Regional Prophylaxis with Teicoplanin in Monolateral or Bilateral Total Knee Replacement: an Open Study

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From January 1991 to June 1997, patients undergoing primary elective monolateral or bilateral total knee replacement (TKR) were consecutively enrolled in a prospective, open clinical study on the efficacy and safety of regional prophylaxis with teicoplanin (TEC). Those scheduled for monolateral TKR (115 patients) received 400 mg of TEC in 100 ml of saline as a 5-min infusion into a foot vein of the leg to be operated on immediately after the tourniquet was inflated to 400 mm Hg (ca. 50 kPa). For patients undergoing bilateral surgery (45 patients), regional administration of TEC was also repeated for the second knee operation. Follow-up ranged from a minimum of 2 years to 8 years. None of the patients experienced local or systemic adverse effects following regional administration of TEC. In the immediate postoperative and 2-year follow-up periods, only one superficial infection of the primary site attributable to intraoperative contamination (prophylaxis failure) out of the 205 prostheses implanted was observed. Deep infections involving the prosthesis did not occur. Infectious complications at distant sites were observed in nine cases (urinary tract infection due to *Escherichia coli* in eight cases, and *Salmonella enteritidis* gastroenteritis in one case) in the immediate postoperative period; they all were rapidly cured after antibiotic treatment. A delayed prosthetic infection, related to hematogenous spread of the etiological agent and therefore not considered a prophylactic failure, was observed in a patient who had undergone TKR 5 years before. Regional administration of TEC in monolateral and bilateral TKR appears to be a safe and valuable prophylactic technique.

In clean prosthetic surgery, the occurrence of deep infectious complications involving the prosthetic device can be devastating, often requiring additional surgical operations (1, 5, 32, 33). Following total knee joint replacement (TKR), deep wound infection rates higher than those for total hip replacement (29) and ranging from <1 to 5% (2, 12) have been reported, depending on the presence of some individual risk factors for infection and reasons for operation. Prophylactic antimicrobial agents are therefore usually given as a standard practice in TKR (2, 11, 25).

Gram-positive cocci are the pathogens most frequently involved in infected orthopedic prostheses; staphylococci account for 75% of infections, and the leading organism is *Staphylococcus epidermidis* (12, 27). The optimal antimicrobial agent for use in total joint replacement has not yet been clearly identified (23). However, as most infections in joint prostheses are caused by staphylococci, the most widely used antibiotics are some cephalosporins and semisynthetic penicillins, by virtue of their excellent activity against the pathogens involved and their favorable pharmacokinetics and safety (7, 21, 22, 24). The preferred agents seem to be cefazolin and cefamandole (26), and multiple doses of cefazolin are presently considered by most authors to be the standard prophylaxis in clean surgical procedures, including elective orthopedic surgery (2, 3, 8, 15, 20, 23). However, methicillin-resistant (MR) coagulase-positive and -negative staphylococci are increasingly being reported as nosocomial pathogens, therefore suggesting the use of antimicrobial agents effective against these MR microorganisms in the prophylaxis for prosthetic orthopedic surgery, particularly in hospitals in which there is high resistance among these nosocomial pathogens (11, 12).

Teicoplanin is a glycopeptide antibiotic available in Europe which displays activity against aerobic and anaerobic gram-positive bacteria, including MR staphylococci. MICs ranging from 0.5 to 1 mg/liter and from 2 to 4 mg/liter have been reported for *Staphylococcus aureus* and for coagulase-negative staphylococci, respectively, irrespective of the susceptibility of these organisms to methicillin (13). Because of its long half-life (45 to 70 h) (4), teicoplanin can be administered once daily and has been shown to be safe and effective in the treatment of bone and joint infections (4, 16, 17). Following intravenous bolus administration of a single 400-mg dose, concentrations likely to be inhibitory to susceptible bacteria have been observed in bone samples (31). Lower levels are achieved in fat (9, 31). Finally, in four comparative trials on prosthetic joint implant surgery, single-dose teicoplanin was found to have efficacy and safety equivalent to those of multiple-dose cephalosporin (cefazolin, cefamandole, or cefuroxime) regimens (26).

The standard surgical technique of TKR requires the use of a tourniquet which completely occludes systemic circulation during the time of surgery, thus preventing further antibiotic penetration from arterial blood into leg tissues. In monolateral and bilateral TKR procedures, we found in a previous study (6) that the injection of 400 mg of teicoplanin into a foot vein of the leg to be operated on after complete occlusion of the systemic circulation (regional prophylaxis) seems to be a safe and valuable prophylactic procedure. Indeed, it provides concentrations in tissues (skin, subcutaneous tissue, bone, and synovia) in the operative field which are 2 to 10 times higher than those achievable by injecting 800 mg of the same antibi-

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otic into an arm vein before application of the tourniquet (systemic prophylaxis).

A prospective, open, noncomparative study was therefore planned in order to define the efficacy and safety of regional prophylaxis with teicoplanin in monolateral and bilateral TKR.

(A preliminary report of this study has been presented previously [F. de Lalla, R. Viola, G. P. Pellizzer, A. Rigon, V. Dal Pizzol, P. Macchi, P. Fabris, and C. Stecca, Abstr. 34th Intersci. Conf. Antimicrob. Agents Chemother., abstr. K3, 1994].)

MATERIALS AND METHODS

From January 1991 to June 1997, patients of both sexes admitted to Center for Knee Surgery, Sandrigo Hospital, Vicenza, Italy, undergoing elective monolateral or bilateral TKR were consecutively enrolled in a prospective, controlled, open clinical study. Exclusion criteria were as follows: history of allergic reactions to glycopeptides, local or systemic infection, treatment with antibiotics within the previous 2 weeks for any proven or presumed infection, renal insufficiency (serum creatinine of >1.6 mg/dl), and previous surgery of the same knee joint. Liver function tests were in the normal range for all subjects prior to surgery (aspartate transaminase, <40 U/liter; alanine transaminase, <45 U/liter; bilirubin, <1.2 mg/dl). Confidential informed consent for the regional administration of prophylaxis was obtained from all subjects. Teicoplanin, 400 mg in 100 ml of saline, was infused over 5 min into a foot vein of the leg to be operated on immediately after the tourniquet was inflated. In those patients scheduled for bilateral operation, regional administration of teicoplanin at the same dosage was repeated for the second knee operation. In both monolateral and bilateral TKR, patients did not receive any concomitant oral or parenteral antibiotic prophylaxis.

The tourniquet was inflated to 400 mm Hg (ca. 50 kPa) for all patients (after the limb was exsanguinated by elevation) immediately before the infusion of teicoplanin and was kept in place for the duration of surgery.

In all cases the operation was performed by the same surgical team (four surgeons) in the same conventional operating room (without laminar flow). The skin in the operative field was shaved using a disposable razor and was cleaned with antiseptic soap just before the patient entered the operating room. An alcoholic solution of povidone-iodine was then applied for 5 min.

Patients were carefully monitored in the postoperative period according to previously published guidelines (12). Briefly, infections within the primary operative incision and/or implanted prosthesis or adjacent bone, as well as any drainage procedure or debridement for infection at the operative site or in and around the prosthesis, were considered failures of prophylaxis. Distant-site infection, such as respiratory tract infection (clinical signs of infection or production of mucous or purulent sputum and radiological signs of infection) and urinary tract infection (clinical signs and symptoms confirmed by at least one positive [>10^5 CFU/ml] culture of clean-catch midstream urine) was also monitored but was not recorded as failure of prophylaxis (12). Febrile morbidity, defined as axillary body temperature of ≥38°C of unknown origin in combination with a lack of clinical symptoms on at least two consecutive measurements at least 6 h apart beyond 48 h after operation, was also monitored. Finally, the use of anti-infective drugs over 1-year period following the surgical procedure was recorded, and any unexplained use of these drugs was regarded as failure of prophylaxis.

A minimum 2-year follow-up was planned. Patients were clinically checked 15 days after discharge from the hospital and then after 1, 2, 4, 6, and 12 months during the first postoperative year; afterwards, they were interviewed by telephone, and clinically checked when necessary, at 6-month intervals.

Statistical analysis of the results was done on a personal computer with the SAS statistical package (SAS Institute, Cary, N.C.).

RESULTS

In the period of the study, 218 patients underwent either monolateral or bilateral TKR, for a total of 277 prostheses implanted. Fifty-eight patients undergoing monolateral (44 patients) or bilateral (14 patients) implantation, for a total of 72 prostheses implanted, were excluded due to one of the following: they had been given antibiotics within 2 weeks prior to surgery (8 patients), had received different dosages of teicoplanin (6 patients), or were undergoing knee reimplantation instead of a primary knee replacement (44 patients). A total of 160 subjects were therefore enrolled. Of these, 115 underwent monolateral TKR and 45 underwent bilateral TKR, for a total of 205 prostheses implanted. All of these 160 patients could be evaluated for both efficacy and safety of teicoplanin prophylaxis. Indeed, none of the eligible patients refused regional prophylaxis.

TABLE 1. Demographic characteristics of the patients, indications for surgery, and operative information

Characteristic	Value
No. (%) of patients enrolled	
Total	160 (100)
Female	141 (88)
Males	19 (12)
Age (yr)	
Mean ± SD	70.4 ± 5.6
Range..	41–89
No. (%) of patients undergoing:	
Monolateral TKR	115 (71.9)
Bilateral TKR..............................	45 (28.1)
Total no. of prostheses implanted	205
No. (%) of patients with indication for surgery:	
Osteoarthrosis.............................	152 (95)
Reumathoid arthritis	6 (3.5)
Other	2 (1.5)
Duration of surgery (min)	
Mean ± SD	150 ± 34
Range..	60–270
No. (%) of patients with anesthesia types:	
General......................................	31 (81.8)
Spinal..	29 (18.2)
Drainage tube (no. of prostheses).........	205
Mean duration of use (days).............	2
Range (days)...............................	1–5
No. (%) of patients undergoing blood transfusion (packed red blood cells)............	132 (82.5)

The demographic characteristics of the patients, the indication for surgery, and some operative information (such as the type of anesthesia, the mean duration of surgery, the use of drainage tubes, and the administration of blood transfusions) are reported in Table 1.

None of the patients experienced adverse effects following regional teicoplanin administration, either during or after surgery.

Deep infections involving the prosthesis did not occur in either the immediate postoperative period or over the 2-year follow-up period. A superficial infection of the II b type (12) which required surgical drainage and antibiotic treatment was observed in a 74-year old female without any particular risk factor for infection (such as diabetes mellitus, obesity, or concurrent corticosteroid therapy) who underwent primary monolateral total knee arthroplasty for osteoarthrosis. On the 6th postoperative day she presented fever (38°C), purulent discharge in the operative incision with local pain, a high C-reactive protein level, and leukocytosis. Surgical drainage and systemic antibiotic therapy (teicoplanin [600 mg once daily] plus amikacin [1,000 mg once daily] for 1 week) were successfully performed, leading to uneventful recovery. Involvement of the prosthesis or adjacent bone did not occur in the course of subsequent 3-year follow-up. Wound swabs were cultured, yielding negative results. Infectious complications at distant sites were observed in nine cases in the immediate postoperative period: urinary tract infections (due to *Escherichia coli*) in eight cases and gastroenteritis due to *S. enteritidis* in one case.

These patients were rapidly cured with either norfloxacin (for urinary tract infection) or trimethoprim-sulfamethoxazole (for salmonellosis). Finally, the 29 patients (14.2%) who had exhibited febrile morbidity were given symptomatic treatment solely, and in no case was unexplained use of anti-infective drugs in the 1-year period following TKR registered.

Patients were followed-up for 2 years (17 prostheses implanted), 3 years (46 prostheses), 4 years (36 prostheses), 5 years (39 prostheses), 6 years (23 prostheses), 7 years (30 prostheses), and 8 years (14 prostheses). In the long-term follow-up period (from 2 to 8 years) a deep prosthetic infection, which required removal of the implant and replacement by another prosthesis, was observed. This complication was caused by a methicillin-sensitive *S. aureus* strain and occurred in a 65-year-old female who had undergone primary bilateral TKR 5 years before.

DISCUSSION

Prophylactic antibiotics are an essential component of successful surgery for total joint replacement. Their usefulness has recently been stressed by a meta-analysis of four randomized controlled clinical trials comparing prophylactic antimicrobial administration with either a placebo or no prophylaxis (10). The optimal duration of prophylaxis in joint replacement procedures, however, is still debatable. The efficacy of single-dose cephalosporin as a prophylactic regimen is uncertain (10), although single-dose prophylaxis with long-half-life agents appears to be reasonable: in four comparative randomized studies, single-dose teicoplanin was found to have efficacy and safety equivalent to those of multiple-dose cephem antibiotic (cefazolin, cefamandole, or cefuroxime) regimens in the prevention of infection following total hip replacement or TKR (28, 30; R. A. B. Mollan, C. H. Webb, and M. Haddock, Program Abstr. 7th Eur. Congr. Microbiol. Infect. Dis., abstr. 758, 1995; P. Periti, G. Stringa, T. Mazzei, E. Mini, and P. Dentico, Abstr. 34th Intersci. Conf. Antimicrob. Agents Chemother., abstr. K4, 1994).

At present, teicoplanin is not considered a first-choice drug for prophylaxis of joint prosthetic surgery. Nevertheless, it displays a good spectrum of activity against primary pathogens responsible for postoperative infection in orthopedic surgery and particularly against both methicilin-sensitive and MR staphylococci, which are the most commonly isolated pathogens in postoperative infectious complications following joint replacement. Teicoplanin can, therefore, be regarded as a reasonable alternative choice whenever an antibiotic that is highly effective against MR staphylococci is required (11), such as in a department with higher risk of nosocomial infections and/or an increased incidence of infection due to MR bacteria (19).

The results of this study on the efficacy and safety of regional prophylaxis seem very favorable: neither local nor systemic adverse effects of regional teicoplanin administration were observed, and the overall rate of infection recorded was similar to or lower than those previously reported for total knee arthroplasty with conventional prophylactic regimens (14, 18). During a mean follow-up period of 4.7 years (ranging from a minimum of 2 to 8 years), only one superficial infection of the primary site and no deep infection attributable to intraoperative contamination were seen out of 205 prostheses implanted. The delayed prosthetic infection observed in a patient who had undergone TKR 5 years before should, indeed, be regarded as hematogenous (12) and not related to prophylactic failure, since the occurrence of late-onset, hematogenous infection of joint prostheses is not influenced by any prophylactic antibiotic regimen given at the time of implantation. This leads to a

99.5% success rate (confidence interval, 98.56 to 100%) of regional prophylaxis, which is certainly above the 95% success rate fixed by the guidelines published previously (12) for the lower end of the confidence interval.

(The power of the study is twice that recommended in the quoted guidelines (12), with 205 implants of prostheses having been studied. At our institution, prior to the use of regional prophylaxis, infection rates ranging from 1 to 1.5% for deep infection and from 1 to 2% for superficial infection following TKR procedures were observed, with a three-dose cefazolin prophylactic regimen administered by the systemic route.)

In monolateral TKR, a high local concentration of antibiotics (especially in the subcutaneous tissue) ensured during surgery by use of the regional route appears to be essential for the prevention of infection, since postoperative infection usually begins in the operative field. Furthermore, the levels of teicoplanin in serum, which during surgery are very low and sometimes undetectable, rise within a few minutes after the tourniquet is released at the end of the surgical procedures (6). The high concentrations of teicoplanin in the serum appear to be sufficient to prevent infection from an occasional bacteremia during the immediate postoperative period.

In conclusion, the results of the present study indicate that in monolateral and bilateral TKR, regional administration of 400 mg of teicoplanin after complete occlusion of the systemic circulation of the leg to be operated on appears to be a safe and valuable prophylactic technique. Apart from providing concentrations of antibiotic in the operative field higher than those achievable by conventional systemic prophylaxis, regional prophylaxis was found to ensure a rate of postoperative infection similar to those achievable with conventional prophylactic regimens. Prospective, randomized trials comparing regional and systemic prophylaxis in larger number of patients could better define the role of this new route of administration of prophylactic drugs in TKR.

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