

Local and Systemic Levels of Tobramycin Delivered from Calcium Sulfate Bone Graft Substitute Pellets

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We asked if tobramycin-loaded calcium sulfate pellets could be used to maintain high local site antibiotic concentrations for an extended period with minimal systemic levels and without adverse effects on vital organs. Calcium sulfate pellets loaded with 10% tobramycin were implanted in contained medullary defects in the proximal humeri of canines. The number of pellets implanted was calculated to yield an equivalent human maximum prescribed dose, and 1.8-fold this dose. These doses converted to approximately 20 mg/kg, and 36 mg/kg, respectively, for the canine. Local and systemic tobramycin levels, pellet resorption, bone response, clinical pathology parameters, and histopathologic responses of potential target organs were analyzed to determine if there was any adverse response for a 28-day period. Serum tobramycin was elevated for less than one day while local levels remained elevated for at least 14 days, and in some animals, 28 days. Tobramycin delivered locally from calcium sulfate pellets had no apparent adverse effect on clinical pathology parameters or on any of the organs that were analyzed. In addition, bone formation and pellet resorption followed patterns typically seen with calcium sulfate materials.

Chronic osteomyelitis is a particularly difficult clinical problem requiring aggressive surgical debridement with or without osseous reconstruction and systemic antibiotic therapy. Debridement of all foreign bodies and necrotic tissues that might represent a nidus for persistent infection often results in large contained or noncontained bone defects. When an organism is identified, systemic intrave-

nous antibiotic therapy is given for a period of 6 weeks based on bacterial sensitivity. Prolonged administration of systemic drugs can be problematic. Usually an indwelling intravenous access is necessary, and there is considerable risk of toxicity from prolonged antibiotic therapy. Systemic delivery of antibiotics to infected bone also is unpredictable. Osteomyelitic bone usually has a poor blood supply, which is needed to deliver the antibiotic. In addition, numerous drugs cannot be delivered systemically because of toxicity to vital organs. This includes the aminoglycosides such as tobramycin and gentamicin, which can cause nephrotoxicity or ototoxicity. The use of systemic antibiotics also may lead to resistant bacterial strains, decreasing the availability of effective antibiotics.

As a result of all of these potential problems with systemic therapy, local antibiotic delivery has been used in the treatment of chronic osteomyelitis. Numerous studies have shown that polymethylmethacrylate can locally deliver antibiotics.^{2–5,13,14,19–22,28} A major disadvantage is that polymethylmethacrylate requires a second procedure to remove the implant after its antibiotic release has fallen below therapeutic levels. For this reason, there is interest in the use of a biodegradable antibiotic delivery matrix that could eliminate the need for removal. A variety of materials including calcium-based bone graft substitutes, synthetic polymers, and protein-based materials have been proposed as alternative delivery vehicles.^{11,12} Among these, medical grade alpha-hemihydrate calcium sulfate holds particular promise. Calcium sulfate has relatively rapid resorption characteristics, which could result in more complete release of an antibiotic such as tobramycin; and calcium sulfate promotes new bone formation in contained defects.^{6,9,15,24} Several animal studies have shown that calcium sulfate pellets are substantially resorbed and replaced with new bone formation by 6 weeks^{15,24,25}; and a similar rate of pellet resorption has been reported in clinical use.^{6,9,24}

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The local and systemic levels of tobramycin delivered from calcium sulfate bone graft substitute pellets and the potential effects on vital organs have not been thoroughly studied.^{15,18} Although local antibiotic delivery generally has been thought to be effective, continued caution has been recommended due to limitations of existing clinical and laboratory studies.^{10,11,22,29} Two recent reports of renal toxicity following local delivery of gentamicin, one from a combination of beads and block polymethylmethacrylate in one patient²⁶ and the other from biodegradable bovine collagen sponges in three patients,²³ underscore the importance of understanding the release rate of locally delivered antibiotics and the potential for systemic toxicity. In vitro studies of drug elution are limited in their ability to model wound conditions. McLaren et al^{10,11} questioned the effect of laboratory sampling methods on characterizing the elution of tobramycin from calcium sulfate and the reliability of in vitro elution data in general in predicting the in vivo release of antibiotics. Local site effects are also of concern. Although neither the optimal level of antibiotic nor the duration of its release has been established, it is generally believed that very high local levels of antibiotic are responsible for the apparent effectiveness of local antibiotic therapy.^{11,14,15,22} This is consistent with maximizing the bactericidal effectiveness of an aminoglycoside such as tobramycin, which is concentration dependent. However, the effect of such high local levels of antibiotics on the ability of calcium sulfate to enhance the healing of bone defects is largely unknown.^{15,18}

In this study, we asked if tobramycin-loaded calcium sulfate pellets could be used to maintain high local site antibiotic concentrations for an extended period while minimizing systemic levels and without adverse effects on vital organs as determined from clinical pathology parameters and from histopathologic examination. In addition, we asked whether or not new bone formation, normally associated with calcium sulfate pellets, could occur in the presence of high antibiotic concentrations. Our hypothesis was that delivery of tobramycin from calcium sulfate pellets would be effective in maintaining high antibiotic levels locally with low systemic concentrations and without clinical or histological evidence of adverse systemic effects. Additionally, we hypothesized that new bone formation in association with the calcium sulfate material would occur in a bone defect, even in the presence of high antibiotic concentrations.

MATERIALS AND METHODS

Sterile, circular pellets (approximately 4.7 mm in diameter × 3 mm in length) of calcium sulfate hemihydrate loaded with 10% by weight of tobramycin sulfate were implanted into a medullary

axial defect surgically created in both proximal humeri in 10 skeletally mature male hound dogs weighing 27 to 40 kg. Using a computer-generated randomization scheme, five of the dogs were assigned to receive the maximum prescribed human dose of tobramycin (MPD), and the other five dogs received a multiple of the maximum prescribed dose (ie, 1.8-times the MPD). The animals were observed postoperatively for 28 days. Radiographs and blood sample collections for tobramycin levels and clinical pathology and local samples aspirated from the implant site were obtained at various time points throughout the study as described below. The animals were killed using an intravenous injection of a supersaturated solution of pentobarbital. Complete necropsies were conducted on each animal, and selected tissues were collected, fixed, processed, and evaluated microscopically. The study was conducted using an approved Institutional Animal Care and Use Committee protocol.

The MPD of tobramycin when delivered from calcium sulfate pellets is 10 mg/kg body weight in humans.¹⁷ For dogs, this converts to a MPD of approximately 20 mg/kg, or 36 mg/kg for the 1.8-fold MPD group, based on a surface-area-to-body-weight conversion from human to canine.²⁷ The individual dosage of the pellets was based on body weight. The body weight rounded to the nearest whole kilogram was used to determine the number of implanted pellets required to achieve the appropriate dose (either MPD or 1.8-fold MPD) for each animal. Each pellet weighed approximately 98.8 mg and therefore contained 9.88 mg of tobramycin sulfate. Because tobramycin-free base represented approximately 65.5% of the molecular weight of tobramycin sulfate, each pellet nominally contained 6.47 mg of free tobramycin. The mean number of pellets implanted was 102 for animals in the MPD group and 184 for the 1.8-times MPD group. The pellets were divided equally between the two humeri.

A cranial surgical approach to the greater tubercle of each humerus was done under general aseptic technique. The procedure was conducted under general inhalation anesthesia using subcutaneous acepromazine (0.05 mg/kg) and morphine (0.5 mg/kg), intravenous thiobarbiturate (8–16 mg/kg), and isoflurane to maintain the surgical plane. A cylindrical cavity was drilled axially through the greater tubercle into the medullary canal to a dimension of 13 mm in diameter and 100 mm in length. The calculated number of pellets was inserted into the medullary defect of each humerus. After implantation of the pellets, the supraspinatus tendon was closed over the defect in the greater tubercle, and the wound was closed in layers in a routine fashion. After the surgical procedure, analgesia, antibiotics, and intravenous fluids were maintained under the care of the veterinary staff. Postoperative analgesia was provided using subcutaneous buprenorphine (10 to 30 µg/kg) at 12-hour intervals for 2 days and afterward on an as needed basis. Acetaminophen was administered thereafter to any dogs exhibiting clinical signs of pain. A cephalosporin antibiotic was administered intravenously (1 gm) during the surgical procedure and orally three times daily for 5 postoperative days (22 mg/kg). The animals were allowed unrestricted weight bearing in the postoperative period.

Pellet resorption and bone response were assessed from serial clinical radiographs obtained preoperatively, immediately post-

operatively, and at 7, 14, and 28 days. Local tobramycin levels were obtained from samples obtained under anesthesia at 1, 3, and 24 hours and at 7, 14, and 28 days by aspirating the medullary canal using a spinal needle under radiographic control with orthogonal views. Systemic tobramycin levels and serum chemistry, hematology, and coagulation parameters were obtained at 0, 1, 3, 4, 8, 16, and 24 hours and at 2, 4, 7, 14, and 28 days, after an overnight fast. Baseline values for local and systemic tobramycin and for clinical pathology parameters were determined from samples obtained just before insertion of the pellets.

For the serum chemistry evaluation, approximately 10 mL of blood was collected in a tube without anticoagulant. The sample was allowed to clot and then centrifuged to obtain serum. The serum was analyzed for the following parameters: sodium, potassium, chloride, calcium, phosphorus, glucose, bile acids, total bilirubin, alkaline phosphatase, cholesterol, aspartate aminotransferase, urea nitrogen, creatinine, total protein, albumin, globulin, and albumin/globulin ratio. For hematology parameters, 2.8 mL of blood was collected in EDTA-containing tubes. The whole blood samples were analyzed for the following: red blood cell counts, white blood cell (total and differential), hemoglobin concentration, hematocrit, red cell morphology, mean cell hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, and platelet counts. For the coagulation parameters approximately 1.8 mL of blood was collected in tubes containing sodium citrate anticoagulant. The samples were centrifuged to obtain plasma, and the samples were analyzed for activated partial thromboplastin time and prothrombin time.

The local and systemic concentrations of tobramycin were determined in our institution's clinical biochemistry laboratory using Fluorescence Polarization Immunoassay (FPIA) technology (AxSYM Tobramycin Assay, Abbott Laboratories, Abbott Park, IL). Initial specimen assays indicated that the tobramycin levels of several local site samples exceeded the analytical range of the instrument. Therefore, the samples were analyzed using manual dilution under the clinical laboratory's standard operating procedures for the tobramycin assay. The detection limit for tobramycin using this system was 0.2 $\mu\text{g/mL}$.

For purposes of comparing pharmacokinetic parameters, a pharmacokinetic analysis of the local and systemic levels of tobramycin was performed to determine the maximum concentration (C_{max}), time at maximum concentration (T_{max}), area under the curve (AUC), and half-life ($T_{1/2}$).

After euthanasia, a complete necropsy was done. The liver, lungs, kidneys, rib with marrow, and each humerus were collected for histopathologic analysis using light microscopy of sections stained with standard hematoxylin and eosin. Additionally, undecalcified, plastic embedded, ground sections, stained with basic fuchsin and toluidine blue, were prepared from each defect. These sections were evaluated using light microscopy to characterize the nature of new bone and residual pellet material in the defects. A bone marrow smear was collected from the rib of all animals. Bone marrow smears were fixed in methanol, stained with a Wrights-Giemsa stain, and evaluated microscopically to determine the myeloid:erythroid (M:E) ratio.

Nonparametric methods were used to analyze the local and systemic tobramycin concentrations as well as the serum chemistry, hematology, and coagulation parameters. The Friedman test was used to compare different time points, and the Mann-Whitney test was used to compare the MPD and 1.8-fold MPD groups at each time point. A 0.05 significance level was used for all statistical tests.

RESULTS

No intraoperative or postoperative complications occurred, and all surgical sites healed normally. All animals were bearing weight with normal ambulation within 48 hours and maintained normal function throughout the study.

A progressive resorption of the pellets was evident in the serial plain film radiographs. The implanted pellets were apparent throughout the created defects immediately postoperatively (Fig 1A). A progressive resorption of the pellets was evident at the 7- and 14-day time points (Figs 1B, C). At 28 days, the pellets almost were undetectable, and the medullary defects appeared to be filled with bone (Fig 1D). Postmortem contact radiographs of the isolated humeri confirmed that the pellets had resorbed, and the medullary defect was filled with new bone. No differences were observed in the relative pellet resorption rates between the MPD and 1.8-times MPD treatment groups.

Local site tobramycin levels achieved and maintained high concentrations for 14 days. The local tobramycin levels for the two antibiotic dosages exhibited similar profiles with the 1.8-times MPD group having consistently higher elevations at the implant site (Fig 2). The local levels were highest at the initial 1-hour sampling time point (MPD: 1,099 $\mu\text{g/mL}$; 1.8-times MPD: 5,527 $\mu\text{g/mL}$), declined slowly over 24 hours, and continued to maintain therapeutic levels at 7 days (MPD: 3.1 $\mu\text{g/mL}$; 1.8-times MPD: 6.9 $\mu\text{g/mL}$) and at 14 days (MPD: 2.6 $\mu\text{g/mL}$; 1.8-times MPD: 4.5 $\mu\text{g/mL}$). Tobramycin was still detectable locally (MPD: 0.4 $\mu\text{g/mL}$; 1.8-times MPD: 0.3 $\mu\text{g/mL}$) in 2 of the 10 dogs at 28 days postimplantation.

Both dosage groups had highly significant changes in local tobramycin levels compared with preoperative baseline levels with time ($p < 0.0005$). At 14 days, the local tobramycin level remained elevated over the baseline level for both groups ($p = 0.025$ for each group). At 28 days, no significant difference was found in the local tobramycin level, compared to the baseline level, for either group ($p = 0.32$).

Serum tobramycin levels (Fig 3) rose quickly and peaked during the first hour (MPD, 30.3 $\mu\text{g/mL}$; 1.8-times MPD, 46.7 $\mu\text{g/mL}$), declined rapidly for the next 8 hours, and were undetectable after 24 hours. Compared with baseline levels, the MPD and 1.8-times MPD groups

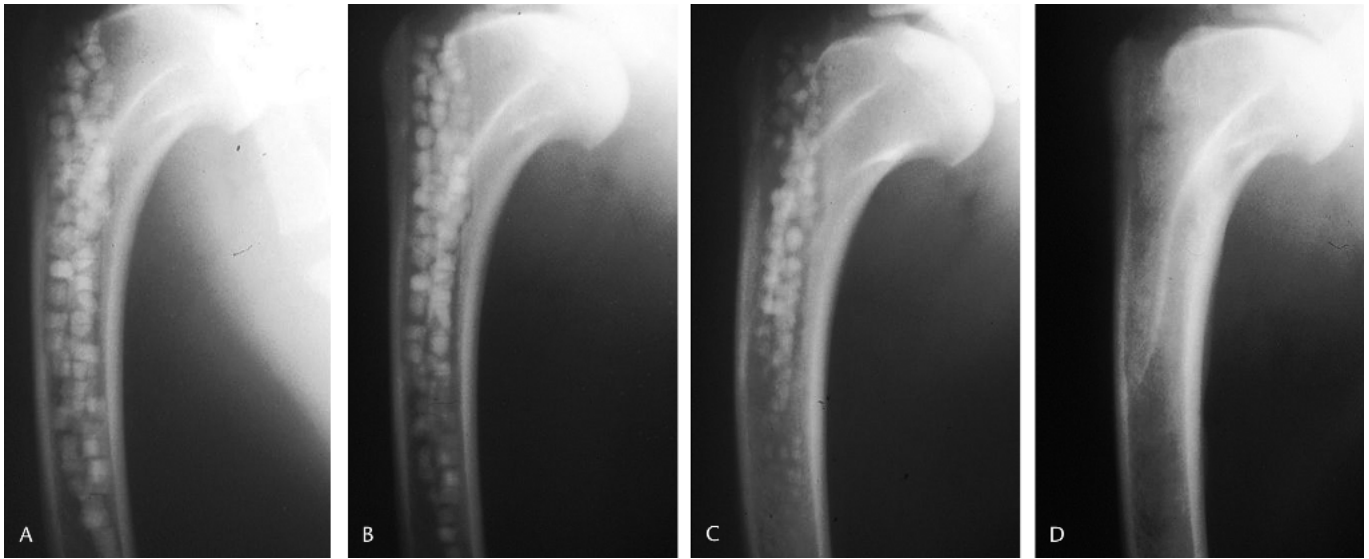


Fig 1. Serial clinical radiographs of the bilateral defects in the proximal canine humerus showed progressive resorption of the calcium sulfate pellets containing tobramycin and their replacement with newly formed bone. (A) The pellets were visible in the immediate postoperative radiographs. (B) Progressive pellet resorption was noted at 7 days and (C) 14 days postoperatively. (D) At 28 days, the pellets were virtually undetectable, and the medullary defects appeared to be filled with new bone.

showed highly significant changes in systemic tobramycin levels ($p < 0.0005$). For both groups, there still was a significant increase in the systemic tobramycin level at 16 hours compared with the baseline level ($p = 0.025$). At 24 hours, however, there was no significant change from the baseline level for the MPD group ($p = 0.56$), but the level for the 1.8-times MPD group remained slightly elevated

over the baseline level ($p = 0.025$). At 2 days, no significant difference was found in the systemic tobramycin level compared with baseline level for either group ($p = 0.32$).

The pharmacokinetic analysis revealed that systemic exposure to tobramycin (C_{max} and AUC) was increased in a dose-proportional manner between the MPD and 1.8-times MPD dose groups (Table 1). The time to maximum serum concentration was similar for both dose groups (ie, 1.2–1.6 hours), and the half-life of tobramycin in serum

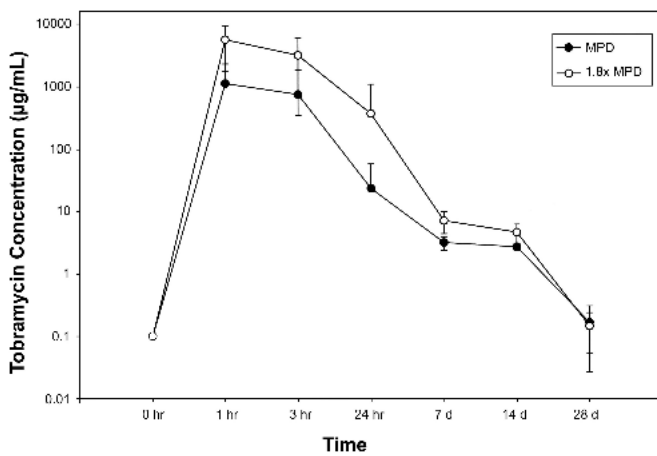


Fig 2. The local site concentration of tobramycin is shown. The data points represent mean values at each time point with standard error bars. hr = hour; d = days 0 hr = immediately before insertion of the pellets; MPD = 20 mg/kg; 1.8 × MPD = 36 mg/kg.

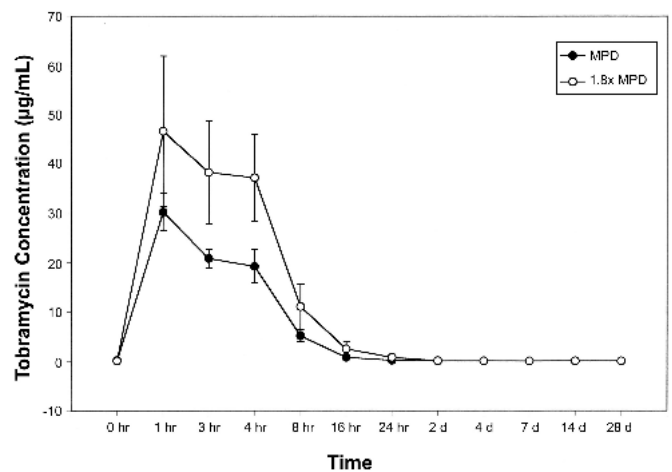


Fig 3. Serum tobramycin levels are shown. The data points represent mean values at each time point with standard error bars. hr = hour; d = days; 0 hr = immediately before insertion of the pellets; MPD = 20 mg/kg; 1.8 × MPD = 36 mg/kg.

TABLE 1. Pharmacokinetic Analysis of Local and Serum Tobramycin in MPD and 1.8-times MPD Dogs

Pharmacokinetic Parameter	Local Tobramycin		Serum Tobramycin	
	MPD	1.8 × MPD	MPD	1.8 × MPD
C _{max} (µg/mL)	1139	5579	31	50
T _{max} (hours)	1.3	1.15	1.2	1.56
AUC (µg-hr/mL)	6309	39846	163	302
T _{1/2} (hours)	52	25	2.7	2.9

AUC = Area under the curve

was relatively rapid (2.7–2.9 hours). Local site samples showed a dose-related increase in tobramycin concentration as expected.

The serum chemistry, hematology and coagulation parameters were unaffected by delivery of tobramycin from calcium sulfate pellets. Hematologic changes included a transient increase in white blood cell counts (principally neutrophils) in both groups that was considered secondary to surgical stress and unrelated to treatment with the test article. These changes were well within the clinically acceptable range, especially in light of rapid return by Day 2 to the normal values in all dogs. There was no increase in the serum calcium in spite of the large number of calcium sulfate pellets implanted.

Examination of lungs, kidneys, liver, and bone marrow indicated there were no gross or microscopic lesions considered secondary to treatment with tobramycin or calcium sulfate. Renal granulomas in two dogs in the MPD group most likely were related to ascarid parasites. Bone marrow smears revealed no difference between the M:E ratios from the MPD and 1.8-fold MPD groups. There were no other histopathologic findings that were considered related to the test material and/or surgical procedures.

Histologic sections of decalcified local implant sites revealed newly mineralized bone and osteoid formation, basophilic amorphous residual implant material with osteoclastlike cells along its margins, variable degrees of fibroplasia, and hemorrhage reflecting the terminal aspiration of cavity fluid. The incidence and degree of all these findings were similar in the MPD and 1.8-times MPD groups.

Evaluation of the stained, undecalcified histologic sections from the proximal and mid-defect levels revealed residual implant material and new bone filling the medullary defects in a similar manner in both the high and low dose groups. Bone that formed in relation to the resorbing pellets often occurred as circular lamellae that appeared in a concentric pattern. This pattern as well as the mineralized nature of the new bone was confirmed in high-

resolution contact radiographs of the undecalcified sections (Fig 4). Bone was seen in apposition to and incorporating residual implant material (Fig 5). Woven and lamellar bone was present. A slight to mild periosteal new bone deposition was present in the paired humeri of both groups.

DISCUSSION

In this study, calcium sulfate used as an osteoconductive, medicated bone graft substitute achieved a predictable local response with long-term release of tobramycin for weeks without adverse systemic effects and with undetectable systemic levels after 24 hours. There were no adverse serum chemistry elevations or abnormal pathology at autopsy, indicating a safe and effective method of local antibiotic treatment and dead-space management in bone. A dose effect was shown in which an increasing number of pellets correlated to increased systemic and local levels. Regardless of the number of pellets implanted, systemic levels dissipated to below detectable limits (0.2 µg/mL) after 24 hours. The present study also indicates that the ability of calcium sulfate to enhance the healing of large medullary defects as seen in previous studies persists even in the presence of high local levels of antibiotics.^{24,25}

This study was designed to determine if there were any adverse local or systemic effects of tobramycin released from calcium sulfate pellets at a dosage equivalent to the maximum prescribed human dose, and 1.8-fold this dose, and was not a model of osteomyelitis. Specifically, the effects evaluated included periodic local site and systemic

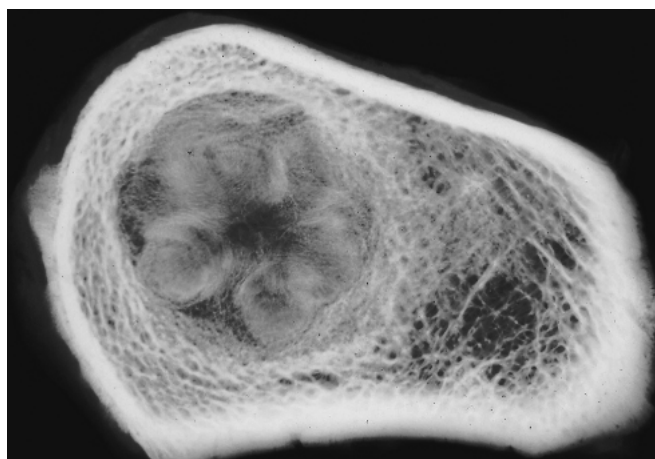


Fig 4. A high-resolution contact radiograph of a transverse section through a proximal humerus after 28 days shows that new bone in the defect formed in relation to the resorbing pellets and often occurred as circular lamellae that appeared in a concentric pattern.



Fig 5. New bone formation in the defect was seen in apposition to and incorporating residual implant material. Woven and lamellar bone and osteoid were present. (Undecalcified, plastic embedded, ground section, stained with basis fuchsin and toluidine blue, magnification $\times 300$)

tobramycin concentrations, clinical pathology parameters throughout the course of the study, radiographic and histological assessment of new bone formation within the bone defect, and histopathologic examination of potential target organs postmortem. Bilateral humeral defects were chosen because there was considerable previous experience evaluating calcium sulfate bone graft substitutes in the canine proximal humerus model.^{24,25} In order to achieve the required dosages, it was necessary to extend the length of the defect from 50 mm to 100 mm to accommodate the large number of pellets. It was also necessary to load the pellets with 10% by weight of the antibiotic. In this respect, the pellets used in this study differed from the calcium sulfate pellets containing 4% tobramycin (Osteo-set® T, Wright Medical, Arlington, TN) that are marketed in Europe, Asia and elsewhere, but which currently are not approved for distribution to surgeons in the United States. A previous study from our laboratory,¹⁸ also using the canine humeral defect model, measured local and systemic concentrations of tobramycin released from calcium sulfate pellets containing 2% and 4% tobramycin and showed release profiles similar to the findings in the present study using pellets containing 10% by weight of tobramycin. In both of these studies, serum tobramycin concentrations fell to undetectable levels ($< 0.2 \mu\text{g/mL}$) within 24 hours, while local levels remained elevated for up to 28 days. Additionally, Nelson et al¹⁵ reported similar findings using a *Staphylococcus aureus*-infected radius defect model in the rabbit. They found that, following treatment of the defect with calcium sulfate pellets containing 10% tobramycin, serum tobramycin was undetectable after 1 day,

while high local tobramycin levels were maintained for the first 7 days, which was the longest postoperative time for local site measurements.

The greatest experience with local delivery of antibiotics to bone, clinically^{2-5,8,14,19,20,22,28} and in laboratory testing,^{13,16,21} is with polymethylmethacrylate. The amount of antibiotics that polymethylmethacrylate can locally deliver varies based on the type of bone cement used and the manner of preparation. Nelson et al¹³ compared the elution of gentamicin from commercially prepared Septopal (Merck, Darmstadt, Germany) polymethylmethacrylate beads to the elution of gentamicin from laboratory-manufactured beads made from Simplex (Stryker Orthopaedics, Mahwah, NJ), Palacos (Schering-Plough, Kenilworth, NJ), or Zimmer dough-type cement (Zimmer, Warsaw, IN). They found in a 30-day study, that the commercially prepared Septopal polymethylmethacrylate beads eluded more total antibiotics and maintained higher concentrations than the implants fabricated in the laboratory. Scott et al²¹ examined the effectiveness of polymethylmethacrylate delivery in vitro by testing Simplex P antibiotic implants against 99 strains of bacteria. The implants were effective in inhibiting the growth of most of these organisms and suggested that clinical use may be warranted.

There have been many published reports on the clinical use of polymethylmethacrylate containing antibiotics for bone infections that describe a staged treatment program for chronic osteomyelitis.^{2-5,8,14,19,20,22,28} The first procedure is to debride the bone and soft tissues and place antibiotic-loaded polymethylmethacrylate implants into the wound either in the form of beads or bead pouch.⁸ The majority of the patients also received systemic intravenous therapy and then a second surgical procedure was done to remove these implants and then reconstruct the bone when necessary. Patzakis et al²⁰ had no recurrent infections in 12 patients with bone defects treated for chronic osteomyelitis using gentamicin-containing Septopal beads and up to 5 days of systemic antibiotic therapy. They found the antibiotic beads to be effective as a temporary means of dead space management before bone grafting. Ostermann et al¹⁹ reported an overall rate of acute infection and/or chronic osteomyelitis of 3.7% (31 of 845 cases) after systemic antibiotic prophylaxis and supplementary local use of tobramycin-impregnated polymethylmethacrylate beads for severe open fractures. In 381 of these cases, severe soft tissue defects were treated using the antibiotic bead pouch technique.⁸ Walenkamp et al²⁸ found 17 infection relapses after a mean followup of 5 years in 100 patients treated for osteomyelitis with debridement and gentamicin-loaded polymethylmethacrylate beads. In 55% of the operations, systemic antibiotic treatment also was given when the pa-

tient was septic or when there was extensive local soft tissue involvement.

One of the substantial disadvantages in the use of polymethylmethacrylate as an antibiotic delivery system has been the need to remove the implants. Because they represent foreign bodies, they can be a nidus for either residual or recurrent infections.⁷ In addition, polymethylmethacrylate implants do not completely release their antibiotics and thus continue to elute sub-therapeutic levels of antibiotic over prolonged periods, potentially increasing the risk of developing antibiotic resistant organisms.¹⁶ Polymethylmethacrylate implants also do not aid in the bone repair. For these reasons, there has been recent interest in the use of a biodegradable antibiotic delivery matrix such as calcium sulfate to eliminate some of these problems.

Calcium sulfate is a commonly used biodegradable implant for a contained osseous defect. Medical grade calcium sulfate is a hemihydrate crystal that becomes a hardened implant by the hydration process. Any pharmaceutical that can dissolve in water can be incorporated into the matrix of the hemihydrate crystal and thus become part of an antibiotic implant. Calcium sulfate is biocompatible and fully biodegradable over a period of approximately 6 weeks and therefore potentially can deliver antibiotics locally to bone for a prolonged period of time. Because it is degradable, it does not need to be removed, and calcium sulfate also acts as a scaffold for bone repair for a contained osseous defect.^{15,24,25} These bioceramic implants are fully degraded, and as a result, all antibiotic incorporated into the matrix is theoretically delivered.

Studies in animals support the beneficial role of antibiotic impregnated calcium sulfate implants for local treatment of osteomyelitis and contaminated fractures. Nelson et al¹⁵ reported that calcium sulfate pellets containing tobramycin were effective in eradicating infection in an experimental osteomyelitis model in rabbits. Ten percent tobramycin-loaded calcium sulfate implants were 85% effective in eradicating the bone infection. These implants were significantly better than calcium sulfate placebo, calcium sulfate placebo with intramuscular tobramycin, and debridement alone. Beardmore et al¹ reported that the combination of calcium sulfate pellets with 10% tobramycin and demineralized bone matrix was 100% effective in preventing intramedullary *Staphylococcus aureus* infection in a contaminated fracture model in goats.

The current animal study showed a consistent in vivo delivery of tobramycin from calcium sulfate pellets. It further showed that the maximum prescribed dose and 1.8-times maximum prescribed dose implants delivered antibiotics in vivo 28 days with undetectable serum levels after 24 hours. There were no adverse local or systemic effects attributed to the implants. The calcium sulfate im-

plants were completely incorporated with significant bone repair by 28 days. Implant incorporation and aided bone repair are not seen with polymethylmethacrylate. These features are potential added values. The next important question to answer is: can calcium sulfate antibiotic pellets be used alone without systemic antibiotics for osteomyelitis? If proven true, there can be considerable savings in morbidity and economic costs in treating osteomyelitis.

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