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Regional and Systemic Prophylaxis with Teicoplanin in Monolateral and Bilateral Total Knee Replacement Procedures: Study of Pharmacokinetics and Tissue Penetration

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Twenty-four patients undergoing monolateral or bilateral total knee replacement (TKR) procedures were randomized to receive teicoplanin (T) either systemically or regionally. Subjects scheduled for systemic prophylaxis and undergoing monolateral (six patients) or bilateral (five patients) TKR received a single 800-mg dose of T in 100 ml of saline as a 5-min infusion into a forearm vein 2.5 h before surgery. For regional prophylaxis, patients undergoing monolateral surgery (eight subjects) received 400 mg of T 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. For the five patients scheduled for bilateral operation and regional prophylaxis, the administration of T was also repeated for the second knee operation. The tourniquet, as the standard TKR surgical technique, was inflated to 400 mm Hg (c. 50 kPa) in all 24 patients immediately before the beginning of surgery and kept in place for the duration of the operation. Samples of serum, bone, skin, synovia, and subcutaneous tissue were collected at timed intervals during surgery. They were microbiologically assayed for T by using *Bacillus subtilis* as the test organism. Overall, the mean T concentrations obtained with regional route prophylaxis were found to be 2 to 10 times higher than those achieved following systemic prophylaxis. Moreover, peak levels in different tissues after regional prophylaxis were significantly higher ($P < 0.05$). None of the patients experienced adverse effects due to regional or systemic T administration; no prosthetic or wound infections were observed in the follow-up period (from 12 to 26 months).

In total hip or knee joint replacement (TKR), deep wound infection rates ranging from <1 to 5% (2, 7) have currently been reported, depending on the presence of some individual risk factors for infection and reasons for the operation. Although for the standard primary replacement procedure the risk of infection is at present low, the consequences of infection can be disastrous. Prophylactic antimicrobial agents are therefore considered essential for successful surgery and are usually given as a standard practice in total hip replacement or TKR (2, 6, 13).

The pathogens most frequently involved in infected orthopedic prostheses belong to aerobic gram-positive cocci; staphylococci account for 75% of infections, and the leading organism is *Staphylococcus epidermidis* (7).

The optimal antimicrobial agent for use in total joint replacement has not been clearly identified (12). Cefazolin or oxacillin is commonly administered as an antistaphylococcal agent (2). However, methicillin-resistant (MR) staphylococci are increasingly being reported. Therefore, the use of antimicrobial agents effective against these MR microorganisms has also been suggested for prophylaxis of prosthetic orthopedic surgery, especially in hospitals in which there is high resistance among these nosocomial pathogens (6, 7).

Teicoplanin is a glycopeptide antibiotic recently marketed in Europe for the treatment of infections due to 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 for *Staphylococcus aureus* and coagulase-negative staphylococci, respectively, have been reported, irrespective of the susceptibility of these organisms to methicillin (8). Because of its long half-life (45 to 70 h) (3), teicoplanin can be given once daily and has been shown to be safe and effective in the treatment of bone and joint infections (3, 10, 11). Following bolus administration of a single 400-mg intravenous dose, concentrations likely to be inhibitory to susceptible bacteria have been reported in bone samples (17). Lower levels are achieved in fat (5, 17).

The 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.

Since 1908, it has been recognized that the injection of drugs into a vein of a limb isolated by a tourniquet (regional route) provides higher concentrations in the limb's tissues than those achievable by administering the same drugs systemically (1). Furthermore, Hoddinott et al. (9) recently demonstrated that in monolateral TKR regional administration of prophylactic cefuroxime into a foot vein is effective in achieving and maintaining concentrations in bone and fat significantly higher than those obtained by giving a larger dose of a similar cephalosporin (cefamandole) by systemic injection to the same patients.

The penetration mechanisms from the venous compartment to the tissues in a limb to which systemic circulation is completely interrupted have not been fully clarified (9, 14). Nevertheless, the potential advantages of regional route

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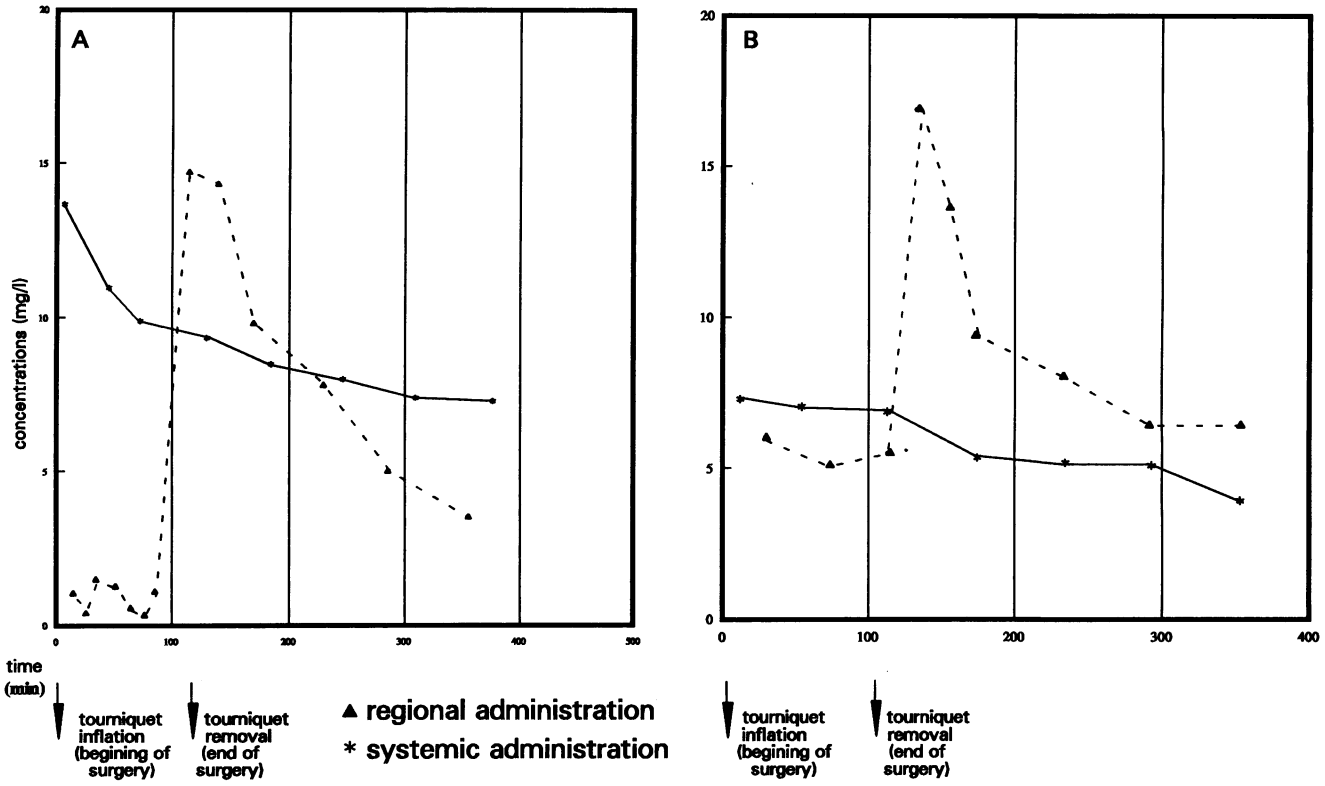

FIG. 1. Mean concentrations of teicoplanin in serum in monolateral and first of bilateral TKR (A) and second of bilateral TKR (B) following administration of teicoplanin by regional (400 mg) (for each prosthetic implantation in bilateral surgery) or systemic (800 mg as single dose) route. Samples were taken during surgery and up to 4 h after the operation.

prophylaxis in TKR are the higher and more-sustained levels of the antimicrobial agent in tissue at the site of operation and/or the reduced amount of prophylactic antibiotic to be given.

The purpose of this study was to compare teicoplanin levels in serum and tissues with administration by either the systemic or regional route as a prophylaxis in monolateral and bilateral TKR.

(A preliminary report of this study has been presented previously [4]).

MATERIALS AND METHODS

Study population. From January 1991 to February 1992, 24 patients (mean age ± standard deviation, 69 ± 6 years; 4 males and 20 females) undergoing elective monolateral (14 subjects) or bilateral (10 subjects) TKR, for disabling chronic degenerative joint disease, under general anesthesia, were enrolled. Renal function (serum creatinine, <1.2 mg/dl) and liver function (aspartate transaminase, <40 U/liter; alanine transaminase, <45 U/liter; bilirubin, <1.2 mg/dl) were in the normal range for all subjects prior to surgery. No patient had received any antimicrobial agent during the week before surgery. Confidential informed consent was obtained from all subjects for the random administration of teicoplanin prophylaxis either by the regional or systemic route. Teicoplanin, 800 mg in 100 ml of saline, was infused over 5 min into a forearm vein as a single-dose prophylaxis in 11 patients (8 females and 3 males; mean age, 70 ± 6 years; mean weight, 71 ± 9.5 kg; and mean height, 165 ± 5 cm)

TABLE 1. Concentrations (milligrams per liter) of teicoplanin in serum at the end of surgery (after tourniquet removal)

Monolateral and 1st of bilateral TKR prophylaxis				2nd of bilateral TKR prophylaxis			
Regional (n = 13)		Systemic (n = 11)		Regional (n = 5)		Systemic (n = 5)	
Observation time (min)	Mean concn ± SD	Observation time (min)	Mean concn ± SD	Observation time (min)	Mean concn ± SD	Observation time (min)	Mean concn ± SD
10.3 ± 0.7	14.7 ± 5.6	9.9 ± 0.3	9.3 ± 3.5	9.7 ± 0.5	16.9 ± 4.0	11.2 ± 2.4	5.6 ± 1.4
34.7 ± 14.6	14.3 ± 1.2	ND[a]	ND	26.5 ± 5.5	13.6 ± 5.1	ND	ND
64.5 ± 4.7	9.8 ± 4.0	66.3 ± 8.9	8.5 ± 3.9	62.3 ± 5.2	9.4 ± 4.4	59.8 ± 0.4	5.4 ± 1.6
122.0 ± 5.9	7.8 ± 4.1	125.0 ± 8.7	8.0 ± 3.5	121.9 ± 6.5	8.0 ± 3.3	120.0 ± 1.3	5.2 ± 1.0
178.2 ± 10.9	5.0 ± 1.9	186.0 ± 13.3	7.4 ± 2.1	178.8 ± 3.7	6.4 ± 3.4	180.0 ± 0.6	5.1 ± 1.1
248.6 ± 15.9	3.5 ± 1.6	252.7 ± 17.9	7.3 ± 2.1	241.0 ± 1.7	6.4 ± 3.0	240.0 ± 0.6	3.9 ± 1.0

[a] ND, not determined.

TABLE 2. Mean concentrations (milligram per kilogram) of teicoplanin in skin, subcutaneous tissue, bone, and synovia with monolateral bilateral TKR following the administration of 400 mg of teicoplanin by regional route or 800 mg by systemic route

TKR type and sample	Regional administration				Systemic administration				
	Time (± SD) (min)	No. of samples	Mean (± SD)	95% CI[a]	Time (±SD) (min)	No. of samples	Mean (± SD)	95% CI	P[b]
Monolateral and 1st of bilateral									
Skin	17 (4.2)	10	7.1 (3.6)	4.2–10.0	6 (2.8)	9	1.0 (0.7)	0.3–1.7	
	49 (8.5)	8	8.0 (4.8)	3.3–12.6	39 (7.1)	6	1.0 (0.5)	0.4–1.6	0.003
	68 (6.1)	9	7.9 (4.6)	3.9–11.8	65 (7.8)	6	2.0 (0.9)	0.8–3.2	
	104 (20.4)	12	8.2 (4.3)	5.2–11.2	110 (14.1)	6	1.4 (0.7)	0.4–2.3	
Subcutaneous tissue	16 (3.7)	7	11.1 (4.3)	6.5–15.8	6 (2.7)	8	1.4 (1.0)	0.5–2.4	
	44 (9.3)	8	12.8 (11.0)	2.2–23.3	43 (9.2)	8	1.8 (0.9)	0.9–2.6	0.000
	69 (5.8)	6	14.6 (3.8)	9.8–19.4	65 (4.0)	6	2.3 (1.1)	0.9–3.8	
	101 (16.3)	13	18.6 (6.9)	14.0–23.2	95 (19.4)	4	2.2 (1.2)	−0.3–4.7	
Bone	17 (3.5)	8	7.5 (4.4)	3.3–11.7	6 (2.9)	10	2.5 (2.0)	0.8–4.1	
	42 (8.7)	9	9.0 (4.3)	5.3–12.8	39 (7.7)	6	2.2 (0.8)	1.2–3.2	0.000
	69 (5.1)	8	9.2 (4.1)	5.3–13.1	59 (3.3)	3	2.2 (0.8)	0.2–4.3	
	101 (23.3)	5	12.7 (4.6)	5.5–19.8	90 (10.0)	2	1.3 (0.2)	−1.9–4.6	
Synovia	17 (4.7)	8	13.3 (10.2)	3.6–23.0	6 (2.9)	9	2.8 (0.9)	2.0–3.6	
	43 (9.4)	5	9.1 (1.5)	6.7–11.4	43 (8.3)	8	2.8 (1.0)	1.9–3.8	0.034
	83 (11.5)	6	14.3 (5.6)	7.2–21.3	93 (22.5)	2	2.9 (0.4)	−4.3–10.1	
2nd of bilateral									
Skin	21 (8.2)	15	4.1 (1.3)	2.0–6.2	6 (3.0)	5	1.6 (0.8)	0.3–2.8	
	71 (9.8)	5	9.4 (5.7)	0.5–18.2	42 (13.3)	4	3.0 (1.4)	−0.1–6.0	0.047
	110 (9.9)	4	7.1 (4.1)	−1.6–15.9	100 (27.4)	4	2.5 (0.9)	0.5–4.5	
Subcutaneous tissue	25 (9.6)	5	5.1 (2.4)	1.4–8.8	7 (3.8)	5	1.9 (0.4)	1.3–2.5	
	72 (7.6)	4	7.3 (2.7)	1.6–13.6	50 (15.2)	6	3.0 (1.9)	0.6–3.5	0.006
	100 (15.8)	5	14.4 (7.7)	2.5–26.3	107 (27.4)	4	2.7 (0.8)	1.0–4.3	
Bone	21 (5.6)	3	3.9 (0.8)	0.8–7.1	7 (2.5)	5	2.1 (0.9)	0.7–3.5	
	50 (17.9)	4	15.4 (7.5)	−0.5–31.3	45 (13.3)	4	1.8 (1.2)	−0.7–4.3	0.007
	103 (13.1)	3	8.8 (3.7)	−5–22.7					
Synovia	22 (7.8)	5	9.7 (5.1)	0.7–18.7	7 (2.7)	4	2.7 (0.9)	0.7–4.6	
	100 (13.7)	4	21.1 (9.1)	1.8–40.5	43 (13.2)	4	4.1 (1.8)	0.3–7.9	0.011

[a] CI, confidence interval.
[b] By Student's unpaired *t*-test.

scheduled for systemic prophylaxis and undergoing monolateral (6 patients) or bilateral (5 patients) TKR. Thirteen subjects (12 females and 1 male; mean age, 68.5 ± 5.6 years; mean weight, 72.6 ± 7 kg; and mean height, 164.5 ± 4.5 cm), 5 undergoing bilateral TKR and 8 undergoing monolateral TKR, were scheduled for regional prophylaxis. They received 400 mg of teicoplanin 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. In those patients scheduled for bilateral operation and regional prophylaxis, the administration of teicoplanin was repeated for the second knee operation.

The tourniquet was inflated to 400 mm Hg (c. 50 kPa) in all patients (after the limb was exsanguinated by elevation) immediately before the administration of teicoplanin when the drug was administered regionally and at 2.5 h after teicoplanin infusion in those patients who received systemic prophylaxis. The tourniquet was kept in place for the duration of surgery.

Blood samples from an arm vein were collected before teicoplanin administration as well as every 10 to 15 min during the operation while the tourniquet was in place and then at 10 min and every 1 h up to 4 h after the end of surgery and the tourniquet had been released. Samples of skin, subcutaneous tissue, bone, and synovia from the operative field were obtained every 10 to 20 min during the operation. Tissue specimens which appeared to be highly contaminated with blood were discarded; bone specimens were sampled either from the tibial plate or from femoral condyles.

Laboratory procedures. Venous blood samples were kept at 4°C before being processed; serum was separated within 1 h. Tissue samples were rinsed with sterile saline to remove excess blood within minutes of removal and then dried. Soft tissues were weighed, diluted 1:1 (wt/vol) in sterile normal saline (pH 6.3), homogenized with a Polytron PT 10-35 Homogenizer (Kinematica, Lucerne, Switzerland), and centrifuged at low speed, and the supernatant was used for the assay. Bone specimens (cortical and cancellous bone) were dissected free of muscle and blood vessels, scraped free of marrow, and rinsed in saline to remove excess blood. Bone samples were weighed, crushed to fine powder with a grinder, extracted in sterile normal saline, and homogenized in the same manner as soft tissues. Hemoglobin levels in tissue homogenates were determined spectrophotometri-

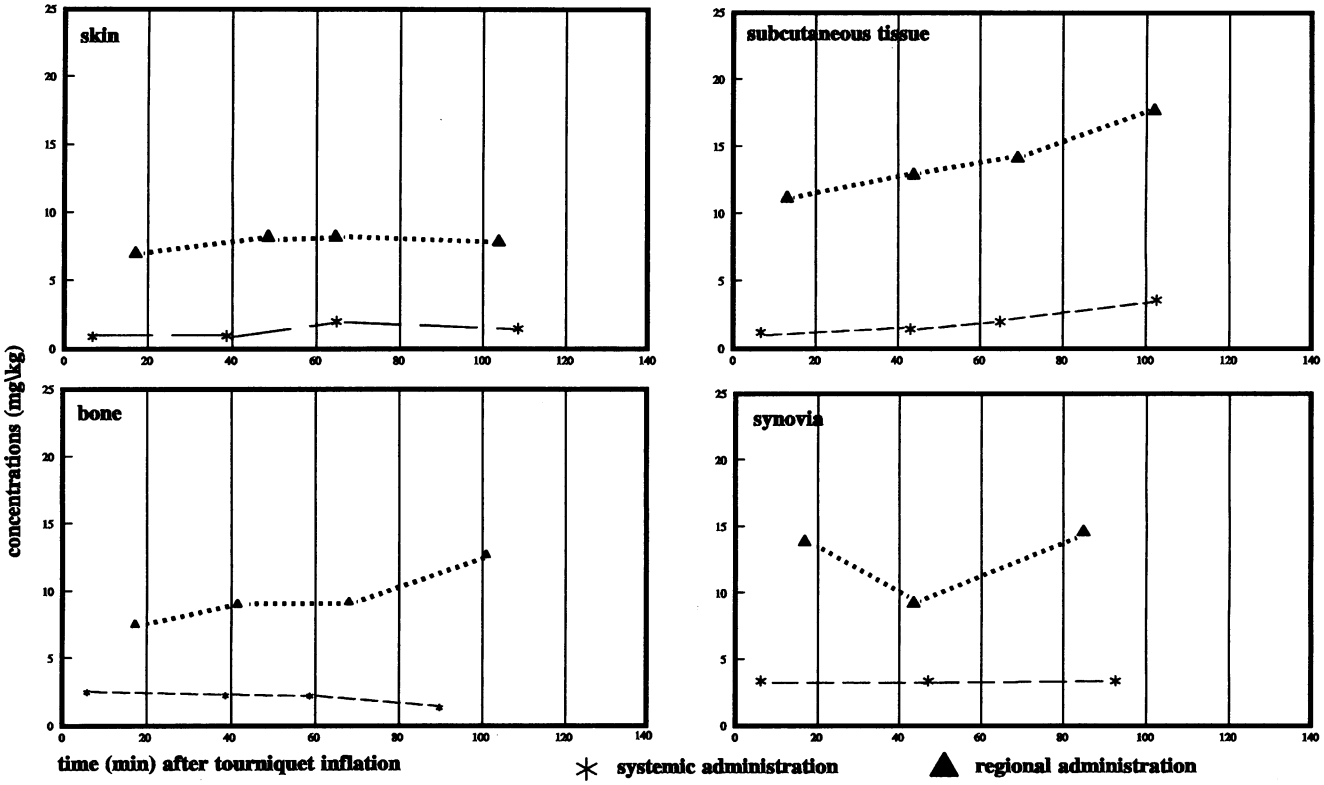

FIG. 2. Mean concentrations of teicoplanin in skin, subcutaneous tissue, bone, and synovia samples following the administration by regional (400 mg) or systemic (800 mg) route. Samples were taken during monolateral TKR and the first of bilateral TKR.

cally at 540 nm by measuring methemoglobin derived from hemoglobin oxidation by potassium ferricyanide (15), and teicoplanin concentrations in tissue were corrected for blood contamination. Serum and tissue samples were stored at −80°C until assayed. Standards with final concentrations of 16, 12, 8, 6, 4, 3, 2, 1, 0.75, 0.5, and 0.25 mg/liter were prepared daily in pooled human serum for blood samples and in normal saline (pH 6.3) for tissue specimens. Teicoplanin concentrations in serum and tissue were determined in triplicate by a standard large-plate agar diffusion technique, with Antibiotic Medium 8 (Difco) (final pH 5.9) and *Bacillus subtilis* ATCC 6633 as the test organism, with a lower limit of sensitivity of 0.5 mg/liter (16). The seeded medium was poured into plates (25.0 by 13.7 cm), set up horizontally on leveled supports, and allowed to harden. Thirty-two wells (diameter, 6 mm) were punched at equal distances, according to a preestablished pattern. Plates were incubated overnight at 35°C in air, and the inhibition zone diameter was determined to the nearest 0.2 mm with a caliper. Best-fit standard curves were obtained by linear regression analysis. The linearity between 0.5 and 16 mg/liter was Log Y = 0.18 × −1.76, r = 0.99 (where Y is the concentration in milligrams per liter) for serum samples, and Log Y = 0.14 × −1.31, r = 0.99 for tissues. Intra-assay precision ranged from 4.2 to 7.5%, with a deviation of measured values from nominal concentrations between −3.4 and 5%, for serum and from 2.9 to 7.5%, with a deviation of −2 to 6%, for tissues samples. Interassay precision at a level of 2 mg was 4.2 and 2.9% for serum and tissues, respectively.

Statistics. Statistical analysis of the results was done on a personal computer with the SAS statistical package (SAS Institute, Cary, N.C.). Means, standard deviations, and the 95% confidence limits were calculated for the teicoplanin concentrations in the different samples. Different tissue and serum samples were pooled according to timed intervals of collection. Comparison of the mean peak levels of teicoplanin in the different tissues after systemic or regional administration was done (Student's unpaired t-test). Data related to the first of the bilateral joint replacement were pooled with those of monolateral surgery. Thus, the number of samples analyzed for the second joint implantation are fewer than those related to the monolateral and to the first of bilateral TKR.

RESULTS

None of the patients experienced adverse effects due to regional or systemic teicoplanin during and after surgery.

No prosthetic or wound infections were reported in the immediate postoperative or 1-year follow up. The mean duration of surgery (± standard deviation) was 113 min (± 30) min (range, 73 to 178 min).

The mean concentrations (milligrams per liter) of teicoplanin in serum following either systemic or regional prophylaxis are shown in Fig. 1. As expected, for the patients who underwent regional prophylaxis (400 mg of teicoplanin), very low or less than detectable values were found in the serum samples taken from forearm veins during monolateral implantation.

The concentrations 10 min after tourniquet release were 14.7 (± 5.6) and 16.9 (± 4.0) for the regional prophylaxis group and 9.3 (± 3.5) and 5.6 (± 1.4) for the systemic prophylaxis group for the monolateral TKRs and the second of the bilateral TKRs, respectively (Table 1). As can be seen

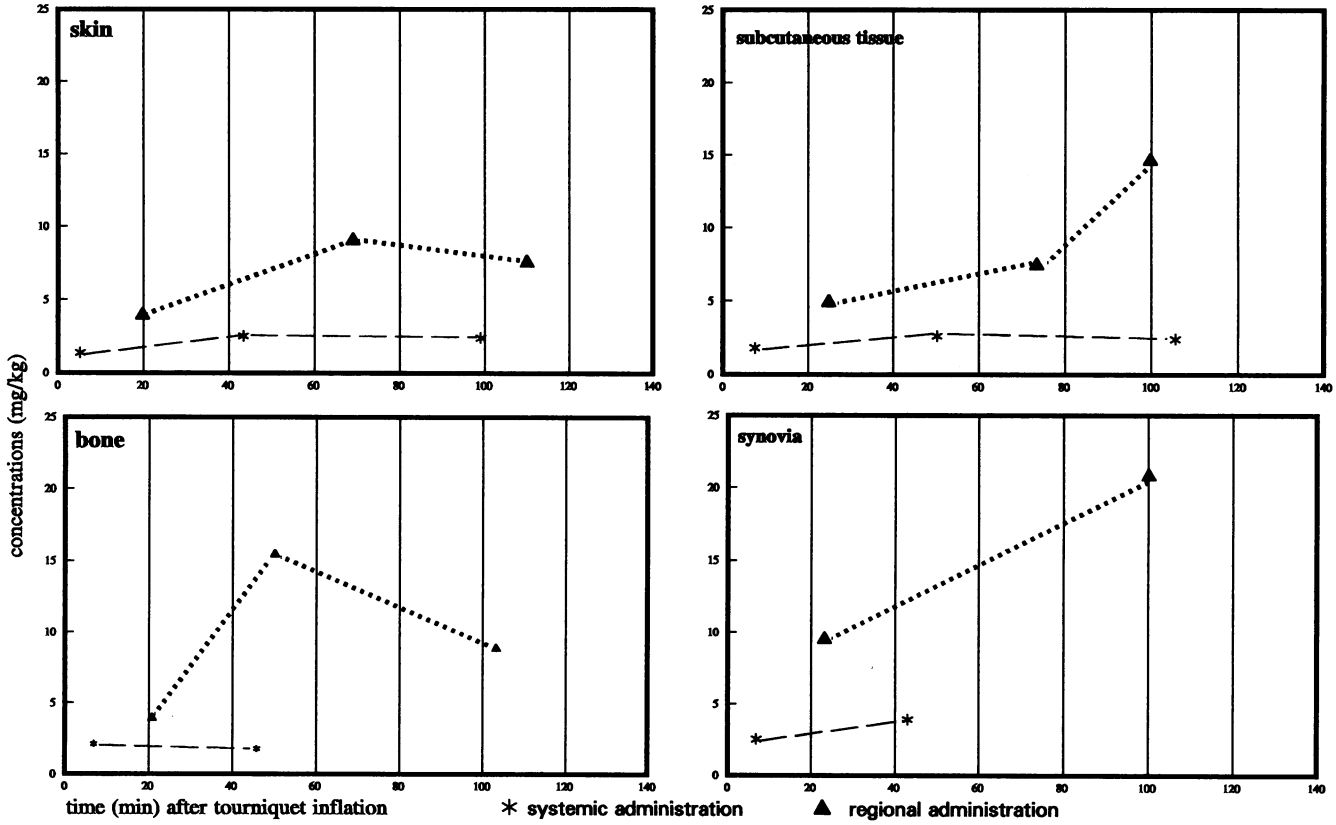

FIG. 3. Mean concentrations of teicoplanin in skin, subcutaneous tissue, bone, and synovia samples during the second of bilateral TKR following systemic (single dose, 800 mg) or regional (400 mg each, for first and second TKR) prophylaxis.

in the graph (Fig. 1), the antibiotic given regionally flowed into the systemic circulation after the removal of tourniquet similarly to an intravenous systemic injection and reached very high concentrations.

The mean levels of teicoplanin in serum after administration both by regional and systemic routes measured at regular intervals (every 30 min for 2 h and every 60 min for another 2 h) during the postoperative period (after tourniquet release) were not significantly different (Student's unpaired t-test, $P > 0.05$) in the monolateral TKR. Meanwhile, for the second prosthesis of bilateral TKR, significantly higher ($P < 0.05$) levels were found in the patients receiving regional prophylaxis (Table 1). During the postoperative observation period (4 h after tourniquet release) the concentrations of the systemically (800 mg) and regionally (400 mg, for each implantation) administered antibiotic in serum tended to become similar (Fig. 1 and Table 1).

Taking into consideration the concentrations in serum, our results showed that the additional dose of teicoplanin that we administered as a regional prophylaxis for the second prosthesis in bilateral TKR did not bring about a significant increase in levels in serum (Table 1 and Fig. 1).

The mean concentrations of teicoplanin and 95% confidence limits at different times (every 20 to 30 min for monolateral TKR and from 20 to 70 min for the second prosthesis) during surgery are shown in Table 2 and Fig. 2 and 3.

Mean values (milligrams per kilogram of body weight) ranged from 7.1 (± 3.6) to 8.2 (± 4.3) in skin, from 11.1 (± 4.3) to 18.6 (± 6.9) in subcutaneous tissue, from 7.5 (± 4.4) to 12.7 (± 4.6) in bone, and from 13.3 (± 10.2) to 14.3 (± 5.6) in synovia at different times following regional prophylaxis (Table 2, monolateral TKR). The corresponding values for systemic prophylaxis varied from 1.0 (± 0.7) to 1.4 (± 0.7) in skin, from 1.4 (± 1.0) to 2.2 (± 1.2) in subcutaneous tissue, from 1.3 (± 0.2) to 2.5 (± 2.0) in bone, and from 2.8 (± 0.9) to 2.9 (± 0.4) in synovia (Table 2, second of bilateral TKR).

Overall, the mean concentrations obtained by the regional route prophylaxis were 2 to 10 times higher than those achieved with the systemic route. The peaks of the mean levels in the different tissues after regional administration were significantly higher than those obtained by the systemic route (Student's unpaired t-test; $P < 0.05$). The intraoperative levels of teicoplanin in subcutaneous, skin and bone tissues (1 to 3 mg/kg) obtained by systemic administration (800 mg) might not have been adequate to inhibit some strains of coagulase-negative staphylococci, whose MICs ranged from 2 to 4 mg/liter (8).

DISCUSSION

Prophylactic antibiotics are an essential component of successful surgery for total joint replacement. Although it is agreed that the choice of the antibiotic must mainly be based on its activity against *S. aureus* and *S. epidermidis*, timing and the duration of prophylaxis should also be based on the pharmacokinetics and tissue penetration of the drug for total joint replacement. At present, teicoplanin is not considered a first-choice drug for prophylaxis of joint prosthetic surgery. Nevertheless, it can be regarded as a reasonable

alternative choice whenever an antibiotic highly effective against MR staphylococci is required (6).

Following the observations of Bier (1), regional delivery of drugs was empirically introduced 5 years ago and then adopted by some in the therapy of bacterial superinfection of diabetic neuropathic foot ulcers (14). Our study shows that regional injection of 400 mg of teicoplanin is safe and can provide significantly higher concentrations than those obtained by giving 800 mg of the same antibiotic by the systemic route. Moreover, following a single 400-mg regional administration, mean peak levels (milligrams per kilogram) ± standard deviations of 8.2 ± 4.3 in skin, 18.6 ± 6.9 in subcutaneous tissue, 12.7 ± 4.6 in bone, and 14.3 ± 5.6 in synovia were obtained. These values are well above the MICs for susceptible microorganisms, including MR staphylococci, and suggest that a single preoperative regional application of a suitable antibiotic is all that is required in this surgery.

Following regional prophylaxis in monolateral TKR, the antibiotic levels in serum during surgery were found to be very low and sometimes the antibiotic was undetectable in serum. However, postoperative infections usually begin in the operative field, and high local concentrations of antibiotic, especially in the subcutaneous tissue, during the surgical procedure could be essential for the prevention of infection. Moreover, the mean levels in serum rose to 14.7 ± 5.6 mg/liter after the tourniquet was released. The high concentrations of teicoplanin within a few minutes after the end of surgery could be sufficient to prevent infection from an occasional bacteremia during the immediate postoperative period.

Owing to the small number of patients in our study, we cannot comment on the effect of this particular technique on infection rates following TKR. Although very few data relating to antibiotic levels in tissue and the rate of postoperative infection are available, the achievement of higher antibiotic concentrations in the operative field during the entire surgical procedure while using a lower antibiotic dose is of genuine interest. Moreover, regional prophylaxis in TKR can be used with any antibiotic which can be administered as an intravenous bolus. Indeed after the tourniquet is released, the levels in serum rise sharply; antimicrobial agents, such as vancomycin and fluoroquinolones, which must be administered only by slow infusion cannot therefore, be administered by the regional route under tourniquet inflation.

In conclusion, in monolateral and bilateral TKR, regional administration of 400 mg of teicoplanin after complete occlusion of the systemic circulation seems to be a safe and valuable prophylactic technique. It provides concentrations in tissue in the operative field which are 2 to 10 times higher than those achievable by injecting 800 mg of the same antibiotic systemically. However, prospective and randomized trials comparing regional and systemic prophylaxis in TKR are needed in order to better define the role of regional prophylaxis.

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