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Randomized Prospective Study Comparing Vancomycin with Teicoplanin in the Treatment of Infections Associated with Hickman Catheters

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In 72 episodes of suspected or proven Hickman-catheter-associated infection occurring in 59 patients with various hematological disorders, patients were assigned to treatment with either vancomycin or teicoplanin in a randomized nonblinded prospective study. Of 60 episodes evaluable for response, 28 were treated with vancomycin and 32 were treated with teicoplanin. Sixteen infective episodes were microbiologically documented in the vancomycin group, and twenty-one were microbiologically documented in the teicoplanin group. Microbiologically and clinically documented infections treated with vancomycin had an 80% response rate, compared with a 69% response rate for those treated with teicoplanin ($P = 0.316$). Adverse events occurred in nine (25%) of the episodes in the vancomycin group, compared with three (8%) in the teicoplanin group ($P = 0.044$). Teicoplanin may provide an effective alternative to vancomycin in the treatment of Hickman-catheter-associated infection in patients with hematological malignancies.

The use of permanent indwelling venous catheters providing easy, rapid, and repeatable venous access has become a fundamental part of patient management in hemato-oncology (1, 10, 25). The Hickman catheter is the most widely used permanent indwelling catheter in adult practice and can be used to administer chemotherapy, antimicrobial agents, and blood products as well as to sample blood. The use of the Hickman catheter and similar catheters has been associated with an increase in the incidence of infection with gram-positive organisms, with coagulase-negative staphylococci, particularly *Staphylococcus epidermidis*, predominating (2, 11, 18, 19, 26). Gram-positive organisms now account for approximately 60% of the significant blood culture isolates in our unit, in agreement with other groups (2, 12, 14, 23, 27).

A proportion of patients may also develop soft tissue infection, most frequently at the catheter exit site, with extension into the subcutaneous tunnel in some instances. Such soft tissue infections cause significant morbidity (16, 24).

Vancomycin, a glycopeptide antibiotic, is currently widely used to treat infections associated with gram-positive organisms (11, 13, 15, 27, 30). Its use, however, is associated with a clinically significant spectrum of side effects (4, 15, 20), and consequently careful supervision of drug administration and monitoring of drug levels is required.

Teicoplanin, which is also a glycopeptide antibiotic (32), has been shown to be effective in treating infections associated with coagulase-negative staphylococci (7, 17, 21, 31, 32); however, experience with the use of teicoplanin in treating Hickman-catheter-associated infections is limited (31). No prospective study has yet been performed comparing vancomycin and teicoplanin in the treatment of Hickman-catheter-associated infections in patients with hematological malignancies. The aim of this study, therefore, was to evaluate these two agents in this clinical setting.

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MATERIALS AND METHODS

Over an 18-month period, patients fulfilling the study entry criteria were prospectively randomized to receive either vancomycin or teicoplanin for the treatment of Hickman-catheter-associated infection in a nonblinded, single-center study. All patients gave written informed consent prior to entry into the study, which was approved by the local ethical committee.

Single-lumen Hickman catheters were inserted as previously described (8). The catheters were used for the administration of chemotherapy, antimicrobial agents, and blood products; for parenteral alimentation; and for sampling blood.

Classification of episodes studied. (i) Microbiologically documented infection. Infections with definite signs and symptoms of either local or systemic infection that could be microbiologically proven by cultures from blood or from the Hickman catheter exit site or tunnel were microbiologically documented infections.

(ii) Clinically documented infection. Infections with definite signs and symptoms of infection at the Hickman catheter exit site or tunnel but without microbiologic proof of the etiologic agent were clinically documented infections.

(iii) Possible infection. Infections with equivocal signs and symptoms of infection without an identifiable site and with negative microbiologic data were possible infections. Infection classification was adapted from the Antimicrobial Therapy Project Group (14).

Clinically and microbiologically documented infections were subdivided by site of infection into the following: (i) exit site infections, if inflammation was localized to within 2 cm of the catheter exit site; (ii) tunnel infections, if these signs extended a distance of greater than 2 cm from the exit site or along the subcutaneous tract of the catheter; and (iii) septicemias, if microbiologically documented bloodstream infections occurred in the absence of soft tissue infection. These criteria were adapted from those of Press et al. (24).

Possible infection was considered to be present when fever that was unresponsive to 48 h of empirical broad-

spectrum therapy with either a ureidopenicillin and an aminoglycoside or a broad-spectrum cephalosporin and an aminoglycoside occurred in patients with neither clinical nor microbiological evidence to localize the site of infection.

Entry and exclusion criteria. Pyrexia sufficient for trial entry was defined as fever of greater than 38°C measured on two consecutive occasions 2 h apart or a single spike of fever greater than 38.5°C that was not related to the administration of blood products.

Patients who were neutropenic (as defined by an absolute neutrophil count of $<0.5 \times 10^9$/liter) at the time of entry into the study or those expected to become neutropenic during the course of the study received gentamicin and piperacillin as well as the study drug.

Patients with a previous history of vancomycin allergy were excluded from the study. No patient could be entered into the study if they had received treatment for a Hickman-catheter-associated infection in the preceding 28 days. No patients entered into the study were receiving systemic prophylactic antimicrobial agents.

Investigation and treatment schedule. After randomization, full hematological and biochemical profiles, chest radiography, urinalysis, creatinine clearance tests, and pure-tone audiometry were performed. Samples for microbiologic culture were taken with a moistened swab from an area within a 2-cm radius of the exit site and from any site of inflammation along the subcutaneous tract of the catheter. Pairs of blood cultures were taken from the Hickman catheter and from peripheral veins. Exit site swabs and blood cultures were repeated after 72 h of therapy and at the end of the study. All bacteriological samples were repeated approximately 1 week after completion of treatment with the study drug. Pure-tone audiometric studies and assessments of hematological and biochemical parameters were performed at the end of the study period.

After the initial evaluation, patients were randomly assigned to receive either 1 g of vancomycin in 250 ml of normal saline infused over 2 h twice daily or teicoplanin as an intravenous bolus. The first 11 episodes in 10 patients randomized to receive teicoplanin were treated with 400 mg of teicoplanin in 10 ml of saline intravenously as a loading dose on day 1 and a 200-mg intravenous bolus once daily on following days. Subsequent episodes were treated with 800 mg of teicoplanin on day 1 and 400 mg once daily on following days. Teicoplanin levels were measured immediately before and 30 min after dose 5 and were assessed retrospectively.

Aminoglycoside dosage was adjusted to maintain a trough level of <2 μg/ml and a peak between 6 to 10 μg/ml. Vancomycin levels were measured immediately before and 1 h after the completion of the third infusion. The dose was adjusted to maintain a trough level of 5 to 10 μg/ml and peak levels between 20 and 40 μg/ml. Levels were repeated twice weekly thereafter or as otherwise indicated.

Evaluation of response. Responses to the study drugs were classified as follows.

Complete response was resolution of fever and complete resolution of soft tissue infection with eradication of the infecting organism.

Failure was lack of resolution of fever and/or progression of soft tissue infection. Removal of the Hickman catheter necessitated by progressive soft tissue infection was also deemed a study failure.

Those patients with possible infection were evaluated at 72 h for response, as unresponsive patients in this group underwent further therapeutic treatments at this stage.

TABLE 1. Patient episodes included and excluded from study analysis

Episode type	No. of episodes in:	
	Vancomycin group	Teicoplanin group
Protocol entry violation	1	4
Death before assessment	2	1
Premature termination of protocol	4	0
Evaluable episodes	28	32

Evaluation of toxicity. Mucocutaneous reactions and their relationship to drug administration were recorded. Nephrotoxicity was defined as a rise in serum creatinine of greater than 44.2 μmol/liter above the baseline value associated with treatment with the study drug and not attributable to other events or systemic hypotension (28). Hepatotoxicity was defined as rises of greater than twice the prestudy levels of bilirubin, alanine aminotransferase, and alkaline phosphatase in the absence of any other discernible cause. Hearing loss was assessed from pre- and posttreatment pure-tone audiograms.

Statistical analysis. The significance of differences between the study groups was evaluated by using the two-sample *t* test and the Fisher exact test when appropriate by using the Epistat statistical package.

RESULTS

Study population characteristics. During an 18-month period, 72 consecutive episodes of presumed Hickman-catheter-associated infection occurred in 59 patients. Seven episodes in the vancomycin group and five in the teicoplanin group were inevaluable for response, the reasons being shown in Table 1. There were two deaths in the vancomycin group and one in the teicoplanin group; all were attributable to the underlying hematological disorder.

Patients evaluable for response were equally matched for age, sex, and underlying hematological condition (Table 2). All patients had underlying hematological malignancies. There were a similar number of patients undergoing autologous bone marrow transplantation in both groups, but four patients in the teicoplanin group underwent allogeneic transplantation.

The duration of therapy with the study drug was similar for both groups, the median number of days of treatment being 7 for vancomycin and 8 for teicoplanin. Seventy-eight percent of the patients in the teicoplanin group and eighty-four percent of the patients in the vancomycin group were neutropenic at some time during the study. There was no significant difference in the duration or severity of neutropenia while on the study drug (two-sample *t* test, $P = 0.29$). Four patients in the vancomycin group and five patients in the teicoplanin group received single-agent therapy. The remainder received gentamicin and piperacillin as well as the study drug. Two patients with a history of allergy to ureidopenicillins received a broad-spectrum cephalosporin instead of piperacillin.

The distribution of infection types is shown in Table 3.

The overall outcome for each study group and outcome related to infection type are detailed in Table 4. The response rates for microbiologically and clinically documented infections were 80% for vancomycin and 69% for teicoplanin ($P = 0.316$).

The four exit site failures in the teicoplanin group were due to deteriorating soft tissue infection. Three resolved

TABLE 2. Clinical characteristics of patients evaluable for response

Characteristic	Study group	
	Vancomycin	Teicoplanin
No. of evaluable episodes	28	32
Mean age (range) (yr)	45 (26–78)	40 (17–77)
Sex (no. of males/females)	14/14	15/17
No. of patients with the following hematological disorder:		
Acute lymphoblastic leukemia	3	3
Acute myeloid leukemia	14	20
Myelodysplasia	1	0
Myeloma	1	0
Hodgkin's disease	9	7
Chronic myeloid leukemia	0	1
High-grade NHL[a]	0	1
No. of allogeneic BMT[b] patients	0	4
No. of autologous BMT patients	7	6
Median no. of days (range) of treatment	7 (5–28)	8 (4–32)
Median no. of days (range) of neutropenia	6 (5–27)	7 (4–32)
No. of patients receiving combination antimicrobial agents	24	27

[a] NHL, Non-Hodgkin's lymphoma.
[b] BMT, Bone marrow transplant.

TABLE 4. Overall responses and response by infection site

Infection type and site	No. of complete responders/no. of episodes (%) with:	
	Vancomycin	Teicoplanin
Total	20/28 (71)	21/32 (66)
Clinically documented	4/4 (100)	3/5 (60)
Microbiologically documented	12/16 (75)	15/21 (71)[a]
Possible	4/8 (50)	3/6 (50)
Exit site		
Clinically documented	4/4 (100)	3/3 (100)
Microbiologically documented	6/6 (100)	4/8 (50)[b]
Tunnel		
Clinically documented		0/2
Microbiologically documented	0/4	3/5 (60)[c]
Microbiologically documented septicemias	6/6 (100)	8/8 (100)

[a] No significant difference ($P = 0.52$) between total number of responders for clinically and microbiologically documented infections in either study group.
[b] No significant difference in outcome for all exit site infections in either group ($P = 0.055$).
[c] No significant difference in outcome for tunnel infections in each group ($P = 0.21$).

after a change in therapy (all received vancomycin) without loss of the Hickman catheter. One patient required Hickman catheter removal and a prolonged course of teicoplanin to resolve the infection. Although there was a trend for exit site infections to do less well when treated with teicoplanin, the difference did not reach significance ($P = 0.055$).

There were no responders with tunnel infections in the vancomycin group, compared with three in the teicoplanin group. The duration of treatment for tunnel infections varied from 4 to 27 days for vancomycin and from 4 to 10 days for teicoplanin. Again, there was no significant difference in outcome for tunnel infections between the two groups ($P = 0.21$).

All septicemic episodes responded to vancomycin or teicoplanin. The group treated for possible infection with vancomycin had a 50% response rate at 72 h. Of the four failures, three went on to receive amphotericin B. One patient had a subclavian vein thrombosis, and fever resolved with removal of the Hickman catheter. A 50% response rate was also seen in the group receiving teicoplanin for possible infection. Two of these failures received antifungal therapy. The other patient's fever settled with neutrophil recovery.

Two patients relapsed within 28 days of completing treatment with vancomycin for soft tissue infections. The first patient received 28 days of vancomycin for an *S. epidermidis* exit site infection, only to develop an *S. epidermidis* bacteremia 14 days after stopping the study drug. The second patient had a recurrent *Staphylococcus aureus* exit site infection after a complete response following 8 days of vancomycin.

Microbiological evaluation. Significant microbiological isolates were obtained from 16 patients in the vancomycin group and from 21 patients in the teicoplanin group. The breakdown of these isolates by species, site of isolation, and response to therapy is summarized in Table 5. Five microbiologically documented infections involved mixed organisms. The elimination rate for both groups was similar. Isolates were eliminated in 14 of 16 (87%) patients receiving vancomycin and 17 of 21 (80%) patients receiving teicoplanin. The recovery of persistent organisms was related to continuing clinically defined soft tissue infection in all cases.

Toxicity. All patients were evaluated for toxicity. Nine patients receiving vancomycin and three patients receiving

TABLE 3. Distribution of infection types by site in each study group

Infection type	No. of infections[a] with:	
	Vancomycin ($n = 28$)	Teicoplanin ($n = 32$)
Exit	10 (6)	11 (8)
Tunnel	4 (4)	7 (5)
Septicemia	6 (6)	8 (8)
Possible	8	6

[a] Number in parentheses is number of microbiologically documented infections.

TABLE 5. Microbiological isolates and relation to site of infection and outcome

Organism(s) isolated	No. of isolates (no. eliminated[a]) and source from either study group			
	Vancomycin		Teicoplanin	
	Soft tissue	Blood	Soft tissue	Blood
Coagulase-negative staphylococci	5[b] (4)	6 (6)	8 (7)	7 (7)
S. aureus	2[b] (2)	1 (1)	2[b] (2)	1 (1)
Coagulase-negative staphylococci + diphtheroids	2 (1)		3[b] (0)	1 (1)
Diphtheroid species	1[b] (1)	3 (3)		
Enterococcus species				1 (1)

[a] Remainder were all persistent isolates.
[b] Blood isolate was indistinguishable from that at exit site.

TABLE 6. Adverse reactions

Reaction	No. of episodes with:	
	Vancomycin (n = 35)	Teicoplanin (n = 37)
Severe mucocutaneous reaction	4	0
Minor skin rash	0	1
Hearing loss	0	0
Renal impairment	5	1
Hepatotoxicity	0	1

teicoplanin experienced an adverse reaction (P = 0.047). Four of these reactions in patients receiving vancomycin were deemed serious enough to necessitate a change in therapy.

The toxicity data for the two groups are summarized in Table 6. Severe mucocutaneous reactions were seen in four of the patients receiving vancomycin. They consisted of one severe anaphylactoid reaction involving bronchospasm, hypotension, and lip edema and three episodes of the "red man syndrome." Moderate renal impairment was seen in five patients from the vancomycin group and in one patient from the teicoplanin group. The maximum serum creatinine recorded was 240 μmol/liter, and renal function recovered to prestudy levels within 1 week with modification of drug dosage as appropriate. These patients had all received aminoglycosides as well as the study drug. The duration of treatment with vancomycin in the patients with renal impairment varied from 4 to 27 days. No patient receiving teicoplanin experienced a therapy-limiting adverse reaction. Of the 50 patients who had pre- and poststudy pure-tone audiometric examinations, no cases of reduced auditory acuity were detected.

DISCUSSION

This study, as far as we are aware, is the largest prospective study comparing two agents in the treatment of Hickman-catheter-associated infections. The study was carried out in a single center with consistent data collection and review.

Vancomycin has been used for the treatment of severe staphylococcal and other gram-positive infections for many years (11, 13, 15, 26, 27, 30). While vancomycin remains an extremely valuable drug, its use is associated with significant toxicity. A relatively high incidence of severe mucocutaneous reactions was seen in this study, despite great care being taken to ensure the correct preparation and rate of infusion. The incidence of mucocutaneous reactions might have been lower had a 6-hour rather than a 12-hour dosing regimen been used. Additionally, the more widespread use of chromatographically purified vancomycin preparations may further improve the toxicity profile. The incidence of nephrotoxic events in this study is comparable with that reported by Farber et al., in which vancomycin was given with an aminoglycoside (4); however, renal impairment was not therapy limiting. The etiology of the renal impairment in the patients in this study (many of whom were undergoing intensive myeloablative chemotherapy) is complex and multifactorial, but combinations of potentially nephrotoxic agents should be avoided if suitable alternatives exist.

Experience with teicoplanin is increasing (7, 17, 21, 29). Webster et al. reported 19 microbiologically documented Hickman-catheter-associated infections treated with teicoplanin (31). Although a lower dose of teicoplanin was used in their study, the response rate was encouraging. However, three early relapses were seen on discontinuing therapy. This experience is in contrast to the poor results seen in two other studies which also used low doses of teicoplanin to treat deep-seated and severe staphylococcal infections (3, 6).

Teicoplanin is well tolerated. The reported incidence of adverse reactions varies from 13.2 to 9.3% (17, 29), which is comparable with our experience. The commonest side effects are skin rashes and transient elevation of liver transaminases.

The incidences of exit site infections (43%), tunnel infections (25%), and septicemic infections (31%) in this study are comparable with those reported by Press et al. in a review of 143 similarly documented Hickman catheter infections (24).

For the lower dose of teicoplanin given to the first 10 patients in the study, the mean peak and trough teicoplanin levels were 12.9 and 5.1 μg/ml, respectively. For the higher dose administered to subsequent patients, mean peak levels increased to 21.2 μg/ml, with a trough of 5.3 μg/ml. Two of the exit site failures treated with teicoplanin occurred on the lower-dose regimen and may have been related to suboptimal teicoplanin dosage.

Septicemic episodes responded well without catheter removal as has been previously reported (9, 21, 31). For septicemic infections, the median duration of treatment was relatively short (7 days for teicoplanin and 9 days for vancomycin), and therapy was discontinued before neutrophil recovery in three patients in each group. Although this practice is controversial (9, 24), no early relapses occurred. This suggests that shorter courses of treatment may be effective in Hickman-catheter-associated septicemic infections with gram-positive organisms of low pathogenic potential in the absence of soft tissue infection. Termination of treatment before neutrophil recovery in such infections may not necessarily be associated with early clinical or microbiological relapse.

While tunnel infections appeared to do better when treated with teicoplanin, this difference was not statistically significant. These data suggest that a therapeutic trial of antimicrobial therapy is worthwhile for tunnel infections associated with coagulase-negative staphylococci and diphtheroids before Hickman catheter removal is considered.

It was of interest to evaluate the proportion of patients presenting with possible infection that could be salvaged by the addition of an antimicrobial agent specific for gram-positive organisms after failure of 48 h of empirical broad-spectrum therapy. The study is open to the criticism that a 48-h assessment time after initiating empirical therapy is early and that consequently some of the febrile episodes would have resolved without additional antimicrobial agents. This aside, 50% of such episodes resolved in each group. In only one case did this response coincide with granulocyte recovery.

It is apparent that gram-positive infections in our center are suboptimally treated by the empirical antimicrobial regimen used, as less than 30% of the gram-positive isolates in this study were susceptible to piperacillin or gentamicin. In view of the increasing proportion of such isolates seen in our center, we are now exploring the approach adopted by Karp et al. of including an antimicrobial agent specific for gram-positive organisms in the initial empirical antimicrobial regimen in febrile neutropenic patients who have a Hickman catheter in situ (11). The availability of an equally efficacious but less-toxic alternative to vancomycin that can be given once daily without monitoring levels in serum makes this policy more attractive. This strategy is not, however, uni-

versally accepted (27) and runs the risk of the possible emergence of resistant gram-positive organisms, although none was encountered during the present study.

In conclusion, teicoplanin appears to be a safe, well-tolerated alternative to vancomycin in the treatment of Hickman-catheter-associated infections in patients with hematological malignancies. Its ease of administration with subsequent savings in staff time and consumables is an advantage.

The exact timing of the introduction of specific gram-positive cover in the management of febrile episodes in the neutropenic patient with a Hickman catheter in situ but no evidence of soft tissue infection has yet, however, to be properly defined in formal prospective studies.

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