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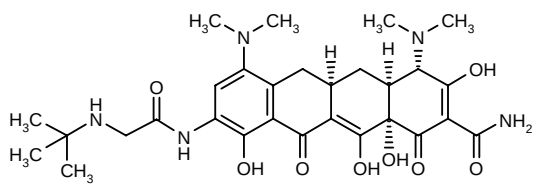
GAR-936

Tetracycline Antibiotic

Tigacycline
TBG-MINO
WAY-GAR-936

(4*S*,4a*S*,5a*R*,12a*S*)-9-(*N*-*tert*-Butyl-glycylamino)-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12-octahydronaphthacene-2-carboxamide

9-(*N*-*tert*-Butylglycylamido)-6-demethyl-6-deoxy-7-(dimethylamino)tetracycline



$C_{29}H_{39}N_5O_8$ Mol wt: 585.6630

CAS: 220620-09-7

EN: 213617

Synthesis*

Nitration of minocycline (I) with KNO_3 and H_2SO_4 gives the 9-nitro derivative (II), which is reduced with H_2 over Pd/C in 2-methoxyethanol/2N H_2SO_4 to provide 9-aminominocycline (III) (1). Acylation of compound (III) with 2-bromoacetyl bromide (IV) in *N*,*N*-dimethylpropyleneurea (DMPU) affords 9-(2-bromoacetamido)minocycline (V). Finally, this compound is treated with *tert*-butylamine (VI) to yield, after purification, GAR-936 (2, 3). Scheme 1.

Alternatively, 9-aminominocycline (III) is acylated directly with *N*-*tert*-butylglycyl chloride (VII) to give GAR-936 (2). This method has been applied to the scale-up synthesis of GAR-936. Scheme 1.

Introduction

Tetracyclines are a group of broad-spectrum antibacterial antibiotics, originally discovered in the 1940s and 1950s. Chlortetracycline was one of the earliest antibiotics to be isolated, first announced in 1948, and the related compounds oxytetracycline followed in 1950 and tetracycline in 1953. The complexity of the four-ring molecules has hampered extensive chemical modifications, but the semisynthetic derivative doxycycline was produced as early as 1958 and minocycline a few years later, in 1964. Both of these compounds have been marketed widely. Until more recently, however, few other semisynthetic or synthetic tetracycline analogues have been progressed. The mode of action of this group is to inhibit protein synthesis by binding to the bacterial 30S ribosomal subunit. This blocks the entry of aminoacyl *t*-RNA into the ribosome and by preventing the incorporation of amino acid residues into the peptide chains, thus limits their elongation. As a consequence of the broad spectrum of action of this group, both the semisynthetic and the natural products have been very widely used in human medicine but in recent decades their value has been eroded by the development of resistance to them in many bacterial species. There are two modes of resistance to the tetracyclines; an efflux mechanism, particularly prevalent in strains of *Escherichia coli*, and ribosomal protection.

The glycylcyclines are synthetic analogues of tetracyclines with a glycylamido substituent in the 9-position and were developed to overcome this growing problem of resistance. Earlier compounds with a 9-dimethylglycylamido (DMG) group were found to have good activity but the most promising compound currently is the 9-*tert*-butylglycylamido derivative of minocycline, TBG-MINO or GAR-936.

Pharmacological Actions

In vitro *activity*

The activity of GAR-936 has been tested extensively *in vitro*, including organisms with known resistance

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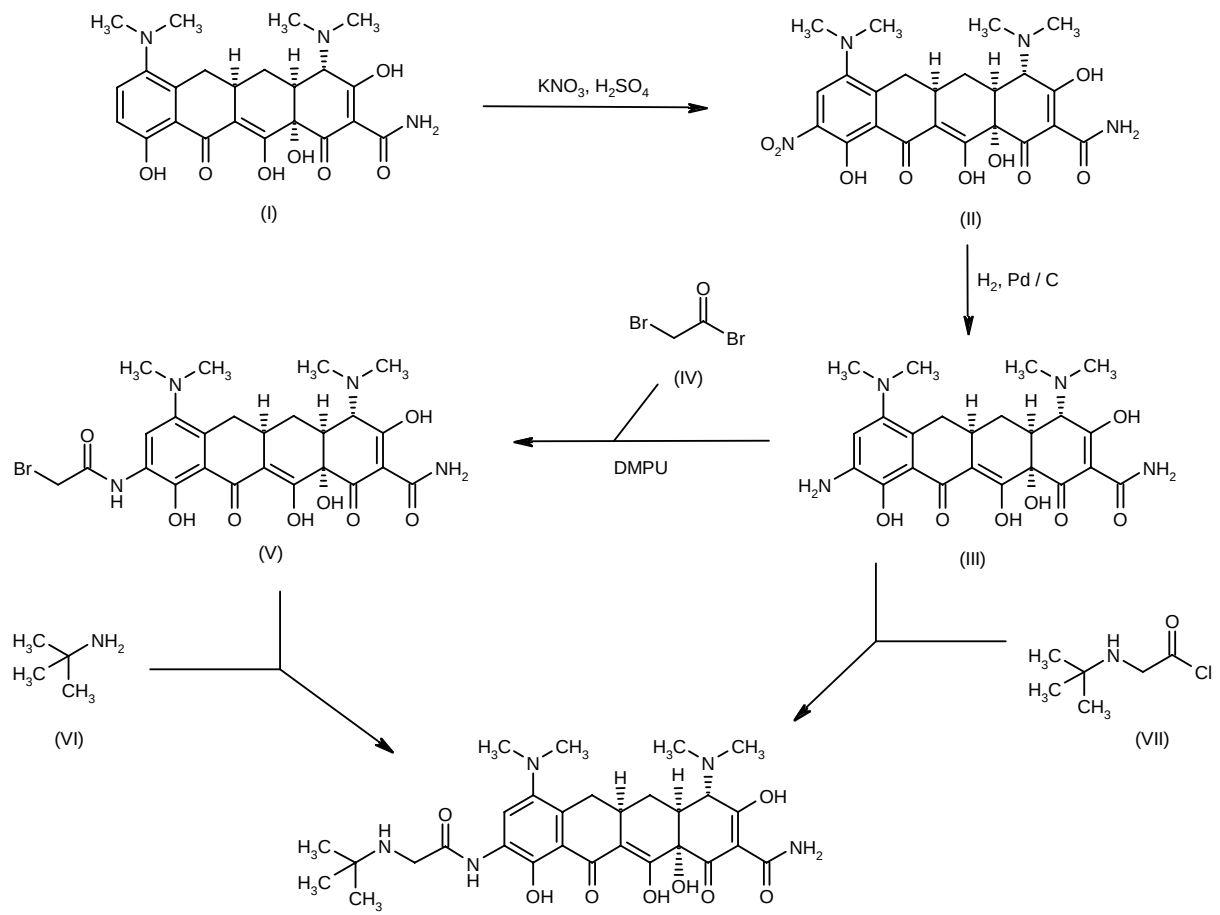
Scheme 1: Synthesis of GAR-936



mechanisms to tetracyclines, such as the ribosome protection resistance determinant, *tet*M and the various efflux resistance determinants, *tet*A, *tet*B, *tet*C, *tet*D and *tet*K. Comparisons have been made with the earlier glycylcyclines, DMG-minocycline (DMG-MINO) and DMG-dimethyl-deoxytetracycline (DMG-DMDOT), with minocycline and tetracycline and with various other antibacterial agents.

Petersen *et al.* (4) tested GAR-936 against a comprehensive range of tetracycline-resistant strains of *E. coli*, *Staphylococcus aureus*, *Enterococcus faecalis* and *Neisseria gonorrhoeae* in comparison with DMG-MINO, DMG-DMDOT, minocycline and tetracycline. The three glycylcyclines were as active against the resistant strains as they were against the tetracycline susceptible strains. GAR-936 was more active than the other two glycylcyclines against *E. coli* strains carrying the efflux determinants *tet*A and *tet*C, with minimum inhibitory concentrations (MICs) of 0.25-0.5 mg/l compared with MICs of 2 mg/l. The three glycylcyclines had similar activity against the other strains. Overall, GAR-936 had the most consistent activity, with MICs in the range of 0.25-0.5 mg/l against all strains tested (Table I).

A wide range of clinical isolates was tested: 126 Gram-positive species, 236 Gram-negative species, including 30 non-fermentative isolates, 51 fastidious Gram-negative cocci and cocco-bacilli and 72 anaerobic species. As well as the tetracyclines and glycylcyclines, GAR-936 was compared with ciprofloxacin, vancomycin and erythromycin against staphylococci and enterococci, with vancomycin against the streptococci, with ciprofloxacin, imipenem and ceftazidime against the Gram-negatives and fastidious organisms, and with cefoxitin and imipenem against the anaerobic species.

GAR-936 had good activity against all the Gram-positive species tested, including methicillin- and erythromycin-resistant *S. aureus* and coagulase-negative staphylococci, vancomycin-resistant enterococci and penicillin-resistant pneumococci. MIC_{90} values for GAR-936 were 0.5-1.0 mg/l against staphylococci, 0.25-0.5 mg/l against enterococci, 0.12 mg/l against pneumococci and 0.25 mg/l against *Streptococcus*

Table I: Activity of GAR-936, minocycline and tetracycline against strains with characterized tetracycline resistance determinants.

Species	Resistant determinant	GAR-936	Minocycline	Tetracycline
		MIC (mg/l)		
E. coli	*tet*A	0.5	4	32
	*tet*B	0.5	16	>32
	*tet*B	0.5	8	>32
	*tet*C	0.25	4	>32
	*tet*D	0.25	8	>32
	*tet*M	0.25	>32	>32
	sensitive	0.25	1.0	1.0
	sensitive	0.25	0.5	1.0
S. aureus	*tet*K	0.5	0.25	>32
	*tet*M	0.5	4	>32
	*tet*M	0.25	4	>32
	*tet*M	0.25	2	32
	sensitive	0.25	0.06	0.12
	sensitive	0.5	0.06	0.25
E. faecalis	*tet*M	0.25	16	>32
	sensitive	0.25	1.0	8
N. gonorrhoeae	*tet*M	1.0	16	32

pyogenes and *Streptococcus agalactiae*. GAR-936 had the most consistent activity of the three glycylcyclines and was more active than minocycline against many streptococcal isolates and most enterococci. Against Gram-negative species GAR-936 was markedly more active than minocycline against *Citrobacter diversus*, *E. coli*, *Morganella morganii*, *Providentia* spp., *Shigella* spp. and *Salmonella* spp. It was equal to or slightly more active than minocycline against *Burkholderia cepacia*, *Citrobacter freundii*, *Enterobacter*, *Klebsiella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Serratia marcescens*. It was, however, less active than minocycline against *Stenotrophomonas maltophila*.

GAR-936 and the other glycylcyclines were highly active against the fastidious pathogens, especially *Moraxella catarrhalis*. Minocycline was slightly more active against *Haemophilus influenzae*, but a number of strains of *N. gonorrhoeae* were resistant to minocycline (MIC_{90} = 32 mg/l), whereas all were susceptible to GAR-936 (MIC_{90} =1 mg/l). The glycylcyclines were less active than ciprofloxacin and ceftazidime against these three species, although they were more active than imipenem against *H. influenzae*. Activity of all the tetracyclines and analogues against anaerobic species was variable, but GAR-936 was more active than minocycline against *Bacteroides* spp., *Clostridium difficile*, *Prevotella* spp. and anaerobic Gram-positive cocci. GAR-936 and minocycline had similar variable activity against *Clostridium perfringens*.

These results have been confirmed by a number of other authors. Boucher *et al.* (5) tested GAR-936 in comparison with tetracycline, doxytetracycline and minocycline against 527 clinical isolates of Gram-positive species. These authors tested a wider range of enterococci, including *Van*A, *Van*B and *Van*D *E. faecium*, *E. avium*, *E. casseliflavus*, *E. gallinarum* and *E. raffinosus*, and confirmed the good activity of GAR-936. They also tested *Listeria monocytogenes*, *Lactobacillus* spp., *Leuconostoc* spp., *Pediococcus* spp. and JK diphtheroids. With the exception of 2/20 JK diphtheroid isolates, which required 4 mg/l for inhibition, GAR-936 was highly active against these species. Patel *et al.* (6) tested 37 vancomycin-resistant enterococci, 26 methicillin-resistant staphylococci (MRS) and 30 isolates of pneumococci with high-level penicillin resistance. Their results confirm the good activity of GAR-936, with only the MRS requiring 1 mg/l to inhibit all isolates. Hoellman *et al.* (7) looked at the activity of GAR-936 against 201 pneumococci in comparison with minocycline, doxycycline and tetracycline. Other agents included for comparison were four β-lactams, clarithromycin and vancomycin. Of the pneumococci tested, 51 were susceptible to penicillin, 72 were of intermediate resistance and 78 were fully resistant to penicillin. The activity of the three marketed tetracyclines varied widely, with many isolates requiring levels of 16-128 mg/l for inhibition. Although penicillin-resistant strains were the least susceptible to these three conventional tetracyclines, not all penicillin-susceptible strains were fully sensitive to them. In contrast, GAR-936 was quite unaffected by the susceptibility of the strains to penicillin, with excellent activity against all categories of isolates, with MIC values of between less than or equal to 0.016 and 0.125 mg/l against all isolates (Table II). This activity was slightly greater than that of vancomycin, and clearly superior to the other compounds tested. Tetracyclines are normally regarded as bacteristatic compounds, but these authors showed that GAR-936 had a bactericidal effect at concentrations above the MIC, although the reduction in numbers was slower than that seen with penicillins and vancomycin.

A major study of the *in vitro* activity of GAR-936 was published by Gales and Jones (8) who compared its activity against 1203 recent clinical isolates with ten other

Table II: Activity of GAR-936, other tetracyclines and vancomycin against 51 penicillin-susceptible, 72 peniclillin-intermediate and 78 penicillin-intermediate and 78 penicillin-resistant strains of Streptococcus pneumoniae *(adapted from ref. 7).*

Drug		MIC mg/l		
		Range	MIC_{50}	MIC_{90}
GAR-936	S	≤ 0.016-0.125	0.03	0.125
	I	≤ 0.016-0.125	0.03	0.06
	R	≤ 0.016-0.125	0.06	0.125
Tetracycline	S	≤ 0.06-64	0.25	32
	I	≤ 0.06-64	1.0	64
	R	≤ 0.25-128	32	64
Minocycline	S	≤ 0.06-16	0.06	8
	I	≤ 0.06-16	0.25	16
	R	≤ 0.06-16	4	16
Doxycycline	S	0.03-16	0.125	8
	I	≤ 0.06-32	0.5	8
	R	0.125-16	4	8
Vancomycin	S	≤ 0.06-0.5	0.25	0.25
	I	≤ 0.06-0.5	0.25	0.25
	R	0.125-0.5	0.25	0.25

S = susceptible; I = intermediate; R = resistant

antibacterial agents (including minocycline). Their results confirm the higher MICs against some *Proteus* and *Providentia* noted by Petersen *et al*. (4) and the excellent activity seen against the majority of Gram-positive cocci. They tested a wider range of *Streptococcus species*, including *S. viridans*, *S. bovis* and a range of β-hemolytic streptococci. GAR-936 was uniformly highly active against these species with MIC_{90} values of 0.06-0.12 mg/l.

Two large studies have been completed investigating the anaerobic activity of GAR-936. In one study, 327 recent human isolates were tested for susceptibility to GAR-936 in comparison with minocycline and tetracycline, cefoxitin, imipenem, clindamycin and metronidazole (9). Another study included 148 strains isolated from human and animal bite wounds (10). The activity of GAR-936 was compared with that of nine other broad-spectrum agents. These studies confirmed that GAR-936, while not equalling the activity of cefoxitin and imipenem against some species, nevertheless has useful broad-spectrum activity against anaerobic species.

GAR-936 has been shown to have good activity against some atypical pathogens, including *Chlamydia* and *Mycoplasma*. Roblin and Hammerschlag (11) tested the susceptibility of ten isolates of *Chlamydia pneumoniae* and five isolates of *Chlamydia trachomatis* to GAR-936, doxycycline and clarithromycin, both used as standard treatment of infections with these organisms, and ofloxacin. GAR-936 was slightly more active than doxycycline, with MICs of 0.125 and 0.25 mg/l against all isolates of *C. pneumoniae*. Clarithromycin was slightly more active than GAR-936. Against *C. trachomatis*, GAR-936 and clarithromycin were equally active (MICs = 0.03-0.125 mg/l) and both were superior to doxycycline. Tetracyclines have been used as therapeutic agents for most *Mycoplasma* species and *Mycoplasma pneumoniae* remains susceptible to tetracyclines, but in recent years some *Mycoplasma hominis* and *Ureaplasma urealyticum* isolates have acquired the *tet*M resistance determinant. Kenny and Cartwright (12) showed that GAR-936 was more active than minocycline and tetracycline against *M. pneumoniae* (MIC_{90} values = 0.25, 1.0 and 1.0 mg/l respectively). GAR-936 was unaffected by the presence of the tetM gene in *M. hominis*, with MICs of 0.125-0.25 mg/l, whereas MICs for minocycline and tetracycline were all above 32 mg/l. Interestingly, GAR-936 was not as active as the other two compounds against *U. urealyticum*, with MICs of 1-16 mg/l.

GAR-936 has been shown to produce a postantibiotic effect (PAE) on treated bacteria; this refers to an inhibitory effect on bacterial growth seen following exposure to an antibacterial even after the removal of that compound. If a compound exerts a PAE, it can mean that longer dosage intervals may be appropriate. A significant PAE was seen when staphylococci and *E. coli* strains were exposed to GAR-936 at a concentration of approximately eight times the MIC for that strain (13). Against staphylococci, both tetracycline-susceptible and tetracycline-resistant isolates, the PAE was greater than 3 h (Table III). This was substantially greater than the PAE with minocycline against the strain carrying the tetM determinant. PAEs against *E. coli* were between 1.8 and 2.9 h, again greater than those seen with minocycline.

In vivo *activity*

GAR-926 has been shown to have promising activity against a range of bacterial pathogens in a number of experimental animal infections, including acute mouse infections, localized thigh infections in mice, mouse pneumonia, rat endocarditis, rabbit endocarditis and rabbit meningitis. Preliminary experiments using acute intraperitoneal infections in mice indicated that GAR-936 was

Table III: The postantibiotic effect (PAE) of GAR-936 and minocycline against Staphylococcus aureus *and* Escherichia coli *strains susceptible and resistant to tetracyclines (from ref. 13).*

Organism		Conc. (mg/l)	PAE (h)
S. aureus - sensitive	Minocycline	0.5	2.7
	Minocycline	2.0	3.2
	GAR-936	2.0	4.1
S. aureus - *tet*K	Minocycline	2.0	2.9
	GAR-936	4.0	3.5
S. aureus - *tet*M	Minocycline	64	1.0
	GAR-936	2.0	>3.0
E. coli - sensitive	Minocycline	4.0	1.7
	GAR-936	2.0	2.9
E. coli - *tet*B*	GAR-936	4.0	2.6
E. coli - *tet*M*	GAR-936	2.0	1.8

*Minocycline not tested; MIC values too high

Table IV: Activity of GAR-936 and minocycline in mouse acute peritoneal infections. ED_{50} values of compounds dosed intravenously in a single dose at 0.5 h postinfection. (adapted from ref. 4).

		ED_{50} mg/kg	
Species	Type of strain	GAR-936	Minocycline
S. aureus	*tet*M	1.0	1.8
	*tet*K	2.1	2.0
	MRSA	0.79	0.31
	MRSA *tet*M	0.84	1.6
	MRSA *tet*K *tet*M	2.3	16
S. pneumoniae	penicillin S	1.3	3.9
	penicillin I	1.7	3.5
	penicillin R	0.61	20
E. coli	tetracycline S	1.7	3.2
	*tet*A	1.6	16
	*tet*C	1.5	14
	*tet*M	3.5	>32
	*tet*B	3.9	>32
	minocycline R	1.6	>32

active by both the subcutaneous and the intravenous route, but that, unlike minocycline and the earlier tetracyclines, activity was greatly diminished when the compound was administered by the oral route. In this model, Petersen *et al.* (4) tested five strains of *S. aureus* (including MRSA strains and those carrying the *tet*M and *tet*K resistance determinants), three strains of *S. pneumoniae* (penicillin resistant, intermediate and susceptible) and six strains of *E. coli* (including those carrying the *tet*A, *tet*B, *tet*C and *tet*M determinants). The estimated doses to protect 50% of infected mice (ED_{50}) for GAR-936 and for minocycline are given in Table IV. In these experiments, the compounds were administered intravenously in a single dose given at 0.5 h postinfection. GAR-936 was particularly active against *S. pneumoniae* infections and was more effective than minocycline even though the MIC values for the two compounds against the penicillin-susceptible and penicillin intermediate strains were identical (0.12 mg/l). Additional experiments reported by Projan (13) included a strain of *E. faecalis* carrying three resistant determinants (*tet*L, *tet*M, *tet*S). Minocycline had poor activity with a subcutaneous ED_{50} of 25 mg/kg in contrast to GAR-936, which had an ED_{50} of only 1.0 mg/kg.

The good activity of GAR-936 against *S. pneumoniae* acute mouse infections was confirmed when the compound was tested in a mouse pneumonia model (13), where GAR-936 was superior to minocycline, vancomycin and amoxicillin against an infection with a penicillin-susceptible strain of *S. pneumoniae*. The compounds were dosed subcutaneously (GAR-936, minocycline and vancomycin) or orally (amoxicillin) once a day for 3 days postinfection. Complete protection was seen with a dose of only 1 mg/kg/day of GAR-936, in contrast to 16, > 5 and > 8 mg/kg/day of vancomycin, amoxicillin and minocycline, respectively. A dose of 0.5 mg/kg/day of GAR-936 gave 80% protection compared with 4, 5 and 8 mg/kg/day of vancomycin, amoxicillin and minocycline, respectively. Using this model, Mikels *et al.* (14) calculated the protective dose for 50% of the animals (PD_{50}) and performed counts on the lungs of mice infected with either a penicillin-sensitive (PSSP) or a penicillin-resistant (PRSP) pneumococcus. The PD_{50} for GAR-936 against the PSSP was only 0.4 mg/kg in contrast to 3.3, 1.9 and 0.5 mg/kg of minocycline, vancomycin and amoxicillin, respectively. Against the PRSP, using two different dosing schedules, the PD_{50} of GAR-936 was 0.5 and 0.2 mg/kg compared with 1.8 and 1.6 mg/kg of vancomycin and 13.1 and 2.8 mg/kg of amoxicillin. Minocycline was inactive against this strain. In confirmation of these excellent protective effects, a dramatic fall in the numbers of *S. pneumoniae* was seen in the lungs of mice treated with GAR-936 and killed at intervals.

Mikels *et al.* (15) also used a mouse pneumonia model to test GAR-936 against *P. aeruginosa*. Gentamicin and piperacillin were included as comparator drugs. The strain of *P. aeruginosa* tested was susceptible to 8 mg/l of GAR-936, 1 mg/l of gentamicin and 4 mg/l of piperacillin. Lungs were removed from infected and treated animals to determine the numbers of organisms remaining at varying intervals. Dosing was at 3 h and then twice daily for 2 days postinfection by the subcutaneous route. GAR-936 and gentamicin produced a similar fall in numbers in the lungs of mice killed at 48 h, but when the agents were given in combination, a greater fall was seen. A dose of 10 mg/kg (x 4) of GAR-936 produced 100% survival of infected mice over a 14-day period in contrast to 75% survival with gentamicin. At 5 mg/kg (x 4) gentamicin protected 50% of the mice and GAR-936 40%. The combination of GAR-936 and gentamicin at 5 mg/kg gave 80% protection.

The mouse thigh lesion model has been used to determine the efficacy of GAR-936 against a number of species, including *S. pneumoniae*, *S. aureus*, *Klebsiella pneumoniae* and *E. coli* (16). Neutropenic mice were

Table V: Pharmacokinetic parameters in healthy male subjects following a 1-h i.v. infusion of GAR-936 (adapted from ref. 21).

Dose	Fasted or fed	C_{max} (mg/l)	$AUC_{(0-\infty)}$ (mg·h/l)	C_L (l/h)	V_{ss} (l)	$t_{1/2}$ (h)
100 mg	Fasted	0.91	6.4	16	684	38
200 mg	Fasted	1.6	12.4	17	764	42
200 mg	Fed	1.5	11.7	18	1004	53
300 mg	Fed	2.8	17.8	17	820	45

used and treated for varying intervals over 24 h to allow pharmacodynamic and pharmacokinetic parameters to be determined. Using this model, ED_{50} values were higher than those reported in the acute model. No standard comparator drugs were included. *S. pneumoniae* strains were the most susceptible, but *K. pneumoniae* and some strains of *S. aureus* required far greater doses for protection. The authors calculated that the time above a factor of the MIC was the best correlate with therapeutic efficacy.

Activity against *E. faecalis* and *S. aureus* has been evaluated in a model of rat endocarditis (17). Vancomycin-resistant (a *Van*A and a *Van*B strain) and vancomycin-susceptible *E. faecalis* strains (VREF and VSEF) were used, as well as a MRSA strain. GAR-936 was highly active *in vitro* against all four strains used and was more active than vancomycin. In this model, efficacy is judged by the reduction in numbers of organisms recovered at intervals from the infected cardiac vegetations. GAR-936 produced substantial falls in the numbers of all species recovered from the cardiac tissue, and in all cases these falls were superior to those seen with vancomycin, even against the vancomycin-susceptible strains.

Another endocarditis study used rabbits infected with enterococci (a vancomycin-susceptible *E. faecalis*, a *Van*A strain of *E. faecalis* and a *Van*B strain of *E. faecium*). These authors (18) treated the infected rabbits intravenously with 14 mg/kg/day of GAR-936 for 5 days twice daily starting 48 h after infection. No comparator compounds were included. A reduction of almost 2 logs in the numbers of organisms recovered from the cardiac vegetations was seen. In addition, using radiolabeled compound, GAR-926 was shown to have penetrated into the cardiac tissues and vegetations at levels in excess of those found in the plasma.

Fang *et al.* (19) tested GAR-936 and vancomycin using a rabbit meningitis model with an infection caused by a recent human isolate of a highly penicillin-resistant strain of *S. pneumoniae*. Treatment was by the intravenous route starting 18 h after infection. GAR-936 was given either once or twice at doses ranging from 10-50 mg/kg. The numbers of organisms surviving in the cerebrospinal fluid and in the blood were determined 6 h after treatment. GAR-936 produced a significant fall in bacterial numbers in the CSF although the doses required to produce this effect (2 x 30 mg/kg or 50 mg/kg single dose) were higher than vancomycin doses (5 and 20 mg/kg).

Pharmacokinetics and Metabolism

Animal studies using radiolabeled material have indicated that GAR-936 penetrates tissues well, with levels in a range of tissues exceeding those in plasma. Tombs *et al.* (20) looked at the distribution of GAR-936 into rat tissues, where the highest levels were found in bone, followed by liver, spleen and kidney. The high levels found in bone are consistent with other tetracyclines which chelate calcium and adhere to bone. Levels persisted in tissues longer than in plasma, indicating a high volume of distribution. The half-life was calculated as 36 h in plasma, 208 h in bone, 128 h in thyroid and 77 h in kidney. In the rabbit endocarditis study noted above, GAR-936 penetrated into cardiac tissue in infected rabbits with a ratio of cardiac tissue/plasma of approximately 4.8.

An ascending single-dose intravenous infusion study in healthy male subjects showed that kinetics were linear for doses of 12.5-200 mg (21). A validated HPLC method with a range of 25-12,500 ng/ml with UV detection at 350 nm was used. The main pharmacokinetic parameters are detailed in Table V. As in rats, the half-life was long (38-45 h) and the volume of distribution was very high. Food had little effect on the pharmacokinetics of GAR-936. Little effect of age and gender on the pharmacokinetics of GAR-936 was seen when a single intravenous dose of 100 mg was used (22). Age groups of 18-50, 65-75 and over 75 were used.

Less than 15% of the compound was excreted unchanged in the urine. No details are available on metabolism and routes of excretion.

Safety and Tolerability

Side effects in healthy subjects are claimed to be typical of tetracyclines, namely, nausea, vomiting and headache, but the maximum tolerated dose is only 100 mg. Tolerance is stated to be improved by food, with the maximum tolerated dose increasing to 200 mg. Infusions of 4 h do not improve tolerance compared with 1-h infusions.

Clinical Studies

GAR-936 is in phase II clinical trials as an injectable antibiotic for the treatment of serious polymicrobic

infections in hospitalized patients where resistant pathogens are known or suspected (23).

Manufacturer

American Home Products Corp. (US).

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