

## Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylicyclines

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The pharmacokinetics of tetracyclines and glycylicyclines are described in three groups. Group 1, the oldest group, represented by tetracycline, oxytetracycline, chlortetracycline, demeclocycline, lymecycline, methacycline and rolitetracycline is characterized by poor absorption after food. Group 2, represented by doxycycline and minocycline, is more reliably absorbed orally, while group 3, represented by the glycylicycline tigecycline, is injectable only, with an improved antibacterial spectrum compared with the tetracyclines. Though incompletely understood, the pharmacodynamic properties of the tetracyclines and glycylicyclines are summarized.

Keywords: pharmacokinetics, pharmacodynamics, tetracyclines

### Introduction

The tetracyclines including the glycylicyclines represent a large group of antibacterials, some of which were first introduced into clinical practice in the 1950s (tetracycline) while others have recently been approved (the glycylicycline, tigecycline) or are in pre-clinical development (the aminomethylcycline, PTK 0796). Given the duration over which these drugs have been developed and clinically used it will be no surprise that the available information on the pharmacokinetics of individual agents is patchy and comparisons are often difficult. There is also a lack of robust information on the pharmacodynamic properties of the class; the last member to be introduced into clinical practice, minocycline, in the early 1970s, pre-dates the development of modern pharmacodynamics concepts by more than a decade.

In general the tetracyclines can be divided into three groups based on their pharmacokinetic and antibacterial properties.

Group 1: This group consists of the older agents which have reduced absorption and are less lipophilic than newer drugs in group 2. Examples are tetracycline, oxytetracycline, chlortetracycline, demeclocycline (demethyl chlorotetracycline), lymecycline, methacycline and rolitetracycline. All can be administered orally except for rolitetracycline.

Group 2: These drugs are more or less completely absorbed and are 3–5 times more lipophilic than drugs in group 1. This may improve their tissue distribution but convincing data is absent. They are available in oral and intravenous formulations. Examples are doxycycline and minocycline.

Group 3: This group includes the developmental compounds aminomethylcyclines (e.g. BAY73-6944/PTK 0796) which are yet to enter clinical trials and the recently approved glycylicycline tigecycline. These antibiotics are active *in vitro* against many bacteria with acquired resistance to tetracyclines.

In this review we will concentrate on the pharmacokinetics of each group in turn and then discuss the pharmacodynamics of the class as a whole. The focus is primarily on the older tetracyclines as there are a number of reviews of tigecycline already published and more importantly new data will become available for this drug over the next few years. The data presented on tetracyclines should make it possible to place tigecycline in an appropriate context. With the older agents, it is important to note that the antibiotic assay methodologies used may not meet present standards; this may be partly responsible for the difference noted between studies.

### Pharmacokinetics

**Group 1: tetracycline, oxytetracycline, chlortetracycline, demeclocycline, lymecycline, methacycline and rolitetracycline**

HPLC assays and spectrofluorometric methods are available for most of these agents<sup>1,2</sup> but many investigators have used microbiological assays.<sup>3,4</sup> A range of formulations is available, but rolitetracycline is the only one to be available as intravenous only. In many European markets these drugs are only available

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## Review

**Table 1.** Pharmacokinetics of tetracyclines<sup>6-13</sup>

Agent	Formulations	Percentage absorption	Doses (mg)	Peak concentration ( $C_{\max}$ ) (mg/L)	Time to peak concentration		Protein binding (%)	Volume of distribution (L/kg or L)	Elimination (%)	
					( $t_{\max}$ ) (h)	( $t_{1/2}$ ) (h)			urinary	faecal
Tetracycline	po/iv	77-88	250	2	2-4	6-11	55-64	1.3 L/kg or 108 L	30	20-60
			300	2.5	3	7.8				
			500	3-5	2	8.5				
Oxytetracycline	po/iv	58	250	2	3	9.2	27-35	128 L	-	50
			500	4						
Chlortetracycline	po	25-30	500	1.4	3	5.6	50-55	100 L	-	>50
Demeclocycline	po	66	150	1.2	4	-	75-91	1.7 L/kg or 121 L	40	43
			300	1.7	4	10-17				
			500	2.5	6	13				
Lymecycline	po	-	300	2.1	3	8	-	-	25	-
Methacycline	po	58	300	2-3	3	14	75-78	-	33	-
Rolitetracycline	iv	none	275	2-4	-	5-8	-	-	>50	-
			300	4-6						

in oral formulations. Topical preparations are also marketed, but are not discussed here.

### Absorption, distribution, metabolism and excretion

Absorption is variable ranging from 0% to almost 90%; however, for most agents it is in the range 25-60%.<sup>5</sup> Serum concentrations rise slowly after oral administration with absorption occurring in the stomach, duodenum and small intestine.  $C_{\max}$  (mg/L) depends on dose, but is generally in the range 1-5 mg/L (Table 1).  $t_{\max}$  is in the range 2-4 h except for demeclocycline whose  $C_{\max}$  is delayed until 4-6 h.

All these tetracyclines form insoluble complexes with calcium, magnesium, iron and aluminium, which markedly reduces absorption.<sup>14</sup> The effect of disease on the absorption of these drugs is unknown. Protein, fat and carbohydrate meals reduce the absorption of tetracycline by about 50%.<sup>2</sup> The volume of distribution ( $V$ ) for these agents is in the order of 1.3-1.7 L/kg or a total volume of distribution of 100-130 L. These data imply some concentration in tissues; however, most data on tissue penetration are of poor quality, making firm conclusions about their relative distribution difficult. Protein binding is variable. None of these agents undergoes metabolism with the exception of tetracycline, 5% of which is excreted as the metabolite  $\Delta$ -epitetracycline.<sup>1</sup> Unchanged drugs are excreted by renal and biliary routes. Renal elimination ( $CL_R$ ) is related to glomerular filtration for most agents, the exception being chlortetracycline.<sup>15,16</sup> The amount of drug excreted in the urine is <50%; rolitetracycline is said to have high renal elimination. Greater than 40% appears in the faeces after biliary elimination and most drugs have some enterohepatic circulation.<sup>5</sup> Biliary concentrations can exceed blood by a factor of 5.<sup>17</sup>

### Serum concentration time profiles

Tetracycline concentrations in blood follow a plateau-shaped course with a slow rise and a slower drop,<sup>6</sup> the serum half-life ( $t_{1/2}$ ) being in the range 6-10 h for tetracycline, oxytetracycline, chlortetracycline and lymecycline. The half-lives of demeclocycline and methacycline are longer, 10-17 h. There has been little

formal assessment of dose-linearity with these drugs, but serum concentrations clearly increase with increasing dose.<sup>12</sup> There is very little data on areas under the serum time curves, but 300 mg of tetracycline or lymecycline produced AUCs of  $26.9 \pm 6.0$  and  $21.9 \pm 4.3$  mg·h/L, respectively.<sup>11</sup> Five hundred milligrams of tetracycline on an empty stomach, as tablets or dissolved in water, produced average AUC in the range 55-75 mg·h/L.<sup>2</sup>

### Special groups

There are no data on the effect of age, sex, obesity or low body weight on the pharmacokinetics of these drugs. There are no data on the effect of infection, other co-morbidities or liver impairment with the agents. Exercise increases serum concentrations and reduces renal clearance of tetracycline but the clinical significance of this is hard to judge.<sup>18</sup>

Renal failure is known to reduce the elimination of tetracycline<sup>16</sup> but not chlortetracycline where the serum half-life in patients with chronic renal failure is similar to those with normal renal function.

### Group 2: doxycycline and minocycline

There is a significant published database on the pharmacokinetics of doxycycline<sup>19-22</sup> and minocycline<sup>20</sup>—therefore, these agents will be discussed separately.

### Doxycycline

HPLC, biological and fluorometric assays for doxycycline have been described.<sup>2,20,23,24</sup> At present, only the oral formulation is available in most countries, though an iv form of doxycycline has been developed and used clinically.

### Absorption, distribution, metabolism and excretion

Doxycycline is said to be almost completely absorbed with a bioavailability of more than 80%<sup>19</sup> with an average of ~95%.<sup>20</sup> However, some authors comparing intravenous (iv) and oral (po) doses of doxycycline felt absorption was lower—in the range 73-77%.<sup>25</sup> Absorption takes place in the duodenum.<sup>20</sup>

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**Table 2.** Pharmacokinetics of doxycycline

Dose (mg) and route	Single dose (SD) or multi-dose (MD)	Peak concentration ( $C_{\max}$ ) (mg/L)	Time to peak concentration ( $t_{\max}$ ) (h)	Half-life ( $t_{1/2}$ ) (h)	Area under serum time curve (AUC) (mg·h/L)	Volume of distribution (V) (L or L/kg)	Clearance (mL/min)			Reference
							total	renal	non-renal	
100 po	MD	2.0 ± 1.0	1.8 ± 1.1	12 ± 3	13 ± 5	–	–	–	–	26
100 po	SD	1.7	2.5–3	14.3 ± 14.6	37–40	–	–	–	–	27
200 po	SD	5.9 ± 1.8	2.6 ± 0.8	16 ± 4	113 ± 46	–	–	–	–	28
200 po	SD	5.2 ± 1.5	2.7 ± 0.8	13 ± 5	90 ± 16	0.7 ± 0.1	–	–	–	29
200 po	SD	4.8 ± 0.3	–	–	81 ± 5	–	–	–	–	18
200 po	SD	5.7 ± 2.6	2.6 ± 1.0	25 ± 19	123 ± 81	–	30 ± 13	–	–	30
200 po	SD	2.6 ± 0.2	2.9 ± 0.4	20 ± 6	41 ± 6	62 ± 18	–	–	–	31
200 po	SD	2.6 ± 0.7	–	14 ± 7	54 ± 32	–	78 ± 38	–	–	32
200 iv	SD	–	–	16.3	92 ± 18	50 ± 9	37 ± 6	23 ± 4	14 ± 4	33
200 iv	SD	9.3	–	14	112	–	–	–	–	34
200 iv	MD	1.9–3.5	–	17 ± 7	61 ± 23	79 ± 11	63 ± 20	–	–	35
100 iv	6.9 ± 0.7	–	16 ± 2	8.8 ± 9	0.7 ± 0.1	30 ± 3	14 ± 3	14 ± 2	–	36

The half-life of absorption is  $0.85 \pm 0.41$  h.<sup>29</sup> The peak concentration ( $C_{\max}$ , mg/L) varies with dose being 15.3 mg/L 4 h after a dose of 500 mg orally (Table 2).<sup>37</sup>

Doxycycline–metal ion complexes are unstable at acid pH, therefore more doxycycline enters the duodenum for absorption compared with the earlier compounds.<sup>38</sup> In addition, food has less effect on absorption than on absorption of earlier drugs<sup>10</sup> with doxycycline serum concentrations being reduced by ~20% by test meals compared with 50% for tetracycline.<sup>2</sup> The volume of distribution is 50–80 L or 0.7 L/kg (Table 2) and the protein binding is 82–93%,<sup>19</sup> but may be lower in some patient groups.<sup>28</sup> There is little good quality data on tissue penetration. In healthy volunteers, the area under the serum time curve (AUC) ratio of AUC blister/AUC serum is 54% in a suction blister fluid model.<sup>26</sup> All other tissue penetration depends on single time point estimations; however, penetration into sputum is 8–28% estimated over 16 h.<sup>39</sup> Penetration into saliva is poor while biliary concentration exceeds serum by many fold.<sup>17,22</sup> Penetration as assessed by a 3 h post-dose concentration measurement after a single peri-operative dose of doxycycline in orthopaedics indicated levels below that of serum in bone, skin, fat, tendons and muscle.<sup>40</sup> Concentrations are highest in the liver, kidney and digestive tract, that is the excretory organs.<sup>20</sup> There is no significant metabolism and no metabolites have been found in man.<sup>19,20</sup> However, in an interaction study with rifampicin, some patients had reduced doxycycline  $C_{\max}$  and AUC, suggesting there may be some hepatic metabolism.<sup>32</sup> Doxycycline is eliminated unchanged by both the renal and biliary routes. Bile concentrations may be 10–25 times those in serum.<sup>41</sup> About 35–60% is excreted in urine and the remainder in faeces<sup>12,18,30,34</sup> (Table 2).

### Serum concentration time profiles

Doxycycline is slowly absorbed orally, taking 2–3 h to reach peak concentrations. The elimination half-life is long, ranging from 12 to 25 h depending on the study (Table 2). Average AUCs for 200 mg/day oral doses range from 40–123 mg·h/L and 61–112 mg·h/L for iv doses. There is little data on dose-linearity

or the effects of multiple doses on the pharmacokinetics of doxycycline.

### Special groups

The pharmacokinetics of doxycycline have been studied in the elderly, undernourished patients with hyperlipidaemia, infected patients and patients with renal impairment. There are no data on the impact of sex, pregnancy, lactation or liver impairment on doxycycline pharmacokinetics.<sup>20</sup> The impact of age on the pharmacokinetics of 200 mg iv doxycycline was studied in 25 patients over 65 years old—mean age 76, range 65–90 years. The  $t_{1/2}$  was  $15 \pm 9$  h, AUC (mg·h/L) 194 mg·h/L and the volume of distribution  $25 \pm 9$  L. Serum concentrations were higher than those reported in other groups with a  $C_{\max}$  of 8–30 mg/L and concentrations at 10 h in the range 5–10 mg/L. The reason for these increased serum concentrations and reduced volumes of distribution is unclear.<sup>42</sup> Undernourished patients dosed with 200 mg iv doxycycline had lower AUC, shorter serum half-lives, serum concentrations and protein binding. Total and non-renal clearances were increased.<sup>36</sup> Compared with control patients, those with hyperlipidaemia had increased serum AUC and  $C_{\max}$ .<sup>31</sup> The clinical importance and underlying pathophysiology are not determined. Exercise in young, healthy volunteers had the effect of increasing the  $C_{\max}$  of 200 mg doxycycline from  $4.8 \pm 0.3$  to  $6.5 \pm 0.6$  mg/L and the AUC from  $81 \pm 5$  to  $106 \pm 3$  mg·h/L.<sup>18</sup> The reasons for this are unclear.

Several studies have been conducted in patients with various degrees of renal impairment and those with end stage renal disease.<sup>28,34,41,43</sup>

Patients with chronic renal failure have reduced urinary recovery of doxycycline and increased faecal recovery.<sup>34,41,43</sup> However, the serum half-life is not greatly increased, being reported in the range 20–25 h. As expected, AUCs are mostly increased for a 200 mg dose, being on average in the range 120–196 mg·h/L.<sup>34</sup> The  $C_{\max}$  is unchanged<sup>34</sup> but protein binding is significantly reduced in patients with end stage renal disease.<sup>28</sup>

There is very limited information on the effects of haemodialysis, ~10% of the drug was removed in a 7 h dialysis session.<sup>43</sup>

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Dose modification is probably not needed in renal impairment as the hepatic and non-hepatic gastro-intestinal elimination compensate for loss of renal clearance.

Klastersky *et al.*<sup>44</sup> studied the serum of doxycycline 200 mg iv, multiple doses, in patients with severe hospital infections. Peak concentrations were in the range 5–6 mg/L and troughs 1–2 mg/L, not unlike healthy volunteer data.

In more recent times, the pharmacokinetics of doxycycline in 17 patients recovering from severe *Plasmodium falciparum* malaria have been reported.<sup>45</sup> Patients received 200 mg of the drug orally and blood samples were drawn in the acute and convalescent phases. In the acute phase, the  $C_{max}$  (mg/L) was 3.2 (1.6–7.7);  $AUC_{0-24}$  (mg·h/L) 32 (18.7–79.7);  $t_{1/2}$  (h) 10.5 (6.9–17.9); and volume of distribution (L/kg) 1.4 (0.6–3.0). Equivalent values in the convalescent phase were as follows:  $C_{max}$  4.4 (1.5–8.6) mg/L;  $AUC_{0-24}$  48.6 (18.3–69.8) mg·h/L;  $t_{1/2}$  11.6 (8.5–17.2) h and volume of distribution 0.9 (0.5–2.7) L/kg.

### Minocycline

HPLC and biological assays are used to measure minocycline.<sup>3,46</sup> At present, there are only oral formulations available clinically as capsules, tablets, modified release capsules and suspension. An iv formulation has also been investigated.<sup>46</sup>

#### Absorption, distribution, metabolism and excretion

Minocycline is almost completely absorbed (95–100%),<sup>20</sup> mainly in the stomach, duodenum and jejunum. Unlike other tetracyclines, food does not appear to have an effect on either the  $C_{max}$  or AUC.<sup>47</sup> The kinetics of absorption of minocycline follow the same broad pattern as for tetracycline, that is after oral administration a rise to  $C_{max}$  by 2 h.<sup>48</sup> The  $C_{max}$  increases, with increasing dose being 0.65 mg/L after 50 mg, 2.2 mg/L after 150 mg, and 3–3.6 mg/L after a 200 mg dose<sup>12,47–49</sup> (Table 3). After intravenous administration, the  $C_{max}$  concentrations are 3–8.75 mg/L after a 200 mg dose.<sup>29,51–53</sup> Absorption is reduced by iron and antacids containing calcium and magnesium.<sup>46</sup> There is little data on the volume of distribution of minocycline, values of 80–115 L have been reported<sup>53</sup> or 1.17 L/kg.<sup>50</sup> Protein binding is 76%<sup>51</sup> and the effect of disease on protein binding has not been studied. As with other tetracyclines, there is very little good quality data on tissue penetration. However, a tissue/serum concentration ratio of >10 has been reported for liver and bile; 5–10 for duodenum, gall bladder

and thyroid; and <2 for colon, bladder, prostate, uterus, breast, skin, lymph nodes and veins.<sup>51</sup> No minocycline has been detected in saliva and concentrations of <50% serum in CSF have been reported.<sup>52</sup> Minocycline is unusual for a tetracycline in that it has a variety of metabolites; up to six have been described, some of which have antibacterial activity and are found in urine. The principal metabolite is 9-hydroxyminocycline; the other two main metabolites are mono-N-demethylated derivatives. Epimerization of minocycline also results in the formation of 4-epiminocycline.<sup>54</sup> Little minocycline is recovered in the urine—probably 5–12% of the dose. Faecal elimination accounts for about 20–35% of the dose.<sup>12,48,51,53</sup> Renal clearance is about 2.2–1.2 mL/min.<sup>50</sup>

#### Serum concentration time profiles

Minocycline reaches  $C_{max}$  after 2–3 h post-oral dose and then has a prolonged serum half-life of 12–18 h.<sup>34,48,49,53</sup> A summary of the pharmacokinetic parameters is shown in Table 3. The  $AUC_{24}$  after a 200 mg oral dose is ~45 mg·h/L and the equivalent  $AUC_{0-\infty}$  is about 70 mg·h/L.<sup>47,48</sup> After a 200 mg iv dose, the  $AUC_{0-\infty}$  were 70–86 mg·h/L.<sup>50</sup> There is little known on dose-linearity with minocycline or the effect of multiple dosing on pharmacokinetic parameters. Interesting is in one study which reported the data where the serum half-life was increased after multiple doses.<sup>50</sup> The reason for this is not known but may be related to saturation of excretory pathways.

#### Special groups

There are no data on the effects of age, sex, changes in body mass, co-morbidity or infection on the pharmacokinetics of minocycline except for a small number of studies carried out in patients with renal impairment and end stage renal disease. Renal impairment and end stage renal disease have little effect on the serum concentrations and serum half-life or AUC of minocycline<sup>34,50,53,55</sup> in both single dose and short multi-dosing studies. As may be expected, the urinary recovery in renal failure is <1% total dose.<sup>34</sup>

### Group 3: Aminomethylcyclines

BAY 73-6944/PTK 0796 is a compound being investigated and is currently in pre-clinical development. In animal models it is substantially unbound in plasma at concentrations ranging from 0.5 to 10 mg/L. In the presence of liver homogenates it appears to be metabolically stable with no detectable loss of compound over 60 min.<sup>56,57</sup>

**Table 3.** Pharmacokinetics of minocycline

Dose and route	Single dose (SD) or multi-dose (MD)	Peak concentration ( $C_{max}$ ) (mg/L)	Time to peak concentration ( $t_{max}$ ) (h)	Half-life ( $t_{1/2}$ ) (h)	Area under serum time curve (AUC) (mg·h/L)	Reference
50 mg po	SD	0.65	–	–	2.1 (0–6 h)	47
200 mg po	SD	3.1	2	17	43.9 (0–24 h)	48
200 mg po	SD tablet	3.5	2–4	12.9	47.6 (0–24 h)	49
	SD capsule	3.6	2–4	13.1	46.7 (0–24 h)	
200 mg iv	SD	3.0	–	17	85.8 (0–8 h)	50
200 mg iv	MD	4.1	–	21	69.8 (0–8 h)	34
200 mg iv	SD	–	–	14.6	67 (0–7 h)	

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**Table 4.** Mean pharmacokinetic parameters of tigecycline after various single iv doses [mean (% CV)]

	1 h infusion						
	12.5	25	50	75	100	200	300
$C_{max}$ (mg/L)	0.11 (10)	0.25 (25)	0.38 (17)	0.57 (14)	0.91 (29)	1.64 (18)	28 (17)
AUC (mg·h/L)	0.75 (68)	2.26 (45)	2.56 (21)	3.67 (27)	6.40 (10)	12.42 (23)	17.86 (10)
CL (L/h/kg)	0.29 (27)	0.20 (50)	0.28 (14)	0.29 (16)	0.20 (13)	0.25 (22)	0.25 (11)
$V_{SS}$ (L/kg)	2.8 (34)	6.4 (20)	6.4 (31)	7.5 (10)	8.6 (18)	11 (25)	12 (20)
$t_{1/2}$ (h)	11 (84)	32 (64)	18 (21)	21 (25)	38 (14)	42 (28)	46 (13)
$CL_R$ (L/h)	–	–	–	–	2.6 (26)	3.0 (50)	2.7 (23)

$C_{max}$ , peak concentration; AUC, area under the serum time curve; CL, clearance;  $V_{SS}$ , volume of distribution at steady state;  $t_{1/2}$ , half-life;  $CL_R$ , renal clearance.

**Table 5.** Mean pharmacokinetic parameters of tigecycline after various iv doses—multi-dosing [mean (%CV)]

	Tigecycline dose (mg)					
	25		50		100	
	day 1	day 10	day 1	day 10	day 1	day 10
$C_{max}$ (mg/L)	0.26 (14)	0.32 (17)	0.49 (17)	0.62 (15)	0.82 (15)	1.17 (15)
AUC (mg·h/L)	0.80 (8)	1.48 (18)	1.44 (14)	3.07 (12)	2.39 (13)	4.98 (19)
$t_{1/2}$ (h)	–	49.3 (72)	–	36.9 (32)	–	66.5 (34)
CL (L/h/kg)	–	0.20 (17)	–	0.20 (9)	–	0.24 (20)
$V_{SS}$ (L/kg)	–	8.6 (23)	–	7.2 (7)	–	9.1 (32)

$C_{max}$ , peak concentration; AUC, area under the serum time curve;  $t_{1/2}$ , half-life; CL, clearance;  $V_{SS}$ , volume of distribution at steady state.

### Glycylcyclines (tigecycline)

Tigecycline has been assayed by HPLC but more recently by a liquid chromatography/mass spectrometry (LC/MS) assay.<sup>58,59</sup> Pharmacokinetic data are available from healthy volunteer studies and also from Phase 3 clinical trials of therapy in skin and soft tissue infection and intra-abdominal sepsis, hence the data available are much more comprehensive than for the earlier drugs. As yet, there is only an intravenous formulation of tigecycline which is infused over a 1 h period.

### Absorption, distribution, metabolism and elimination

There are no data on absorption of tigecycline, but its oral bioavailability is reported to be limited. A light breakfast did not have a significant effect on iv tigecycline pharmacokinetics.<sup>60</sup> The volume of distribution is large with initial values of volume of distribution at steady state ( $V_{ss}$ ) being >10 L/kg.<sup>61</sup> Total volumes of distribution are ~350 L in women and 500 L in men.<sup>58</sup>

The more recent presentation of a dose ranging study of 12.5–300 mg as single doses or multi-dosing has added significantly to this earlier report.<sup>62,63</sup> For single dose exposures of 12.5, 25, 50, 75, 100, 200 and 300 mg the  $V_{ss}$  (L/kg) were 2.8, 6.4, 6.5, 7.5, 6.8, 13 and 12, respectively, indicating some dose dependency. In the multi-dose studies the  $V_{ss}$  (L/kg) for the 25, 500 and 100 mg doses were 8.6, 7.2 and 9.1, respectively (Tables 4 and 5). The reasons for these differences are at present unclear; however, in the dose range used in man 100 mg loading, then 50 mg 12 hourly, the volume of distribution is somewhere in

the range 2.5–7.0 L/kg.<sup>63</sup> Given tigecycline's large volume of distribution there must be tissues into which it is concentrated. As yet tissue penetration data are limited; however, in 10 healthy volunteers using a cantharidin skin blister model and measuring the  $AUC_{0-12}$  in both blister fluid and serum after a 100 mg iv dose, the penetration was 74% ( $AUC_{0-12}$  blister fluid =  $1.6 \pm 0.2$  mg·h/L;  $AUC_{0-24}$  serum =  $2.2 \pm 0.3$  mg·h/L). The equivalent  $C_{max}$  concentrations were 0.17 mg/L in blister fluid and 0.82 mg/L in serum.<sup>59</sup>

Further studies in adult humans who received 100 mg iv tigecycline have indicated concentrations in lung tissue of 0.8 mg/L at 4 h post-dose, 0.2 mg/L at 8 h, 0.4 mg/L at 12 h and 0.4 mg/L at 24 h. There was significance between subject variability in measured drug concentrations. CSF concentrations in non-inflamed meninges were low being 5% 1 h post-infusion and 41% after 24 h. As may be expected, bile concentrations were high, ranging from 0.16–4.37 mg/L, with bile/serum ratios in the range 606–1997. This is consistent with biliary excretion of tigecycline.<sup>64</sup>

Radiolabelled tigecycline has been administered to Sprague-Dawley rats as a single infusion to study the drug distribution.<sup>65</sup> As expected peak radioactivity was seen at the end of infusion in all the tissues. AUC values were highest in the bone, bone marrow, salivary gland, thyroid, spleen and kidney. The tissue AUC/plasma AUC was >1 for most tissues over the 168 h of the experiments. The tissue/plasma ratios were 2046 for bone, 149 for bone marrow, 90 for thyroid, 45 for spleen and 24 for liver. The high ratio in bone may be related to calcium binding.<sup>65</sup>

## Review

Tigecycline protein binding ranges from 73% at 0.1 mg/L to 79% at 1 mg/L, the reason for this atypical pattern is as yet unknown.<sup>63</sup> The metabolism of tigecycline in man has been studied using radiolabelled tigecycline.<sup>66</sup> There are two major metabolic pathways, the main route being glucuronidation and its inactive epimer producing 5–20% of the radioactivity in human serum. An N-acetyl-9-aminomincycline metabolite is also formed to a less degree.<sup>66</sup> At least five human metabolites have been described in urine, serum, faeces and plasma.<sup>60</sup> Less than 15% of tigecycline is excreted unchanged in the urine<sup>61,67</sup> and renal clearance accounts for <20% total clearance.<sup>60</sup> Radio-labelled tigecycline studies in man indicated that 59% of the radioactivity was found in faeces and 32% in urine. This presumably means that, like some other tetracyclines, there is biliary excretion and perhaps also an enterohepatic circulation.

### Serum concentration pharmacokinetic profile

The serum values of the  $C_{\max}$  (mg/L), AUC (mg·h/L), serum half-life (h) and clearance (L/kg/h) for single doses of 12.5, 25, 50, 75, 100, 200 and 300 mg and 25, 50 and 100 mg multiple doses are shown in Tables 4 and 5. The proposed dosing in man is a 100 mg loading dose followed by 50 mg 12 hourly. This will give a  $C_{\max}$  of  $0.62 \pm 0.09$  mg/L and an AUC at steady state of  $3.1 \pm 0.4$  mg·h/L. The  $C_{\max}$  of the 100 mg dose is 0.9 mg/L and the 50 mg in multi-dosing 0.62 mg/L. The half-life of the 100 mg dose is 22 h in the single dose study and 66 h in the multi-dose, equivalent values for the 50 mg dose are 18 and 38 h, indicating lengthening of the half-life with multiple doses. Drug clearance is usually  $\sim 0.2$  L/h/kg irrespective of the dose or number of doses. There is rough linearity with dose in terms of AUC and  $C_{\max}$  values. Steady state is reached within 3 days.<sup>62</sup>

Using the single and multiple dose data from Phase 1 subject populations, pharmacokinetic models have been developed.<sup>68</sup> For single dose data a three-compartment model with zero order input and first order elimination adequately described the data, despite the presence of secondary peaks in some profiles. However a two-compartment model provided the most unbiased estimates of AUC<sub>0–12</sub> and is therefore most appropriate to multi-dose studies in patients.

### Special groups

The effects of age, gender, excretory organ failure and infection on the pharmacokinetics of tigecycline have been studied. The effect of age and gender has been studied in healthy volunteers in three age groups, 18–50, 65–75 and >75 years old.<sup>58</sup> A single 100 mg 1 hourly infusion was given and the mean  $C_{\max}$  was 0.85–1.0 mg/L in all groups. The lowest AUC was in males under 50 years (mean AUC 4.2 mg·h/L) and the highest in those over 75 years (means AUC 5.8 mg·h/L). The mean AUC for women was  $\sim 5$  mg·h/L in all the groups. Studies have been conducted on subjects with severe renal impairment (creatinine clearance < 30 mL/h) and those with end stage renal disease maintained by haemodialysis. These data were compared with those from healthy volunteers. A single 100 mg infusion over 1 h was administered. The  $C_{\max}$  and AUC values are shown in Table 6. Haemodialysis had no effect on the pharmacokinetics of tigecycline and only 5% of unchanged drug was recovered from the urine of those with severe renal impairment compared with 16% from the healthy volunteers.<sup>67</sup>

**Table 6.** Pharmacokinetics of tigecycline 100 mg infusion in healthy subjects, those with severe renal impairment and those with end stage renal disease

	Peak concentration ( $C_{\max}$ ) (mg/L)	Area under the serum time curve (AUC) (mg·h/L)
Healthy volunteers	0.60	3.3
Creatinine clearance < 30 mL/min	0.6	4.7
End stage renal disease on haemodialysis	0.96	4.0

There are no published data as yet on the impact of liver impairment on the pharmacokinetics of tigecycline. A non-compartmental pharmacokinetic analysis was performed on 15 patients in the Phase 3 study in complicated skin and soft structure infections.<sup>69</sup> The dosing regimen was 100 mg loading dose on day 1 followed by 50 mg 12 hourly until day 14.

The patients' weights varied from 57 to 200 kg; mean 80 kg. The  $C_{\max}$  was  $0.63 \pm 0.28$  mg/L,  $C_{\min}$   $0.16 \pm 0.05$  mg/L, AUC<sub>ss</sub> (0–12 h)  $3.04 \pm 0.81$  mg·h/L, total clearance  $17.5 \pm 4.2$  L/h and CL/kg  $0.22 \pm 0.06$  L/h/kg. These data are in very close agreement with data from treated patients with intra-abdominal sepsis and from healthy volunteers in Phase 1 and Phase 2 studies.<sup>63,70</sup>

Co-administration of digoxin plus tigecycline or warfarin plus tigecycline in healthy male volunteers had no impact on the pharmacokinetics of either agent.<sup>71,72</sup>

### Pharmacodynamics

Pharmacodynamics is the relationship between measurements of antimicrobial exposure in body fluids with the antibacterial and toxicological effects of the drug.<sup>73</sup> The most important measure of drug potency is still the minimum inhibitory concentration (MIC, mg/L); however, several other antibacterial effect measures are important. These include the pattern of bacterial killing, persistent effects and data from *in vitro* and animal pharmacokinetic/pharmacodynamic models.<sup>74,75</sup> Pharmacodynamic indices (AUC/MIC,  $C_{\max}$ /MIC,  $t > \text{MIC}$ ) can be related to bacteriological outcomes and specific pharmacodynamic index sizes used to predict clinical outcomes and establish clinical breakpoints.<sup>76</sup>

In general the pharmacodynamics of tetracyclines is understudied in comparison with some drug classes such as  $\beta$ -lactams, fluoroquinolones and aminoglycosides. The pattern of the antibacterial killing effect of doxycycline, minocycline and tigecycline has been studied using time–kill curve methods. Doxycycline produces a 0.5 log reduction in viable count of *Staphylococcus aureus* over 24 h at a concentration of  $2\times$  MIC. Increasing the concentration to  $16\times$  MIC results in 1–2 log kill. Against *Streptococcus pneumoniae* doxycycline produces no killing over 24 h at  $2\times$  MIC but this increases to  $>4$  log kill at the  $16\times$  MIC concentration. Doxycycline produces no net effect against *Escherichia coli* at  $4\times$  MIC concentration over 24 h, but a 3 log kill at MIC 8–16.<sup>77</sup> The patterns of killing of minocycline and tigecycline were compared against *S. aureus*

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( $n = 9$ ), *E. coli* ( $n = 6$ ) and *Klebsiella pneumoniae* ( $n = 6$ ) in time–kill curves at  $4\times$  MIC concentration over 24 h. Minocycline produced a  $-1.5 \pm 1.0$  log kill against *S. aureus*,  $-2.0 \pm 0.8$  log kill against *E. coli* and  $+0.3 \pm 1.8$  log growth with *K. pneumoniae*. Equivalent values for tigecycline were  $-2.0 \pm 1.3$  log kill for *S. aureus*,  $-0.7 \pm 0.7$  log kill for *E. coli* and  $+0.4 \pm 1.5$  log growth for *K. pneumoniae*.<sup>92</sup>

At the concentration designed to mimic those achievable in man, tigecycline 2 mg/L, 0.5–0.7 log reductions in *Enterococcus faecium* and 0.7–1.4 log reductions in glycopeptide intermediate *S. aureus* were observed over 24 h.<sup>78</sup>

MBCs (mg/L) are 2-fold higher than the MIC for *S. pneumoniae* and 2–4 times the MIC for *S. aureus* of both minocycline and tigecycline. In contrast with *Enterococcus faecalis* tigecycline's MBC is  $>16$  times the MIC.<sup>79,80</sup> Tigecycline produces  $\leq 0.5$  log killing against *E. faecalis* with most strains in time–kill curves over 24 h;<sup>81</sup> however, kill is enhanced by the addition of serum.<sup>77</sup>

Bacterial inoculum appears to have a modest effect on tigecycline MICs which are 1–2 dilutions higher with 10- to 100-fold increases in inoculum.<sup>82</sup> Data for other tetracyclines are absent.

Persistent antibiotic effects have been studied with tetracyclines *in vitro* and *in vivo*; however, the significance of persistent antibiotic effects such as the post-antibiotic effect (PAE) remains to be established. Doxycycline has a PAE against *S. aureus*, *S. pneumoniae* and *E. coli* which increases with increasing concentrations of exposure. At  $2\times$  MIC to  $4\times$  MIC concentrations the PAE for *S. aureus* is 0.7–1.2 h, *S. pneumoniae* 2.2–2.8 h and *E. coli* 1.0–1.4 h.<sup>77</sup> Tigecycline has been reported to have a longer PAE than minocycline against *S. aureus* and *E. coli* by an average 0.6–2 h at  $8\times$  MIC concentrations.<sup>83</sup>

*In vivo* using a murine model, tigecycline at a dose of 3 mg/kg single dose,  $C_{max}$  0.42 mg/L, AUC 0.68 mg·h/L, and  $t_{1/2}$  0.25 h had PAE of 8.9 h against *S. pneumoniae* and 4.9 h against *E. coli*.<sup>79</sup> Tigecycline's PAE against *E. faecalis* is 1–4.5 h at  $1-20\times$  MIC concentrations using time–kill *in vitro* studies.<sup>81</sup>

There is very little data on the use of *in vitro* pharmacokinetic or animal pharmacokinetic/pharmacodynamic models to describe the antibacterial effects of tetracyclines. Using a hollow fibre *in vitro* model to simulate free drug serum concentrations of oral minocycline 200 mg/day in man, the 24 h antibacterial effect was a  $-1.8 \pm 0.2$  log reduction in count by 24 h against UK EMRSA-16.<sup>84</sup>

Similar data to those of Bowker *et al.*<sup>84</sup> were reported by Garrison and Neumiller<sup>85</sup> in their *in vitro* model where tigecycline at concentrations associated with human dosing produced a 1.5 log drop in viable counts at 24 h. Tigecycline produced a greater antibacterial effect against fluoroquinolone-resistant *S. pneumoniae* than levofloxacin and against vancomycin-resistant enterococci than vancomycin.<sup>84</sup>

Van Ogtrop *et al.*<sup>79</sup> studied minocycline and tigecycline in a murine neutropenic thigh infection model against a number of strains of *S. pneumoniae*, *S. aureus* and *E. coli*; tigecycline's MICs were 0.06–0.12, 0.12–0.5 and 0.12 mg/L, respectively. The dose of tigecycline for a 24 h static effect was 0.8–5.9 mg/kg/day with *S. pneumoniae* but 25 times greater for *S. aureus* and *E. coli* (4.3–23 mg/kg/day) despite similar MIC values. Against *K. pneumoniae* the bacteriostatic dose was higher yet at 65–151 mg/kg/day. These data with that from time–kill curves suggest that the drug exposures to clear different bacterial species with tigecycline may be different, with *S. pneumoniae*

**Table 7.** Successes and failures in man with iv doxycycline according to bacterial species and expected MIC<sub>50</sub>

Species	MIC <sub>50</sub> (mg/L) of representative strains	Success	Failure
<i>S. pneumoniae</i>	0.1	16	1
Group A streptococci	0.2	2	0
<i>S. aureus</i>	0.3	4	0
<i>E. coli</i>	12.0	3	2
<i>Klebsiella/Enterobacter</i> spp.	25.0	5	7
<i>Proteus</i> spp.	$>50.0$	2	9

requiring the lowest exposures, *S. aureus* and *E. coli* higher and *K. pneumoniae* higher yet. In this murine model AUC and  $t > MIC$  could be related to antibacterial effect using non-linear regression analysis. The drug exposure to produce 80% of maximal effect was calculated as a free drug time greater than MIC of more than 50% of the dosing interval for tigecycline.<sup>79</sup>

More recently, based on likely drug exposures in man, tetracyclines have been classified as AUC driven agents.<sup>73</sup> As yet no AUC/MIC static effect targets have been published for any tetracyclines or tigecycline; such data from animal or *in vitro* models would be of help in determining clinical breakpoints.<sup>76</sup>

There are four studies relating tetracycline serum concentrations, pathogen MIC and species to clinical outcomes. Klustersky *et al.*<sup>44</sup> used iv doxycycline to treat a group of about 50 patients with a variety of infections including urinary tract infection, pneumonia, wound infection and septicaemia. Peak serum doxycycline concentrations were in the range 5–6 mg/L and trough concentration was 1–2 mg/L. Table 7 shows the successes and failures by species and the MIC<sub>90s</sub> of representatives of those species performed by the authors. Of those bacteria which had an MIC of  $\leq 0.3$  mg/L (26) 25 infections were cured while if the MIC was  $\geq 12$  mg/L (30) 12 infections were cured.

In a different indication, Q fever endocarditis, 16 patients were studied over 1 year. *Coxiella burnetii* MIC, doxycycline serum concentrations and serological response (phase 1, *C. burnetii*) antigens were correlated. Those patients with a serum doxycycline to MIC ratio of  $\geq 1$  showed a more rapid decline in phase 1 antibodies than those with values between 0.5 and 1. Serum AUC values were not calculated and it was obviously difficult to generalize from this infection to others.<sup>86</sup>

The relationship between tigecycline AUC, MIC and microbiological outcome has been explored using data from three trials in complicated skin and soft tissue infection.<sup>87,88</sup> Two different dose regimens were used: 100 mg load plus 50 mg 12 hourly and 50 mg load plus 25 mg 12 hourly. The serum AUC<sub>0–24</sub> at steady state was median 5.16, range 2.81–9.36 mg/L (high dose) and median 2.33, range 1.49–4.98 (low dose). The pathogens isolated were divided into several groups, the most useful for the analysis being all Gram-positive pathogens ( $n = 36$ ). One patient who failed tigecycline had a mesh graft for a hernia repair which was not removed. This patient was, very reasonably, excluded from outcome analysis. If the AUC/MIC value was  $<25$ , 5 patients failed therapy and 10 were cured, if the AUC/MIC was  $>25$ , no patients failed and 20 were cured. Classification and regression tree (CART) analysis identified an AUC/MIC of 12.3 for both

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microbiological and clinical responses. In a further analysis including patients with polymicrobial infection and MICs of tigecycline up to 16 mg/L the probability of cure was >0.9 if the AUC/MIC was >30.<sup>87,88</sup>

Given an AUC/MIC breakpoint of ~12–18 for infection mainly caused by *S. aureus*, the pharmacodynamic breakpoint would be ≤0.25 mg/L,<sup>89</sup> which is in close agreement with the breakpoint suggested from animal models of *S. pneumoniae*, *S. aureus* and *E. coli* infection.

A similar analysis was performed on patients in three trials of complicated intra-abdominal infection ( $n = 71$ ). Patients received 100 mg iv tigecycline and then 50 mg twice daily, and the median AUC was 5.6 mg-h/L. APACHE score predicted microbiological and clinical outcomes and an AUC/MIC of 6.96 was significant in CART analysis for both microbiological and clinical outcomes. An AUC/MIC of >30 was associated with >90% chance of success in the final model.<sup>90</sup> These data were used to try to develop a pharmacodynamic breakpoint for *E. coli*. Several AUC/MIC targets were used, 6.96, 8.4 and 11.1; there was a 95% probability that the true AUC/MIC target was between 5.7 and 11.5. For an MIC of 0.5 mg/L, the target attainment rates for AUC/MIC ratios of 6.96, 8.4 and 11.1 were 94%, 83% and 54%, respectively.<sup>91</sup>

## Conclusions

Tetracycline and glycylicycline pharmacokinetics and pharmacodynamics represent a relatively under-investigated but interesting area of antimicrobial chemotherapy. Until recently our understanding was poor and little progress had been made until tigecycline entered clinical development. We are still unclear as to the relative importance of serum versus tissue levels in predicting outcomes for the tetracyclines and glycylicyclines but this may be important given their large volumes of distribution. Much work could be done to improve our pharmacokinetic/pharmacodynamic knowledge of these agents, and as tigecycline enters clinical use it is to be hoped that this experience will add to our knowledge in the area.

## Transparency declarations

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