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Penetration of Daptomycin into Bone and Synovial Fluid in Joint Replacement

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Daptomycin exhibits clinical activity in the treatment of infections with Gram-positive organisms, including infections due to methicillin-resistant *Staphylococcus aureus*. However, little is known about its penetration into bone and synovial fluid. The aim of our study was to assess the penetration of daptomycin into bone and synovial fluid after a single intravenous administration. This study was conducted in 16 patients who underwent knee or hip replacement and received a single intravenous dose of 8 mg of daptomycin per kg of body weight prior to surgery. Plasma daptomycin concentrations were measured 1 h after the end of daptomycin infusion and when bone fragments were removed. Daptomycin concentrations were also measured on bone fragments and synovial fluid collected at the same time during surgery. All samples were analyzed with a diode array–high-performance liquid chromatography (HPLC) method. After a single-dose intravenous infusion, bone daptomycin concentrations were above the MIC of daptomycin for *Staphylococcus aureus* in all subjects, and the median bone penetration percentage was 9.0% (interquartile range [IQR], 4.4 to 11.4). These results support the use of daptomycin in the treatment of *Staphylococcus aureus* bone and joint infections.

Staphylococcal osteoarticular infections are difficult to treat (1, 2). They are caused mainly by *Staphylococcus aureus* and coagulase-negative staphylococci (1–5). Antibiotics are cornerstone of their treatment, but optimal regimens have not been identified, since few controlled trials have been performed to assess and compare different regimens. The high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) and the emergence of strains with decreased susceptibility to vancomycin make it necessary to evaluate newer options in such situations (6).

Daptomycin has many interesting characteristics relative to bone and joint infections, with or without foreign bodies.

First, daptomycin is as a cyclic lipopeptide antibiotic with an spectrum of activity against Gram-positive organisms, including MRSA. Until now, there have been few instances of acquired resistance and rare resistance in vancomycin-heteroresistant *Staphylococcus aureus* (7). Second, daptomycin has a high and very rapid concentration-dependent bactericidal activity (8–11), not affected by decreased susceptibility to vancomycin (12). Third, daptomycin shows an antimicrobial activity in an *in vivo* model of acute osteomyelitis (13) and penetrates rapidly into biofilms (14, 15); also, due to its unique mechanism of action on cell membrane, daptomycin retains antimicrobial activity against both stationary-phase cultures of staphylococci within the biofilm and bacteria in the multiplication phase (16–20). Finally, the safety and tolerability of daptomycin have been established (21–23). Therefore, daptomycin could be a relevant treatment for bone and joint infection, provided that its penetration into bone is satisfactory. The European Cubicin Outcomes Registry and Experience (EU-CORE) database, a large database on real-world daptomycin use, contains data for 220 patients treated for osteomyelitis with daptomycin. It is a quite heterogeneous group of patients that includes those with permanent prosthetic joint infection and those with temporary prosthetic-related infection (i.e., spacer infection) and non-prosthetic-related osteomyelitis. Overall clinical success was achieved in 165/220 patients, who were mostly treated with a daptomycin infusion of 6 mg per kg of body weight per day, and safety and tolerability were good. However, this high rate of clinical success should be viewed in light of the fact that the hindsight was short and clinical success was used to collectively describe patients with an outcome of cure or improvement (24). Despite these clinical results, data on the penetration of daptomycin in human bone are lacking.

The aim of our study was to assess the penetration of daptomycin into bone and synovial fluid after a single intravenous administration of this antibiotic.

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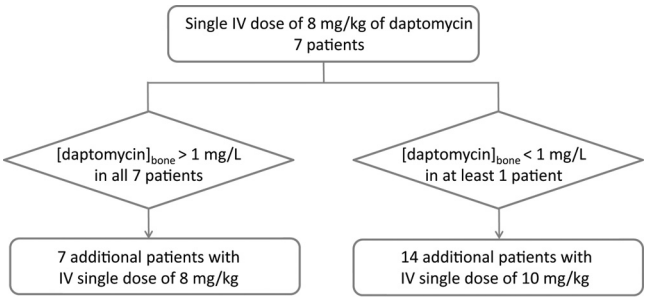

FIG 1 The two-step study design depending on the daptomycin concentrations in bone in the first seven patients.

MATERIALS AND METHODS

Patients. Healthy adults were invited to participate in the study during the preoperative phase of a planned knee or hip surgery. They gave informed written consent to their participation.

Excluded from the study were subjects with either an elevated (≥5× upper limit of normal [ULN]) serum creatinine phosphokinase before surgery, a serum C-reactive protein concentration of >10 mg/liter, a creatinine clearance of <30 ml/min (measured by the Cockcroft-Gault equation), Child-Pugh class C liver failure, a body mass index of >40 kg/m^2, chronic limb ischemia (stage II or higher), chronic osteomyelitis, treatment with statins, fibrates, or cyclosporine, or a known intolerance to daptomycin.

This phase I, open-label, nonrandomized study was carried out at the university hospital in Besançon, France. It was approved by an independent ethics committee (CPP Est-II, Besançon, France) at the session on 25 March 2010 and by the French health authority (AFSSAPS) under the number B100319-77.

Drug administration. Patients received a single dose of daptomycin intravenously between 4 and 12 h before surgery. The delay took into account the linear pharmacokinetics of daptomycin, the half-time of elimination of the drug, around 8 h, and the availability of the operating room.

Because of the uncertainty of optimal daptomycin dosing for adequate bone penetration, we decided to start the study using an 8-mg/kg dose and designed a two-step study that is summarized in Fig. 1. Daptomycin was administered intravenously over 30 min at 8 or 10 mg/kg. In any case of poor tolerance of the infusion and/or an allergic reaction, daptomycin infusion was stopped.

Patients were given a standard intravenous dose of cefuroxime (or clindamycin if they had an allergy to beta-lactams) before surgery, according to the French guidelines for antibiotic prophylaxis in orthopedic surgery (25).

Sample collection. Two blood samples were collected from each patient. In order to minimize the variability of the first rapid phase of distribution of the daptomycin, the first sample (used to determine the concentration at 1 h [C_{1HOUR}]) was taken 1 h after the end of the daptomycin infusion. The second one (used to determine the concentration during surgery [C_{OP}]) was collected during surgery, around the time of bone removal.

For each patient, bone tissues were collected to determine the daptomycin concentration in shinbone and thighbone in cases of knee replacement and in thighbone in cases of hip replacement. Synovial fluid was also collected at the time of bone removal provided that a volume of at least 5 ml was available. Samples were transported within 10 min to the laboratory at room temperature. After treatment, plasma, bone, and synovial fluid samples were frozen at −80°C.

For a total knee replacement, a tourniquet was applied around the thigh immediately after induction of anesthesia.

Daptomycin concentration measurements. (i) Blood and synovial fluids. (*a*) Collection. Blood samples were collected in heparin-containing tubes (volume, 7 ml). Plasma was separated by centrifugation at 1,500 × *g* for 10 min at 4°C, transferred into propylene vials, and stored at −80°C until analysis. Samples of synovial fluid were collected in heparin-containing tubes (volume, 7 ml) and were stored at −80°C until analysis. The daptomycin stability in plasma samples is acceptable with storage at −20°C (26).

(*b*) Extraction. For extraction, 100 μl of plasma (or synovial fluid) were added with ethylparaben (10 μl of a 0.25 g/liter solution) as internal standard. Proteins precipitation was performed by adding 400 μl of methanol. After 30 s of shaking (Vortex), the solution was centrifuged 3 min and 10,000 × *g*. Forty microliters of supernatant was injected into the HPLC system.

(*c*) HPLC quantification. All samples (plasma and synovial fluid) were analyzed with validated photodiode array–high-performance liquid chromatography (PDA-HPLC). Chromatography was carried out with an OmniSphere 5 C_{18} column (150 by 4.6 mm; Agilent France, Les Ulis, France). The chromatographic system included a 717 Plus injector (Waters France, Guyancourt, France), a SpectraSeries P100 pump, and a UV6000LP detector (Thermo Scientific Waltham, MA, USA). The mobile phase was a phosphate buffer (pH 3.8)-acetonitrile (65/35 [vol/vol]) solution. The flow rate was 1 ml/min with an injection volume of 40 μl. The wavelength used for detection was 224 nm. Each sample took 10 min to run.

The HPLC method was validated on a range of daptomycin concentrations from 0.15 to 80 μg/ml. The linearity was validated ($R^2 = 0.9976$). Three internal controls were used (concentrations of 0.2 μg/ml, 20 μg/ml, and 80 μg/ml). The within-run precision was 14.8%, 5.8%, and 0.2%, respectively. The within-run accuracy was 14.6%, 5.2%, and 5.8%, respectively. The between-run accuracy between day 1 and day 5 was 11.2%, 3.7%, and 3.3%, respectively. The limit of quantification was 0.15 mg/liter (the lowest concentration for which the coefficient of variation was above 20%).

(ii) Bone. (*a*) Collection. Bone samples were collected in dry and appropriate packaging. After resection of the bone samples, adhering blood, bone marrow, and soft tissues were removed from the specimen by swabbing, scraping, or rinsing, and samples were immediately stored at −80°C until analysis.

(*b*) Extraction. For extraction, approximately 700 mg (the precise weight of bone sample used for extraction was measured) of cancellous bone was manually crushed and immersed in 1.2 ml of cold phosphate buffer (pH 6). Samples were agitated for 30 s (Vortex) and then ultrasonicated for 10 min. Samples were then stored 2 h at 4°C. They were then shaken for 30 s and centrifuged for 10 min at 10,000 × *g*. This procedure was repeated three times for each bone sample. The 3 supernatants were pooled, and 1,000 μl of supernatant (with addition of 10 μl of a solution of ethylparaben [0.25 mg/liter]) was cleared on Agilent SPE Bond Elud columns with 1,000 μl of methanol. This clear extract was recovered and injected into the HPLC system.

(*c*) HPLC quantification. After extraction of daptomycin from bone, 40 μl of clear extract was injected, with the same HPLC parameters as for plasma and synovial extracts. For each bone sample, the amount of daptomycin (μg) was determined then reported relative to the exact quantity of crushed bone (g) to get the concentration of daptomycin in bone (μg/g).

The HPLC method was validated on a range of daptomycin amounts from 0.15 to 2.4 μg. The linearity was validated ($R^2 = 0.99$). The within-run precision was 1.7%, 1.4%, and 4.7% for amounts of 0.2 μg, 1.2 μg and 2.4 μg, respectively. The within-run accuracy was 9.0%, 4.5%, and 2.1% for amounts of 0.2 μg, 1.2 μg, and 2.4 μg, respectively. The between-run accuracy was 4.7%, 8.5%, and 4.2% between day 1 and day 5 for amounts of 0.2 μg, 1.2 μg, and 2.4 μg, respectively. The limit of quantification was of 0.15 μg (first small amount for which the coefficient of variation was above 20%).

Statistical analysis. We describe the demographic data (age and sex) and surgical site, the results of the pharmacological dosages of daptomycin in bones ($C_{THIGHBONE}$ and $C_{SHINBONE}$), synovial fluid (C_{SF}), and

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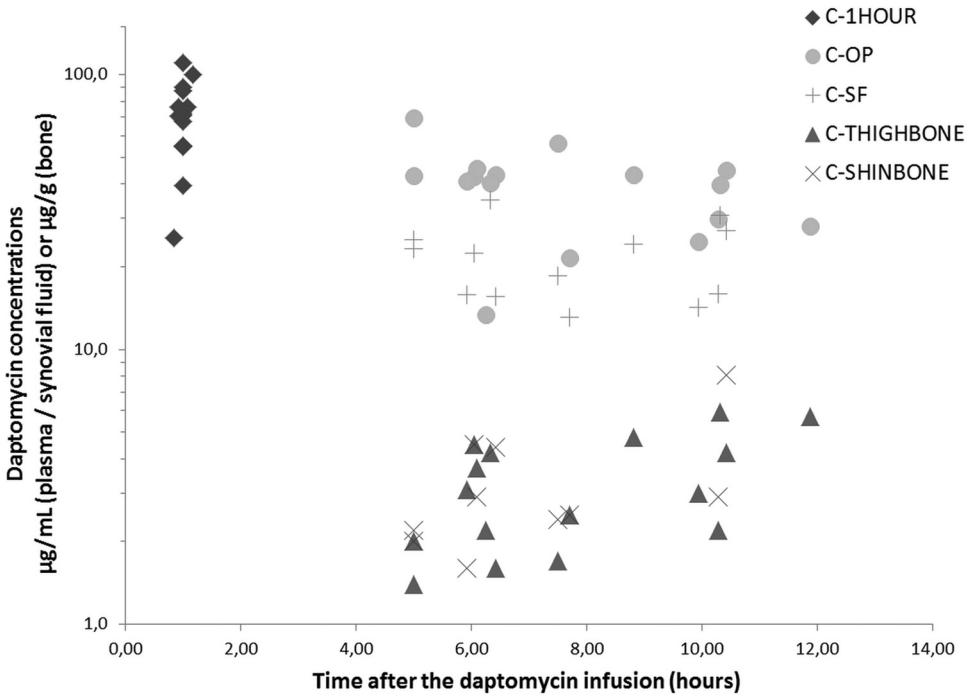

FIG 2 Representation of the daptomycin concentrations in plasma (C_{1HOUR} and C_{OP}) or in synovial fluid (C_{SF}) (μg/ml) and in bones ($C_{THIGHBONE}$ and $C_{SHINBONE}$) (μg/g) versus the sampling time.

plasma (C_{1HOUR} and C_{OP}). Statistical analysis was performed using a dependent *t* test for paired samples with a fixed statistical significance at a 5% level.

We calculated the percentage of penetration of daptomycin into bone and synovial fluid by calculating for each patient the ratio of the bone drug concentration to C_{OP}: C_{SF}/C_{OP} for the daptomycin penetration in synovial fluid, $C_{THIGHBONE}/C_{OP}$ for the daptomycin penetration in thighbone, and $C_{SHINBONE}/C_{OP}$ for the daptomycin penetration in shinbone.

The concentrations of daptomycin and the bone penetration percentages are presented as medians and interquartile ranges (IQR), and the time variables are presented as means and ranges.

RESULTS

At the end of the first step of the study, bone concentrations of daptomycin were found to be above the cutoff threshold of 1 μg/ml in all 7 patients. Consequently, the same dose of 8 mg/kg of daptomycin was used in the patients enrolled in the second step of the study.

Data were obtained from 16 patients. There were six men and 10 women. The median age was 69 years (IQR, 55 to 91). Ten knee and six hip replacements were performed. All the biological samples scheduled were obtained, except that synovial fluid was missing for three patients due to an insufficient volume of synovial fluid.

During the study, one adverse event occurred. It consisted of a bullous pemphigoid diagnosed 28 days after surgery. It was an expected serious adverse event. According to the evaluation of imputability using the WHO global introspection method, the causality assessment of the reported adverse event and daptomycin was classified as possible.

For the whole study, bone tissue, blood for determining C_{OP}, and synovial fluid were collected at the same time from any one patient. For the whole study, bone tissue, blood for C_{OP}, and synovial fluid were taken after a mean of 7.3 h, 7.4 h, and 7.3 h after daptomycin infusion, respectively. For each patient, bone tissues, blood for C_{OP}, and synovial fluid were collected in a median time of 27 min (IQR, 19 to 34). Mean times between the inflation of the tourniquet and the bone samplings were short: 21 min (range, 12 to 43 min) for thighbone and 39 min (range, 27 to 54 min) for shinbone.

Figure 2 presents the concentrations of daptomycin determined in plasma (C_{1HOUR} and C_{OP}), in synovial fluid (C_{SF}) and in bones ($C_{THIGHBONE}$ and $C_{SHINBONE}$) plotted against the time of sampling. Table 1 displays the concentrations of daptomycin determined for each patient. The mean values (± standard deviation [SD]) were 70.3 (±21.5), 39.3 (±13.6), and 21.6 (±6.8) μg/ml for C_{1HOUR}, C_{OP}, and C_{SF}, respectively. In bone samples, the mean values (± SD) were 3.3 (±1.5) and 3.4 (±1.9) μg/g for $C_{THIGHBONE}$ and $C_{SHINBONE}$, respectively. C_{SF} and C_{OP} were statistically significantly different ($P < 0.0001$) (Table 2).

The median synovial fluid penetration percentage was 54% (IQR, 38 to 60%). In thighbone, it was 9.5% (IQR, 6.5 to 11.7%), and in shinbone, it was 8.2% (IQR, 4.4 to 10.5%) (Table 3).

DISCUSSION

Our single-center pilot study showed that daptomycin penetrates synovial fluid well and that it also penetrates cancellous bone in healthy volunteers.

Even though there is currently no validated method to measure bone concentrations of any antibiotics, the method we used resembles in part the current state-of-the-art methods described by Landersdorfer et al. (27). The daptomycin concentrations were determined in only one type of bone, the cancellous bone. The bone samples were rather large operating

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TABLE 1 Daptomycin concentrations in plasma (C_{1HOUR} and C_{OP}), in bones ($C_{THIGHBONE}$ and $C_{SHINBONE}$), and in synovial fluid (C_{SF})

Patient	Replacement	C_{1HOUR} (μg/ml)	C_{OP} (μg/ml)	Time between C_{1HOUR} and C_{OP} (h:min)	$C_{THIGHBONE}$ (μg/g bone)	$C_{SHINBONE}$ (μg/g bone)	C_{SF} (μg/ml)
1	Knee	71.3	43.0	04:00	1.4	2.0	23.3
2	Knee	110.3	69.9	04:00	2.0	2.2	25.0
3	Knee	67.8	43.4	05:25	1.6	4.4	15.6
4	Knee	72.6	42.5	05:03	4.5	4.5	22.4
5	Knee	100.3	56.4	06:20	1.7	2.4	18.5
6	Knee	39.4	21.6	06:42	2.5	2.5	13.1
7	Hip	76.2	40.4	05:15	4.2		35.0
8	Hip	87.6	43.4	07:49	4.8		24.1
9	Knee	70.5	44.8	09:30	4.2	8.1	27.0
10	Hip	90.3	39.9	09:19	5.9		30.8
11	Hip	55.0	24.7	08:56	3.0		14.2
12	Hip	54.6	28.2	10:53	5.7		
13	Knee	71.3	41.0	04:55	3.1	1.6	15.8
14	Knee	76.4	45.6	05:11	3.7	2.9	
15	Knee	55.3	29.8	09:17	2.2	2.9	15.9
16	Hip	25.4	13.4	05:25	2.2		

specimens of noninfected bone (around 700 g), and the samples used for extraction were taken, whenever possible, from the center of the bone. The bone samples were finely homogenized using a mortar and then vortexed and ultrasonicated. These extraction conditions ensured stability of the drug and the achievement of the best extraction possible. Finally, we used a validated HPLC-UV (photodiodes array) method for the quantification of the daptomycin. Our results showed that daptomycin penetrates synovial fluid well, with a median penetration percentage of 54% (IQR, 38 to 60%). But most of all, our results showed that daptomycin also penetrates cancellous bone in healthy volunteers. The median penetration of daptomycin into cancellous bone was 9.0% around 8 h after an 8-mg/kg infusion. Regardless of the samples and the sampling times, daptomycin concentrations have always been found to be above 1 μg/g. We had chosen the value of 1 μg/g, which is equivalent to the MIC breakpoint for clinical isolates of *Staphylococcus aureus* for daptomycin (1 μg/ml) (28), and this was achieved after an unique intravenous single dose of 8 mg/kg daptomycin.

However, there are limitations to our study. First, it was a single-center pilot study. Second, noninfected bone was used, and one cannot be sure that bone penetration would be the same in infected bone. Moreover, we could not study the antimicrobial activity of daptomycin in the bone samples and correlate this activity to the bone concentration of daptomycin. Third, the study design (one bone sample per patient taken during joint replacement surgery) did not allow us to determine the kinetics of daptomycin in bone, in contrast to the microdialysis technique or animal models. Finally, in knee replacement, the tourniquet was applied to the leg to be operated on just before surgery but at least 4 h after the daptomycin infusion and a few minutes before the plasma and bone samples were taken. Even if the tourniquet could decrease blood circulation to the site of surgery and therefore could affect the rate of bone penetration (29, 30), it certainly had a small impact in our study.

To our knowledge, only one study assessed the penetration of daptomycin into bone tissue of diabetic patients with bacterial foot infections requiring surgical debridement (31). But this study used a different design and assay method. Indeed, Traunmüller et al. (31) used the microdialysis technique with a probe inserted during surgery into cancellous healthy metatarsal bone and a reference probe inserted into an unaffected region of subcutaneous adipose tissue of the same lower limb. Daptomycin concentrations in microdialysates were measured by HPLC with UV detection. Thanks to the microdialysis technique, many samples were collected for each patient, and thus

TABLE 2 Daptomycin concentrations in plasma (C_{1HOUR} and C_{OP}), in bones ($C_{THIGHBONE}$ and $C_{SHINBONE}$), and in synovial fluid (C_{SF})

Measurement[a]	C_{1HOUR} (μg/ml)	C_{OP} (μg/ml)	$C_{THIGHBONE}$ (μg/g bone)	$C_{SHINBONE}$ (μg/g bone)	C_{SF} (μg/ml)
Mean	70.3	39.3	3.3	3.4	21.6
SD	21.5	13.6	1.5	1.9	6.8
Median	71.3	41.8	3.1	2.7	22.4
Minimum	25.4	13.4	1.4	1.6	13.1
Q1	55.2	29.4	2.2	2.3	15.8
Q3	79.2	43.8	4.3	4.0	25.0
Maximum	110.3	69.9	5.9	8.1	35.0

[a] Q1 and Q3, first and third quartiles, respectively.

TABLE 3 Percentage of daptomycin penetration into bone (thighbone and shinbone) and synovial fluid sampled in a mean time of 7.3 h after the perfusion of 8 mg/kg of daptomycin. The results are expressed by the mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3); min and max

	Penetration (%) in:			
Measurement[a]	Thighbone (n = 16)	Shinbone (n = 10)	Bone (n = 26)	Synovial fluid (n = 13)
Mean	9.5	8.2	14.1	53.9
SD	5.0	4.7	11.9	15.9
Median	9.9	8.0	11.1	54.2
Minimum	2.9	3.1	3.0	32.8
Q1	6.5	4.4	6.6	38.5
Q3	11.7	10.5	17.3	60.3
Maximum	20.2	18.1	50.4	86.6

[a] Q1 and Q3, first and third quartiles, respectively.

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the authors were able to calculate the area under the curve of the daptomycin concentration in bone and plasma. Unlike our study, in which uninfected patients received only one infusion of daptomycin at 8 mg/kg, the nine patients with diabetic foot infections received 4 to 5 daptomycin infusions at 6 mg/kg/day before surgery. The degree of bone penetration was assessed by calculating the ratio of the area under the concentration-time curve (fAUC) of free daptomycin in bone to the fAUC of free daptomycin in plasma. The mean ratio was 1.08 for infected bone. Thus, although the results of the study by Traunmüller et al. (31) cannot be directly compared with ours, both studies suggest good penetration of daptomycin into bone tissue.

Our data show that concentrations of daptomycin in noninfected bone and synovial fluid are above 1 μg/g and 10 μg/ml, respectively, after a unique dose of 8 mg/kg of daptomycin. Considering the daptomycin MIC breakpoint (1 μg/ml) defined by EUCAST for *Staphylococcus aureus*, daptomycin may be a useful agent in the management of prosthetic joint infection and could be an alternative to glycopeptides. But it should be interesting to do more studies in infected patients to correlate the antimicrobial efficacy and the concentrations of daptomycin in bone tissues and to explore the daptomycin concentrations in bone after numerous administrations.

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