments were performed with different strains of *E. coli*, *K. pneumoniae*, *S. pneumoniae* and *S. aureus*, and mice were rendered neutropenic before being infected with these organisms. Dosages of tigecycline in the range of 0.19–24 mg/kg/day for were used for *S. pneumoniae*, and for all other bacterial strains, dosages of 0.19–192 mg/kg/day were used. Antibacterials were administered subcutaneously 2 hours after thigh inoculation and on initiation of therapy, the mean $\log_{10}$ number of organisms in the thigh was 6.84 cfu/thigh. After 24 hours, the mean $\log_{10}$ number of organisms in the control animals was 8.99 cfu/thigh and the organisms grew in this group by 2.16 $\log_{10}$ cfu/thigh, on average. Death occurred at 18 to 24 hours post infection in most of the control groups infected with *S. pneumoniae* and *K. pneumoniae*. The ED_{50} (dose providing one-half of the maximum effect, in mg/kg/day) and BD (bacteriostatic dose, in mg/kg/day) for tigecycline were determined against different strains of the test organisms, and these results are listed in table VIII. These results demonstrate that tigecycline was most effective against various strains of *S. pneumoniae*, with bacteriostatic doses of *E. coli* and *S. aureus* being up to 25-fold higher than those for *S. pneumoniae*, and tigecycline was only marginally effective against *K. pneumoniae*.[73]

Murphy et al.[43] studied the efficacy of tigecycline in a rat model of endocarditis caused by *E. faecalis* (three strains studied) as well as a strain of MRSA. Endocarditis was produced by inserting a cannula through the right carotid artery into the left ventricle and 48 hours after implantation, 1mL of bacterial solution was injected intravenously (infection was then verified by plate counts). Antibacterial treatment was initiated 24 or 36 hours after bacterial challenge and treatments were delivered subcutaneously every 12 hours for 3 days. The dosages ranged from 0.5 to 80 mg/kg/day for tigecycline and 40 to 240 mg/kg/day for vancomycin, with control rats receiving injections of phosphate-buffered saline. All rats were killed 24 hours after the last treatment, at which point the hearts were removed and bacterial titres expressed as $\log_{10}$ cfu/heart were determined (results listed in table VIII). Against *E. faecalis* GC6181, tigecycline doses of ≥14 mg/kg/day resulted in an average $\log_{10}$ decrease of >2.0 cfu/heart from the controls, while vancomycin dosages of 40 to 240 mg/kg/day resulted in an average $\log_{10}$ decrease of <1.5 cfu/heart compared with controls. Tigecycline at dosages of 14 mg/kg/day exhibited a $\log_{10}$ reduction from the controls of 2.68 cfu/heart against *E. faecalis* GC6191, whereas vancomycin at 240 mg/kg/day had no significant effect. Tigecycline was effective against *E. faecalis* GC6207, with a $\log_{10}$ cfu reduction from the controls of 4.7 cfu/heart at a dosage of 14 mg/kg/day. Against MRSA, tigecycline 14 mg/kg/day was more effective than vancomycin 40 mg/kg/day, with reduction in bacterial titres of 4.5 and 0.69 $\log_{10}$ cfu/heart, respectively.[43]

A study was conducted by Lefort et al.[74] to determine the activity of tigecycline in experimental endocarditis due to VanA-type *E. faecium* (table VIII). Catheters were inserted through the carotid artery of rabbits and were inoculated with bacteria 24 hours after insertion. Forty-eight hours after in-

oculation, rabbits were treated intravenously with tigecycline in dosages of 14 mg/kg twice daily, 14 mg/kg once daily or 7 mg/kg once daily for a duration of 5 days (control animals were left untreated). The log cfu/g of vegetation was calculated for each group of rabbits, including the control, the 14 mg/kg twice daily group, the 14 mg/kg once daily group and the 7 mg/kg once daily group, giving results of 8.5±1.4, 4.8 ± 0.9, 5.3 ± 1.2 and 5.4 ± 1.0 log cfu/g of vegetation, for each respective group. This study concluded that once daily regimens were as effective as the 14 mg/kg twice daily regimen.[74]

Lefort et al.[80] conducted another study to assess the activity and diffusion of tigecycline in endocarditis, using two strains of *E. faecalis* and one of *E. faecium* (table VIII). Endocarditis was produced in rabbits with each strain and, 48 hours after inoculation, the rabbits were treated with tigecycline 14 mg/kg twice daily for 5 days (controls were left untreated). Results from this study are listed in table VIII for the treated and control groups, and the study concluded that tigecycline was active both *in vitro* and *in vivo* against enterococci, and that tigecycline concentrated into cardiac vegetations and displayed a homogenous distribution.[80]

The *in vivo* activity of tigecycline and minocycline against different strains of *S. aureus*, *S. pneumoniae* and *E. coli*, was evaluated in a study conducted by Petersen et al.[44] (table VIII). Mice received an intraperitoneal injection of a bacterial suspension and then 0.5 hours later received various different doses of the antibacterial intravenously (for mice infected with *E. coli*, a second dose was given 3 hours later). In each test, five animals were treated with each dose and all of the untreated controls died within 48 hours of infection. The ED_{50} was determined for tigecycline and minocycline for each test organism, and the ranges for the different strains are listed in table VIII. When administered intravenously, tigecycline was as effective as minocycline against infections caused by minocycline-susceptible bacteria; however, the ED_{50} of tigecycline against infections caused by MRSA that also contained *tet*(M) were lower than those of minocycline. *E. coli* strains carrying *tet*(A), *tet*(B), *tet*(C) or *tet*(M) were more responsive to tigecycline treatment than minocycline. Tigecycline demonstrated poor activity when oral doses were administered.[44]

Mikels et al.[40] conducted a study in mice to determine the reduction of bacterial counts in lung tissue after administration of tigecycline, gentamicin and piperacillin, both alone and in combination (table VIII). Mice (three to five per group) were infected intranasally with *P. aeruginosa* and 3 hours later were administered antibacterial subcutaneously, either two doses 24 hours apart or four doses 12 hours apart. Log_{10} reductions were then calculated from control bacterial counts, and the results from the different regimens and combinations are listed in table VIII. This study concluded that tigecycline demonstrated excellent activity against *P. aeruginosa* in the murine model. Tigecycline and gentamicin displayed similar reductions of lung counts and an additive effect was observed when the two agents were used in combination. When tigecycline and piperacillin were dosed together twice daily there was an additive effect over each agent dosed alone twice daily but this additive effect was not seen when tigecycline and piperacillin were dosed together once daily compared with alone once daily.[40]

Another study conducted by Mikels et al.[81] determined the therapeutic efficacy of tigecycline against various bacteria in both murine thigh and lung infection models (table VIII). Static doses for tigecycline in thigh infections 1.5 hours after infection were determined with the following results: 16 mg/kg for MSSA, 23 mg/kg for MRSA, 5.2 mg/kg for PSSP, <1 for PRSP, <1 mg/kg for vancomycin-resistant *E. faecalis*, 11 mg/kg for *E. faecium*, and 12–76 mg/kg for *E. coli* and *K. pneumoniae*. The therapeutic efficacy of tigecycline was compared with that of vancomycin, amoxicillin and minocycline against a *S. pneumoniae* lung infection in mice. The results of these studies are listed in table VIII. The minimum effective dose required to achieve 100% survival in mice infected with PSSP or PRSP was determined to be 1 mg/kg given subcutaneously.[81]

To date, two studies have been performed in humans, the first of which was conducted by Muralidharan et al.[64] to assess the safety and tolerability of tigecycline in healthy volunteers. This was a randomised, double-blind, placebo-controlled study (n = 6 active, n = 2 placebo per group), which used ascending single intravenous doses of 12.5, 25,

50, 75, 100, 200 and 300mg of tigecycline. The 12.5 through 200mg doses were administered in the fasting state as a 1-hour infusion, whereas 200 and 300mg doses were administered with food as either a 1- or 4-hour infusion. Blood samples were taken up to 96 hours post-dose and these samples, as well as urine samples, were analysed for tigecycline by validated high performance liquid chromatography (HPLC) methods. Tigecycline was safely administered at all dose levels, infusion times and feeding status tested. The maximum tolerated dose, which is defined as the highest dose level at which <50% of the individuals had gastrointestinal adverse effects, was 100mg in the fasting state and 200mg in the fed state. The observed dose-dependent adverse effects due to tigecycline therapy were typical of the tetracyclines as a class, and included nausea, vomiting and headache, and prolonging the length of the infusion (i.e. 1 hour vs 4 hours) did not improve the tolerability.[64]

The second study in humans was also conducted by Muralidharan et al.,[68] and was designed to determine the effects of age and gender on the pharmacokinetics, safety and tolerability of tigecycline in healthy volunteers. This open-label, non-randomised, single-dose study was conducted in healthy male and female volunteers belonging to various age groups, including 18–50 years, 65–75 years and >75 years. Each volunteer received a single 100mg intravenous dose of tigecycline infused over 1 hour, which was administered 30 minutes after a medium fat breakfast with water being permitted *ad lib*. Patients in the 18–50 year old group were not allowed to take concomitant medications, while for the patients over 65 years of age, previously prescribed medications were allowed provided they did not interfere with the adsorption, distribution, metabolism or excretion of tigecycline. If concomitant medications were required, they were administered 2 hours before or 4 hours after the start of the study drug administration. Serial blood samples were collected for pharmacokinetic analyses up to 120 hours post dose. Tigecycline was safely used and well tolerated by all groups, and the adverse effects experienced were typical of the tetracyclines (nausea, vomiting, and headache). Women in the 18–50 age group experienced slightly more nausea than other groups, while nausea was mild for both sexes, with the exception of one individual who experienced moderate nausea. The incidence of adverse effects improved with age, with none of the eight male participants in the >75 age group experiencing nausea or vomiting, and only one woman in this age category reporting mild nausea. This study concluded that tigecycline can safely be administered to both sexes across all age groups tested with no necessary dosage adjustments required.[68]

7. Adverse Effects

Little data are available regarding the adverse effects resulting from tigecycline therapy since most of the clinical trial data remains unpublished. Phase 1 clinical trials by Muralidharan et al.[68] have reported that tigecycline was well tolerated in healthy volunteers. Adverse effects similar to the tetracycline class include were reported including nausea, vomiting and headache which were unrelated to the length of the infusion (i.e. 1 hour vs 4 hours).[63,71] The following information briefly summarises the adverse effects that occur with tetracyclines as they are also likely to occur with tigecycline. However, it should be mentioned that only through clinical trails and post-marketing surveillance will the true incidence of adverse effects be observed with tigecycline. Postier et al.[76] reported that nausea and vomiting were the most frequent adverse effects in a multicentre, open-label study of hospitalised patients with complicated SSSI. Murray et al.[77] also reported that nausea and vomiting were the most frequent adverse effects in a multicentre, open-label study of hospitalised patients with complicated intra-abdominal infections.

7.1 Gastrointestinal

Nausea, vomiting, diarrhoea, abdominal pain and heartburn are dose-dependent effects that are common with the use of tetracyclines.[26,35,38,52,59-62,79,82] Nausea and vomiting may be a result of the irritant effect of the medication on the gastric mucosa.

7.2 Central Nervous System

Light-headedness, dizziness, vertigo, ataxia, drowsiness and fatigue are observed with minocycline therapy, with 30–90% of patients being affected and women more likely to experience these

effects.[52,59-61] Tinnitus, hearing loss and visual disturbances have been reported with tetracycline use.[59,60] Tetracycline, doxycycline and minocycline have all been reported to increase intracranial pressure, although this is rare, with <1% of patients experiencing this effect.[26,59-62]

7.3 Effects on Teeth and Bone

All of the tetracyclines are deposited in teeth and bone during calcification, which can lead to dental staining and inhibition of bone growth in children.[26,35,38,52,60-62] Children may be affected if their mother receives a tetracycline during pregnancy (most affected if the antibacterial is taken after the fifth month of pregnancy), or if the child receives single or multiple courses of tetracyclines during early childhood.[26,38,52,59-62] Dental staining occurs primarily in secondary dentition and, although it may be cosmetically disconcerting, the clinical significance is minor.[26,38,57] To prevent tooth discolouration and bone growth inhibition, tetracyclines should be avoided in children <8 years of age. Minocycline has been reported to cause permanent tooth discolouration in adults taking the medication for prolonged periods of time and is thought to occur via a different mechanism than in children.[83-85]

7.4 Hepatic

Hepatic toxicity mainly occurs in patients who are receiving high dosages of tetracyclines.[26,38,52,59-62] Several deaths have been reported in pregnant women with acute pyelonephritis, who developed fatty degeneration of the liver upon treatment with tetracyclines at dosages >2 g/day.[26,38,52,59-61] Hepatotoxicity has also been observed in patients without any predisposing conditions (such as pregnancy or renal impairment), and tetracycline-induced pancreatitis has been observed in association with hepatotoxicity.[38,59,60]

7.5 Renal

Patients with impaired renal function receiving tetracyclines may develop acute renal failure, which is dependent on the degree of renal impairment, and the dose and duration of treatment.[26,38,52,60-62] The tetracyclines inhibit protein synthesis, which results in azotaemia from metabolism of amino acids, with an observed increase in blood urea nitrogen (serum creatinine may or may not be affected).[38,52,60,61]

7.6 Hypersensitivity Reactions

Hypersensitivity reactions to the tetracyclines are rare, but may involve urticaria, angioneurotic oedema, anaphylaxis, pericarditis, exacerbation of systemic lupus erythematosus and serum sickness-like reactions.[26,38,52,59-62]

7.7 Haematological

Rarely, tetracyclines may cause mild leukopenia, vascular purpura, thrombocytopenia, modification of clotting factors, neutropenia, eosinophilia and anaemia.[38,60,62]

7.8 Miscellaneous

Photosensitive skin reactions have been reported in patients receiving tetracyclines exposed to periods of sunlight or tanning equipment.[86-88] Onycholysis with and without association with photosensitivity have been reported.[89,90]

8. Drug Interactions

As with adverse effects associated with tigecycline, there is also a paucity of drug interaction data. The following information briefly summarises the drug interactions that occur with tetracyclines in general as they are likely to occur with tigecycline.

8.1 Antacids, Calcium, Magnesium, Iron, Sodium Bicarbonate and Binding Resins

The use of antacids, calcium supplements, multivitamins, iron supplements, magnesium salicylates, magnesium-containing laxatives, sodium bicarbonate, cholestyramine or colestipol while undergoing tetracycline therapy may cause nonabsorbable complexes to be formed.[26,59,60,62,82] Antacids and sodium bicarbonate may also decrease the absorption of tetracyclines by increasing the intragastric pH. Therefore, these products should be administered 2 hours before or after the tetracycline.[59,60,82]

8.2 Anticoagulants

The tetracyclines may enhance the effects of oral anticoagulants, such as warfarin.[60,62,82] Patients

prescribed tetracyclines should be monitored by having international normalised ratio or prothrombin times tested more frequently, and the dosage of warfarin adjusted accordingly.

8.3 Antidiarrhoeal Agents

Products containing kaolin and pectin or bismuth subsalicylate can significantly reduce the bioavailability of the tetracyclines by inhibiting their absorption in the gastrointestinal tract.[60,62,82] Concomitant use of these agents with tetracyclines should be generally avoided.

8.4 Anticonvulsants

The concomitant administration of barbiturates, carbamazepine or phenytoin may increase the rate of metabolism of doxycycline by enzymatic induction.[26,59,60,62,82] Other tetracyclines do not appear to be affected largely because of their renal excretion.

8.5 Digitalis Glycosides

The tetracyclines may inhibit the conversion of digoxin to inactive metabolites through alteration of the gut flora, which may result in increased serum digoxin concentrations (less than 10% of patients may be affected).[38,59,60,62,82] The impact on gut flora and the formation of digoxin reduction products may last several months after discontinuing tetracycline therapy.[91]

8.6 Diuretics

The use of tetracyclines and diuretics may cause an increase in BUN levels (both agents can independently cause increases in BUN).[59,60,62,82] The rise in BUN is most significant in patients with previous renal impairment, and it is therefore recommended that these patients receive an antibacterial from another class.[59,60,62,82]

8.7 Insulin

The tetracyclines may reduce the insulin requirements in patients with diabetes mellitus. Patients should be monitored for signs of hypoglycaemia and therapy adjusted as necessary during tetracycline treatment.[60,82]

8.8 Methoxyflurane

The co-administration of tetracyclines and the anaesthetic methoxyflurane has been shown to cause nephrotoxicity, which has lead to death in some patients.[26,59,60,62,82]

8.9 Oral Contraceptives

Tetracyclines may reduce the effectiveness of oral contraceptives and also increase the incidence of breakthrough bleeding, although this interaction remains controversial.[26,38,59,60,62,82] It is nevertheless recommended that women use a back up contraceptive method through the rest of the cycle in which a tetracycline was used in order to prevent pregnancy.[60,82]

8.10 Penicillin

The concurrent use of tetracycline and penicillin is not recommended because bacteriostatic drugs like tetracycline can interfere with the bactericidal action of penicillin when a rapid response may be necessary.[59,60,62,82]

9. Role of Glycylcyclines

The glycylcyclines exhibit antibacterial activities typical of earlier tetracyclines, and are active against organisms resistant to tetracyclines as well as other pathogens including methicillin-resistant staphylococci (MRSA and MRSE), PRSP and VRE. Tigecycline displays good pharmacokinetic and pharmacodynamic properties, and has been shown to be effective at treating various infections in different animal models. Phase 2 clinical trials have investigated tigecycline therapy in complicated SSSI, as well as in complicated intra-abdominal infections, and have produced positive results. Consequently, tigecycline may be of use clinically in treating infections resistant to other antibacterials, as well as in the treatment of SSSI and intra-abdominal infections. However, until more human clinical trial data become available regarding *in vivo* efficacy, adverse effects and interactions, the potential use of tigecycline clinically cannot be fully ascertained. Currently, tigecycline can only be administered by injection, and an oral formulation of the drug would

further expand the potential role of tigecycline therapy in clinical practice.

Acknowledgements

The authors would like to express their sincere thanks to Drs Alice Marshall, Ray Testa and Andrew Trofa of Wyeth (Canada and US) for their assistance in obtaining information used in this review. Drs Zhanel, Embil and Hoban have received research funding from Wyeth.

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