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Pharmacokinetics of topical gentamicin in total hip arthroplasty

Two different ways of administering topical gentamicin were examined in patients undergoing total hip arthroplasty. 160 mg gentamicin, dissolved in isotonic saline, was instilled into the wounds of five out of ten patients. In the other five patients, the components of the prostheses were inserted by means of gentamicin-containing cement, 0.5 g per 40 g powder. Both the serum concentrations and the wound concentrations of gentamicin were determined constantly during the postoperative period. The average half-lives of gentamicin in the surgical wounds of the two groups of patients were found to be 3½ and 25h, respectively. The average wound concentration was found to be higher than the minimum inhibitory concentration for staphylococci and aerobic Gram-negative rods for 18 and 11 h, respectively, in the group of patients treated with gentamicin solution compared with 160 and 67 h, respectively, in the group treated with the gentamicin-containing cement.

Key words: antibiotics; cement; gentamicin; hip prosthesis; wound infection.

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The use of gentamicin-containing bone cement in total hip arthroplasty (THA) significantly reduces the number of deep postoperative wound infections (Josefsson et al. 1981). Similar controlled studies involving other types of operations have shown that other ways of administering topical antibiotics can have a prophylactic effect on wound infections (Moylan 1980).

The present work is a study of the pharmacokinetics in serum and wound fluid of topical gentamicin in THA. The gentamicin was applied in two different ways: either as a solution instilled into the wounds or mixed with the cement used for the fixation of the prostheses.

Patients and methods

After giving their informed consent, ten patients undergoing THA (Stanmore prosthesis) took part in the study. All the patients had normal serum creatinine values. Suction drainage was used in all the operations, the drain being placed in contact with the prosthesis. Five of the patients had their prosthesis components fixed by means of gentamicin-containing cement (Palacos), 0.5 g gentamicin per 40 g powder. In the other five patients, gentamicin-free cement was used for the fixation of the prostheses and, after closing the muscle fascias, 160 mg gentamicin dissolved in 100 ml isotonic saline was instilled through the drain. The drain was then clamped until the operation had been completed. The average period of clamping was 22 (15–30) min. The Drevac suction drainage system (Seely et al. 1979) was applied and modified to enable collection of samples of wound fluid for determination of the concentrations, and to calculate the passage times of the wound fluid samples from the surgical wound through the drain to the sampling place. A rubber membrane was inserted into the drain. Approximately 150 µl of wound fluid per sample was aspirated through the membrane by means of a syringe. A bacterium-proof air filter on a small side-tube provided with a clamp was inserted between the rubber membrane and the suction bellows, approximately 15 cm from the latter. The flow rate of the wound fluid in the drain was measured in the following way: The drain on the patient's side of the air filter was clamped and the connection to the filter opened. Consequently, the part of the drain between the filter and the suction bellows was emptied as the wound fluid was aspirated into the suction bellows. By restoring the original conditions, it was

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possible to measure the flow rate of the fluid in the emptied part of the drain (mm/min). Wound fluid samples were taken 1, 2, 6, 10, 14, 22, 26, 30 and 34 h after the application of the topical gentamicin. The flow rate of the wound fluid in the drain was measured simultaneously. After removal of the drains 2–3 days after the operation, the length of the drain from the wound to the rubber membrane was measured and the times for the collection of fluid samples were corrected with consideration to the passage time through the drain.

Five blood samples were taken from each of the patients in order to determine the serum concentrations. The samples were taken ½, 1, 2, 6 and 10 h after the application of the topical gentamicin.

An agar diffusion method with filter paper discs (diameter 6 mm) was employed in order to measure the concentrations of gentamicin. The wound fluid samples were centrifuged and measured on the supernatants. Antibiotic medium number 5 (Difco) was used as test medium and *Pseudomonas aeruginosa* as test strain. Standard concentrations for determination of the concentrations in the wound fluid samples were prepared in pooled wound fluid supernatants from patients not treated with gentamicin. Standard concentrations for the measurement of the serum concentrations were prepared in pooled human serum. All samples were double-checked. The smallest measurable concentration was 0.3 µg/ml.

According to Atkinson (1980), 95 per cent of *E. coli, Klebsiella, Enterobacter* and *Proteus mirabilis*, and 75 per cent of *Ps. aeruginosa* have a minimum inhibitory concentration (MIC) of gentamicin which is ≤4.0 µg/ml, and 100 per cent of *Staph. aureus* and *Staph. epidermidis* have a MIC of gentamicin which is ≤0.8 µg/ml. The measured concentrations in the wound fluid are evaluated on the basis of these MIC-values by estimating the time during which the concentration is above 4.0 and 0.8 µg/ml.

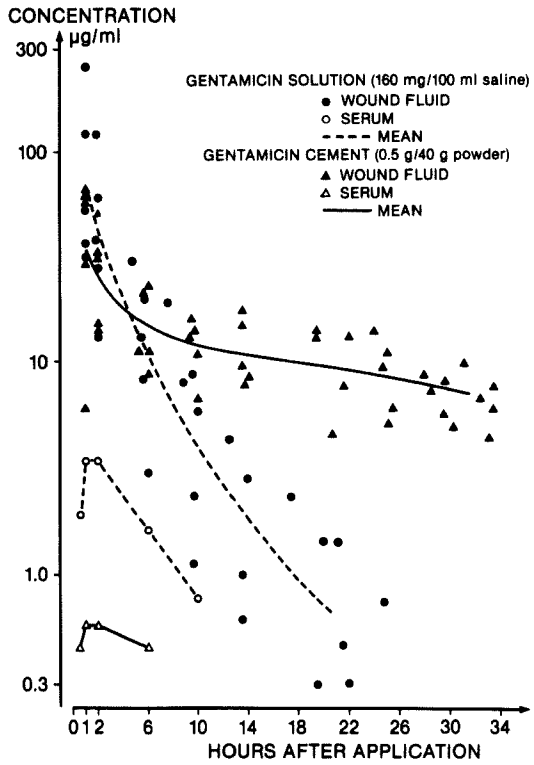

Figure 1. Concentration of gentamicin in serum and wound fluid. For serum only mean concentrations are indicated.

Results

The individual concentrations measured in the wounds as well as the mean concentrations in serum can be seen in Figure 1. At 10 h, three patients with gentamicin-containing cement had serum concentrations below measurable level. In all patients the serum concentrations were lower than the wound concentrations. In eight of the patients, the highest wound concentration measured was found in the first wound fluid sample taken 1 h after the application of the gentamicin. In the remaining two patients, both treated with gentamicin-containing cement, the highest wound concentration was seen 2 and 6 h, respectively, after the application.

After 6 h the wound concentration curves could be regarded as exponential and the half-lives as well as the duration of time after the gentamicin was applied until the concentration

Table 1. Pharmacokinetic data in wound fluids for topical gentamicin applied in two different ways, expressed as mean value and range

	Half-life hours	Hours after the application until the concentration falls below	
		0.8 µg/ml	4.0 µg/ml
Gentamicin solution	3.5 (2.5–4.5)	18 (13–22)	11 (5.5–14.5)
Gentamicin cement	25 (12–80)	160[1] (63–277)	67[1] (35–117)

1. This result has been reached by extrapolation.

fell below 4.0 and 0.8 μg/ml were calculated by linear regression of the logarithm of the concentrations on the time (Table 1).

Discussion

Several studies seem to indicate that there has to be a certain number of contaminating bacteria in the wound area for a postoperative wound infection to occur (Polk & Lopez-Mayor 1969, Krizek & Robson 1975). The favourable effect of prophylactic antibiotics on the frequency of postoperative wound infections, which has been seen in several controlled studies, is probably due to the fact that the antibiotics reduce the number of contaminating bacteria in the wound to below an infectious level (DiGiglia et al. 1970).

The circumstances which influence the effect of antibiotics in such a prophylaxis are partly that the concentrations reached in the wound are above MIC and partly that such concentrations remain in the wound for as long as it takes to reduce the number of bacteria sufficiently.

By using antibiotics topically, it is possible to obtain much higher concentrations in the wounds than by using systemic administration which carries a higher risk of toxic side effects. We found in our study that in the first hours after application of the gentamicin the concentrations in the wounds were much higher than those obtained by others after parenteral administration (Reichelt et al. 1976).

In the first hours after the application the concentrations in the wounds were similar for the two groups of patients, but the fall in the concentration of gentamicin was much slower in the group of patients treated with gentamicin-containing cement. The same difference could be observed in the period after the application, during which there was a therapeutic concentration of gentamicin in the wounds. Thus, in the group treated with the gentamicin solution the concentration in the wounds was found to be higher than MIC for aerobic Gram-negative rods and staphylococci for 11 and 18 h, respectively, after the application, compared with 67 and 160 h, respectively, in the group treated with gentamicin-containing cement. However, the latter periods were calculated by extrapolation and since the last measurements of the concentrations took place approximately 34 h after the insertion of the cement, these figures should be considered with some caution. Other workers have found therapeutic concentrations in the tissue near the cement for several months after the operation (Wahlig & Dingeldein 1980).

In the group of patients treated with gentamicin solution, the serum concentrations corresponded to those found after intramuscular administration of normal therapeutic doses. With respect to any toxic side effects, it thus does not seem to be possible to increase the amount of gentamicin applied in this way.

Based on the pharmacokinetic results obtained in this work, the use of gentamicin-containing cement seems to be preferable to that of a gentamicin solution, due to the considerably slower decrease of the concentrations in the wounds. This does not, however, throw any light on whether there will be a similar difference with regard to the prophylactic effect on infections. This will depend on how quickly the concentrations of gentamicin obtained in the wounds are able to reduce the number of contaminating bacteria to below the level causing infection. To the authors' knowledge, no data elucidating this matter have yet been published.

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