Acta orthop. scand. 47, 144–148, 1976

THE *IN VITRO* ELUTION OF GENTAMICIN SULPHATE FROM METHYLMETHACRYLATE BONE CEMENT

A Comparative Study

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The *in vitro* elution of gentamicin from three brands of bone cement has been studied. One was found to have a much longer lasting activity than the other two. This activity and the possible deleterious side effects from the use of gentamicin in bone cement as a routine procedure are discussed.

Key words: bone cement; gentamicin; postoperative infection; total hip replacement

Accepted 18.xi.75

For a number of years the use of methylmethacrylate as a means of fixation of total hip prostheses has been an established part of the procedure.

It has however been troubled by an unusually high number of infections, the prevention of which has led to expensive and complicated procedures such as special sterile operating enclosures and special ventilating systems, and even vaccination against staphylococci.

It is commonly believed that the infections of total hip replacement (THR) show themselves in two different clinical entities: the immediate postoperative infection as seen with other types of surgery and a late infection with an insidious onset after a latent period of up to 1 year or more. These infections often necessitate the removal of the prosthesis with considerable loss of function as the result.

The late type of infection is believed by some to be derived from bacteria of low virulence, perhaps sometimes anaerobics, from the skin flora mostly, that have been introduced into the wound at the time of surgery (Charnley 1972, Ericson et al. 1973, Kamme et al. 1974) while others hold the view that a haematogenic infection can occur at a *locus minoris resistentia* (Buchholz & Gartmann 1972).

Hessert & Ruckdeschel (1970) tried to mix methylmethacrylate bone cement (Palacos®) with tetracycline, a mixture of penicillins, and with gentamicin sulphate. Eluting the antibiotic from the polymerized bone cement in 0.8 per cent NaCl they found no trace of tetracycline. Of the penicillin mixture, about 5 per cent was found in the solution after 24 hours, but up to 80 per cent of the gentamicin was recovered. They used 1 g of

gentamicin in one package of bone cement, concluding that with the use of such a cement a liberation of about 800 mg of gentamicin could be expected. Wahlig & Buchholz (1972) carried out similar experiments using Palacos® as the cement, a phosphate buffer solution as the eluting fluid, and gentamicin as the antibiotic. They found a very long lasting release of gentamicin, lasting for over one year. Buchholz & Engelbrecht (1970) tested the antibiotic effect of penicillin-G, erycin-heptogluconate, rolitetracycline, and gentamicin sulphate in Palacos® with dextrose agar as the solvent. They found good antibiotic activity with penicillin, lasting for over one year. No tetracycline activity was demonstrated. With gentamicin an initially very high concentration was found in the broth. The concentration decreased over 10–12 days to a low value that stayed constant for more than 2 months.

The total amount of gentamicin recovered was about 6 per cent of the initial amount. Wahlig & Buchholz (1972) also examined the serum levels and urine concentrations in rats and dogs after implantation of cement containing gentamicin and measured the same parameters in 20 patients who had THR with gentamicin in the cement. They found very low serum levels for only 1–2 days in both animals and humans. The rats had traceable gentamicin activity in the urine for 22 weeks, whereas the effect in dogs only lasted about 2–3 weeks, the difference presumably being due to characteristics of the species. In two patients in whom the excretion of gentamicin was followed it was no longer traceable in the urine after about 3 weeks, the total excreted amount being about 6 per cent of the amount implanted.

Eicher (Knight, personal communication) mixed the injectable preparation of gentamicin into the cement and by using chromatography, he was able to demonstrate small amounts of the drug in the patients' urine. Wahlig & Hahmeister (1973) tested the liberation of gentamicin from Palacos®. Their results were similar to those of other workers, viz., that small amounts of the antibiotic are set free for very long periods of time. Their experiments lasted for up to 30 months. They implanted the cement in dogs and found concentrations varying from 1 to 54 μg/ml in the wound secretion taken from a cavity in the cement. Sattel & Nabert-Bock (1973) in a comparative study found the release of gentamicin from CMW to last about 4 months whereas Refobacin-Palacos® showed antibiotic activity for a much longer period of time. They also examined the contents of gentamicin in the wound drainage after the use of Refobacin-Palacos® in three patients and found concentrations from 20 to 10 μg/ml. They further aspirated the THR's in 30 patients and found antibiotic activity after 264 days with concentrations of 0.2–0.04 μg/ml. Stöhr et al. (1973) were able to demonstrate gentamicin concentrations in wound secretions of 1–2 μg/ml up to 21 months after insertion of Palacos® with gentamicin. Gartenmann et al. (1973) tested the antibiotic effect of Nebacetin (a mixture of neomycin and bacitracin) in combination with Palacos® and CMW Bone Cement® and found a high level of activity after 7 days with the Palacos® mixture. The results with CMW Bone Cement® were significantly poorer. Their clinical results showed no primary infections in 100 cases. A long-term follow-up of their material has not yet been done.

MATERIAL AND METHODS

A package of CMW Bone Cement® powder was mixed with 1 g of gentamicin sulphate powder by thorough stirring. The monomer was added and the cement was mixed according to the manufacturer's instructions. The cement was then cast into rods of 10×4×110 mm in a mould. After removal from the mould the samples were machined on one side to the exact thickness of 4 mm. A package of Surgical

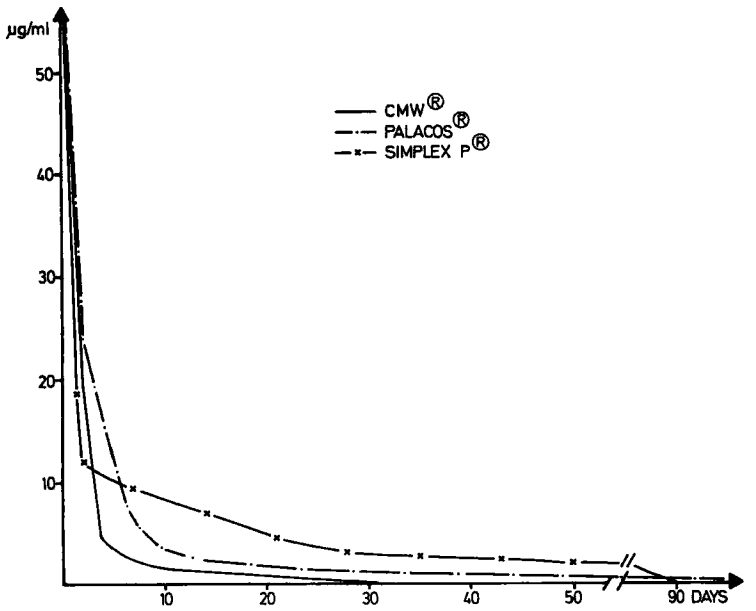

Figure 1.
The concentration of gentamicin eluted from three brands of bone cement.

Simplex® mixed with 0.5 g of gentamicin sulphate and a package of Refobacin Palacos® were prepared in a similar manner.

The samples then underwent mechanical testing to determine the modulus of elasticity and the breaking strength. (Results not yet published). The fragments weighing about 1.8 g each were then analyzed as to their antibiotic activity. A total of 80 specimens were examined.

Determination of antibiotic activity

The rods were placed in tubes surrounded by human serum. The tubes were then placed in a rolling-machine in an incubator at + 35° C. The serum was changed every 24 hours.

The method used for measuring the concentration of gentamicin has been described previously by Rosdahl et al. (1970). First daily, and then later weekly samples were taken. Results are shown in Figure 1.

RESULTS

The release of gentamicin from all the specimens shows a common pattern in that the release is greatest in the first hours after adding the serum and then slowly decreases until the serum is changed, when there again is a sharp rise in output per hour. This underlines the simple fact that the release of antibiotic is a diffusion process.

In evaluating the results it was considered that although many experiments were carried out each specimen consisted of a portion of the same batch. It was therefore felt that although the variations in results from sample to sample were sometimes considerable (up to 2–300 per cent) it would be justifiable to give the results as mean values, the individual variations being due to such factors as uneven mixing of the cement and gentamicin powder or even the presence of a lump of powder on the cement surface. This might also occur in the case of clinical use so that the diagrams express the rate of elution from the whole portion of cement (Figure 1). The results show, in accordance with the findings of Wahlig & Hameister (1973), that the gentamicin is initially released in large amounts giving rise to very high concentrations locally. In the case of CMW the release diminished to a low level after about 10 days and the activity had ceased after 30 days. The Surgical Simplex showed a similar curve although the release was somewhat higher and lasted about 4 months. Refobacin-Palacos® also

gave a high initial dosage, but then continued with a slow release for 3 months after which time the experiment was discontinued. This level of release corresponded to about 0.5 μg gentamicin per gram of cement per day.

DISCUSSION

The present results confirm the findings of others although there are differences in the results of various investigators. Sattel & Nabert-Bock (1973) found that Palacos® not only had a longer lasting release of gentamicin, but also a higher release. This last observation has not been confirmed in the present study, but it seems logical that differences in shape and size of the test bodies, differences in eluting fluids, and in the frequency of fluid change may alter the results. In clinical use the release of antibiotic will depend on two factors: the surface area of the cement involved and the diffusion gradient, i.e. the turn-over of tissue fluid surrounding the cement. This also explains why in the present study the antibiotic activity in CMW had ceased after about 30 days while other investigators (Sattel & Nabert-Bock 1973) found a much longer lasting activity since they used cement pieces with irregular surfaces and of twice the size as were used by us.

The concentration of antibiotic inside the cement will undoubtedly remain very high and any water absorbed into the acrylic cement and possibly filling the "vacuoles" in the cement will be saturated with gentamicin.

The concept of using a long lasting depot antibiotic in the bone cement rests on the theory of haematogenous infection as the cause of late infections in the THR.

The most common type of bacteria in infected THR's is a staphylococcus of some variety or other, but also a number of anaerobics have been found as listed by Buchholz & Gartmann (1972).

Whether this large variety of bacteria, some 20 different kinds, are most likely found in the circulating bloodstream or whether they enter the wound at the time of operation is debatable. That haematogenous infection can occur cannot be completely denied, but in the light of present knowledge it is the authors' belief that peroperative infection still seems the most likely route.

The claims of Buchholz & Engelbrecht (1970) and of Wahlig & Hameister (1973) that the possibility of toxic and systemic side effects can be ruled out cannot be supported. If a THR is implanted using gentamicin in the cement the body will receive and excrete small amounts of gentamicin every day. It has yet to be demonstrated that no allergic or long-term toxic effects arise from this procedure, especially since the indications for THR tend to include much younger age groups now than some years ago. The well-known development of allergies in, for instance, chemical and industrial workers to various substances after 10 to 20 years of exposure may be a warning sign. Also the risk of developing resistant strains of bacteria must be considered. From the point of view of prophylaxis it might therefore be preferable to choose a cement type that does not have the very long-lasting effect.

It has however been demonstrated (Ericson et al. 1973) that through prophylactic usage of systemic antibiotics of proper choice and in adequate dosage the avoidance of infection can be achieved—and this treatment can be discontinued at will. It must also be remembered that gentamicin is virtually without effect on anaerobic bacteria. However, the excellent results achieved by Buchholz (Buchholz & Gartenmann 1972) show the value of using a bone cement with a long-lasting antibiotic effect as a therapeutic measure in trying to salvage an already infected THR.

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