ORIGINAL RESEARCH ARTICLE

Clin Pharmacokinet 2004; 43 (6): 405-415
0312-5963/04/0006-0405/$31.00/0

Teicoplanin in Patients with Acute Leukaemia and Febrile Neutropenia

A Special Population Benefiting from Higher Dosages

Federico Pea,[1] *Pierluigi Viale*,[2] *Anna Candoni*,[3] *Federica Pavan*,[1] *Leonardo Pagani*,[4] *Daniela Damiani*,[3] *Marco Casini*[5] and *Mario Furlanut*[1]

1 Department of Experimental and Clinical Pathology and Medicine, Medical School, Institute of Clinical Pharmacology and Toxicology, University of Udine, Udine, Italy
2 Department of Medical and Morphological Research, Medical School, Clinic of Infectious Diseases, University of Udine, Udine, Italy
3 Department of Medical and Morphologic Research, and Division of Hematology, Medical School, Chair of Hematology, University of Udine, Udine, Italy
4 Division of Infectious Diseases, Bolzano General Hospital, Bolzano, Italy
5 Division of Hematology, Bolzano General Hospital, Bolzano, Italy

Abstract

Objective: To define the optimal dosage regimen of teicoplanin that ensures early therapeutically relevant trough concentrations (C_{min}) [>10 mg/L at 24 hours and possibly close to 20 mg/L at 48 hours] in patients with acute leukaemia who develop febrile neutropenia after chemotherapy.

Design: Prospective observational pharmacokinetic study.

Participants: Adult patients (n = 33) with normal renal function previously treated with antineoplastic chemotherapy because of acute lymphocytic or acute nonlymphocytic leukaemia, and subsequently developing febrile neutropenia treated with empirical antimicrobial therapy.

Design: First, the standard dosage group (n = 11) was administered standard loading and maintenance doses of teicoplanin (400mg every 12 hours for three doses followed by 400mg once daily). Blood samples were collected at defined times as part of routine monitoring and assessed for teicoplanin plasma concentration by fluorescence polarisation immunoassay. Secondly, the high dosage group (n = 22) received a high loading regimen (800 + 400mg 12 hours apart on day 1, 600 + 400mg 12 hours apart on day 2) followed by a high maintenance regimen (400mg every 12 hours) from day 3 on.

Results: In the standard dosage group, no patient had the recommended teicoplanin C_{min} of ™10 mg/L within the first 72 hours, and only five of the 11 patients (45%) had a C_{min} of ™10 mg/L after 120 hours. No patient had a C_{min} of ™20 mg/L. In the high dosage group, teicoplanin C_{min} averaged ™10 mg/L within 24 hours, and this value was achieved within 48 hours in all but one patient. Of note, C_{min} at 72 hours exceeded 20 mg/L in ten of the 22 patients (45%). No patient experienced significant impairment of renal function.

Conclusions: In this patient group, therapeutically relevant C_{min} may be achieved very early in the treatment period with loading doses of 12 mg/kg and 6 mg/kg 12 hours apart on day 1, and 9 mg/kg and 6 mg/kg 12 hours apart on day 2, regardless of renal function. Subsequently, in patients with normal renal function a maintenance dosage of 6 mg/kg every 12 hours may be helpful in ensuring C_{min} close to

20 mg/L. Assessment of C_{min} after 4872 hours may be useful to individualise teicoplanin therapy. Factors increasing volume of distribution and/or renal clearance of teicoplanin (fluid load, hypoalbuminaemia, leukaemic status) may explain the need for higher dosages.

Patients with haematological malignancies are immunocompromised hosts with a high risk of developing life-threatening bacterial infections. In the last 20 years, the aetiology of bacterial infections in haematological patients has changed substantially, with Gram-positive micro-organisms progressively increasing and exceeding Gram-negative bacteria, which were the most frequently involved agents in the late 1980s.[1] This upward trend of Gram-positive bacteria may be related to several factors, including: (i) antimicrobial prophylaxis with oral fluoroquinolones;[2] (ii) the wide empirical use during the nadir of the neutropenic period of third-generation cephalosporins directed against Gram-negative organisms; and (iii) the frequent use of indwelling central venous catheters.[3]

For Gram-positive bacteremia in neutropenic haematological patients, a major role for a glycopeptide (teicoplanin or vancomycin) in the antimicrobial regimen, as either first- or second-line therapy, has been advocated by several authors.[4-6] Since meticillin-resistant staphylococci may be responsible for increased infection-related mortality rate in haematological patients,[2,7] undertreatment with teicoplanin may be of great concern in this setting. Additionally, several antibacterials are known to present unusual pharmacokinetic behaviour in haematological patients. Higher than expected dosages of both aminoglycosides[8-11] and ceftazidime,[12] mainly due to increased volume of distribution and/or renal clearance, were needed to ensure therapeutic concentrations of these hydrophilic antibacterials in febrile neutropenic patients. Similar results were also observed with the glycopeptides. De Gatta et al.[13] showed that higher dosages of vancomycin were needed for the treatment of febrile neutropenic patients. Likewise, in a population pharmacokinetic study, Lortholary and coworkers[14] estimated that 62% of patients with haematological malignancies receiving standard dosages of teicoplanin had trough concentrations (C_{min}) at 48 hours of <10 mg/L, mainly as a result of increased renal clearance.

Additionally, in a retrospective study[15] involving more than 200 critically ill patients, we have recently shown that the lack of appropriate loading may be a major cause of significant underexposure to teicoplanin (C_{min} < 10 mg/L) early in the treatment period in severely ill patients, this probably being a cause of clinical failure for teicoplanin therapy. Of note, this delay in achieving a therapeutically relevant C_{min} of teicoplanin might be of major concern when using standard doses in patients with acute leukaemia, since the potentially increased volume of distribution and/or renal clearance might contribute to lowering C_{min}.

Although a teicoplanin C_{min} of 10 mg/L is generally accepted as the standard of care, particularly for combination therapy, a C_{min} of >20 mg/L is currently recommended for some settings, namely for teicoplanin monotherapy[16] and/or for the treatment of *Staphylococcus aureus* endocarditis and bone or prosthetic infections.[17-20] In a retrospective study, MacGowan et al.[21,22] showed that favourable clinical outcome of *S. aureus*-related deep infections treated with teicoplanin was associated with C_{min} values of >20 mg/L. Recently, Weinbrein and Struthers,[23] commenting on the possible causes of the emergence during teicoplanin therapy of meticillin-resistant *S. aureus* with reduced susceptibility, proposed that higher than currently recommended dosages of teicoplanin, targeted to a C_{min} of 20 mg/L, might be beneficial for the treatment of *S. aureus* septicaemia, particularly when less susceptible micro-organisms with a minimum inhibitory concentration (MIC) close to the breakpoint for teicoplanin may be involved.

Accordingly, considering the worrying emergence in patients with acute leukaemia of coagulase-negative staphylococci with reduced susceptibility to teicoplanin,[24-27] we believe that this higher threshold for teicoplanin might be also beneficial for this special population, when multiresistant,

Gram-positive-related, deep-seated infections due to *S. aureus* and/or to other micro-organisms with reduced susceptibility may be the concern.

Finally, patients with acute leukaemia, due to their immunosuppressed status, probably need higher dosages of teicoplanin for successful outcome,[14] as suggested also by experimental animal data showing that teicoplanin dosages required to protect mice challenged with *S. haemolyticus* were 4-fold higher in immunocompromised than in normal animals.[28]

On these bases, we planned a pharmacokinetic study to define the appropriate dosage regimen that ensures early therapeutically relevant C_{min} of teicoplanin in patients with acute leukaemia.

Patients and Methods

Patients

This study was carried out in haematological patients previously treated with antineoplastic chemotherapy because of acute lymphocytic or acute nonlymphocytic leukaemia. Patients were eligible for empirical antimicrobial therapy if they had a severe neutropenia with a cell count <100/mm^3 and an expected duration of >5 days, and had a fever of unknown origin >38.5μC on one occasion or >38μC on at least two occasions. Criteria for inclusion of anti-Gram-positive coverage with teicoplanin in the first-line broad spectrum combination therapy were: (i) previous prophylaxis with a fluoroquinolone;[2] (ii) presence of central venous catheterisation;[2] and/or (iii) grade 3 or 4 mucositis.[6] All patients were administered teicoplanin therapy for the first 72 hours. Afterwards, if Gram-positive bacteria susceptible to teicoplanin were isolated from normally sterile sites and/or a defervescence was documented within 72 hours, teicoplanin therapy was continued for at least 8 days. On the other hand, whenever Gram-negative bacteria and/or yeasts and/or moulds were isolated, teicoplanin therapy was withdrawn. The study was approved by a review board and informed consent was obtained from each patient.

Study Design

Considering that appropriate loading doses are mandatory to enable early optimal exposure (C_{min} > 10 mg/L) with teicoplanin,[14,15,29] and that C_{min} >20 mg/L have been advocated with the intent of ensuring successful treatment of Gram-positive-related sepsis with teicoplanin[16,19,20,22,23,28] and of preventing the emergence of breakthrough resistance for *S. aureus* in severely ill patients,[23] the objectives of our study were to identify what loading dosages of teicoplanin may enable early therapeutically relevant C_{min} exceeding 10 mg/L and approaching 20 mg/L in acute leukaemic patients, and what maintenance doses must subsequently be administered in patients with normal renal function to maintain these concentrations.

Standard Dosage Group

In Italy, as in many other countries, the licensed dosage of teicoplanin for severe infections in patients with normal renal function is three loading doses of 6 mg/kg every 12 hours followed by a maintenance dose of 6 mg/kg every 24 hours, irrespective of the underlying disease. Consistently, in the first part of the study (carried out at the Division of Haematology of Bolzano General Hospital), in order to assess the exposure ensured by this standard dosage regimen of teicoplanin, a group of leukaemic patients with normal renal function (n = 11) was administered standard loading and maintenance doses of teicoplanin (400mg every 12 hours for three doses followed by 400mg once daily. The administration procedure was intravenous infusion over 15 minutes) [figure 1].

Exclusion criteria were: age >75 years; creatinine clearance (CL_{CR}) estimated on the basis of the Cockcroft and Gault formula[30] <50 mL/min; presence of extensive pleural, pericardic or peritoneal effusions; previous teicoplanin therapy in the former 14 days. Blood samples for therapeutic drug monitoring (TDM) of plasma concentrations were collected at the following defined times: 1 hour after the first dose to assess peak plasma concentration (C_{max}), and at 12, 24, 48, 72, 96, 120 and 144 hours to assess C_{min}. Since standard teicoplanin doses were not expected to induce overexposure in patients with normal renal function,[19] in order to better appreciate the C_{min} achievable at or near

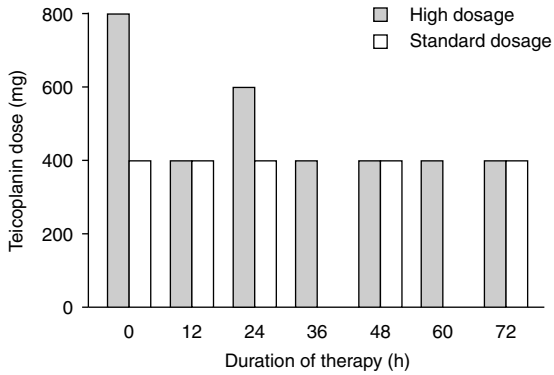

Fig. 1. Dosage regimen of teicoplanin during the first 3 days of therapy in the standard (n = 11) and the high (n = 22) dosage groups, respectively.

steady state with this standard regimen, no dosage adjustment based on TDM results was performed in this group.

High Dosage Group

Because with the standard teicoplanin regimen no patient appeared to have adequate C_{min} values (see the Results section), the second part of the study was subsequently carried out at the Division of Hematology of the Udine University Hospital.

To define the new dosage regimen, sparse data obtained from the multiple-trough sampling of the standard dosage group were used to estimate the population pharmacokinetic parameters of teicoplanin by means of P-Pharm version 5.1 software (Innaphase, Champs sur Marne, France). Akaike's information criterion[31] was used to discriminate among models and a two-compartment open model with first-order elimination was chosen. The estimated parameters (table I) suggested that in patients with acute leukaemia, similar to the findings of Lortholary et al.[14] in a previous population pharmacokinetic study, both clearance and volume of distribution show very high interindividual variability and may be increased.

Accordingly, two loading doses of 12 mg/kg every 12 hours were estimated as appropriate to achieve teicoplanin C_{min} values exceeding 10 mg/L and approaching 20 mg/L early in the treatment course. However, although teicoplanin is only moderately nephrotoxic, the drug burden of these patients often includes several nephrotoxic drugs such as amphotericin and aminoglycosides and, in order to limit further toxicity and to meet clinicians' wishes, a more conservative combination of loading doses was chosen (800 + 400mg 12 hours apart on day 1, and 600 + 400mg 12 hours apart on day 2; figure 1) in this second group of leukaemic patients (n = 22).

Subsequently, from day 3 on, considering the higher clearance of teicoplanin and the larger interindividual variability estimated in our haematological patients (0.86 L/h, coefficient of variation [CV] of 38%) than in healthy volunteers (0.73 L/h, CV of 11%),[14] higher maintenance doses of 400mg every 12 hours were administered in order to ensure sustained C_{min} values close to 20 mg/L.

The 2 **:** 1 sample size of the high dosage (test) group and the standard dosage (control) group (n = 22 vs 11) was chosen considering that sparse data about C_{min} in haematological patients treated with standard doses of teicoplanin have recently become available in the literature[14,29] and that in this way much more information would be gathered for the high dosage group. Despite the theoretically long elimination half-life of teicoplanin due to its high plasma protein binding,[32] the total daily dosage of teicoplanin was divided into two doses with the intent of ensuring the highest possible C_{min}, since the frequent hypoalbuminaemia of leukaemic patients[33] may be responsible for both a more rapid distribution and a higher clearance of teicoplanin.

Exclusion criteria and teicoplanin sampling times were the same as for the standard dosage group, but in this group adjustment of teicoplanin therapy according to the TDM results was allowed from day 3 on with the purpose of maintaining the desired C_{min} between 20 and 30 mg/L.

This approach was based on previous clinical findings,[22,23] but it was also consistent with the

Table I. Population pharmacokinetic parameters in neutropenic patients. Data are expressed as means (% coefficient of variation)

CL (L/h)	V_c (L)	k_{12} (h^{-1})	k_{21} (h^{-1})	Reference
0.86 (38)	7.31 (16)	1.21 (20)	0.07 (43)	Present study
0.88 (43)	5.75 (33)	1.08 (34)	0.14 (30)	Lortholary et al.[14]

CL = total body clearance; $\mathbf{k_{12}}$ = transfer rate constant from central to peripheral compartment; $\mathbf{k_{21}}$ = transfer rate constant from peripheral to central compartment; $\mathbf{V_c}$ = volume of distribution of the central compartment.

principles of pharmacodynamics. Teicoplanin is a time-dependent bactericidal antibacterial whose efficacy is mainly related to the time during which plasma concentrations persist above the MIC for the bacterial aetiological agent (time > MIC).[34]

To evaluate the influence of teicoplanin therapy on renal function, at baseline and then daily, an assessment of serum creatinine concentration was performed, and CL_{CR} was estimated on the basis of the Cockcroft and Gault formula.[30] Significant reduction in renal function was defined as an increase in serum creatinine of ™0.5 mg/dL or a reduction of CL_{CR} by <30 mL/min.

Analytical Procedures

After centrifugation, plasma samples were stored frozen at 80 µC and subsequently analysed at the Institute of Clinical Pharmacology and Toxicology of the University of Udine by means of a fluorescence polarisation immunoassay (FPIA) [Opus Diagnostics, Fort Lee, NJ, USA] using a TDx analyser (Abbott, Rome, Italy).[35,36] The interday and intraday CVs of the assay were less than 10%.

Statistical Analysis

The Kolmogorov-Smirnov test was performed to assess whether data were normally or non-normally distributed. Accordingly, descriptive data were expressed as mean β SD or as median and range. Statistical analysis comparing data between groups were performed using a parametric (unpaired Student's t-test) or a nonparametric test (Mann-Whitney Rank Sum Test) for normally or non-normally distributed data, respectively, by means of SigmaStat software (SPSS Science Software GmbH, Erkrath, Germany). A value of $p < 0.05$ was required to achieve statistical significance.

Results

The characteristics of the 33 leukaemic patients involved in this study, 11 in the standard dosage group and 22 in the high dosage group, respectively, are shown in table II. No statistically significant differences in age, sex, bodyweight and albuminaemia occurred between the two groups, whereas significantly lower serum creatinine concentrations, and consequently higher estimated CL_{CR}, were observed either at baseline or in the following days in the high than in the standard dosage group.

Hypoalbuminaemia (defined as albuminaemia <3.5 g/dL) was present in 68% and 63% of patients in the high and in the standard dosage groups, respectively. Intravenous fluid load averaged 1800 and 2700 mL/day in the high and in the standard dosage groups, respectively, this difference being mainly due to the higher number of patients receiving total parenteral nutrition in the latter group.

Mean total teicoplanin dosages administered in the high and the standard dosage group, respec-

Table II. Patient characteristics at baseline. Data are expressed as means β SD

Parameter	Standard dosage (n = 11)	High dosage (n = 22)	p-Value
Age (years)	45 β 11	48 β 15	0.591
Sex (male/female)	6/5	12/10	
Weight (kg)	67.3 β 14.4	68.0 β 13.5	0.900
Albuminaemia (g/dL)	3.3 β 0.6	3.2 β 0.4	0.585
Serum creatinine (mg/dL)	0.96 β 0.22	0.67 β 0.19	<0.001
CL_{CR} (mL/min/kg)	1.34 β 0.28	1.92 β 0.65	0.008
Body temperature (µC)	38.3 β 1.1	38.2 β 0.5	0.136
Underlying disease	3 ALL, 8 ANLL	4 ALL, 18 ANLL	
Days with teicoplanin therapy	8 (8–9)[a]	6 (3–11)[a]	0.001
Concomitant antibacterials	7 piperacillin/tazobactam + amikacin; 3 ceftazidime + amikacin; 1 meropenem + amikacin	22 ceftazidime	

a Median and range.

ALL = acute lymphocytic leukaemia; **ANLL** = acute nonlymphocytic leukaemia; **CL_{CR}** = estimated creatinine clearance by means of the Cockcroft and Gault formula.

tively, were 18.4 and 12.5 mg/kg on day 1, 15.3 and 6.2 mg/kg on day 2, and 12.6 and 6.2 mg/kg/day during the maintenance period. The median days of teicoplanin therapy for the high and the standard dosage groups, respectively, were 6 and 8.

Mean β SD teicoplanin C_{max} observed after the first dose, and C_{min} observed during the overall treatment period in the two study arms, are shown in figure 2. At all TDM sampling times, teicoplanin plasma concentrations were significantly higher ($p < 0.001$) in the high than in the standard dosage group. In the standard dosage group, despite the lower average CL_{CR}, no patient presented with C_{min} of ™10 mg/L within the first 72 hours, and only 5 out of 11 (45%) exceeded this recommended threshold after 120 hours. The difference in mean estimated CL_{CR} between the standard and the high dosage groups could make comparison of these results difficult. However, since the patients in the standard dosage group had lower CL_{CR}, they would be expected to have slower elimination of teicoplanin. Despite this, most of them (10 out of 11) did not exceed the C_{min} threshold of 10 mg/L after 96 hours of repeated administration. This suggest that in the presence of higher CL_{CR}, as observed in the high dosage group, C_{min} values with standard dosages would have been even lower, further supporting the necessity for higher teicoplanin dosages.

In the high dosage group, teicoplanin C_{min} averaged ™10 mg/L within 24 hours (the percentage of patients with C_{min} ™10 mg/L was 18.2% [4/22] after the first loading dose and increased to 59.1% [13/22] after the second loading dose), and this value was achieved in all but one patient within 48 hours. In the high dosage group, C_{min} at 72 hours exceeded 20 mg/L in 45.4% of cases (10/22). In patients having a C_{min} at 72 hours of <20 mg/L and continuing with teicoplanin therapy (6/22), the daily maintenance dosage was increased to 500 or 600mg twice daily (corresponding to 13.16 and 18.75 mg/kg/day), so that C_{min} exceeded 20 mg/L in 50% (8/16) and 90% (9/10) of cases at 96 and 120 hours, respectively. On the other hand, in one patient, mainly due to a low bodyweight (47kg), the 400mg twice daily maintenance dosage of teicoplanin caused a C_{min} of 31.6 mg/L, so that the maintenance dosage was reduced to 300mg twice daily (corresponding to a reduction in dosage from 17.0 to 12.8 mg/kg/day), with the intent of enabling appropriate comparison of her teicoplanin C_{min} with those of the other patients continuing to receive twice daily administration because of hypoalbuminaemic status.

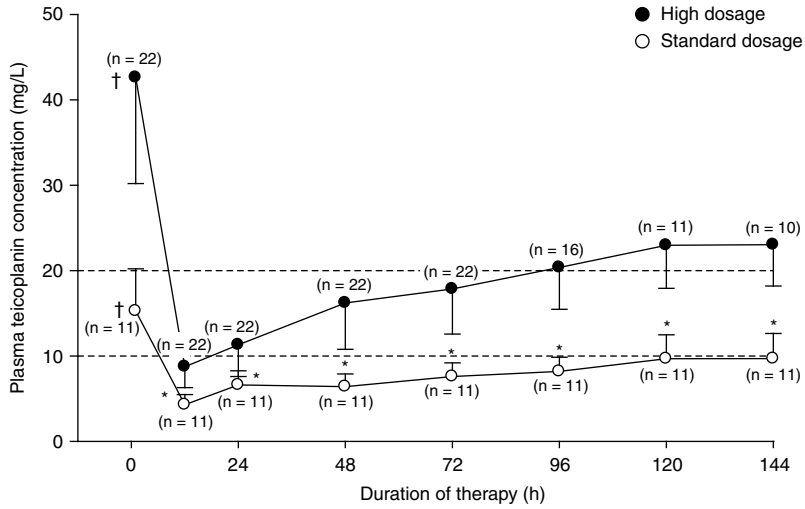

Fig. 2. Plasma teicoplanin concentrations during the overall treatment period in the standard and the high dosage groups. Values are means β SD. The horizontal broken lines show the minimum recommended trough concentration (C_{min}) for the standard of care (10 mg/L) and the suggested C_{min} for immunocompromised hosts (20 mg/L). * indicates a statistically significant difference ($p < 0.001$); † indicates peak concentration at 1 hour after the first dose.

A moderate to good inverse linear relationship between teicoplanin C_{min} and estimated CL_{CR} was observed at all the TDM sampling times in both groups (r between 0.48 and 0.67), no clear relationship between teicoplanin C_{min} and either albuminaemia or fluid load was found.

Interestingly, despite the administration of high loading doses, one patient in the high dosage group presenting with high estimated CL_{CR} of between 140 and 172 mL/min, hypoalbuminaemia of 2.6 g/dL and receiving a high daily intravenous fluid load of 15002000mL, at the end of the loading period had very low teicoplanin C_{min} (7.6 mg/L at 48 hours) which increased to therapeutically relevant concentrations (17.5 mg/L at 120 hours) only after increasing the maintenance dosage up to 600mg twice daily for 3 days (corresponding to a dosage of 18.8 mg/kg/day). This suggests that the interindividual pharmacokinetic variability of teicoplanin in this special population could not always be efficaciously predicted.

No patient in the standard or high dosage groups experienced significant renal impairment during or after teicoplanin treatment (figure 3). An appropriate evaluation of haematological adverse effects (drug-related thrombocytopenia) was not possible because of the particular setting of the studied population (presence of severe pancytopenia related to the antineoplastic chemotherapy).

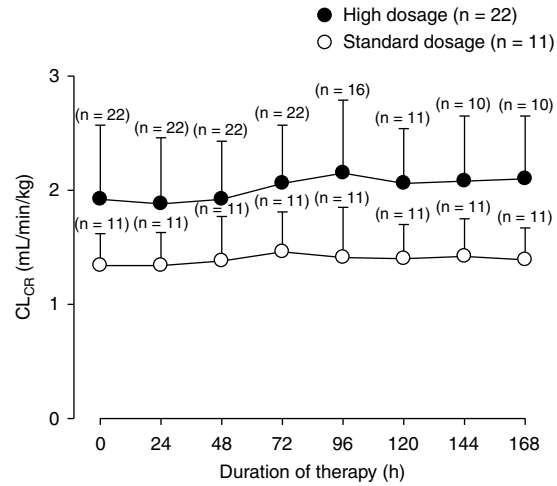

Fig. 3. Trend of estimated creatinine clearance (CL_{CR}) on the basis of the Cockcroft and Gault formula during the overall treatment period in the standard and the high dosage groups. Values are means β SD.

Discussion

Our findings suggest that in patients with acute leukaemia higher than currently recommended loading doses of teicoplanin may be appropriate in order to enable early therapeutically relevant C_{min}. Subsequently, in patients with normal renal function, higher maintenance dosages should be administered to maintain highly effective C_{min}.

The results of the standard dosage group suggest that the standard regimen of teicoplanin will lead to much lower concentrations in patients with acute leukaemia than in healthy volunteers.[37] Interestingly, comparing concentrations obtained after the first 400mg intravenous dose in our patients with those found after a single 400mg intravenous dose in our previous study in healthy volunteers,[38] even though the two groups were comparable in terms of bodyweight and estimated CL_{CR}, 12-hour C_{min} was significantly lower in acute leukaemic patients (4.3 β 1.2 versus 7.1 β 1.8, $p < 0.001$). The findings of increased population-estimated volume of distribution and clearance of teicoplanin in the standard dosage group are in agreement with no patient having the recommended C_{min} (10 mg/L) in the first 72 hours and are consistent with the suggestions of other authors that the licensed dosages of teicoplanin might be underestimated for this special population. In 11 neutropenic patients administered standard loading doses of teicoplanin, Gimenez and coworkers[29] showed that C_{min} at 48 hours ranged between 5.6 and 13.1 mg/L, and concluded that higher loading doses of teicoplanin should be administered. Likewise, in a population pharmacokinetic study carried out in patients with haematological malignancies, Lortholary et al.[14] estimated that a prolonged loading period (400mg every 12 hours for at least four doses) would have probably result in C_{min} at 48 hours of >10 mg/L in most of the patients. Of note, our study included only patients with acute leukaemia whereas these two other studies considered more heterogeneous populations with various haematological malignancies (lymphomas and multiple myeloma, other than leukaemia). This may possibly explain some differences with our findings, for example the fact that C_{min} at 48 hours was <10

mg/L in 100% of our patients versus 62% of those in Lortholary et al.[14]

Although most of the severe bacterial infections responsible for mortality in haematological patients are usually due to Gram-negative micro-organisms,[39,40] several studies reported that *S. viridans*,[41] meticillin-resistant *S. aureus*[7] and coagulase-negative staphylococci[2] may be associated with significant mortality rate in this population. Underexposure to antimicrobials in the first days of therapy may be a factor affecting successful antibacterial treatment of multiresistant Gram-positive-related infections.[23,42] In critically ill patients, breakthrough resistance to glycopeptides during treatment has been reported,[25,43-45] and also in patients with haematological malignancies the emergence of coagulase-negative staphylococci resistant more frequently to teicoplanin than to vancomycin has increasingly been pointed out.[24-26,46] Of note, for micro-organisms presenting with an MIC close to the breakpoints of susceptibility,[23] the situation may be critical since relatively low plasma concentrations of teicoplanin (in terms of actual free C_{min} > MIC), by exposure to subinhibitory concentrations, might produce selective pressure for the emergence of intermediate susceptible strains.[23,42] Accordingly, MacGowan et al.[21,22] showed that the percentage of successful outcome for teicoplanin therapy greatly increased when C_{min} of >20 mg/L was ensured in critically ill patients. Thus, our choice of teicoplanin C_{min} > 10 mg/L and close to 20 mg/L early in the treatment of these severely immunocompromised hosts may be beneficial from either a clinical or a pharmacological point of view.

The findings in the high dosage group suggest that in most patients with acute leukaemia and normal renal function a more aggressive regimen of teicoplanin (average loading doses of 12.2 and 6.1 mg/kg 12 hours apart on day 1, and of 9.2 and 6.1 mg/kg 12 hours apart on day 2, followed by a daily maintenance dosage of 6.1 mg/kg every 12 hours) may enable effective C_{min} values just exceeding 10 mg/L at 24 hours and approaching 20 mg/L at 72 hours.

Several factors causing an increase of either volume of distribution or renal clearance of teicoplanin may explain the need for an increased dosage of teicoplanin in patients with acute leukaemia. First, these patients are frequently administered a high fluid load by means of saline infusions and/or parenteral nutrition, leading to haemodilution and/or an expansion of the extracellular fluid. Consequently, in such conditions an increase in volume of distribution may be expected, particularly for those drugs presenting with a limited extracellular distribution, for example the hydrophilic antibacterials such as aminoglycosides, -lactams and glycopeptides. In a study carried out in critically ill adult patients,[47] mainly because of an expansion of extracellular water caused by parenteral nutrition and/or fluid therapy, the volume of distribution of gentamicin was shown to be increased, this leading the authors to conclude that higher doses of gentamicin are needed for patients on total parenteral nutrition. Likewise, a marked increase in volume of distribution in patients with haematological malignancies was also found for amikacin[8] and meropenem.[48] Consistently, in both our study arms, an increased volume of distribution of teicoplanin might have occurred due to the high fluid load administered to all of the patients during the overall treatment.

Secondly, leukaemic patients are frequently hypoalbuminaemic,[33] this increasing the unbound fraction of teicoplanin and enabling both a more rapid distribution and an enhanced renal clearance.[49,50] In a renal transplant patient undergoing continuous veno-venous haemofiltration, we have recently shown that hypoalbuminaemia significantly affected both distribution and elimination of teicoplanin.[51] In a recent population pharmacokinetic study on amikacin,[10] despite the negligible plasma protein binding, hypoalbuminaemia was proven to be one of the most important covariates explaining the interindividual pharmacokinetic variability in patients with haematological malignancies. Consistently, in both of our study groups, about two-thirds of the patients were hypoalbuminaemic.

Thirdly, several authors have shown that renal clearance of hydrophilic antibacterials may be substantially enhanced in patients with haematological malignancies. Fernandez De Gatta et al.[13] showed that in patients with haematological malignancies and normal renal function, due to an enhanced renal elimination of vancomycin, higher dosages (38 mg/kg/day) should be administered to guarantee therapeutic concentrations. Similar results were found by

other authors in both adult[52] and paediatric[53] haematological patients. Zeitany et al.[11] highlighted that in patients with acute leukaemia the percentage of bone marrow blast cells at the time of diagnosis significantly correlated with increased clearance of amikacin and that the required dosage to maintain therapeutic concentrations of amikacin, averaging 27.5 mg/kg/day, was almost doubled in these patients compared with healthy volunteers. Likewise, in patients with acute myeloblastic leukaemia, Romano and coworkers[10] found that amikacin clearance was increased, and that the simultaneous presence of hypoalbuminaemia required a more than 2-fold increase in the total daily dosage to enable optimal therapy with amikacin in these patients. Interestingly, these two latter studies on aminoglycoside pharmacokinetics suggest that acute leukaemia may induce some pathophysiological factor responsible for enhanced renal clearance of hydrophilic antibacterials. Among the possible explanations, we hypothesise that in these patients, at least early in the post-chemotherapy period, the enhanced renal clearance might be due to an increased glomerular filtration rate counteracting the huge renal load of protein-derived cellular catabolites derived from lysis of circulating cells. This may be consistent with protein load being shown to increase both renal blood flow and glomerular filtration rate in humans.[54] Other authors have suggested that the enhanced renal clearance observed in febrile neutropenic patients might be caused by fever and/or by the acute infectious disease, and not by the leukaemic status.[48] However, the heterogeneity of the enrolled populations in these studies, including patients with leukaemia, multiple myeloma and non-Hodgkin's lymphoma, might represent a confounding factor and explain some of the differences in our findings.

From a safety standpoint, no patient in either the standard or the high dosage groups experienced a significant impairment of renal function during or after teicoplanin treatment. This is consistent with teicoplanin being a well tolerated glycopeptide, particularly at the renal level.[15,55-58]

We recognise that our work has some limitations. First of all, patients were not randomly assigned to the two study arms, but they were enrolled during two subsequent periods at different sites. Secondly, since this was an observational study based on TDM results, extensive assessment of most classic pharmacokinetic parameters of teicoplanin was not carried out. Finally, the small number of patients observed did not enable a pharmacodynamic evaluation, even if this is a major endpoint of our forthcoming studies. Apart from these limitations, the findings generally support our conclusions.

Conclusions

At the end of the loading period in the high dosage group, we observed an average C_{min} at 48 hours of 16.2 mg/L after total daily loading doses of 18.4 mg/kg on day 1 and 15.3 mg/kg on day 2. Our findings suggest that, in patients with acute leukaemia, therapeutically relevant C_{min} values, exceeding 10 mg/L and close to 20 mg/L, may be achieved very early in the treatment period if, in the first 2 days of therapy, higher than presently recommended loading doses of teicoplanin are administered, regardless of renal function, to all patients. The suggested loading regimen is 12 mg/kg and 6 mg/kg 12 hours apart on day 1, and 9 mg/kg and 6 mg/kg 12 hours apart on day 2. Subsequently, from day 3 on, in patients with normal renal function, continuing with maintenance doses of 6 mg/kg every 12 hours may be helpful in ensuring a C_{min} close to 20 mg/L. Assessing C_{min} after 48–72 hours may be useful for the purpose of tailoring teicoplanin therapy to the individual patient. Given the high renal clearance and the frequent hypoalbuminaemia of this special population, administration every 12 hours may be helpful, from a pharmacokinetic point of view, in maintaining adequate C_{min} for the entire dosage interval.

Further clinical studies are warranted to assess the pharmacodynamics of this enhanced regimen of teicoplanin and to confirm its potential benefit in preventing the worrying emergence of staphylococci with reduced susceptibility to teicoplanin in patients with acute leukaemia.

We should emphasise that this teicoplanin regimen has been assessed for patients with acute leukaemia, and might not be suitable for patients with other haematological malignancies, such as multiple myeloma, lymphomas or myelodysplastic syndromes, due to the possible presence of quite different pathophysiological conditions. In general, to

ensure appropriate therapy, a population-tailored regimen should be defined for each single subpopulation of critically ill patients according to the special features of the particular underlying disease or pathophysiological condition. Subsequently, TDM may be helpful to ensure adequate plasma concentrations in the individual patient.

Acknowledgements

The authors have provided no information on sources of funding or on conflicts of interest directly relevant to the content of this study.

References

1. Viscoli C, Castagnola E. Treatment of febrile neutropenia: what is new? Curr Opin Infect Dis 2002; 15 (4): 377-82
2. Horvathova Z, Spanik S, Sufliarsky J, et al. Bacteremia due to methicillin-resistant staphylococci occurs more frequently in neutropenic patients who received antimicrobial prophylaxis and is associated with higher mortality in comparison to methicillin-sensitive bacteriemia. Int J Antimicrob Agents 1998; 10 (1): 55-8
3. Pagano L, Tacconelli E, Tumbarello M, et al. Bacteremia in patients with hematological malignancies: analysis of risk factors, etiological agents and prognostic indicators. Haematologica 1997; 82 (4): 415-9
4. Davies JM. A review of the use of teicoplanin in haematological malignancy. Eur J Haematol Suppl 1998; 62: 2-5
5. Egerer G, Goldschmidt H, Streich N, et al. Ceftazidime in combination with glycopeptide antibiotic is an effective first-line therapy for patients undergoing high-dose therapy with autologous peripheral blood stem cell support. Support Care Cancer 1999; 7 (5): 336-42
6. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002; 34 (6): 730-51
7. Gonzalez-Barca E, Carratala J, Mykietiuk A, et al. Predisposing factors and outcome of staphylococcus aureus bacteremia in neutropenic patients with cancer. Eur J Clin Microbiol Infect Dis 2001; 20 (2): 117-9
8. Kaojarern S, Maoleekoonpairoj S, Atichartakarn V. Pharmacokinetics of amikacin in hematologic malignancies. Antimicrob Agents Chemother 1989; 33 (8): 1406-8
9. Tod M, Lortholary O, Seytre D, et al. Population pharmacokinetic study of amikacin administered once or twice daily to febrile, severely neutropenic adults. Antimicrob Agents Chemother 1998; 42 (4): 849-56
10. Romano S, Fernandez de Gatta MM, Calvo MV, et al. Population pharmacokinetics of amikacin in patients with haematological malignancies. J Antimicrob Chemother 1999; 44 (2): 235-42
11. Zeitany RG, el Saghir NS, Santhosh-Kumar CR, et al. Increased aminoglycoside dosage requirements in hematologic malignancy. Antimicrob Agents Chemother 1990; 34 (5): 702-8
12. Nyhlen A, Ljungberg B, Nilsson-Ehle I. Pharmacokinetics of ceftazidime in febrile neutropenic patients. Scand J Infect Dis 2001; 33 (3): 222-6
13. Fernandez de Gatta MM, Fruns I, Hernandez JM, et al. Vancomycin pharmacokinetics and dosage requirements in hematologic malignancies. Clin Pharm 1993; 12 (7): 515-20
14. Lortholary O, Tod M, Rizzo N, et al. Population pharmacokinetic study of teicoplanin in severely neutropenic patients. Antimicrob Agents Chemother 1996; 40 (5): 1242-7
15. Pea F, Brollo L, Viale P, et al. Teicoplanin therapeutic drug monitoring in the critically ill patients: a retrospective study emphasizing the importance of a loading-dose. J Antimicrob Chemother 2003; 51 (4): 971-5
16. Wilson APR, Gruneberg RN, Neu H. A critical review of the dosage of teicoplanin in Europe and the USA. Int J Antimicrob Agents 1994; 4 Suppl. 1: S1-S30
17. Begg EJ, Barclay ML, Kirkpatrick CM. The therapeutic monitoring of antimicrobial agents. Br J Clin Pharmacol 2001; 52 Suppl. 1: 35S-43S
18. Schaison G, Graninger W, Bouza E. Teicoplanin in the treatment of serious infection. J Chemother 2000; 12 Suppl. 5: 26-33
19. Wilson AP. Clinical pharmacokinetics of teicoplanin. Clin Pharmacokinet 2000; 39 (3): 167-83
20. Wilson AP, Gruneberg RN, Neu H. Dosage recommendations for teicoplanin. J Antimicrob Chemother 1993; 32 (6): 792-6
21. MacGowan AP, White LO, Reeves DS, et al. A retrospective review of serum teicoplanin concentrations in clinical trials and their relationship to clinical outcome. J Infect Chemother 1998; 2: 197-208
22. MacGowan AP, Bowker KE. Pharmacodynamics of antimicrobial agents and rationale for their dosing. J Chemother 1997; 9 Suppl. 1: 64-73
23. Weinbren M, Struthers K. Emergence of Staphylococcus aureus (MRSA) with reduced susceptibility to teicoplanin during therapy. J Antimicrob Chemother 2002; 50 (2): 306-7
24. Cercenado E, Garcia-Leoni ME, Diaz MD, et al. Emergence of teicoplanin-resistant coagulase-negative staphylococci. J Clin Microbiol 1996; 34 (7): 1765-8
25. Cunningham R, Gurnell M, Bayston R, et al. Teicoplanin resistance in Staphylococcus haemolyticus, developing during treatment. J Antimicrob Chemother 1997; 39 (3): 438-9
26. Pagano L, Tacconelli E, Tumbarello M, et al. Teicoplanin-resistant coagulase-negative staphylococcal bacteraemia in patients with haematological malignancies: a problem of increasing importance. J Antimicrob Chemother 1997; 40 (5): 738-40
27. Sloos JH, Dijkshoorn L, van Boven CP. Septicaemias caused by a strain of staphylococcus haemolyticus exhibiting intermediate susceptibility to teicoplanin in multiple intensive care unit patients. J Antimicrob Chemother 2000; 45 (3): 410-1
28. Torney HL, Balistreri FJ, Kenny MT, et al. Comparative therapeutic efficacy of teicoplanin and vancomycin in normal and in neutropenic mice infected with staphylococcus haemolyticus. J Antimicrob Chemother 1991; 28 (2): 261-9
29. Gimenez F, Leblond V, Nguyen J, et al. Variations of teicoplanin concentrations in neutropenic patients. J Clin Pharm Ther 1997; 22 (3): 187-90
30. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16 (1): 31-41
31. Yamaoka K, Nakagawa T, Uno T. Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. J Pharmacokinet Biopharm 1978; 6 (2): 165-75
32. Dykhuizen RS, Harvey G, Stephenson N, et al. Protein binding and serum bactericidal activities of vancomycin and teicoplanin. Antimicrob Agents Chemother 1995; 39 (8): 1842-7
33. Eriksson KM, Cederholm T, Palmblad JE. Nutrition and acute leukemia in adults: relation between nutritional status and infectious complications during remission induction. Cancer 1998; 82 (6): 1071-7
34. MacGowan AP. Pharmacodynamics, pharmacokinetics, and therapeutic drug monitoring of glycopeptides. Ther Drug Monit 1998; 20 (5): 473-7

35. Awni WM, St Peter WL, Guay DR, et al. Teicoplanin measurement in patients with renal failure: comparison of fluorescence polarization immunoassay, microbiological assay, and high-performance liquid chromatographic assay. Ther Drug Monit 1991; 13 (6): 511-7

36. Cox H, Whitby M, Nimmo G, et al. Evaluation of a novel fluorescence polarization immunoassay for teicoplanin. Antimicrob Agents Chemother 1993; 37 (9): 1924-6

37. Outman WR, Nightingale CH, Sweeney KR, et al. Teicoplanin pharmacokinetics in healthy volunteers after administration of intravenous loading and maintenance doses. Antimicrob Agents Chemother 1990; 34 (11): 2114-7

38. Pea F, Furlanut M, Poz D, et al. Pharmacokinetic profile of two different administration schemes of teicoplanin: single 400mg intravenous dose vs double-refracted 200mg intramuscular doses in healthy volunteers. Clin Drug Invest 1999; 18: 47-55

39. Collin BA, Leather HL, Wingard JR, et al. Evolution, incidence, and susceptibility of bacterial bloodstream isolates from 519 bone marrow transplant patients. Clin Infect Dis 2001; 33 (7): 947-53

40. Sparrelid E, Hagglund H, Remberger M, et al. Bacteraemia during the aplastic phase after allogeneic bone marrow transplantation is associated with early death from invasive fungal infection. Bone Marrow Transplant 1998; 22 (8): 795-800

41. Tunkel AR, Sepkowitz KA. Infections caused by viridans streptococci in patients with neutropenia. Clin Infect Dis 2002; 34 (11): 1524-9

42. Schentag JJ. Antimicrobial management strategies for Gram-positive bacterial resistance in the intensive care unit. Crit Care Med 2001; 29 (4 Suppl.): N100-7

43. Elsaghier AA, Aucken HM, Hamilton-Miller JM, et al. Resistance to teicoplanin developing during treatment of methicillin-resistant Staphylococcus aureus infection. J Antimicrob Chemother 2002; 49 (2): 423-4

44. Hassan IA, Chadwick PR, Johnson AP. Clinical isolates of methicillin-resistant staphylococcus aureus (MRSA) with reduced susceptibility to teicoplanin in Northwest England. J Antimicrob Chemother 2001; 48 (3): 454-5

45. Fridkin SK. Vancomycin-intermediate and -resistant staphylococcus aureus: what the infectious disease specialist needs to know. Clin Infect Dis 2001; 32 (1): 108-15

46. Spanik S, Trupl J, Studena M, et al. Breakthrough nosocomial bacteraemia due to teicoplanin-resistant staphylococcus haemolyticus in five patients with acute leukaemia. J Hosp Infect 1997; 35 (2): 155-9

47. Ronchera-Oms CL, Tormo C, Ordovas JP, et al. Expanded gentamicin volume of distribution in critically ill adult patients receiving total parenteral nutrition. J Clin Pharm Ther 1995; 20 (5): 253-8

48. Nyhlen A, Ljungberg B, Nilsson-Ehle I. Pharmacokinetics of meropenem in febrile neutropenic patients: Swedish Study Group. Eur J Clin Microbiol Infect Dis 1997; 16 (11): 797-802

49. Rowland M. Clinical pharmacokinetics of teicoplanin. Clin Pharmacokinet 1990; 18 (3): 184-209

50. Pea F, Furlanut M. Pharmacokinetic aspects of treating infections in the intensive care unit: focus on drug interactions. Clin Pharmacokinet 2001; 40 (11): 833-68

51. Pea F, Brollo L, Lugano M, et al. Therapeutic drug monitoring-guided high teicoplanin dosage regimen required to treat a hypoalbuminemic renal transplant patient undergoing continuous venovenous hemofiltration. Ther Drug Monit 2001; 23 (5): 587-8

52. Le Normand Y, Milpied N, Kergueris MF, et al. Pharmacokinetic parameters of vancomycin for therapeutic regimens in neutropenic adult patients. Int J Biomed Comput 1994; 36 (1-2): 121-5

53. Chang D. Influence of malignancy on the pharmacokinetics of vancomycin in infants and children. Pediatr Infect Dis J 1995; 14 (8): 667-73

54. Cirillo M, Anastasio P, Spitali L, et al. Effects of a meat meal on renal sodium handling and sodium balance. Miner Electrolyte Metab 1998; 24 (4): 279-84

55. Charbonneau P, Harding I, Garaud JJ, et al. Teicoplanin: a well-tolerated and easily administered alternative to vancomycin for gram-positive infections in intensive care patients. Intensive Care Med 1994; 20 Suppl. 4: S35-42

56. Wood MJ. Comparative safety of teicoplanin and vancomycin. J Chemother 2000; 12 Suppl. 5: 21-5

57. Fanos V, Mussap M, Khoory BJ, et al. Renal tolerability of teicoplanin in a case of neonatal overdose. J Chemother 1998; 10 (5): 381-4

58. Sidi V, Roilides E, Bibashi E, et al. Comparison of efficacy and safety of teicoplanin and vancomycin in children with antineoplastic therapy-associated febrile neutropenia and gram-positive bacteremia. J Chemother 2000; 12 (4): 326-31

Correspondence and offprints: Dr *Federico Pea*, Institute of Clinical Pharmacology and Toxicology, DPMSC, University of Udine, P. le S. Maria della Misericordia 3, 33100 Udine, Italy.
E-mail: federico.pea@med.uniud.it