Treatment of osteomyelitis with antibiotic-soaked porous glass ceramic

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We have developed a new drug delivery system using porous apatite-wollastonite glass ceramic (A-W GC) to treat osteomyelitis. A-W GC (porosity, 70% and 20% to 30%), or porous hydroxyapatite (HA) blocks (porosity 35% to 48%) used as controls, were soaked in mixtures of two antibiotics, isepamicin sulphate (ISP) and cefmetazole (CMZ) under high vacuum.

We evaluated the release concentrations of the antibiotics from the blocks. The bactericidal concentration of ISP from A-W GC was maintained for more than 42 days, but that from HA decreased to below the detection limit after 28 days. The concentrations of CMZ from both materials were lower than those of ISP. An in vivo study using rabbit femora showed that an osseous concentration of ISP was maintained at eight weeks after implantation. Osteoconduction of the A-W GC block was good.

Four patients with infected hip arthroplasties and one with osteomyelitis of the tibia have been treated with the new delivery system with excellent results.

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The surgical treatment of chronic osteomyelitis often produces large bone defects which should be filled to reduce recurrence. Various antibiotic carrier systems have been developed, particularly antibiotic-impregnated polymethylmethacrylate (PMMA) beads which are widely used.^{1,2} When such beads are used for chronic osteomyelitis, a

subsequent removal operation is required. Recently, drug delivery systems (DDSs) using resorbable materials such as collagen,³ fibrinogen⁴ and polylactic acid⁵ have been developed. These do not require removal, but do not replace bone grafting.

We have developed a new DDS using an antibiotic-soaked porous A-W glass ceramic (GC) block which has previously been shown to form a chemical bond with living bone and to have a mechanical strength almost equal to that of cancellous bone.⁶

Materials and Methods

In vitro study. Two types of porous A-W GC (Nippon Electric Glass Co, Ltd, Otsu, Japan) were made into 8 mm³ blocks. They had a porosity of 70% (A-W GC 70) and 20% to 30% (A-W GC 20-30) and pore sizes of 200 µm and 10 to 50 µm, respectively. The chemical composition of A-W GC in terms of weight percentage is MgO 4.6, CaO 44.9, SiO₂ 34.2 and CaF₂ 0.5. It contains oxyfluorapatite and β-wollastonite. Apatite accounts for approximately 35% of the weight, wollastonite for 40% and glass for 25%. The method of synthesis has previously been reported by Kokubo et al.⁷ Porous hydroxyapatite (HA) blocks of the same size (porosity, 35% to 48%; pore size, 50 to 300 µm; Sumitomo Pharmaceutical Co, Ltd, Tokyo Japan) were used as controls. The compressive strength of A-W GC 70 is 20 MPa, that of A-W GC 20-30 is 236 MPa and that of HA is 45 to 70 MPa.

We used two antibiotics, isepamicin sulphate (ISP; Asahi Chemical Industry Co, Ltd, Osaka, Japan) and cefmetazole (CMZ; Sankyo Co, Ltd, Tokyo, Japan). The minimum inhibitory concentration against *Staphylococcus aureus* was 0.39 µg/g for ISP and 1.56 µg/g for CMZ.^{8,9}

The three types of porous ceramic block were placed in a bone cement mixer (Mixovac II High Vacuum System; Stryker, Michigan) into which solutions of 100 mg/ml of ISP or CMZ were poured until all the blocks were covered. A vacuum of 500 mmHg was sustained for 10 minutes. To evaluate the elution ability of the porous blocks, each block was placed in a test tube (15 ml), covered with 3 ml of phosphate-buffered saline (PBS) (pH 7.4) and stored in a thermostatic chamber at 37°C. The PBS was replaced every two days and the preserved PBS was then frozen at -20°C

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Fig. 1a

Fig. 1b

In vitro release of ISP (a) and CMZ (b) from A-W GC 70, A-W GC 20-30 and HA.

until assayed. The concentrations of antibiotic in each eluate were assayed by high-performance liquid chromatography.

In vivo study. The porous A-W GC 70 cylinders (4 mm/diameter, 4 mm/height) were soaked under vacuum with the ISP or CMZ solution (100 mg/ml). A hole about 4 mm in diameter was drilled into the bone-marrow cavity of the intercondylar region of the right femur of four groups of three mature male rabbits weighing 3 to 3.5 kg. Seven small cylinders of antibiotic-soaked porous A-W GC were inserted, and the opening was closed with bone wax. The groups were killed at 1, 2, 4 and 8 weeks after implantation, and the right femur and blood were collected. Slices of bone were obtained from the proximal, middle and distal thirds of each femur. After removal of soft tissue and bone marrow, the cancellous and cortical bone was pulverised, homogenised with PBS, and centrifuged. The supernatant fluid was collected for evaluation.

Results

To obtain the absorption rate the change in weight of a ceramic block from before soaking to after soaking was divided by its weight before soaking. The antibiotic absorption ratio of A-W GC 70 was 76.1%, that of A-W GC 20-30 21.8% and that of HA 25.3%. The absorption ratio was thus roughly proportional to the porosity for the A-W GC material but not for the HA block.

In the in vitro study, the highest level of ISP was released from A-W GC 70, and the bactericidal concentration was maintained for 42 days. The concentration released from HA decreased to below the detection limit after 28 days. A-W GC 20-30 showed an intermediate release concentration (Fig. 1). The concentration of CMZ was lower than that of ISP and decreased to below the level of detection after 14 days for all three types of ceramic.

To calculate the release ratio, the total amount of anti-

biotic released in PBS was divided by the antibiotic soaked up in the ceramic blocks before elution in PBS. All ceramic blocks showed a release ratio of 90% to 100% for ISP, but of only 40% to 50% for CMZ.

The osseous concentration of ISP in rabbit femora decreased gradually at first, but then increased eight weeks after implantation. The distal part of the femur showed the highest levels (Fig. 2) while the serum concentrations did not reach toxic levels. By contrast, the concentration of CMZ remained below the detection limit for eight weeks.

Formation of new bone in the centre of the cylinder was

Fig. 2

The osseous concentration of ISP in the rabbit femur.

Fig. 3a

Fig. 3b

Scanning electron micrograph of A-W GC 70 eight weeks after implantation. New bone is formed in the centre of the block and bonded to the ceramic without any fibrous layer ((a) $\times 16$; (b) $\times 78$; A-W, A-W GC; B, bone).

Fig. 4a

Fig. 4b

Radiographs of a 35-year-old man with osteomyelitis of the right tibia which recurred nine years after the primary operation. Figure 4a – One week after implantation of ISP-soaked porous A-W GC blocks. Figure 4b – Two years after implantation. The borders between the A-W GC and bone are unclear.

observed in the rabbit femora two months after implantation. SEM showed bone formation along the circumference of the pores without any intervening fibrous layer (Fig. 3).

Pilot clinical study. We used these antibiotic-soaked ceramic blocks to treat five patients, four with infected arthroplasty and one with osteomyelitis of the proximal tibia. In one case, a 34-year-old-man with recurrence of osteomyelitis had curettage of the infected focus and implantation of antibiotic-soaked A-W GC 70 blocks into the defect. Two years later, the border between the bone and ceramic blocks had become almost indistinguishable (Fig. 4). In another, a 64-year-old woman with an infected total hip replacement had revision. A large acetabular defect was filled with antibiotic-soaked A-W GC 70 and the new socket was fixed with PMMA bone cement and a Kerboul cross shell; there was an excellent result at 1.5 years. The other three patients all had excellent results

Discussion

The use of antibiotic-impregnated PMMA beads for the treatment of chronic osteomyelitis has been reported,¹⁰⁻¹³ but the disadvantages include low biocompatibility, a very low release ratio and possible thermal damage to the antibiotics. Hoff, Fitzgerald and Kelly¹⁴ reported that the total amount of antibiotic released from PMMA bone cement was very low, with only 5% elution of penicillin or gentamicin from the cement.

We have shown that antibiotic-soaked porous A-W GC blocks had good osteoconductive properties in clinical studies of the correction of large bone defects in the iliac crest and for the replacement of vertebrae.^{15,16} Ijiri et al⁶ have reported ectopic bone formation in porous A-W GC combined with bone morphogenetic protein in rats.

Our study has shown that 90% to 100% of total ISP and

40% to 50% of total CMZ were released from the porous A-W GC 70 or HA blocks. Antibiotic-soaked porous ceramic blocks are thus a more efficient DDS than antibiotic-impregnated PMMA bone cement. The release ratios of the two antibiotics were quite different, possibly because ISP has a positive charge and CMZ a negative charge in solution.¹⁸ We speculate that the difference may be related either to their affinity for the ceramic blocks or to their solubility.

Gentamicin is used with PMMA bone cement mainly because it is resistant to the heat produced by the polymerisation of the cement but A-W GC blocks cause no thermal damage and therefore any antibiotic may be used.

There have been several reports of a DDS using porous HA and antibiotic. Shinto et al¹⁹ studied antibiotics in powder form placed in a cylindrical cavity in calcium HA blocks. Itokazu et al²⁰ used similar porous HA blocks to ours, and soaked them with antibiotic by centrifugation. Slow release of antibiotics from HA blocks has also been reported, but our in vitro study showed that A-W GC 70 blocks absorbed and released a larger quantity of antibiotics than HA blocks, which may be related to differences in porosity and pore size. Although the porosity of A-W GC 70 is higher than that of HA, the compression strength of A-W GC 70 is nearly equal to that of human cancellous bone. A-W GC 70 has a uniform pore size of 200 μm , but HA has interconnecting pores of small diameter and thus cannot absorb a large quantity of antibiotics in spite of its porosity.

Our findings suggest that a DDS with porous A-W GC 70 blocks is better than systems using PMMA beads or porous HA blocks. Our pilot clinical study showed that antibiotic-soaked A-W GC blocks appeared to be useful for the treatment of chronic osteomyelitis or infected arthroplasties with bone defects.

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