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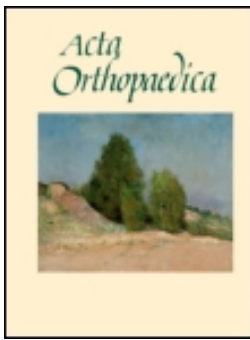
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Published online: 08 Jul 2009.

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In vivo pharmacokinetics of a gentamicin-loaded collagen sponge in acute periprosthetic infection

Serum values in 19 patients

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Background　The in vivo pharmacokinetics of gentamycin-loaded collagen fleeces in humans have not been described in the current literature. We therefore analyzed in vivo pharmacokinetics of these fleeces when used in the treatment of periprosthetic infections.

Patients and methods　Gentamycin concentrations were measured in 19 consecutive patients with an acute periprosthetic infection. Each patient received 2–5 fleeces (130 mg gentamycin/fleece).

Results　Initially, the blood concentration increased to 3.2–7.2 mg/L, depending on the number of fleeces that were applied. The serum peak concentrations resulted in peak/MIC ratios of 2.5–36 for *P. aeruginosa, S. aureus,* and *Klebsiella* spp. Subsequently, the serum values decreased almost linearly below 0.3 mg/L in 18 to 62 hours. After 24 hours, the serum levels of gentamicin dropped below 2 mg/L, the toxicity threshold.

Interpretation　The application of 2 to 5 130-mg gentamycin-loaded collagen fleeces may be useful as an adjuvant treatment for implant-related infections, since no toxic concentrations were measured 24 hours postoperatively.

■

In early postoperative deep hip prosthesis infections, according to the criteria of Smyth and Emmerson (2000), debridement, irrigation drainage, and systemic high-dose antibiotics (aminoglycosides) while retaining the prosthesis may be effective if the treatment is initiated within 24–36 hours of the onset signs of infection (Buchholz et al. 1981, Anttipoika et al. 1990). In infected prostheses, bacteria adhere to the surfaces of implants, producing a biofilm that has a protective effect against many antimicrobial agents because of their reduced metabolic activity (Brown et al. 1990, Habash et al. 1999). As a result, the minimum inhibitory concentration (MIC) is increased. Local antibiotics can be used to achieve a high concentration (up to 1,000 fold) at the local site (Diefenbeck et al. 2006).

Aminoglycosides (e.g. gentamicin) have a narrow therapeutic index. After intravenous administration, bioavailability is 100% and peak serum concentrations occur at the end of a 30-min infusion. After intramuscular administration, bioavailability is also 100% and peak serum concentrations occur after 30–90 min. Gentamicin administered intravenously has a half-life of 2 (0.5–3) h in adults. The therapeutic serum level is in the 4–10 mg/L range. Within 24 h, 30–100% of the gentamicin is eliminated by renal excretion in unchanged form. Gentamicin accumulates in the lysosomes of kidney proximal tubular cells and causes apoptosis at clinically relevant doses (Servais et al. 2006). Intravenous administration at levels of more than 2 mg/L is generally considered to be toxic for the patient, and is known to have adverse systemic effects such as ototoxicity and nephrotoxicity (Siber et al. 1975, Isselbacher et al. 1994).

In a kinetic release model, 95% of gentamicin was found to be released from collagen fleeces after 1.5 hours, compared to only 8% from poly(methyl methacrylate) (PMMA) beads (Sørensen et al. 1990). In local application, this carrier substance results in initially high local gentamicin concentrations for the first 4 hours, falling over a maximum of 4 days (Mehta et al. 1996, Wachol-Drewek et al. 1996). Although not controlled and not randomized, clinical results of the application of gentamicin-loaded collagen fleeces indicate that they appear to be of value for treatment of osteomyelitis (Diefenbeck et al. 2006). There are no data available in the drug information of the Royal Dutch Association for the Advancement of Pharmacy on the in vivo pharmacokinetics of this locally administered gentamicin-loaded collagen fleece in humans; nor have we found any such information in the literature.

We analyzed the in vivo pharmacokinetics of a gentamicin-loaded collagen fleece in a cohort of acute periprosthetic infections.

Patients and methods

From 1998 to 2004, 19 patients with a hip or knee arthroplasty endured an acute surgical site infection. They were included in this study after obtaining written informed consent. The treatment considered of open surgical debridement, pulsative irrigation, retention of the prosthesis and application of two or more gentamicin-loaded fleeces (Garacol; Schering-Plough, Maarssen, the Netherlands) in the artificial jointe before closing the wound (Table 1). An acute (deep or superficial) surgical site infection (SSI) was diagnosed within 1 year after implanttion of the prosthesis, according to the criteria of Smyth and Emmerson (2000).

Two or more gentamicin-loaded collagen fleeces in combination with surgical debridement, irrigation while retaining the prosthesis were applied. In addition, empirical systemic administration of antibiotics other than gentamicin was started and subsequently adjusted to the sensitivity of the microbial species involved. The collagen fleece measures 10 × 10 × 0.5 cm and contains an equivalent of 130 mg gentamicin sulfate. It is a bovine collagen, which is fully biodegradable. Application of a maximum of 5 fleeces in case of osseous infections is advised

Table 1. Characteristics of the 19 patients with infected arthroplasties

Gender	
Male	2
Female	1
Age at operation, years (range)	73 (48–83)
Weight, kg (range)	77 (62–98)
Height, cm (range)	163 (148–178)
Body mass index	30 (19–41)
Infected prosthesis (n)	
Primary total hip arthoplasty	14
Revision total hip arthroplasty	3
Total knee arthroplasty	1
Hemiarthroplasty	1
ASA [a] classification	
1	1
2	8
3	8
4	0

[a] ASA: American Society of Anesthesiologists physical status classification (Owens et al. 1978).

by the manufacturer. The number of sponges used was decided peroperatively by the surgeon, based on the extent of the infected tissue. No drainage system was used. No additional systemic gentamicin was administered postoperatively.

Cultures were taken before debridement. Inflammatory parameters, creatinine levels, and the gentamicin serum concentrations were measured postoperatively at 6, 12, 18, and 24 h and after each consecutive 24-h period until gentamicin was no longer detectable. Serum gentamicin was measured by fluorescence polarization immunoassay (AxSYM analyzer; Abbott Laboratories, Diagnostics Division, Abbott Park, IL) according to the instructions for gentamicin provided with the instrument. The sensitivity, defined as the lowest measurable concentration that can be distinguished from zero with 95% confidence, was 0.30 µg/mL. The variation coefficients between runs were less than 7% for concentrations between 1.0 and 8.0 mg/L. As a toxicity reference, 2 mg/L gentamicin in serum was used. Creatinine clearance was calculated according to the Cockcroft-Gault formula (1976). In order to demonstrate the effectiveness of the concentration of gentamicin measured, the measured peak serum concentration was divided by the minimum inhibitory concentration for each microorganism cultured.

Table 2. Observations

Case no	No. of sponges	Gentamicin used (mg)	Peak serum gentamicin concentration (mL/min)	Creatinine clearance (mg/L)
1	3.5	455	7.1	50
2	3	390	NR [a]	NR
3	3	390	3.7	121
4	3	390	4.8	78
5	3	390	7.2	NR
6	4	520	4.5	68
7	2	260	1.0	62
8	4	520	3.2	51
9	3	390	2.7	51
10	4	520	5.7	64
11	5	650	0.6	99
12	5	650	2.4	68
13	5	650	3.0	68
14	5	650	6.9	49
15	2	260	4.7	89
16	2	260	1.4	106
17	5	650	6.4	41
18	3	390	6.8	53
19	4	520	NR	34
Average (SD)	3.6 (1.0)	469 (138)	4.2 (2.2)	68 (24)

[a] NR: not reported.

Statistics

Pearson rho correlation analysis and descriptives were performed using SPSS software, version 15.0.

Results (Table 2)

Initially, the serum concentration increased to 3.2–7.2 mg/L in 4.5 to 6 h. The values subsequently decreased almost linearly below 0.3 mg/L in 18 to 62 h. After 24 h, the gentamicin levels dropped below the 2 mg/L reference toxicity concentration in all cases (Figure 1).

The culture specimens contained *P. aeruginosa, S. aureus* and/or *Klebsiella* spp. The peak concentrations measured in the serum gave peak/MIC ratios of 3.5:1 to 8:1 for *P. aeruginosa* (MIC 0.9 mg/L), 16:1 to 36:1 for *S. aureus* (MIC 0.2 mg/L) and 2.3:1 to 5.1:1 for *Klebsiella* spp. (MIC 1.4 mg/L), which are representative values for members of the Enterobacteriaceae family (Lorentzen et al. 1996). Apart from 2 patients with reduced clearances (cases 17 and 19 in Table 1), all patients had renal clearances within the normal range.

There was no association between the number of fleeces applied and subsequent gentamicin peak serum concentrations. There was an inverted relation between weight and the peak serum concentration of gentamicin in this series (p
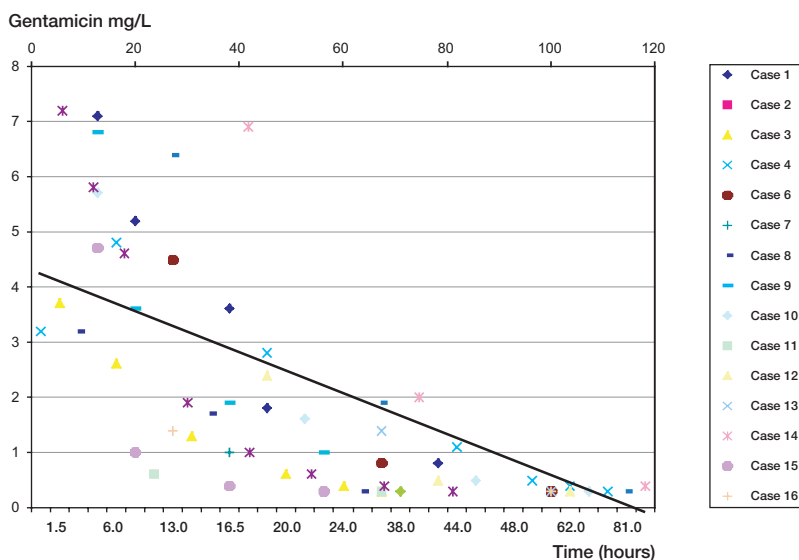

Figure 1. Time course of gentamicin serum concentrations in different patients.
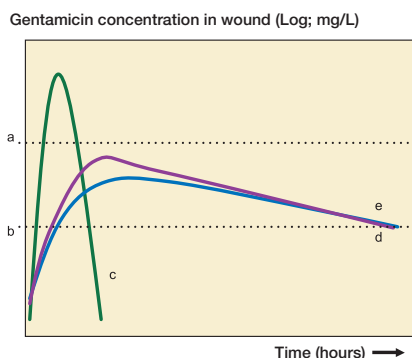
Figure 2. The pharmacokinetics of local deliverers of gentamicin.
a Gentamicin concentration that is bactericidal in the case of resistant pathogens (300 mg/L).
b Minimal concentration that is inhibitory to sensitive pathogens (4 mg/L).
c Fleeces (Garacol).
d Beads.
e Minibeads.

< 0.001) (Figure 3), which is in accordance with the formula described by Cockcroft and Gault (1976) for calculation of renal clearance.

Discussion

We found that the gentamicin serum levels decreased to non-toxic levels 1 day after application of gentamicin-loaded fleeces. Authors of in vitro studies of gentamicin-loaded fleeces (Garacol) have reported a quick release of gentamicin in the first 6 h after application (Blanc 1992).

Although there is quick release of gentamicin from its carrier, the bioavailability of gentamicin from collagen fleeces is different from that after intramuscular administration. The release from collagen appears to accelerate in a medium or environment with a rising pH (Firsov 1987). At the surgical site, the pH is lower than physiological pH, suggesting a slower release in vivo than in vitro (Sorensen et al. 1990, Blanc 1992). Because of these differences in pharmacokinetic behavior of the drug, a comparison between local application of gentamicin and intramuscular infiltration is warranted. Several authors have reported bactericidal gentamicin levels higher than 300 mg/L at the surgical site after application of gentamycin fleeces (Young and Hewitt, 1973, Von Hasselbach 1989,
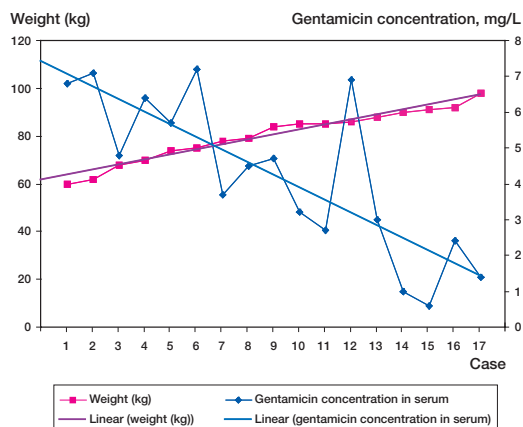

Figure 3. Plots of weight and gentamicin peak concentration for each patient (plotted in order of increasing weight).

Jorgensen et al. 1991, Wernet et al. 1992, Lethsch et al. 1993). These high levels (ranging from 381 to 5,117 mg/L) were maintained for 2 up to 5 days, which suggests that there is slower release than would be predicted by in vitro results (Jorgensen et al. 1991, Wernet et al. 1992). Resorption and diffusion into the blood vessels and the degree of vascularization are the immeasurable determining factors of the bioavailability of gentamicin from collagen fleeces. After intravenous administration, bactericidal gentamicin levels higher than 300 mg/L for gentamicin-resistant microorganisms (Von Hasselbach 1989) cannot be achieved at the surgical site within a few hours and then maintained for 24 h without serious adverse effects such as ototoxicity and nephrotoxicity. Whereas bactericidal concentrations were achieved locally at the surgical site with Garacol (Young and Hewitt 1973, Von Hasselbach 1989, Jorgensen et al. 1991, Wernet et al. 1992, Lethsch et al. 1993), the serum levels of gentamicin were found to decrease to the non-toxic range within 1 day without any risk of adverse effects. Also, in 20 patients treated with netilmicin-impregnated locally impacted cancellous bone in hip or knee revision procedures, extremely high concentrations of the antibiotic were recorded in the wound drainage on the first days after surgery without any adverse systemic effects (Witsø et al. 2004).

The initially very high bactericidal concentrations at the surgical site in the first hours after administration favor the use of gentamicin-loaded

sponges rather than gentamicin-loaded PMMA beads, which do not give these levels (Walenkamp 1989, Walenkamp and Karsemaker 1998). PMMA beads have their maximum serum concentrations after 1 day, which do not reach toxic levels. In vitro Garacol has it peak serum concentration within 6 h of administration, and the toxic serum level falls to less than 2 mg/L within 24 h. Conventional 7-mm PMMA beads slowly release gentamicin, resulting in exudate levels of approximately 30 mg/L within the first day postoperatively, and provide local concentrations of approximately 5 mg/L for 2–3 weeks. These levels are well above the concentrations of 4 mg/L necessary to inhibit sensitive and moderately sensitive pathogens (Young and Hewitt 1973), whereas resistant microbes will not be affected. The effect in tissue approximately 1–2 mm away from the implant, where the concentration will be much lower, is still unclear (Wahlig et al. 1978, Walenkamp 1989, Miclau et al. 1993). The 3-mm × 5-mm mini PMMA beads have a higher and earlier peak serum concentration than the conventional 7-mm PMMA beads, but still no bactericidal concentrations at surgical site are measured for resistant microbes for either (Walenkamp 1989). They do have the same steady state of 5 mg/L at the surgical site for several weeks (Figure 2). The disadvantage of beads is that they must be removed; otherwise they themselves will be an infection site after 2–3 weeks (Neut et al. 2001). When they are mixed with acrylic bone cement, in vitro measurements have demonstrated a high but rapidly falling antibiotic level within the first postoperative week, followed by a slowly decreasing concentration, still with some inhibitory effect after 1 year (Bálint et al. 2004). In vivo studies have shown high bactericidal concentrations of gentamicin in wound exudates for 2 to 5 days without toxic serum concentrations (Wernet et al. 1992, Letsch et al. 1993).

In contrast, a subsequent study conducted in our hospital demonstrated toxic serum concentrations in 7 of 12 patients, resulting in a persistent renal clearance failure in 3 patients (Swieringa and Tulp 2005. In this study group, 4–6 gentamicin-loaded fleeces were applied and mean toxic levels of 4.2 mg/L were measured up to 10 days after application. In the present study, the application was reduced to 2–5 sponges; all cases showed a reduced

gentamicin level below the toxic concentration of 2 mg/L, while a transiently reduced creatinine clearance was observed in only two patients. The difference can be explained by the reduced number of fleeces, which accounts for a relatively shorter period of toxic concentrations, but no relationship was found between the number of fleeces included and serum level of gentamicin. On the other hand, this can be explained by some surgery-related factors, for example as a function of the size of the surface area of the surgical wound after the radical debridement or quality of bleeding cease. The low number of patients may also have had an influence on the results.

Comparison of Garacol with Septocoll was done in a cohort of 40 patients with contaminated wounds. There was a peak value in serum in the Sulmycin (also known as Garacol) group (0.349 mg/L) that was almost three times higher than in the EMD 53155 (later known as Septocoll) group (0.977 mg/L); after 24 h, the curves came increasingly into line (Walenkamp and Karsemaker 1998). After 72 h, the serum concentrations in both cases were below 0.01 mg/L. Although both groups reached concentrations between 800 and 5,000 mg/L in wound secretions, after two days the values in the Sulmycin group were subject to greater fluctuation than those in the EMD 53155 group. Moore et al. (1987) found that the peak/MIC ratio was significantly higher in patients with good clinical responses to therapy than in patients with poor clinical responses. Two years later, Leggett et al. (1989) reported that for a murine pneumonitis and thigh infection model, the log area under the concentration-vs.-time curve (AUC)/MIC was the only parameter predictive of efficacy for the first 6 h, and that peak concentration in itself was not predictive of efficacy. This might suggest that Garacol and Septocoll have equal clinical efficacy, because both have bactericidal concentrations within 6 h and for the first 2 days.

We conclude that the in vivo release of gentamycin from collagen fleeces in humans differs from that of other methods of application—especially the high bactericidal concentrations, without any risk of serious adverse effects. Gentamycin-loaded collagen fleeces may be useful as an adjuvant treatment for implant-related infections.

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