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Review

The comparative efficacy and safety of teicoplanin and vancomycin

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Glycopeptide antibiotics, such as teicoplanin and vancomycin, are active against staphylococci (including methicillin resistant strains), streptococci, enterococci and *Clostridium* spp. Vancomycin and teicoplanin are both widely used in the treatment of infections caused by Gram-positive organisms. Vancomycin can, however, provoke a number of side-effects, and serum concentrations should be monitored during treatment. Teicoplanin has a longer half-life than vancomycin, it can be given as an intravenous bolus or by intramuscular injection, and nephrotoxicity and ototoxicity are relatively uncommon. Treatment with teicoplanin might, therefore, offer advantages over treatment with vancomycin—provided that similar clinical efficacy can be shown. At least 11 clinical trials comparing the efficacy and safety of teicoplanin and vancomycin have been carried out worldwide. Meta-analysis of the combined results from these studies indicates that more than three-quarters of the patients in each of the treatment groups had a clinical response to therapy. Meta-analysis of the numbers of adverse events occurring in each treatment group shows significantly fewer reports of adverse events in patients receiving teicoplanin (13.9%) than in those receiving vancomycin (21.9%). Direct comparisons are difficult because of inherent differences between studies, but available data suggest that teicoplanin is as effective as vancomycin and that its superior tolerability together with advantages such as once-daily bolus administration, intramuscular use and lack of requirement for routine serum monitoring, give it considerable potential for use in clinical practice.

Introduction

Glycopeptide antibiotics are active against staphylococci (including methicillin resistant strains), streptococci, listeria, enterococci and *Clostridium* spp. Teicoplanin is a complex of five closely related glycopeptides with a similar structure to that of vancomycin. It binds to the terminal D-Ala-D-Ala sequence of peptides forming the bacterial cell wall and, by stearically hindering the transglycosylation reaction, inhibits the formation of peptidoglycan (Reynolds & Somner, 1990). Teicoplanin and vancomycin are both large polar molecules and, as they cannot penetrate the lipid membrane of Gram-negative bacteria, they are inactive against these organisms.

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Vancomycin is widely used to treat infections caused by Gram-positive organisms. Its use is, however, associated with a number of clinically significant side-effects (Farber & Moellering, 1983; Kucers, 1984; Mellor *et al.*, 1985). Careful supervision of drug administration and monitoring of serum concentrations are therefore required. Teicoplanin has a longer half-life than vancomycin (159 h *vs* 11 h) and unlike vancomycin, can be given either as an intravenous bolus or by intramuscular injection (Campoli-Richards, Brogden & Faulds, 1990; Thompson *et al.*, 1992). Assay of serum concentrations of teicoplanin is usually only required in those patients with pre-existing renal impairment, as nephrotoxicity and ototoxicity are relatively uncommon (Davey & Williams, 1991). The 'red man' syndrome, resulting from histamine release after vancomycin administration, is very rare in teicoplanin-treated patients. These factors would give teicoplanin a considerable advantage over vancomycin if clinical efficacy were shown to be of a similar order.

Worldwide, at least 11 clinical trials have been conducted comparing the efficacy and safety of teicoplanin with that of vancomycin. The results of these 11 trials have been analysed in an effort to clarify the clinical position of these two agents, and the findings are described in this paper.

Methods

Clinical studies

A total of 1276 patients in Europe and the United States were enrolled into 11 randomized clinical trials (three double-blind and 11 open) comparing vancomycin with teicoplanin (Gerard *et al.*, 1987; Van Laethem *et al.*, 1988; Smith *et al.*, 1989; Cony-Makhoul *et al.*, 1990; Kulmala *et al.*, 1990; Kureshi *et al.*, 1991; Van der Auwera, Aoun & Meunier, 1991; Charbonneau *et al.*, 1994; Hedström, 1994; Menichetti *et al.*, 1994; Neville *et al.*, 1995). Study details are given in Tables I and II. A total of 651 patients received teicoplanin and 625 received vancomycin. Four of these studies were conducted in febrile neutropenic patients (Smith *et al.*, 1989; Cony-Makhoul *et al.*, 1990; Kureshi *et al.*, 1991; Menichetti *et al.*, 1994), and four in patients with severe Gram-positive infections (Van Laethem *et al.*, 1988; Van der Auwera, Aoun & Meunier, 1991; Hedström, 1994; Neville *et al.*, 1995), including one study of severe infection with methicillin resistant *Staphylococcus aureus* (MRSA). The three remaining studies were in patients with vascular catheter-associated bacteraemia (Kulmala *et al.*, 1990), patients in intensive care units (Charbonneau *et al.*,1994), and haematology/oncology patients with staphylococcal infections (Gerard *et al.*, 1987).

Teicoplanin was given at maintenance doses of 200 mg, 400 mg or 6 mg/kg/day for a median period of 7–22 days. In all but one study (Van Laethem *et al.*, 1988), the dose regimen included a loading dose of teicoplanin, either given as 400–800 mg or 8 mg/kg on the initial day of treatment, or as three doses of 6 mg/kg at 12 hourly intervals over a period of 2 h.

The remaining 625 patients received vancomycin at a dose of either 750–1000 mg, or 8–30 mg/kg every 12 h, over a period of 8–16 days. Concurrent use of other antimicrobials was permitted in nine of the 11 studies; the exceptions being the study of Van der Auwera *et al.* (1991) and an unpublished US study (Kulmala *et al.*, 1990).

Table I. Study details

Investigator	Indication	Design	Country
Smith *et al.* (1989)	febrile neutropenics—Hickman catheters	R/O	UK
Kureshi *et al.* (1991)	febrile neutropenics	R/DB	Canada
Charbonneau *et al.* (1994)	intensive care unit patients	R/O	France
Neville *et al.* (1995)	severe Gram-positive infection	R/O	UK
Van der Auwera *et al.* (1991)	immunocompromised patients	R/O	Belgium
Van Laethem *et al.* (1988)	severe MRSA infection	R/O	Belgium
Gerard *et al.* (1987)	staphylococcal infections haematology/oncology	R/O	Belgium
Cony-Makhoul *et al.* (1990)	febrile neutropenics	R/O	France
Hedström (1994)	severe Gram-positive infection	R/O	Sweden
Kulmala *et al.* (1990)	catheter-associated bacteraemia/septicaemia	R/DB	USA
Menichetti *et al.* (1994)	febrile neutropenics	R/DB	Italy

R, Randomized; O, open; DB, double blind

Table II. Study details

Investigator	Total patients	Indication	Teicoplanin dose[a]	Teicoplanin mean duration (days)	Vancomycin dose[a]	Vancomycin mean duration (days)
Smith *et al* (1989)	72	febrile neutropenics	200/400 mg q 24 h	7	1000 mg q 12 h	8
Kureshi *et al.* (1991)	53	febrile neutropenics	6 mg/kg q 24 h	22	15 mg/kg q 12 h	16
Charbonneau *et al.* (1994)	56	ICU patients	6 mg/kg q 24 h	15	8–12 mg/kg q 12 h	13
Neville *et al.* (1995)	54	severe Gram-negative infections	200/400 mg q 24 h	10	750/1000 mg q 12 h	—
Van der Auwera *et al.* (1991)	74	immunocompromised patients	100/400 mg q 24 h	11	1000 mg q 12 h	12
Van Laethem *et al.* (1988)	21	severe MRSA infection	400 mg q 24 h	21	1000 mg q 12 h	15
Gerard *et al.* (1987)	40	haematology/oncology patients	200 mg q 24 h	—	1000 mg q 12 h	—
Cony-Makhoul *et al.* (1990)	59	febrile neutropenics	6 mg/kg q 24 h	—	30 mg/kg q 12 h	—
Hedström (1994)	80	severe Gram-positive	400 mg q 24 h	—	1000 mg q 12 h	—
Kulmala *et al.* (1990)	240	catheter-associated infections	6 mg/kg q 24 h	13	15 mg/kg q 12 h	13
Menichetti *et al.* (1994)	527	febrile neutropenics	6 mg/kg q 24 h	12	1000 mg q 12 h	12

[a]Maintenance dose.

Assessments of efficacy within the studies

The efficacy of treatment was assessed on both clinical and bacteriological criteria. There were minor differences in the assessments performed in each of the trials but the following criteria were broadly adopted in all of the studies.

Clinical efficacy: patients were considered to be clinically cured if signs and symptoms of infection were resolved at the end of treatment. Clinical improvement was defined as a definite reduction in signs and symptoms but incomplete resolution of infection. Clinical recurrence was defined as an initial resolution of signs and symptoms with subsequent worsening of the clinical condition caused by infection after termination of therapy. Failure was defined as an inadequate clinical response.

Bacteriological efficacy: bacteriological efficacy was assessed as follows. Elimination was recorded when the original causative organism was eradicated during therapy. Patients who had a complete clinical resolution of infection rendering a follow up culture impossible (for example, soft tissue infections) were also judged to be bacteriologically cured. Bacteriological failure was defined as the persistence of the initial pathogen during treatment. Elimination with recurrence was defined as the absence of the causative organism from patient cultures at the completion of therapy, with reappearance at the same site during follow up. Elimination with reinfection was defined as the eradication of the causative organism at, or immediately after, the termination of therapy with the appearance of another infecting organism at the same site subsequently. Indeterminate was defined as any response for which bacteriological evaluation was not possible (for example, less than 48 h treatment with the study drug, or administration of another effective antimicrobial drug before follow-up cultures were obtained).

Assessments of safety within the studies

During the 11 studies, patients were monitored diligently to detect the appearance of adverse events. The intensity of these adverse events was graded as mild, moderate or severe and their relationship to the study drug determined by the investigators.

Assay of the serum concentrations of either teicoplanin or vancomycin was undertaken during the studies as deemed necessary by the investigators.

In order to evaluate the clinical nephrotoxicity of the treatment regimens, routine haematological and biochemical laboratory tests were performed at intervals during the studies. Nephrotoxicity was defined variously as a rise in serum creatinine of: $>44.2\ \mu$mol/L over the baseline value (Smith *et al.*, 1989); $>50\%$ over the baseline value (Charbonneau *et al.*, 1994); >0.5 mg/dL over baseline (Kureshi *et al.*, 1991); a rise of >1.1 mg/dL over the normal range for males and >1.0 mg/dl in females (Kureshi *et al.*, 1991); any rise above the normal range (Hedström, 1994; Menichetti *et al.*, 1994); or any rise in serum creatinine over the baseline value (Kulmala *et al.*, 1990). Neville *et al.* (1995) used the criteria laid down by Sage *et al.* (1988) to define nephrotoxicity as a rise of serum creatinine of 100% or more.

Statistical analysis within studies

In each study, patients were compared for baseline characteristics to ensure matched groups. For all of the studies the patients in each treatment group were similar in terms

of age, sex and underlying condition. Responses to therapy and safety parameters were compared using *t*-test, Fisher's exact test, chi-square test with Yates correction for small numbers, the log rank test and a Kaplan-Meier statistic, as appropriate.

Comparison using meta-analysis

At least 15 trials have been conducted to date comparing teicoplanin with vancomycin. The 11 studies reported here were sufficiently similar in design and assessment criteria to enable comparisons to be made by meta-analysis between the combined groups receiving the two antibiotics. The studies reported by Bowley *et al.* (1988) or Al-Wali *et al.* (1992) in patients undergoing continuous ambulatory peritoneal dialysis and data from the study of de Lalla *et al.* (1992) of antibiotic-associated colitis have not been included. The small study of Gilbert, Wood & Kimbrough (1991) was also excluded from this analysis as some of the patients (those with intravascular catheter-associated bacteraemia) were included elsewhere (Kulmala *et al.*, 1990).

Results

Results of analysis within the 11 studies are summarised below. Also summarised are the results of meta-analysis on combined findings.

Clinical evaluation

The clinical response to treatment in evaluable patients is summarised in Table III. Successful response has been defined as those patients who showed either cure or improvement in condition. Clinical response rates varied for teicoplanin from 54% (13/24) in a study of febrile neutropenic patients (Cony-Makhoul *et al.*, 1990) to 92% (11/12 and 23/25) in studies of patients with severe infections with MRSA and febrile neutropenic patients respectively (Van Laethem *et al.*, 1988; Kureshi *et al.*, 1991). The clinical response rates for vancomycin varied from 60% (21/35) in febrile neutropenic patients to 93% (13/14) in patients with severe Gram-positive infections (Cony-Makhoul *et al.*, 1990; Hedström, 1994).

None of the differences in response rates was found to be statistically significant, a finding also supported by the meta-analysis of the combined results (Table IV). In total, 78.8% (435/552) of patients who received teicoplanin were successfully treated, in comparison with 77.2% (404/523) of those who were treated with vancomycin (difference 1.6%; 95% CI −3.4%, +6.6%). In many of the studies, insufficient detail is provided in order for deep-seated infections to be analysed separately but, overall, 45 cases of bone and joint infection (with and without prostheses), mediastinitis, endocarditis, or infected central venous catheters, vascular prostheses, and pacemaker wire could be identified from three of the studies (van Laethem *et al.*, 1988; Smith *et al.*, 1989; Charbonneau *et al.*, 1994). Failure or relapse of infection was noted in 11 of 21 such cases treated with teicoplanin and in 9/24 treated with vancomycin: these response rates were not significantly different. There was also no difference in the proportion of central venous catheters that were removed in bacteraemic patients treated with either agent.

Table III. Clinical response

Investigator	Teicoplanin (*n*)	Vancomycin (*n*)	Clinical response rates teicoplanin	vancomycin	*P* value
Smith *et al.* (1989)	35	37	21/32 (66%)	20/28 (71%)	ns
Kureshi *et al.* (1991)	26	27	23/25 (92%)	21/25 (84%)	ns
Charbonneau *et al.* (1994)	24	32	18/22 (80%)	20/24 (83%)	ns
Neville *et al.* (1995)	26	28	13/17 (76%)	13/19 (68%)	ns
Van der Auwera *et al.* (1991)	37	37	27/36 (75%)	26/35 (74%)	ns
Van Laethem *et al.* (1988)	12	9	11/12 (92%)	9/10 (90%)	ns
Gerard *et al.* (1987)	21	19	13/18 (72%)	14/17 (82%)	ns
Cony-Makhoul *et al.* (1990)	24	35	13/24 (54%)	21/35 (60%)	ns
Hedström (1994)	53	27	27/31 (87%)	13/14 (93%)	ns
Kulmala *et al.* (1990)	118	122	53/60 (88%)	57/64 (89%)	ns
Menichetti *et al.* (1994)	275	252	216/275 (78%)	190/252 (75%)	ns

ns, Not statistically significant; *n*, number of patients.

Table IV. Meta-analysis of the combined results

Parameter	Teicoplanin (%)	Vancomycin (%)	*P* value
Clinical response[a]	435/552 (78.8%)	405/523 (77.2%)	ns
Bacteriological response[a]	220/263 (83.7%)	204/247 (82.6%)	ns
Patients with adverse events	91/651 (13.9%)	137/625 (21.9%)	0.0003
Patients with nephrotoxicity[a]	28/585 (4.8)	58/544 (10.7%)	0.0005

Total number of teicoplanin patients = 651.
Total number of vancomycin patients = 625.
ns, Not statistically significant.
[a]Evaluable patients.

Bacteriological evaluation

Bacteriological response rates for evaluable patients in 10 of the 11 studies are given in Table V (the response rate for one study (Cony-Makhoul *et al.*, 1990) was not given by its authors, and was not calculable from the published data). In this instance, all patients with either elimination or presumed elimination of the causative pathogen were included as bacteriological responders. Response rates for teicoplanin ranged from 71% (10/14) in severe Gram-positive infections and infections in febrile neutropenic patients (Smith *et al.*, 1989; Neville *et al.*, 1995) to 92% (46/50, 12/13 and 11/12) in infections in febrile neutropenic patients and severe infections with MRSA (Van Laethem *et al.*, 1988; Kureshi *et al.*, 1991; Menichetti *et al.*, 1994). For vancomycin, the lowest bacteriological response rate was 66% (23/35) in severe Gram-positive infections (Van der Auwera *et al.*, 1991) and the highest was 100% (9/9) in a study of febrile neutropenic patients (Kureshi *et al.*, 1991).

Again, none of these differences was found to be of statistical significance. Subsequent meta-analysis of the combined figures (Table IV) confirmed these conclusions. Combined response rates were 83.7% (220/263) for teicoplanin and 82.6% (204/247) for vancomycin (difference 1.1%; 95% CI −7.6%, +5.4%). In the studies where details were provided, none of the Gram-positive bacteria that persisted despite glycopeptide therapy had developed glycopeptide resistance.

Evaluation of safety

The numbers of patients experiencing adverse events in each study is given in Table VI. With the exception of Cony-Makhoul *et al.* (1990), all authors noted the appearance of adverse events during treatment with both teicoplanin and vancomycin. No statistically significant difference between the numbers of adverse events with teicoplanin and vancomycin was reported in four of the studies (Van Laethem *et al.*, 1988; Kulmala *et al.*, 1990; Charbonneau *et al.*,1994; Hedström, 1994). Of these, Van Laethem *et al.* (1988) and Hedström (1994) found more adverse events in the teicoplanin arm (5/12 (42%) and 26/53 (49%), respectively) than in the vancomycin arm (3/9 (33%) and 11/27 (41%), respectively). Conversely, Charbonneau *et al.* (1994) and the US study 102-009 (Kulmala *et al.*, 1990) reported higher rates of adverse events in the vancomycin arm (17/32 (53%) and 37/122 (30%), respectively) than in those who were treated with teicoplanin (7/24 (29%) and 32/118 (27%), respectively). In each of the remaining five studies, there were statistically significantly fewer adverse events in the patients treated

Table V. Bacteriological response

Investigator	Teicoplanin (*n*)	Vancomycin (*n*)	Bacteriological response (%) teicoplanin	vancomycin	*P* value
Smith *et al.* (1989)	35	37	15/21 (71%)	12/16 (75%)	ns
Kureshi *et al.* (1991)	26	27	12/13 (92%)	9/9 (100%)	ns
Charbonneau *et al.* (1994)	24	32	17/21 (81%)	21/25 (84%)	ns
Neville *et al.* (1995)	26	28	10/14 (71%)	7/9 (78%)	ns
Van der Auwera *et al.* (1991)	37	37	28/36 (78%)	23/35 (66%)	ns
Van Laethem *et al.* (1988)	12	9	11/12 (92%)	9/10 (90%)	ns
Gerard *et al.* (1987)	21	19	17/21 (81%)	16/19 (84%)	ns
Cony-Makhoul *et al.* (1990)	24	35	not calculable for this study	not calculable for this study	—
Hedström (1994)	53	27	15/17 (88%)	7/8 (88%)	ns
Kulmala *et al.* (1990)	118	122	49/58 (84%)	55/64 (86%)	ns
Menichetti *et al.* (1994)	275	252	46/50 (92%)	45/52 (87%)	ns

ns, Not statistically significant; *n*, number of patients.

Table VI. Adverse events

Investigator	Teicoplanin (*n*)	Vancomycin (*n*)	Number of patients with adverse events (%) teicoplanin	vancomycin	*P* value
Smith *et al.* (1989)	35	37	3/35 (8%)	9/37(26%)	0.047
Kureshi *et al.* (1991)	26	27	2/26 (8%)	11/27 (41%)	0.01
Charbonneau *et al.* (1994)	24	32	7/24 (29%)	17/32 (53%)	0.07
Neville *et al.* (1995)	26	28	7/28 (25%)	16/28 (57%)	0.03
Van der Auwera *et al.* (1991)	37	37	0/37 (0%)	7/37 (19%)	0.011
Van Laethem *et al.* (1988)	12	9	5/12 (42%)	3/9 (33%)	ns
Gerard *et al.* (1987)	21	19	0/21 (0%)	6/19 (32%)	0.007
Cony-Makhoul *et al.* (1990)	24	35	None reported in this study		—
Hedström (1994)	53	27	26/53 (49%)	11/27 (41%)	ns
Kulmala *et al.* (1990)	118	122	32/118 (27%)	37/122 (30%)	ns
Menichetti *et al.* (1994)	275	252	9/275 (3.2%)	20/252 (8%)	0.03

ns, Not statistically significant; *n*, number of patients.

with teicoplanin than in those who received vancomycin ($P < 0.05$). The results of meta-analysis of the combined figures (Table IV) showed that significantly fewer adverse events were experienced by patients treated with teicoplanin than by those who received vancomycin ($P = 0.0003$; difference −8%; 95% CI −12.2%, −3.8%).

Numbers of patients with nephrotoxicity, as defined by the various parameters chosen, have similarly been calculated wherever possible from the information given by the authors. These figures are presented in Table VII. Figures are available for only nine of the studies. No figures are given for the study by Gerard *et al.* (1987). A statistically significant difference between the occurrence of nephrotoxicity in the teicoplanin and vancomycin groups was demonstrated in only one of the nine studies (Kureshi *et al.*, 1991); these authors reported a higher incidence ($P = 0.02$) of nephrotoxicity in patients treated with vancomycin (6/27, 22%) than in those treated with teicoplanin (0/26, 0%). In a further three studies (Smith *et al.*, 1989; Charbonneau *et al.*,1994; Neville *et al.*, 1995), results showed a statistically insignificant trend in favour of teicoplanin ($p < 0.2$). Meta-analysis of these data (Table IV) showed an overall statistically significant difference between the groups ($P = 0.0005$; difference −5.9%; 95% CI −9.0%, −2.8%), with a higher incidence (58/544, 10.7%) in the vancomycin treated patients than in those who received teicoplanin (4.8%, 28/585). It should be noted that aminoglycosides and other drugs with known nephrotoxic potential were equally frequently administered in combination with either vancomycin or teicoplanin in these studies.

Discussion

Vancomycin has been used for the treatment of severe staphylococcal and other Gram-positive infections for many years. Nevertheless, optimal management of these infections remains difficult to establish. Vancomycin is certainly an extremely effective antibiotic but its use is associated with significant toxicity (Kucers, 1984). Teicoplanin has a similar spectrum of activity, but there has been controversy about the appropriate daily dose (Wilson, Grüneberg & Neu, 1994), and doubts about the dose-response relationship have discouraged its use in some centres. In other centres (particularly those in the United States undertaking clinical trials in patients with endocarditis), higher doses of teicoplanin have been used (Wilson *et al.*, 1994).

A double-blind study comparing vancomycin with teicoplanin in the treatment of septicaemia and endocarditis (Gilbert *et al.*, 1991) formed the rationale for higher teicoplanin doses in the USA. Teicoplanin monotherapy was effective in patients with endocarditis or intravenous catheter-associated infections due to coagulase-negative staphylococci, streptococci or enterococci, and also in patients with uncomplicated septicaemia due to *S. aureus*. However, six of eight patients treated with teicoplanin for endocarditis or mycotic aneurysm caused by *S. aureus* failed to respond to therapy, whereas there was only one failure out of the four treated with vancomycin. These differences were not statistically significant. Interestingly, the results of a study of monotherapy in immunocompromised patients with severe Gram-positive infection (Van der Auwera *et al.*, 1991) showed teicoplanin and vancomycin to be of similar clinical and bacteriological efficacy. In this study, equal numbers of patients with *S. aureus* infections failed to respond to therapy with either drug. In a review of all of the studies of teicoplanin available at the time, Wilson *et al.* (1994) suggested that monotherapy with a maintenance dose of 6 mg/kg/day is

Table VII. Reported nephrotoxicity

Investigator	Teicoplanin (n)	Vancomycin (n)	Number of patients with nephrotoxicity (%) teicoplanin	vancomycin	P value
Smith *et al.* (1989)	35	37	1/35 (2.7%)	5/37 (14.3%)	ns[a]
Kureshi *et al.* (1991)	26	27	0/26 (0%)	6/27 (22%)	0.02
Charbonneau *et al.* (1994)	24	32	6/24 (25%)	15/32 (47%)	ns
Neville *et al.* (1995)	26	28	1/28 (4%)	5/28 (18%)	ns[a]
Van der Auwera *et al.* (1991)	37	37	0/37 (0%)	3/37 (8%)	ns
Van Laethem *et al.* (1988)	12	9	2/12 (17%)	2/9 (22%)	ns
Gerard *et al.* (1987)	21	19	no information given	no information given	—
Cony-Makhoul *et al.* (1990)	24	35	none reported in this study	none reported in this study	—
Hedström (1994)	53	27	2/37 (5.4%)	3/21 (14.3%)	ns
Kulmala *et al.* (1990)	118	122	12/111 (11%)	17/101 (17%)	ns
Menichetti *et al.* (1994)	275	252	4/275 (1.4%)	2/252 (0.8%)	ns

ns, Not statistically significant; n, number of patients.

[a] $0.5 < P < 1.0$.

NB: Each study reported had different criteria for defining nephrotoxicity. Details are given in the text.

usually adequate for streptococcal endocarditis, but that up to 12 mg/kg/day should be used for *S. aureus* endocarditis (in order to maintain trough concentrations above 20 mg/L).

Meta-analysis of the combined results of all of the studies was in agreement with the findings of the individual studies with respect to clinical and bacteriological efficacy rates. The analysis showed that more than three-quarters of patients in each of the treatment groups had a positive clinical response to therapy (teicoplanin 78.8%, vancomycin 77.2%). In addition bacteriological cures were obtained in 83.7% of patients treated with teicoplanin and 82.6% of those given vancomycin. No statistically significant difference between the response rates was observed. Unfortunately, details of patients with deep-seated infections were not always provided in the studies analysed. It was possible, however, to identify 45 patients (21 treated with teicoplanin and 24 with vancomycin) with osteomyelitis, mediastinitis, endocarditis or infected intravascular devices. The clinical response rates in these patients (57% for teicoplanin and 62.5% for vancomycin) were lower than the overall response rates but were not significantly different from each other.

Some concern has been expressed about staphylococcal resistance to teicoplanin and/or vancomycin emerging during glycopeptide therapy of deep-seated infections (Kaatz *et al.*, 1990; Chomarat, Espinouse & Flandrois, 1991; Sanyal *et al.*, 1991) but no such strains were reported in any of the studies in this meta-analysis.

On the other hand, meta-analysis of the numbers of adverse events occurring in each treatment group showed significant differences between teicoplanin and vancomycin ($P = 0.0003$), with demonstrably fewer adverse events reported in patients receiving teicoplanin (13.9%) than in those treated with vancomycin (21.9%). This finding agrees with the individual conclusions reached in six of the studies (Gerard *et al.*, 1987; Smith *et al.*, 1989; Kureshi *et al.*, 1991; Van der Auwera *et al.*, 1991; Menichetti *et al.*, 1994; Neville *et al.*, 1995).

Meta-analysis of the incidence of nephrotoxicity in these studies showed that there were significantly fewer cases reported in patients who had been treated with teicoplanin than in those who had received vancomycin. This is of particular importance in severe infections where nephrotoxic agents are likely to be used concurrently. In six of the seven studies where figures were available (Van Laethem *et al.*, 1988; Smith *et al.*, 1989; Kureshi *et al.*, 1991; Van der Auwera *et al.*, 1991; Charbonneau *et al.*, 1994; Neville *et al.*, 1995), fewer cases of nephrotoxicity were reported in teicoplanin treated patients than in vancomycin treated patients; this was statistically significant ($P = 0.02$) in one study (Kureshi *et al.*, 1991). In the seventh study, the incidence of nephrotoxicity was very low and similar with each agent (Menichetti *et al.*, 1994). The low rates of nephrotoxicity in this study were possibly attributable to subtherapeutic aminoglycoside dosages and infrequent use of amphotericin B.

In conclusion, a meta-analysis of comparative studies of vancomycin and teicoplanin has shown them to be of similar clinical and bacteriological efficacy. Furthermore, though direct comparisons are difficult because of inherent differences between studies with respect to the concurrent use of other antimicrobial therapies, the modification of dosage regimens and the diversity of definitions of nephrotoxicity, the analysis has shown that teicoplanin is significantly less likely than vancomycin to be associated with adverse events, including nephrotoxicity.

Thus, the available data suggest that teicoplanin is as efficacious as vancomycin but its superior tolerability, together with advantages such as once daily bolus

administration, intramuscular use and lack of requirement for routine serum monitoring, give it considerable potential for use in clinical practice.

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