ANTIBIOTIC-LOADED ACRYLIC CEMENT

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Laboratory experiments and clinical investigations have confirmed the various claims made originally by Buchholz and Engelbrecht (1970) that antibiotic-loaded acrylic cement releases the antibiotic into the surroundings in useful concentrations. Palacos R cement released higher concentrations than CMW, Simplex and Sulfix brands of cement and over longer periods. Concentrations of gentamycin and facidin were sufficient to penetrate dead cortical bone. These conclusions need to be assessed with animal studies, mechanical testing and clinical results before the ideal place of antibiotic-loaded acrylic cement is established.

The problem of deep infection involving a joint implant, especially when fixed by means of acrylic cement, needs no emphasis. Bacterial contamination can occur at the time of operation by air pollution or by direct contagion: otherwise, it must derive from the patient’s bloodstream, either at the time of operation or later. Control and prevention are effective by an aseptic ritual, by operating only on patients free from overt sepsis, and by using prophylactic antibiotics systemically or locally. The effects of late deep infection (pain and loosening at the bone-cement interface) have to be related to possible primary mechanical failure; it may be that infection sometimes starts this process but, subsequently, organisms are not found. The problem is difficult to assess because there are so many variable factors, and particularly because of the length of time needed for a full assessment of the clinical situation.

The aseptic technique employed varies in sophistication from place to place, but individual results can be compared reliably with those from the Centre for Hip Surgery at Wrightington (Charnley 1972), where a standard technique has been used for several years. There, with the clean air system and no antibiotics, the only source of infection is the patient himself. With available techniques, organisms from this source cannot be excluded and therefore, presumably, they can be dealt with only by the defence mechanisms of the subject or by disinfectants or antibiotics. Antibiotics can be added to the acrylic cement, and the results of this innovation by Buchholz and his colleagues in Hamburg (Buchholz and Engelbrecht 1970) have been substantiated in several subsequent publications.

The purpose of this paper is to describe certain aspects of our laboratory investigations into the basic properties of antibiotic-loaded acrylic cement. Concurrently, clinical trials are in progress, but the following experiments were performed in order to assess, and in some cases to amplify, the various claims asserted by Buchholz and Gartmann (1972), so as to justify the use of the material in our patients who might be exposed to unknown hazards. Strong theoretical advantages would have to be demonstrated before such risks could be justified. For example, it is known that the addition of substances to acrylic cements alters their mechanical properties (Watts and Elson 1976), but we do not know how much alteration is safe; long-term stability of joint implants might be prejudiced. Furthermore, the possibility of dangerous pharmacological effects from implanting large deposits of antibiotic cannot be ruled out other than by a wide-scale clinical trial. Accordingly, our clinical, therapeutic and prophylactic use of antibiotic-loaded cement must continue for a much longer period before any conclusion can be reached, and further mechanical studies are in progress.

In the meantime, we have examined the following questions in laboratory investigations. 1) Do antibiotics elute (leach out) from acrylic cement in useful concentrations and over significant periods of time? 2) Do different brands of acrylic cement vary in the amounts of antibiotic that they release? 3) Do antibiotics vary in their suitability for loading acrylic cement? 4) Are the concentrations of antibiotic liberated sufficient to penetrate dead bone in effective concentrations, assuming that the presence of necrotic bone is one of the basic problems in the chronic osteomyelitis which accompanies deep infection of implants? 5) Can we provide a model animal study which represents the human situation and can be used for testing different combinations of antibiotic-loaded acrylic cement? 6) From investigations of individual patients undergoing operations using antibiotic-loaded cement, can we substantiate that antibiotics are liberated in the human in useful concentrations?

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THE CHOICE OF MATERIALS

At the beginning of this work there were four brands of acrylic bone cement available, and a multiplicity of antibiotics and disinfectants which, it was claimed, were resistant to the heat and chemical effects of the cements.

In the United Kingdom, Gardner (1975) and colleagues had initiated a multicentre trial using fusidin, whereas gentamicin had been used extensively elsewhere in Europe. Accordingly, we restricted the choice of antibiotic to fusidin (diethanolamine fusidate in amounts equivalent to sodium fusidate) and gentamicin (gentamicin sulphate in amounts equivalent to gentamicin base).

It had been stated that Palacos-R acrylic cement released greater quantities of antibiotic than the other brands (Wahlig, Schliep, Bergmann, Hameister and Grieben 1972; Wahlig and Buchholz 1973). The veracity of these statements was confirmed, and we subsequently used Palacos-R for most of our experiments.

Choice of bacteria—The number of species which have been cultured from operation sites of deep infection is large. Staphylococcus aureus is the organism most frequently found and it seemed reasonable to use this organism, choosing a strain which could be readily identified and which was fully sensitive to both fusidin and gentamicin. Later, other organisms were used.

ELUTION OF ANTIBIOTIC IN VITRO

The rate of elution of antibiotics from acrylic cements into distilled water has been measured. Mixtures of antibiotic and cement (fucidin and gentamicin) in appropriate concentrations were made by shaking the powdered polymer in its bag with the antibiotic powder for five minutes. The monomer liquid was then added and mixed in the normal manner, and the cement was allowed to cure in metal moulds. The blocks thus formed were rectangular and in two sizes: 2 cm × 2 cm × 0.5 cm, and 2 cm × 2 cm × 1 cm.

After two to three weeks, the blocks were placed in standard volumes of distilled water which were changed daily, each day's specimen being assayed for antibiotic concentration (Fig. 1). After the tenth day, by which time the amount of antibiotic eluted was low, the blocks were left undisturbed for fourteen days, when one further estimation was made. The concentrations of antibiotic eluted into the distilled water were measured by a standard plate diffusion method (Reeves 1972).

\[ \text{Fig. 1} \]
Method used for measuring antibiotic eluted from acrylic cement.

\[ \text{Fig. 2} \]
Concentrations of gentamicin eluted from blocks of gentamicin-loaded acrylic cements. Figure 2—Comparison of Palacos-R containing 1.0 gram and 0.5 gram per 40-gram powdered polymer, before curing, with CMW and Simplex containing 1.0 gram. Figure 3—Comparison of Palacos-R with Sulfix. From the fourth consecutive day, the concentrations eluted are low, but after leaving the pots undisturbed for about thirteen days, significant concentrations can be measured.

* CMW Orthopaedic Bone Cement, CMW Laboratories Ltd., Blackpool, U.K.
  Palacos-R, Kulzer & Company GmbH, Bad Homburg, West Germany.
  Sulfix-6 Bone Cement, Sulzer Brothers Ltd., Winterthur, Switzerland.
RESULTS

Five specimens of each of the combinations of antibiotic and cement were tested with comparable results. One result is shown (Figs. 2 and 3). From our experience with several combinations, there is no doubt that the experiments are comparable and repeatable, and that Palacos-R cement releases larger quantities of antibiotic over the period of time described. The results for fucidin were similar, but difficulty was encountered in preventing contamination of the pots by moulds.

COMMENT

These experiments show that acrylic cement releases gentamicin and fucidin into distilled water. It is known that this process continues over long periods—even for two years (Grieben 1975). The process is one of diffusion within the polymer substance; it has nothing to do with the pores holes seen on a section of acrylic cement because the pores do not intercommunicate and allow antibiotic solutions to flow between them. The antibiotics are water soluble, and water diffusing in and out of polymethylmethacrylate matrix carries the antibiotics with it.

Why Palacos-R should release more antibiotic than the other cements tested is not clear nor can the manufacturers answer this question. All four brands of cement have different textures and times for curing, but the range of tests conducted here offers no explanation for the phenomenon. Mechanical testing does not suggest that Palacos-R is inferior to the others (Watts and Elson 1976), and we have used it in our clinical studies with good effect.

Sattel and Nabert-Bock (1973) found results similar to ours and Holm and Vejlsgaard (1976) discussed these in the light of their findings which, although comparable in terms of the length of time during which antibiotic was released from Palacos-R, indicated that the concentrations obtained from Palacos-R were less than those from Simplex. On the other hand, Marks, Nelson and Lautenschlager (1976) confirmed our findings with regard to Palacos-R in both respects and mentioned that they had found the pore size (and therefore the "internal" surface area) larger. The pore size must be related to the number of pores if an estimation of surface area is to be made. Our scanning electron microscope pictures show no difference in pore size or number. Marks et al. (1976) used oxacillin and cefazolin in addition to gentamicin, with similar results.

The long-term release of antibiotics from masses of cement comparable in size to those used in human joint replacement operations may be important for long-term protection from blood-borne infection. Antibiotic-loaded acrylic cement has been removed from one of our patients after being in situ for two and a quarter years. The broken surface retained a highly bactericidal concentration of antibiotic, and presumably, although at very low levels of concentration, the surface must have presented some small persisting concentration. Wahlig and Buchholz (1973) suggested that it is from the superficial four millimetres of a mass of cement that the release occurs; but if this is a diffusion process it is difficult to accept that such a threshold exists.

THE PERMEATION OF NECROTIC BONE

This experiment was designed to find out if the concentration of antibiotic eluted from cement implanted in dead human bone was sufficiently high to enable it to diffuse through significant thicknesses of necrotic bone. Segments from the middle thirds of the femora were removed from human cadavers. The cortical bone at this level measured approximately 7 millimetres in thickness and was dense; the length of the segments removed was 16 centimetres. The periosteum was stripped, the medullary cavity evacuated and the endosteal surface curetted thoroughly in each specimen. Immediately, the medullary cavity was packed with an antibiotic-loaded cement preparation and care was taken that the outside was not contaminated by the antibiotic. When the cement had been pumped to within about 1 centimetre of the distal end, the proximal end was evacuated to a similar extent and the cement allowed to cure in the usual manner. Plain cement plugs were inserted into the incompletely filled ends of the medullary cavity.

![Diagram showing method of mounting a segment of shaft of human femur containing antibiotic-loaded acrylic cement in a plastic box. The ends of the bone are outside the box and any antibiotic detected in the water must have permeated through the bone.](image)

Each specimen was mounted in a plastic container, water-tight rubber seals being used so that the container could be filled with distilled water (Fig. 4). The volume of the distilled water required to submerge the bone segment was reduced in one experiment by glass beads, but in three other experiments the same effect was achieved by squashing the plastic box appropriately after it had been heated. In this simple arrangement, the ends of the bone were isolated from the distilled water, being outside the box. The only way in which antibiotic could enter the water was by permeation through the thickness of the wet cortical bone.

The water was sampled daily for the antibiotic, and at the same time the volume removed was replaced. Subsequently the bone was removed from the water, allowed to dry at room temperature and then tested for
antibiotic concentration. Specimens from the cortical bone were obtained using a 4-millimetre drill at ten sites to depths of one-third, two-thirds and full thickness (Fig. 5). Each depth yielded some powdered bone and the yields from the ten sites were collected into three samples, one from each depth. The three groups were assayed for concentrations of gentamicin per unit weight of bone powder by desiccating the sample, weighing the dry sample, then shaking the powder in a known volume of distilled water and finally measuring the concentration of gentamicin in the distilled water by the plate diffusion procedure.

powdered polymer respectively. With any one experiment the comparison between the right and left femora containing the antibiotic was, respectively, between Palacos-R and Simplex.

Figure 6 shows a typical result for Palacos-R and Simplex, each pack containing 1·0 gram gentamicin; the Palacos-R specimen yielded higher amounts of antibiotic through the thickness of the bones than did Simplex. From these two bones, the concentration of antibiotic located in the bone itself, and estimated in the manner described, is shown in Table I. With one variation which we cannot explain, the concentrations of

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\begin{array}{|c|c|c|c|}
\hline
\text{Subject} & \text{Agents implanted} & \mu g \text{ gentamicin per gram of dried bone} \\
& & \text{Inner third} & \text{Middle third} & \text{Outer third} \\
\hline
A & \text{Palacos} + 1·0 \text{ gram gentamicin} & 18-0 & 4-0 & 165-0 \\
& \text{Palacos} + 1·0 \text{ gram gentamicin} & 16-0 & 12-0 & 18-0 \\
B & \text{Simplex} + 1·0 \text{ gram gentamicin} & 9-4 & 8-2 & 9-3 \\
& \text{Simplex} + 1·0 \text{ gram gentamicin} & 9-2 & 7-2 & 9-9 \\
\hline
\end{array}
\]

RESULTS
Four experiments were done, three using gentamicin and one using fusidin. The cements compared were Simplex and Palacos-R. For the purposes of this comparison, the right and left femora from the same human cadaver were used, thus affording two presumably similar bones for comparison, and the same quantities of antibiotic were added to each corresponding pair of bones: 1 gram of fusidin, 1 gram of gentamicin (on two occasions) and one-half gram of gentamicin per 40-gram pack of antibiotic from the Palacos-R are higher. Comparable results were obtained with one-half gram of gentamicin per pack, and 1 gram fusidin per pack, but we did not estimate the concentrations in the bone substance, this being a proposed further study.

COMMENT
This experiment demonstrates that antibiotics released from a cement depot can permeate dense cortical bone in theoretically effective concentrations.
The concentrations recorded could never be reached by systemic administration of the antibiotic unless the living bone had some special tendency to concentrate antibiotic to levels above those in the tissue fluids (as reflected by blood levels).

One obvious criticism concerns the path taken by the antibiotic. We do not know if it passes diffusely through the bone tissue or selectively through the canals therein. The density of the network of blood vessel canals and canaliculi is high, however, and it seems reasonable to assume that the concentration of antibiotic throughout the composite mass of the bone would be fairly uniform. In vivo, it is possible that the antibiotic, when liberated into the bone, would be removed by the blood stream and that the outer layers of bone might not experience adequate concentration of the antibiotic. While we can see no way of disproving this possibility, the observations of Wahlig and Buchholz (1973), in which tissue levels outside the living bone in which gentamicin-loaded cement had been implanted in human hip arthroplasties were studied, suggest that the material diffuses through the bone substance.

Fucidin has been declared particularly effective in achieving useful concentrations in bone sequestra but it is highly likely that those recorded, for example by Chater, Flynn and Wilson (1972), would be vastly exceeded by those yielded from fucidin-loaded cement.

CLINICAL INVESTIGATIONS

It is not the purpose of this paper to record the results of clinical use, but certain observations following joint replacement operations using gentamicin-loaded Palarco-R cement of blood levels, urinary concentration, and tissue fluid as reflected in vacuum drainage effluent, are factual and can be added to other basic research results.

We have measured these concentrations in eighty-seven patients, and it is not necessary to detail these because they are similar to those published elsewhere (Wahlig and Buchholz 1972). For reference in this Journal, however, Figures 7 to 9 shows the typical concentrations and amounts excreted. The variation was considerable, especially in the tissue fluid concentrations, in which no corresponding variation could be found relating to such obviously relevant factors as: 1) whether 1·0 gram per pack of gentamicin had been used; or the more commonly used 0·5 gram per pack concentration; 2) the exact sitting of the deep drains; 3) the weight of cement used; and 4) the diameter of the femoral canal.

We have found that the usual pattern of events is as follows. Gentamicin can be detected in the blood for about three or four days, in the urine for twenty days, and in the drainage fluid for variable periods (even forty-eight days in one case). The levels in the blood stream are below those produced when gentamicin is administered systemically in doses proved adequate by monitoring the blood levels. Such levels as do occur are unlikely to be toxic. The quantities of antibiotic excreted must increase the risk of the emergence of gentamicin-resistant strains of bacteria, not necessarily related to the patient, but to his environment. However, no such example has been recorded here, nor reported elsewhere. Similarly, no instance of allergy or idiosyncrasy has been recorded.
DISCUSSION AND CONCLUSIONS

When the claim was put forward that certain antibiotics could be added to acrylic cement and that subsequently a remarkably long-lasting elution into the surrounding tissue fluid took place, most orthopaedic surgeons inclined initially to the belief that this was merely another example of the ordinary short-lived topical application of an antibiotic.

Buchholz and Engelbrecht (1970) were undoubtedly the first to exploit the potential of antibiotic-loaded cement, and they admit freely that their initial trials were empirical. For example, it was by chance that Palacos-R cement was used first, because this was the brand that was most widely available in Germany.

From the subsequent studies in Hamburg, knowledge of the basic properties of this combination has become widely available. The results of our studies confirm in general all the claims of Buchholz and his colleagues.

Antibiotic-loaded cement is mechanically less strong than plain cement (Watts and Elson 1976), a factor which must be borne in mind when using this combination in joint replacement operations.

The place for antibiotic-loaded cement in clinical practice is becoming rapidly defined. Eventually, the large series accumulating in Europe and America will provide practical guides for its use. In the meantime, the theoretical advantages supported by shorter term laboratory studies need to be weighed with care against the clinical uncertainties.

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REFERENCES


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