Gentamicin-collagen sponge for local applications

10 cases of chronic osteomyelitis followed for 1 year

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A bovine collagen sponge containing gentamicin was applied locally in 10 patients with chronic osteomyelitis who were then followed for 1 year postoperatively. No adverse effects or recurrence of infections was observed. The release of gentamicin from the sponge was more complete and rapid than has been reported with polymethyl methacrylate (PMMA) beads. Compared with previous reports on PMMA beads, a much higher gentamicin concentration in the wound exudate can be expected after implantation of the collagen sponge, which is easy to apply and does not require a second operation for removal.

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In the surgical treatment of chronic osteomyelitis, systemic antibiotics can be supplemented with local antibiotics that will reach the surrounding bone by simple diffusion. The aminoglycoside gentamicin has been the drug of choice for local treatment; bone cement in bulk or beads have been loaded with gentamicin. However, the release of the antibiotic is both slow and incomplete. In addition, the beads often have to be removed by a second operation. Gentacoll® is a new formulation in which gentamicin is incorporated into bovine collagen, which is compatible with human tissue and is resorbable (Remberger and Hübner 1979). Therefore, a second operation is avoided.

We have prospectively evaluated the effect of Gentacoll®.

Patients and methods

During 1987 and 1988, 10 patients were treated for osteomyelitis at the two participating hospitals (Table 1). All the patients had clinical and radiographic signs of osteomyelitis, as well as fistulation to the skin surface. None of the patients had had antibiotics for at least 1 week before the trial.

The patients received Gentacoll®, a bovine collagen sponge with 130 mg of gentamicin (Schering-Plough, Copenhagen, Denmark). Systemic antibiotics were given on the basis of the results of preoperative aspiration cultures from fistulas and were subsequently adjusted according to intraoperative cultures. The operations involved radical excision of fistulas, affected bone tissue, and sequestra if present.

Table 1. Data on 10 patients treated for osteomyelitis

Patient No.	Sex	Age	Location of infection	Duration of infection	Type of infection	Isolated bacteria[a]	No. of Gentacoll® sponges	Systemic antibiotics[b]
1	F	74	Calcaneus	7 yrs	Posttraumatic	*S. aureus*	1	C
2	F	40	Metatarsus	3 mos	Postoperative	*S. aureus*	1	S+M
3	M	78	Hip fracture	4 mos	Postoperative	0	2	C
4	F	76	Hip fracture	1 mo	Postoperative	*S. aureus*	2	S+M
5	F	61	Hip fracture	5 mos	Postoperative	CNS	3	S+M
6	M	18	Femoral fracture	3 yrs	Postoperative	*E. coli*	3	S+A
7	F	34	Proximal tibia	2 mos	Hematogenous	*S. aureus*	3	S+M
8	M	77	Femoral fracture	20 yrs	Posttraumatic	*S. aureus*	3	F+R
9	M	50	Femoral shaft	21 yrs	Postoperative	*S. aureus*	5	P+M+F
10	M	20	Tibial shaft	2 mos	Posttraumatic	*S. aureus*	4	M+F+Cl

[a] CNS Coagulase-negative staphylococci.
[b] A Ampicillin, C Cephalosporins, Cl Clindamycin , F Fusidic acid, M Methicillin, P Penicillin, R Rifampicin, S Streptomycin.

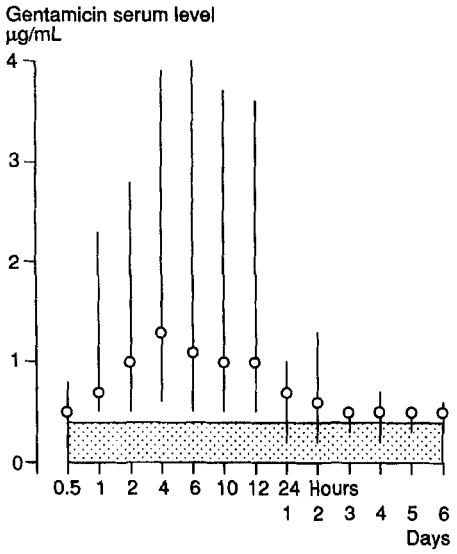

Figure 1. Postoperative serum levels of gentamicin in 10 patients treated for chronic osteomyelitis. Median values and range. Hatching indicates values below the test limit.

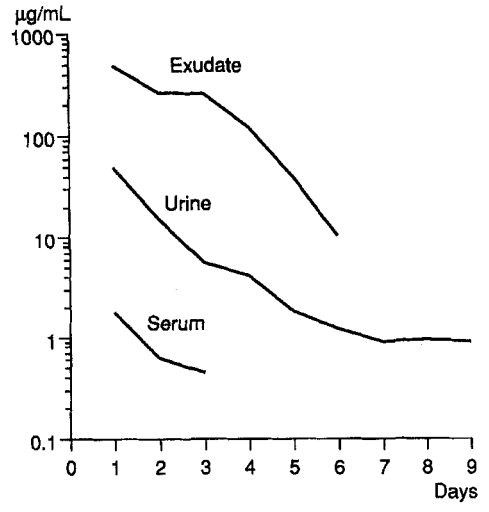

Figure 2. Concentration of gentamicin in serum, urine, and wound exudate in 10 patients after implantation of Gentacoll®.

Gentacoll® sponges were then implanted in the resultant cavity. Surgical overflow drainage was employed in all the cases. Postoperatively, systemic antibiotics were administered parenterally for 5 days and then orally for 7 weeks. Adverse reactions were recorded by daily clinical evaluation during the first 2 postoperative weeks. The gentamicin levels in the blood and urine were followed daily until the values were < 0.5 µg/mL and in the wound exudate until removal of drainage (Essay method: SYVA® Qst™ Sample processor). Serum creatinine, ESR, hemoglobin, and a differential count were recorded once a week during hospitalization and at follow-up examinations after 3, 6, and 12 months.

Results

An average of 351 mg of gentamicin was implanted, and the median serum gentamicin levels were more than 1 µg/mL for 24 hours (Figure 1). Patients treated with only one sponge of Gentacoll® had the lowest levels. The maximum level of 4.0 µg/mL was found in a patient treated with two sponges. Forty-eight hours postoperatively, none of the patients had serum gentamicin levels exceeding 0.7 µg/mL (Figure 2).

One year postoperatively, none of the patients had clinical signs of osteomyelitis, and none of the patients had abnormal blood samples except for the ESR. Three patients had an ESR > 20 mm/h; but in all of these cases, the ESR had decreased as compared with what it had been at the time of the operation and at 3 and 6 months postoperatively. Local or systemic adverse reactions were not observed during the test period. Nephrotoxicity was not observed by clinical or laboratory tests. No complaints of ototoxic actions were recorded (the patients were asked about complaints; an auditory sensitivity test was not performed).

Discussion

The collagen formulation of gentamicin tested in this series of 10 patients with chronic osteomyelitis has proved to be safe, as no adverse reactions occurred. In none of the cases was a toxic serum concentration of gentamicin reached despite the use of up to five sponges of Gentacoll® with a total of 650 mg of gentamicin. Nephrotoxic or ototoxic side effects are not to be expected, because the serum concentration of gentamicin reaches its maximum level within 4–12 hours postoperatively, after which it declines rapidly.

The effectiveness of Gentacoll® compared with the effectiveness of PMMA beads can only be judged by a large comparative study, but some advantages of the collagen formulation can be pointed out. A high antibiotic level in the tissues surrounding the wound has proved effective in preventing recurrence of osteomyelitis (Hedström et al. 1980). In our series the mean

gentamicin level in wound exudate was 479 µg/mL within the first postoperative day. Even after 6 days, the gentamicin level was 10 µg/mL, five to ten times the MIC for *Staphylococcus aureus* (Damholt 1982). The fact that the gentamicin levels in wound exudate and urine were very high during the first week postoperatively indicates that the gentamicin was released almost completely within 2 weeks. These findings correspond well with the results of the rather few studies on this subject (Stemberger et al. 1987, von Hasselbach 1989). Hedström et al. (1980), who implanted PMMA chains with a mean content of 630 mg of gentamicin, found the mean exudate level of 30 µg/mL within the first day postoperatively, with a decrease to less than 5 µg/mL after 1 week. These levels are lower than those found in our series, although the amount of gentamicin implanted was twice as high.

The release of gentamicin from the carrier depends on the surface from which it is spread to the surrounding tissue by diffusion. According to Walenkamp (1983), the larger the surface of the PMMA beads, the more rapid is the gentamicin released. Accordingly, the rapid release of gentamicin from the collagen sponges is most likely due to their large surface.

The decline of the tissue concentration of gentamicin is correlated with the tissue perfusion of the wound (Sørensen et al. 1990, Jørgensen et al. 1991). This explains the more rapid decline of wound gentamicin concentration in vascular surgery as found by Jørgensen et al. (1991).

Following implantation of PMMA beads, Walenkamp (1983) found that early recurrence of infections, i.e., within 2 weeks postoperatively, was present in 76 percent, whereas late recurrence occurred 3 months or more postoperatively. Thus, a high local concentration of antibiotics would be desirable during the first 2 postoperative weeks. The collagen sponge satisfies this demand, whereas the PMMA beads do not with their slow and incomplete release of gentamicin.

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References

Damholt V V. Treatment of chronic osteomyelitis: A prospective study of 55 cases treated with radical surgery and primary wound closure. *Acta Orthop Scand* 1982; 53 (5): 715–20.

von Hasselbach C. Die chronischenpersistierende Osteomyelitis bessere Chancen mit Sulmycin R Implant? In: *Forum der Traumatologie, Osteitis Therapie* (Eds, Dittrich H G, Steer W) Essex Pharma Ltd, Munich 1989: 18–25.

Hedström S Å, Lidgren L, Törholm C, Önnerfält R. Antibiotic containing bone cement beads in the treatment of deep muscle and skeletal infections. *Acta Orthop Scand* 1980; 51 (6): 863–9.

Jørgensen L G, Sørensen T S, Lorentzen E L. Clinical and pharmacokinetic evaluation of gentamicin collagen in groin wound infections after vascular reconstruction. *Eur J Vasc Surg* 1991; 5: 87–91.

Remberger K, Hübner G. Experimentelle Untersuchungen über Zell und Gewebsreaktionen nach Implantationene von xenogenem Kollagenschaum. *Res Exp Med* 1979; 175: 67–70.

Stemberger A, Ascherl R, Rahn H D. Die Wundinfektion des chirurgischer Sict. Kollagen als Tragersubstanz zur Erzielung hoher lokaler Antibiotikaspiegel. In: *Dia Forum. Weichteilchirurgie.* Essex Pharma Ltd, Munich 1987: 4–7.

Sørensen T S, Sørensen A I, Merser S. Rapid release of gentamicin from collagen sponge. In vitro comparison with plastic beads. *Acta Orthop Scand* 1990; 61 (4): 353–6.

Walenkamp G H I M. *Gentamicin PMMA beads. A clinical, pharmacokinetic and toxicological study.* Thesis, University of Nijmegen, Nijmegen, Netherlands 1983.