Gentamicin concentrations in diagnostic aspirates from 25 patients with hip and knee arthroplasties

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Background **There is little information on long-term release of antibiotics from impregnated bone cement.**

Patients and methods **We assayed joint fluids obtained for diagnostic purposes from 25 patients for the presence of gentamicin. All patients had presented with failing or painful joints up to 20 years following primary hip or knee arthroplasty, using gentamicin-impregnated cement.**

Results **Gentamicin was detected in the joint fluids from 9 of 15 patients with knee prostheses and 4 of 10 patients with hip prostheses. The concentrations ranged from 0.06 mg/L to 0.85 mg/L with no significant differences in concentration between the patients with hip or knee prostheses, or the type of prosthesis. We found no relationship between the gentamicin concentration and the time after primary arthroplasty.**

Interpretation **Although most concentrations were below the levels required to inhibit susceptible pathogens, we conclude that gentamicin release around failing implants may lead to false negative cultures in some patients and provide selective pressure for the emergence of resistance where infection is present in others.**

The use of antibiotic-impregnated cement in joint replacement surgery has contributed to the substantial improvement in implant survival (Malchau and Herberts 1998). As regards gentamicin-impregnated cement, concerns have been raised about the potential of selection for infection with multiple strains of coagulase-negative staphylococci (Hope et al. 1989, Thomas et al. 2002). More recently, studies have shown that although the gentamicin is sequestered in the cement, release of gentamicin occurs when the cement is fractured either in vivo (Powles et al. 1998) or in vitro (Armstrong et al. 2002) and that the use of gentamicin in cement may have consequences beyond the immediate post-operative period.

Although much is known about the initial elution characteristics of antibiotic-impregnated cement (Penner et al. 1999), there is little information about antibiotic activity after the first weeks following implantation.

We report the concentrations of gentamicin found in the joint fluids obtained from 25 patients with failing hip or knee arthroplasties where gentamicin-impregnated cement had been used.

Patients and methods

All samples were collected as part of the routine diagnostic evaluation of patients with painful or loosening prostheses and 25 patients undergoing revision hip or knee arthroplasty participated in the study (Table). In 3 cases, joint fluid was obtained in the weeks (1–3 weeks) preceding surgery as part of a preoperative work-up, and in the remainder, aspiration was performed at the time of revision surgery, but before capsular disruption. In all cases (21 joints) where the type of cement employed at the primary joint replacement surgery could be identified, Palacos R had

been used. Specimens were transported to the laboratory where they were stored at –25 °C for up to 18 months before analysis as a single batch at the end of the study. Gentamicin assays were performed using the reverse dilution procedure with a 5 μL sample volume on the Abbott TDx system (Abbott Laboratories, Chicago, Illinois) (White et al. 1994). None of the patients had received systemic gentamicin for other reasons at any stage in the 6 months before participation in the study. 1 patient (case 5) had a urethral catheter inserted during induction of anesthesia and prophylaxis for this procedure was done by means of the administration of a single 80 mg iv bolus of gentamicin 15 minutes before the fluid sample was obtained. Although the gentamicin concentration found in this fluid sample is shown in the Table, it was not used to calculate the mean values or in the statistical analyses.

In 8 patients, the aspirate was from a joint with evidence of an established infection (case 10) and in 4 cases (2, 6, 13 and 14) in the first part of a two-stage revision. Methicillin-resistant staph. aureus (MRSA) was cultured from tissues and synovial fluid obtained from case 10. This was the only positively infected case in our series. The other four cases (2, 6, 13, 14) were staged revision procedures. However, no cultures and enrichment cultures from consecutive multiple specimens from these cases showed organisms. In all other cases (20/25), routine fluid and tissue cultures taken from the operation site were negative. None of the cases has subsequently developed a proven deep infection.

In the statistical analysis, we used the Student's t-test to compare gentamicin levels from hip and knee prostheses, the Mann-Whitney test to compare the time since primary arthroplasty in patients in whom gentamicin was found with those not having gentamicin in joint fluid, and the Spearman correlation test to determine any possible correlation between the gentamicin concentration and the time since primary arthroplasty.

Results

Detectable (> 0.05 mg/L) concentrations of gentamicin were found in the joint fluids from 9 of 15 patients with knee prostheses and 4 of 10 patients with hip prostheses. The gentamicin concentrations ranged from 0.06 mg/L to 0.85 mg/L with no significant differences (Student's t-test $p > 0.05$) in concentration depending on whether the sample had been collected from a patient with a hip (median 0.11 mg/L; mean 0.14 mg/L; range 0.06–0.27 mg/L) or a knee prosthesis (median 0.12 mg/L; mean 0.21 mg/L; range 0.06–0.85 mg/L). Although too few different types of prosthesis were used for a statistical analysis, we found no clear relationship between any particular type of prosthesis and the presence of gentamicin in the joint fluid (Table).

The time between primary arthroplasty and collection of joint fluid tended to be shorter in patients who had gentamicin in their joint fluid (median time since primary arthroplasty 4 (1.6–16) years) than in those who did not (median time 9 (1–19) years), but this did not reach statistical significance (Mann-Whitney test). Furthermore, no correlation

Patient characteristics and gentamicin concentrations in joint fluid

Case	Sex	Age	Type of implant	Time [a]	Conc.[b]
1	M	61	Kinematic knee	0.9	<0.05
2	M	66	Kinematic knee	1.1	<0.05
3	F	74	Kinematic knee	1.5	0.13
4	F	55	Kinematic knee	1.7	0.07
5	M	52	Kinematic knee	1.8	0.08
6	M	80	IB II Knee	3.1	<0.05
7	F	80	Kinematic knee	3.4	<0.05
8	F	70	Kinematic knee	4.1	0.06
9	M	68	Kinematic knee	4.9	0.12
10	M	76	Kinematic knee	7.0	0.37
11	M	??	Kinematic knee	7.1	<0.05
12	F	82	Kinematic knee	11	<0.05
13	M	75	Thompson hip	2.9	0.06
14	F	60	Charnley hip	3.5	0.07
15	M	54	Muller hip	8.5	<0.05
16	M	62	Muller hip	9.3	<0.05
17	F	78	D Series hip	12	<0.05
18	M	65	Muller hip	12	<0.05
19	F	71	Charnley hip	12	0.27
20	M	80	D Series hip	14	<0.05
21	M	68	D Series hip	16	0.14
22	F	68	Uncertain hip	19	<0.05
23	F	62	Kinematic knee	4.0	0.16
24	M	75	Kinematic knee	10	0.85
25	F	80	Kinematic knee	15	0.08

[a] Year since implantation
[b] Gentamicin (mg/L)

was found between the gentamicin concentrations and the time since primary arthroplasty (Spearman correlation test).

Discussion

Detection of a significant concentration of gentamicin in joint fluid before revision hip arthroplasty has been reported (Powles et al. 1998), but it is not known whether this was an isolated instance. Our study has confirmed this finding and emphasizes that detectable gentamicin concentrations in joint fluid may be found in about half (13/25) of all patients with gentamicin-impregnated cement where there is evidence of prosthetic loosening. When combined with other in-vivo studies which show that gentamicin remains in an active form inside the cement for a great many years (Powles et al. 1998) and in-vitro studies that show gentamicin release when the cement is fractured (Armstrong et al. 2002) this suggests that gentamicin release when prostheses fail may be a significant problem. It seems likely that failing implants cause a number of cement fractures both small and large in surface area, and since substantial amounts of antibiotic can be released from transverse fractures of small cement beams 'in vitro' (Armstrong et al. 2002) the larger mantle of cement around an implant may be a rich source. It can be postulated that successive cracks in the cement mantle may cause 'bursts' of antibiotic release into the synovial fluid over months or even years. Although many of the concentrations of gentamicin found in this study were below those needed to inhibit staphylococci (0.25–1 mg/L) (Phillips et al. 1991), this kind of intermittent release of sub-therapeutic concentrations of antibiotic would be a potent initiator of antibiotic resistance. This may explain the observation of multiple strain infection with coagulase-negative staphylococci having mixed patterns of gentamicin sensitivity that are cultured from failed prostheses (Hope et al. 1989, Thomas et al. 2002). Certainly, failure to grow organisms from joint aspirates in cases otherwise deemed likely to be septic may, in some instances, be due to this phenomenon. Contact should, therefore, occur between orthopaedic surgeons and microbiologists in cases when specimens are being submitted which may be contaminated by gentamicin, however long ago the index operation was performed, as this may prove important in the evaluation of culture results.

From the extended periods over which gentamicin has been found to elute (up to 16 years), it is clear that attempts should continue to identify ways of producing antibiotic-impregnated cements which have a good short-term elution profile, but which do not sequestrate antibiotic only to be released months or years later. In doing so, consideration should be given to potential hypersensitivity reactions when antibiotics are added to cement. This has not been a problem with gentamicin, tobramycin, vancomycin, colistin, erythromycin and flucloxacillin. In the case of most of these, this is probably because they are not commonly associated with hypersensitivity, but as regards flucloxacillin it is probably because of the intolerance to heat of this antibiotic (Armstrong et al. 2002), which leads to rapid degradation when added to proprietary brands during revision operations. New antibiotics are continuously being evaluated, however, and if any of them have a tendency to cause hypersensitivity reactions, these may be encouraged and enhanced by repetitive release of antibiotic from the cement mantle.

In conclusion, we have been able to show the elution of gentamicin from gentamicin-impregnated cement in almost half of patients undergoing revision surgery. In most of these, the concentrations found were unlikely to inhibit sensitive strains of staphylococcus aureus, but may provide a strong pressure selecting for the emergence of resistance. Such findings indicate the potential adverse properties of antibiotic-impregnated cement in orthopedic surgery and the need for a better understanding of the long-term elution of antibiotics from these cements.

No competing interests declared.

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