Journal of Antimicrobial Chemotherapy (1988) **21**, *Suppl. A*, 93–103

Teicoplanin in the treatment of infections caused by coagulase-negative staphylococci

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A total of 88 patients were treated with teicoplanin for infections caused by coagulase-negative staphylococci in open clinical studies in France and the UK. Teicoplanin was administered once daily, with a mean dose of 323 mg, for a mean duration of 16 days. Thirty-nine patients received teicoplanin alone while 49 received combination treatment. Clinical cure or improvement occurred in 79 of 82 evaluable cases (96·3%) and bacteriological elimination in 82 cases (95·1%). Treatment with teicoplanin alone was clinically successful in all cases, including 20 septicaemias, and the elimination rate was 93%. There was no apparent correlation between clinical and bacteriological outcomes and results of in-vitro testing. The variation in MICs between France and the UK was attributed to differences in the methods used.

Introduction

Coagulase-negative staphylococci (CNS) were long considered to be innocuous skin commensals but have recently become important causes of infection in certain susceptible patient groups. Patients particularly at risk include those with implanted foreign bodies including prosthetic heart valves, vascular catheters, other shunt and drainage devices, joint prostheses and those with immunocompromised status (Archer, 1978; Karchmer, 1986). Many of these infections are nosocomial and hence the antibiotic susceptibility patterns of the pathogens are unpredictable and they are often multiresistant; 35–66% of clinically important CNS are currently resistant to methicillin (Richardson & Marples, 1982; Schwalbe, Stapleton & Gilligan, 1987).

The recommended therapy for infections caused by such resistant organisms is usually vancomycin, as monotherapy for less severe cases, or in combination with an aminoglycoside and rifampicin for severe life-threatening episodes (Karchmer, 1986). In addition, allergy to β-lactam antibiotics in some patients infected with methicillin-sensitive strains necessitates the use of alternative agents.

Teicoplanin, a new glycopeptide antibiotic produced by *Actinoplanes teichomyceticus*, is active against most Gram-positive bacteria (Grüneberg *et al.*, 1983) including methicillin resistant CNS. It has a long terminal half-life (*c.* 100 h, Buniva *et al.*, 1986) allowing once daily administration and, unlike vancomycin, it can be given as an iv bolus injection or by the intramuscular route.

Clinical trials with teicoplanin throughout Europe and the USA have shown good efficacy in a wide range of infections coupled with a low incidence of adverse events (Lewis, Garaud & Parenti, 1987; Van Laethem *et al.*, 1987). However, recent attention has been focused on the comparative in-vitro activity of teicoplanin and vancomycin

0305–7453/88/21A093+11 $02.00/0

against some strains of CNS (Grant *et al.*, 1986; Wilson *et al.*, 1986). For thirteen of these strains MICs of teicoplanin ranged from 12·8 to 25·0 mg/l whereas the corresponding range for vancomycin was 0·8–3·2 mg/l.

The aim of this study was to assess the efficacy of teicoplanin, alone or in combination with other antimicrobials, in infections caused by CNS, and to ascertain whether a high MIC (>4 mg/l) of the pathogenic strain is a predictor of clinical and bacteriological failure.

Methods

Eighty-eight patients were recruited into this study, as part of a prospective European open evaluation, from 19 centres in France and the UK. A standard protocol was used, which was approved by the local ethical committees concerned. Patients were included if they had suspected or proven Gram-positive infection. The exclusion criteria were: age less than 14 or greater than 80 years, impaired renal function (defined as serum creatinine greater than 150 μmole), hypersensitivity to glycopeptide antibiotics, pregnancy or likelihood of death within 48 h of starting therapy. Informed consent was obtained from each patient before treatment. For this study, data analysis was restricted to patients with proven infection by CNS. Mixed infections were not included in this analysis.

Dosage and route of administration

The recommended dosage of teicoplanin was 400 mg (6 mg/kg) or 200 mg (3 mg/kg) once daily as a slow bolus iv injection, with an optional loading dose of 400 mg on the first day of therapy. Serum concentrations were monitored routinely and doses adjusted as necessary in order to maintain troughs within the range of 5–15 mg/l.

Criteria for infections

Urinary tract infection (UTI) was defined as bacteruria $>10^5$ cfu/ml in MSU or $>10^3$ in CSU or suprapubic aspirate.

Septicaemia was defined as symptoms of fever (>38·5°C on one occasion), rigors and/or hypotension and bacteriologically confirmed by at least two positive pretreatment blood cultures taken from separate sites.

Bone and joint infections were defined by clinical evidence of osteomyelitis or septic arthritis (including changes suggestive of such infections on X-ray or bone scans) and positive identification of infecting organisms in cultures of blood, bone, aspirated joint or subperiosteal fluid.

Mediastinitis was defined as purulent discharge from the anterior mediastinum occurring within 40 days of open heart surgery, whether or not associated with sternal inflammation or pre-sternal suppuration.

Skin and soft tissue infection was defined as evidence of purulent discharge and/or erythema and/or swelling with a positive aspirate or biopsy culture.

Hickman line infection was defined as bacteraemia associated with inflammation and pus at the cannula insertion site.

Assessment of efficacy

Clinical efficacy was assessed according to the following criteria: (i) Patients were considered to be cured if signs and symptoms of infection were eradicated at the end of

treatment. (ii) Clinical improvement was defined as a definite reduction in signs and symptoms during the study period but incomplete resolution of infection. (iii) Clinical recurrence was defined as an initial eradication of signs and symptoms with a subsequent worsening of the clinical condition (after termination of therapy) caused by infection. (iv) Patients were judged to have failed therapy if they had an inadequate clinical response. (v) If a case was not considered evaluable for any reason the investigator was asked to state the reason(s) for this decision.

Bacteriological efficacy

Bacteriological efficacy was assessed according to the following criteria. (i) Elimination implied that the original causative organism was eradicated during and after therapy. Patients who had a complete clinical resolution of infection so that follow-up culture was impossible, e.g. soft tissue or bone and joint infections, were also judged to have been cured bacteriologically. (ii) Bacteriological failure was defined as the persistence of the initial pathogen during treatment. (iii) Elimination with recurrence was defined as the absence of the causative pathogen from cultures at the completion of therapy with reappearance at the same site during follow-up. (iv) Elimination with re-infection was defined as the eradication of the causative organism at or immediately after termination of therapy but appearance of another infecting organism at the same site subsequently. (v) Indeterminate was defined as any response for which bacteriological evaluation was not possible, e.g., less than 48 h treatment with study drug or administration of another effective antimicrobial drug before follow-up cultures were obtained.

Safety monitoring

The following tests were performed at least weekly during and at the end of therapy: (i) complete blood count with differential leucocyte and platelet counts; (ii) determination of serum electrolytes and glucose; (iii) renal and hepatic function and (iv) urinalysis. Patients were monitored daily to detect any clinical signs or symptoms of adverse events.

Antimicrobial susceptibility testing

CNS isolates were tested routinely for susceptibility to teicoplanin either by Stokes' method (Stokes & Ridgway, 1980) or by the standard agar disc diffusion method (Chabbert, 1982) with discs containing 30 μg teicoplanin.

MICs were determined routinely in liquid or solid media, according to the practice of the laboratory involved, at inocula ranging from 10^4 to 10^7 cfu/ml (liquid media) and 10^4 to 10^5 cfu/spot (solid media) with incubation for 18–48 h at 37°C.

Results

A total of 88 patients (39 in France, 49 in the UK) entered this study, ranging in age from 14 to 79 years (mean $\pm$ S.D. $47 \pm 18{\cdot}5$) and in weight from 43 to 109 kg (mean $\pm$ S.D. $65 \pm 12{\cdot}6$). The main infections comprised 52 septicaemias, 13 Hickman catheter site infections, nine cases of mediastinitis, six skin and soft tissue infections, four UTIs, three joint and bone infections, and one shunt-associated meningitis.

Of 89 pathogens cultured from these 88 sites, there were 64 strains of *Staphylococcus*

epidermidis (MICs of teicoplanin 0·01–16·0 mg/l), two *S. haemolyticus* (MIC 0·5 and 1·0 mg/l), one *S. hominis* (MIC 4·0 mg/l), one *S. cohnii* (MIC 32 mg/l), one *S. simulans* (MIC 0·25 mg/l), and 20 unspeciated strains of CNS (MICs 0·06–4·0 mg/l). Twenty-eight of these strains (32%) were resistant to methicillin. Table I shows the frequency of these strains by diagnosis.

Seventy-seven of the 88 patients had one or more complicating and/or predisposing factors for infection. The most frequent of these were leukaemia (29 cases), solid tumours (13 cases), neutropenia (13 cases), presence of a prosthetic device (22 cases) including prosthetic heart valve in nine cases, recent heart surgery for coronary artery bypass (eight cases), congestive heart failure (six cases), diabetes mellitus or severe burns (five cases each).

Twenty-nine patients received teicoplanin monotherapy for their infections. However, of the 59 patients receiving one or more concomitant antimicrobials for at least a part of their therapeutic course, four were given metronidazole only and in six cases the pathogen was reported as resistant to the other agent(s). Thus the ratio of monotherapy: combination therapy was 39 : 49.

Full details of concomitant antimicrobials are shown in Table II. The most common combination agents were aminoglycosides (42 courses), cephalosporins (22 courses) and metronidazole (17 courses). Teicoplanin was administered by iv route for a mean duration of 16 ± 13 days (range 2–73) days. The unit daily dosage of teicoplanin ranged from 200 to 800 mg (2·2–13·3 mg/kg) with a mean of 323 ± 110 mg ($5·1 \pm 1·9$ mg/kg).

Clinical efficacy

The 82 evaluable patients fell into two groups. Thirty-eight patients received monotherapy and 44 were given a combination. The six non-evaluable cases were four

Table I. Frequency of pathogenic strains by diagnosis

Diagnosis	Organism					
	CNS (unidentified)	*S. epidermidis*	*S. haemolyticus*	*S. hominis*	*S. cohnii*	*S. simulans*
Septicaemia ($n = 52$)	11	37	1	1	1	1
Hickman line infections ($n = 13$)	—	13	—	—	—	—
Mediastinitis ($n = 9$)	6	3	—	—	—	—
Skin or soft tissue infection ($n = 6$)	3	3	—	—	—	—
Joint and bone infection ($n = 3$)	—	3	—	—	—	—
UTI ($n = 5$)	—	4	1	—	—	—
Meningitis ($n = 1$)	—	1	—	—	—	
Total	20	64	2	1	1	1

septicaemias (three combination, one monotherapy) and two mediastinitis (two combination). For each group, full results of clinical outcomes by infection sites are shown in Table III. No differences were observed in cure/improvement rates in patients receiving monotherapy (97·4%) or combination therapy (95·5%). All but one of the infections treated with teicoplanin alone were successfully treated. The clinical success rate was similar between countries (94·6% in France, 97·7% in the UK).

Bacteriological efficacy

Eighty-two patients were considered evaluable for bacteriological outcome. Full results are shown in Table IV. The overall elimination rate was 95·1% and was similar between countries (97·3% in France, 93·2% in the UK).

Four organisms persisted, all in patients receiving teicoplanin monotherapy, the dosage being 3·4, 4·5, 2·5 and 4·0 mg/kg, respectively. These were: *S. epidermidis* Hickman wound infection (MIC 1 mg/l), *S. haemolyticus* septicaemia (MIC 1 mg/l) and two CNS skin and soft tissue infections (MIC 0·125 mg/l). In the group receiving combination therapy no failures were observed but there was one recurrence (CNS septicaemia, MIC 2·5 mg/l) and three patients were reinfected following elimination of the original pathogen. These three cases were: a *S. epidermidis*, Hickman wound infection, reinfected with *Agrobacterium radiobacter* and *Candida albicans*, and one

Table II. Concomitant antimicrobials

Antibiotic class	Antibiotic	No. of courses
Aminoglycosides	gentamicin	21
	amikacin	10
	netilmicin	8
	sissomicin	1
	tobramycin	2
Ureidopenicillins	azlocillin	4
	piperacillin	2
Isoxazolyl penicillins	cloxacillin	5
	flucloxacillin	2
Penicillins	amoxycillin	1
	benzylpenicillin	1
Quinolones	pefloxacin	6
	ciprofloxacin	1
	nalidixic acid	1
Cephalosporins	cefotaxime	1
	ceftazidime	15
	cefuroxime	6
Others	metronidazole	17
	rifampicin	8
	erythromycin	1
	chloramphenicol	1
	co-trimoxazole	2
	fosfomycin	2
	fusidic acid	1
	pristinamycin	1
	trimethoprim	1

case each of *S. epidermidis* and CNS mediastinitis, both reinfected with other Gram-positive bacteria.

Clinical and bacteriological outcomes were also analysed for various MIC ranges to see if any differences existed between efficacy rates at low and high MICs (Tables V and VI). It can be seen that there was no difference in either clinical or bacteriological efficacy according to the MIC ranges chosen; indeed, 100% clinical and bacteriological success was only achieved for pathogens with MICs greater than 4 mg/l. In addition, bacteriological persistence and clinical failure were more often associated with MICs less than 1 mg/l.

In order to clarify these observations an analysis was made comparing MIC results and determination techniques for the CNS strains from the two countries involved in this study. Figure 1 shows the frequency distribution of CNS MICs by country and Table VII shows the differences in techniques by country (medium and method used, duration of incubation, inoculum size).

Discussion

With the advent of multiresistant CNS as pathogens in nosocomial infection, the correct choice of appropriate antimicrobial agents is paramount. The data from this study show that teicoplanin alone or in combination is an effective agent for the therapy of moderate to severe infections with CNS. The clinical success rate in 82 evaluable patients was 97·4% for monotherapy and 95·5% for combination therapy; the overall bacteriological success rate was 95·1%. These results are particularly satisfactory since the high incidence of methicillin resistance (32%) agrees well with that reported in other studies of nosocomial infection (Christensen *et al.*, 1982). In

Table III. Clinical outcomes by infection site

Site	M/C*	Clinical response				Cure/Imp. Rate (%)
		Cure	Improvement	Recurrence	Failed	
Septicaemia	M	21	2			100·0
	C	22	2	1		96·0
Hickman site wound infection	M	3	1			100·0
	C	6	3			100·0
Mediastinitis	M	1				100·0
	C	4	1		1	83·3
Skin or soft tissue	M	3			1	75·0
	C	2				100·0
UTI	M	3				100·0
	C	1				100·0
Bone or joint	M	2				100·0
	C		1			100·0
Meningitis	M	1				100·0
	C					
Total	M	34	3		1	97·4
	C	35	7	1	1	95·5

*M, Monotherapy; C, combination therapy.

Table IV. Bacteriological outcome by infection site

Infection site	Bacteriological response					Elimination rate
	Elimination	Elimination with recurrence	Elimination with reinfection	Persistence	Indeterminate	
Septicaemia	46	1		2	3	95·9
Wound (Hickman site)	10		1	1	1	91·7
Mediastinitis	6		2		1	100·0
Bone or joint	2				1	100·0
Skin or soft tissue	5			1		83·1
UTI	5					100·0
Meningitis	1					100·0
Total	75	1	3	4	6	95·1

Table V. Clinical outcomes by MIC range

Clinical outcome	MIC range (mg/l) ≤0·5	>0·5–1·0	>1·0–4·0	>4·0
Cure	15	14	24	4
Improvement	1	5	2	1
Recurrence	0	0	0	0
Failure	2	0	1	0
Not evaluable	0	0	4	0
Total	18	19	31	5
Cure/improvement rate (%)	89	100	96	100
Recurrence/failure rate (%)	11	0	4	0

Table VI. Bacteriological outcomes by MIC range

Bacteriological outcome	MIC range (mg/l) ≤0·5	>0·5–1·0	>1·0–4·0	>4·0
Elimination	16	14	26	5
Elimination with recurrence	0	0	1	0
Elimination with reinfection	1	1	1	0
Persistence	1	2	1	0
Indeterminate	0	2	2	0
Total	18	19	31	5
Elimination rate (%)	89	82	90	100
Recurrence /reinfection rate (%)	6	6	7	0
Persistence rate (%)	5	12	3	0

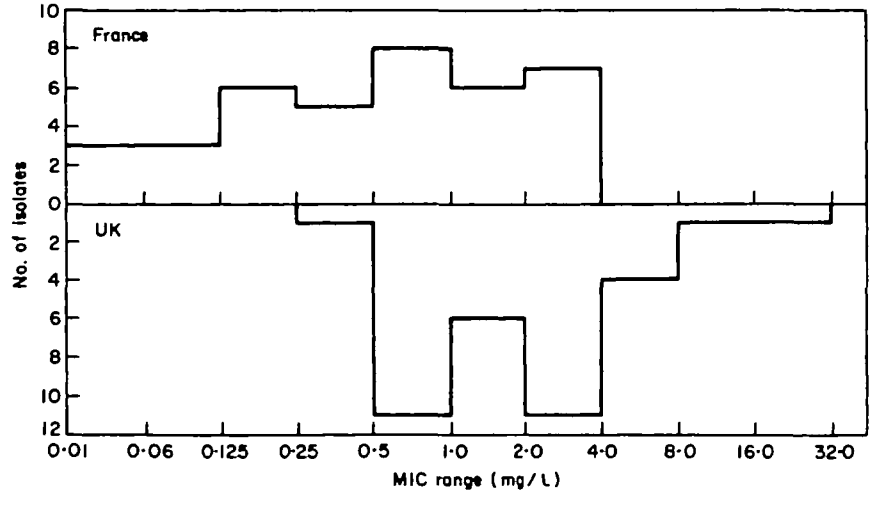

Figure 1. Frequency distribution of MICs of teicoplanin for CNS by country.

Table VII. MIC determination for teicoplanin against CNS strains. Differences in techniques between France and the UK

Parameter		UK	France	*P* value*
Incubation time (h)	18–24	12	38	<0·0001
	48	23	0	
Inoculum size	10^4–10^5	35	23	<0·0001
	10^6–10^7	0	15	
Method	solid	32	9	<0·0001
	liquid	3	29	
Medium	Mueller–Hinton	0	38	<0·0001
	Iso-Sensitest	35	0	

*Chi-square test with Yates' correction.

addition, the poor clinical status of the patients is a reflection of the usual population in which nosocomial infections develop. Furthermore, in other clinical trials conducted in Europe, teicoplanin has been shown to be as efficacious as vancomycin; the overall elimination rate for CNS was 82·4% for teicoplanin (22 patients) and 77·8% for vancomycin (19 patients) (data on file, Merrell Dow Research Institute).

Attention has been focused recently on the comparative activity of teicoplanin and vancomycin against CNS and, in particular, *S. haemolyticus*. Grant *et al* (1986) reported a strain of *S. epidermidis* from a CAPD patient with an MIC of teicoplanin of 12·8 mg/l (1·6 mg/l for vancomycin) whilst Wilson *et al.* (1986) isolated a strain of *S. haemolyticus* from a pacing wire tip with an MIC of teicoplanin of 16 mg/l (2 mg/l for vancomycin). In neither case was teicoplanin being administered, although in the latter patient teicoplanin had been used as prophylaxis for cardiac surgery (three doses).

Early studies on teicoplanin showed conflicting results for in-vitro activity of teicoplanin against CNS; Pallanza *et al.* (1983) found the MIC_{90} against *S. epidermidis* to be 1·6 mg/l (3.1 mg/l for vancomycin), whilst Fainstein, Le Blanc & Bodey (1983) found it to be 12·5 mg/l (3·12 mg/l for vancomycin). Recently, Arioli & Pallanza (1987) reported an MIC_{90} for *S. epidermidis* of 2 mg/l to both teicoplanin and vancomycin and confirmed earlier suggestions that *S. haemolyticus* was less susceptible to teicoplanin. In our study, the MIC_{90} for teicoplanin was 4 mg/l (range 0·01–32) and for vancomycin 2·5 mg/l (range 0·5–2·5).

It is apparent that differences exist in MIC values according to the techniques used; both Bauernfeind & Petermüller (1982) and Fietta *et al.* (1983) found that pH and inoculum size influenced results. However, the major discrepancy was seen in comparisons between solid and liquid media (Mueller–Hinton), where the MIC for *S. epidermidis* could be increased by up to 32 fold by using a solid medium. Fietta *et al.* (1983) also found that Mueller–Hinton broth gave lower MIC values than either nutrient broth or Penassay Y broth. Recently, Felmingham *et al.* (1987) have shown that these differences in results with different media are particularly enhanced for *S. haemolyticus*.

In our study, no differences were observed for clinical and bacteriological outcomes between the two countries, although an important discrepancy was seen in the MIC values. These differences may be explained by the different routine techniques used. There were statistically significant differences in inoculum size ($P < 0·0001$), incubation

time ($P < 0.0001$), the use of solid or liquid medium ($P < 0.0001$) and the choice of medium itself ($P < 0.0001$).

Consequently the interpretation of high MIC values (>4 mg/l) seems difficult in terms of sensitivity or resistance since patients who failed to respond to therapy were infected with organisms with MICs <4 mg/l, whereas the five patients with infections due to organisms with MIC >4 mg/l were cured. Two of these were treated with monotherapy (MICs, 5 and 16 mg/l) and one other (MIC, 32 mg/l) received cefuroxime and gentamicin for one day only.

The great variation in media, inoculum range and incubation time makes comparisons between the results of different investigators difficult to interpret, but it appears that in-vitro resistance does not necessarily equate with in-vivo results. Since it is unlikely that the two CNS populations in this study differ radically in their susceptibility to teicoplanin, further co-operative work should be undertaken in Europe to define a standard technique for determination of MICs of teicoplanin.

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