Novel way of specific local antibiotic treatment of suppurative bone infections with polymethylmetacrylate capsule carriers

PhD thesis

László Zoltán Börzsei M.D.

Leader of the PhD project: Prof. Judit Nagy M.D., PhD., D.Sc.
Program leader: Prof. Erzsébet Rőth M.D., PhD., D.Sc.
Topic leader: Prof. József Nyárády M.D., PhD.

University of Pécs, Faculty of Medicine

Pécs, 2006.

Introduction

The number of severe chronic bone, joint and soft tissue suppurations has been dramatically increasing recently due to the more frequent high-energy injuries accompanying motorization. Tissue damage promotes bacterial multiplication and invasion. While a few decades ago the most common type of bone infection was haemathogenic osteomyelitis, nowadays the number of exogenous osteitises, osteomyelitises shows permanently increasing tendency.

Nevertheless the treatment of chronic osteomyelitis is based on appropriately radical surgical debridement and long-lasting specified parenteral antibiotic therapy, different techniques of local antibiotic defense (PMMA bead chains, spacers, biodegradable implants) have been more commonly used recently. Since in this manner antimicrobal agents act directly on the affected area and only a small fraction of the applied dose gets into the circulation, the systemic toxic effects of antibiotics can be reduced significantly.

The most commonly used material for local antibiotic therapy is the bone cement. Different types of bone cement consist of two components, usually they are the mixture of solid polymethylmetacrilate (PMMA) and a polymerizing / stabilizing component, mixtures of other compositions are rarely used. Cement stores antibiotics like a sponge, but the exact mechanism of binding has not yet been accurately described. In this form of local antimicrobal therapy, antibiotics have to be water soluble and resistant to heat, because temperature sometimes exceeds 100°C during polymerization of the bone cement. In addition antibiotics must not influence mechanical characteristics of PMMA and has to be available in powder form. The aim of the present study was to develop a novel technique which provides specific, long-lasting local antibacterial effect in cases of osteomyelitis regardless of characteristics of antibiotics that were obligatory for being used in cement.

Supposing that several antibiotics are able to penetrate through the wall of a capsule made of PMMA, not only the water-soluble, heat-stable antibiotics available in powder form could be used for local treatment, but theoretically any antibacterial compounds, too. Consequently, after identification of the infective bacteria and determination of its antibiogram, it would be possible to put the most appropriate antibiotic into the previously produced and sterilized PMMA capsules and use them directly at the site of infection.

Aims of the study

PMMA is a generally used antibiotic carrier material in orthopedic and traumatologic surgery. This bone cement is commonly used in the treatment of bone and joint suppurations (e.g. chronic osteomyelitis). It is commercially available as local antibiotic carrier in the form of Gentamycin-containing beads or spacers. For this purpose exclusively some heat-stable and water-soluble antibiotics available in powder form can be used, because the 80-100 °C heat produced during PMMA polymerization might destroy the drugs.

If capsules are produced from PMMA sheets after the polymerization procedure, any kind of antibiotics can be filled into these carriers according to the sensitivity spectrum of the respective microorganisms isolated from the purulent secretion. The chosen antibiotics can be inserted into the preformed sterile capsules before and also during the operation. This technique provides novel perspectives in local antibiotic treatment.

1. The aim of the present series of experiments was to produce antibiotic-containing PMMA capsules from which the drugs can be released in high concentrations fror long period.
2. Antibiotic penetration through PMMA walls of different diameters is examined *in vitro.*
3. We analyse the correlation between PMMA wall thickness and time-dependent antibiotic permeability.
4. The most appropriate carrier is designed and developed.
5. Time-dependent antibiotic release from capsules with different wall thickness is studied.
6. Comparative studies on antibiotic outflow from PMMA beads and capsules containing the same amount of drugs are performed.
7. *In vivo* experiments are performed to examine the effect of Tazocin-filled PMMA capsules in rabbit osteomyelitis.
8. In this animal model we study if locally administered antibiotic is able to get into the systemic circulation.

Materials and Methods

Production of PMMA Bone Cement Sheets

Howmedica Surgical Simplex P Radiopaque Bone Cement (Howmedica, Rutherford, U.K.) consists of two sterile components containing radiodense material, it has been used in practice for a long time, therefore its characteristics have been thoroughly investigated. The fluidy methylmetacrylate monomer N, N-dimethyl para-toluidine hydroquinone component is sterilized by membrane filtration. The other component of powder consistance, methylmetacrylate-styrene copolimer, PMMA-barium sulphate is sterilized by gamma irradiation. After mixing the two components, the cement mass was placed within two slides localized certain distance from each other: small glass pieces of 0.1 mm width were placed on a slide in two columns, the space between them was filled with bone cement and it was covered by a second slide. After getting dry, the slides were removed from the cement sheets. The PMMA sheets were embedded in silicone and placed as midwalls of small tanks. Water resistance of these walls was previously tested with physiological saline and the tanks were sterilized with gas sterilization. Sheets having 0.2-0.8 mm thickness were produced.

Examination of clindamycin penetration through the cement walls

Changes of clindamycin concentration in the two compartments of the tanks at different periods, which refers to penetration through the cement walls of different thickness, were examined with microbiological methods under standard conditions. One compartment of the tanks was filled with 2 ml 200 or 300 μg/ml clindamycin (Pharmacia & Upjohn, N. U/ S. A. PUURS, Belgium) and the other compartment was filled with 2 ml physiological saline. Samples were taken every hour and from the third day every 24 hours from the saline and antibiotic concentration was determined, as described below.

Production and filling of bone cement capsules

Capsules of the same size (15 mm long, 6 mm diameter, 0.3 mm wall thickness) were produced with a pressing machine made of bacelite and aluminium designed and laid out by us. Water soluble form dividing solution was used at the end of the procedure. After removing this solution from the capsules, they were sterilized, filled with 1 ml solution of different

antibiotics and closed with sterile silicone plugs. In each group 6 capsules were filled with one of the following antibiotics with the help of a 2 ml syringe and 23 G needle:

a. clindamycin: 0.06 g (Pharmacia Upjohn, N. U/S. A. PUURS, Belgium)
b. amoxicillin-clavulanic acid: 0.02 g + 0.005 g (Richter-Gedeon Ltd., Hungary)
c. amikacin: 0.1 g (Bristol-Meyers Squibb, Italy)
d. cefotaxime: 0.1 g (Pfizer, Italy)
e. piperacillin-tazobactam: 0.08 g (Wyeth, U.K.)

Production of antibiotic-containing bone cement beads

Surgical Simplex P Radiopaque PMMA Bone cement (5 g powder + 2 ml solvent, Howmedica, Rutherford, UK) was mixed with the respective antibiotic and 6 beads were made by hand under sterile conditions. The average weight of each bead was 1 g and the average diameter was 12 mm. The same antibiotics were used in the same dose as in the capsules.

Examination of antibiotic penetration from the PMMA capsules and beads

The preformed, closed and sterilized capsules filled with the respective antibiotic solution and the antibiotic-containing PMMA beads were placed into 1 ml physiological saline medium. Amount of antibiotics penetrating from the capsules and the beads was measured with standard microbiological technique as described below.

Measurement of antibiotic concentration of the medium with a standard microbiological technique

The antibiotic concentration of the medium, which refers to the diffused amount through the PMMA sheets or the release from the capsules and beads, was measured with a standard microbiological technique. In one series of experiments samples were taken every day from the saline by dipping of Macherey-Nagel (MN3) filter discs (Macherey-Nagel Limited U.K.) having 6 mm diameter. In another series, the saline was changed every day after sampling, so the amount of antibiotics released during one day could be determined this way. These discs were placed on Mueller- Hinton agar (OXOID Limited, U. K.) cultures of *Micrococcus luteus* ATCC 9341 test strain and the inhibitory zones were detected after 24 h incubation period on 37°C. Qualitative sign of antibiotic content of the solutions was the presence of inhibitory zones, the width of the zones quantitatively referred to the concentration. The diameter of the

inhibitory zones was measured after 24 h incubation at 37°C and convered to μg/ml antibiotic concentration using standart dilution series. The minimal inhibitory concentration (MIC) was determined with tube dilution technique in case of every antibiotic.

Each experiment was done in triplicate, results are shown as means ± standard error of means. Statistical evaluation of the data has been performed by one-way analysis of variance (ANOVA) followed by Bonferroni's modified t-test, p values below 0.05 were considered significant.

Production of Tazocin-containing PMMA capsules for in vivo studies

A pressing machine made of Bakelite and aluminum has been designed and laid out by us for the production of bone cement capsules. Capsules of the same size (8 mm long with 6 mm in diameter), but different wall thickness (0.2-0.6 mm) were produced. Water-soluble form dividing solution was used at the end of the procedure. After removing this solution from the capsules, they were sterilized, filled with 100 μl solution of Tazocin (0.02 g piperacillin-sodium + 0.005 g tazobactam; Wyeth-Lederle Pharma, USA) and closed with sterile elastic silicone plugs.

Examination of the effect of locally inserted Tazocin-containing PMMA „mini capsules" in experimental osteomyelitis of the rabbit

Induction of osteomyelitis:

Chronic osteomyelitis was evoked in the left tibia of 25 domestic rabbits after a 2-week-acclimatization period in the Central Animal House of University of Pécs. All the rabbits were male, their average weight was 2.6 kg (2.2-3.2 kg) and they were 7 months old when they got involved in the experiment. Animals in this study were used in accordance with the University Medical School of Pécs Guidelines of Animal Experimentation. Operation was performed under diazepam (Seduxen 0.5 mg/kg i.m.,;Richter Gedeon Rt. Hungary) – ketamine (Calypsol 5 mg/kg i.m.,; Richter Gedeon Rt., Hungary) anaesthesia. The area of the operation was shaved, disinfected with polyvidon-jodide (Betadine; Mundipharma AG, Switzerland) and infiltrated with 2-3 ml 1% lidocaine (Lidocain, ÉGISZ, Hungary). The anterior surface of the proximal part of the tibia was opened through a 2-3 cm incision. A bone sheet of 4-8 mm was resected at the level of the tibial tuberosity, the medullar cavity was curetted and washed with physiological saline. The removed small cortical piece was placed in a hot bath of

physiological saline for 5 minutes. This devitalized bone segment was placed into the medullar cavity as a preformed sequester, accompanied by 1 ml (10^9 /ml) injection of *Staphylococcus aureus* OKI 118003 suspended in saline. The wound was closed in 2 layers. The animals were physically examined every week and symptoms like weakness, loss of appetite, decreased mobility, degeneration of the operated limb or flexion contracture of the affected knee joint have been noted. Radiographs were taken 6 weeks after the operation to confirm osteomyelitis.

Insertion of the PMMA capsules:

The proximal end of the tibia was opened, sequestrectomy, soft tissue debridement and curettage of the medullar cavity were done under anesthesia after taking bacteriological samples. Tazocin-containing PMMA mini capsules (0.02 g piperacillin + 0.005 g tazobactam in 0.1 ml volume) were placed into the medullar cavity and the wound was closed in 2 layers (n=12). Animals of the control group underwent only debridement, sequestrectomy and curettage with no PMMA capsule implantation (n=7). Six rabbits died due to septic complications within four weeks after induction of osteomyelitis, so they were excluded from any further examination. Hence every result and conclusion below are based on the examination of the remained 19 animals.

Microbiological examinations:

Bacteriological examination was immediately performed from the surgical samples, which were directly inoculated onto blood agar, chocolate agar, eosine-methylene blue agar plates as well as aerobic and anaerobic Holman media. The colonies were identified by microscopic and biochemical tests. Blood samples were taken every third day and Tazocin concentration was examined by microbiological agar diffusion technique in order to detect the antibiotic level in the circulation. The sensitivity of this method is 0.5 μg/ml. The minimum inhibitory concentration (MIC) of Tazocin on *Micrococcus luteus* ATCC 9341 was determined by tube dilution method.

Radiological examination:

The first radiographs were taken 6 weeks after infection of the medullar cavity with *Staphylococcus aureus* to prove the development of osteomyelitis. The second series of radiological studies were performed 8 weeks after the second operation in order to assess the healing of the osteomyelitis. One observer, who had no knowledge of the type of the second

operation, evaluated all roentgenograms. The X-Ray pictures have been evaluated according to a semiquantitative scoring system described by Norden et al. Five parameters (sequestral bone formation, presence of periosteal new bone, presence of bone destruction, presence of soft tissue calcification, presence of soft tissue swelling) were determined for each bone. Using the criteria shown in Table 1, a numerical score was assigned to each variable, and the five scores have been added to form a composite radiological score with a maximum of 6 for representing radiographic severity.

Histological examination:

The rabbits were sacrificed by cervical dislocation and the hindlimbs were dissected for histological studies 9 weeks after the therapeutic operation.

Semiquantitative scoring of the histological slides based on the number of granulocytes and the extent of necrosis, trabecular/ cortical destruction, reparation signs and soft tissue involvement has been performed with an expert pathologist blinded from the study.

For comparing the results of both the radiological and the histological evaluation regarding the treated and control groups, statistical analysis has been performed with unpaired Student's t-test, where p values <0.05 were considered significant.

Results

Penetration of clindamycin through PMMA membrane

Clindamycin both from the 200 and 300 μg/ml solutions diffused through the bone cement wall into the saline in detectable amount after 4-5 days.

Release of clindamycin from PMMA capsules and beads

From the capsules high antibiotic outflow (2000-5000 μg/ml) was detected during the whole examination period of 32 days. On the contrary, in the case of the beads, much smaller concentrations (100-500 μg/ml) were measured in the medium for shorter time (17 days). When the medium was changed every day, we experienced that more than 53% of the total antibiotic content of the capsules was released within the first day. The dynamics of the outflow from the beads was also slower, only 12% of the total content was released during the first day and gradually decreasing amount

was measured till the 15th day. The MIC value for *Micrococcus luteus* was 0.1 μg/ml. The capsules remained intact *in vitro*, we noticed no damage, perforation or microfractures upon their macroscopic examination.

Release of amoxicillin-clavulanic acid from the capsules and beads

From the capsules these antibiotics were released during 10 days in a gradually decreasing manner, a rapid decline was observed from 5 to 1.5 μg/ml on the 6th day and no release was detectable from the 19th day. On the other hand, there was only minimal release from the beads, the concentration did not go above 0.1-0.25 μg/ml. The first day release from the capsules was 72% of the total dose, then very small concentrations were measured till the 12th day. Meanwhile, the dynamics of the release from the beads was minimal throughout 10 days, which is likely to be due to the damage of the antibiotics induced by the heat during polymerization of the PMMA. The MIC value for *Micrococcus luteus* was 0.1 μg/ml.

Release of amikacin from capsules and beads

The outflow of amikacin from the capsules was high (850 μg/ml) till the 15th day, then decreased and stabilized at the concentration of 180-200 μg/ml. In case of the beads, smaller, 200-250 μg/ml concentrations were measured in the medium till 15th day, then it gradually decreased to 0. Within the first day, 56% of the total antibiotic content of the capsules was released, then gradually decreasing concentrations were detected every day till the 9th day. The daily antibiotic outflow from the beads decreased gradually till the 8th day. The MIC value for *Micrococcus luteus* was 0.1 μg/ml.

Release of piperacillin-tazobactam from capsules and beads

The release of piperacillin-tazobactam from the capsules was high with the maximum of 750 μg/ml till the 15th day, then after a steep decline no detectable antibiotic concentration could be observed. In case of the beads, markedly smaller, maximum 180 μg/ml concentrations were measured in the medium till 15th day, then it gradually decreased to 0. Within three days, 69% of the total antibiotic content of the capsules was released, then gradually decreasing concentrations were detected every day till the 12th day. From the beads 38% was released during three days, then

decreased gradually till the 12th day. The MIC value for *Micrococcus luteus* was 0.8 μg/ml.

Release of cefotaxim from capsules and beads

The release of cefotaxime was detectable from both the capsules and the beads, but it was higher from the capsules (60-150 μg/ml) than from the beads (12-50 μg/ml). From the capsules, 10% was released during 3 days, while 87% was released during 10 days. On the contrary, 63% of the total content flew out during the first three days and no antibiotics remained after the sixth day. The MIC value for *Micrococcus luteus* was 0.1 μg/ml.

Effect of Tazocin-containing PMMA capsule implantation on experimental osteomyelitis of the rabbit tibia

The animals were controlled by physical examination every week after the induction of osteomyelitis. On the third week after the operation loss of appetite, weakness, signs of atrophy of the operated limb and flexion contracture of the knee joint were observed in cases of 5 animals. Six rabbits died within the first four weeks due to septic complications, therefore they were excluded from any further evaluation. We could isolate the *S. aureus* OKI 118003 from the pus collected from the osteomyelitis. Radiographs taken on the sixth postoperative week confirmed osteomyelitis in all the remaining 19 cases. The composite radiological scores 6 weeks after the induction of the osteomyelitis did not differ significantly, they were 5.5±0.2 in the control and 5.3±0.03 the later antibiotic-treated groups. It means that basically all the animals showed severe osteomyelitis by radiographic evaluation before the second surgery. The next series of radiological examination carried out eight weeks postoperatively revealed that the bone was more swollen, wider and the cortical area was thinner at the site of injury in control animals compared to the findings of rabbits treated with PMMA capsules. Physical symptoms were parallel with the radiological signs: in control rabbits the left hindlimb was atrophic, there was a contracture in the left knee joint and a solid fistula was seen at the site of incision. On the contrary, from the animals treated with Tazocin-containing PMMA capsules, 7 were completely cured both physically and radiologically, in 5 cases atrophic left hindlimbs and minimal contracture of the knee joints were detected by physical examination and radiographs showed only small swelling of the medullar region. The score

values showed marked difference between the two groups representing 4.8±0.04 in control and 2.9±0.03 in PMMA capsule-treated rabbits, respectively (p=0.006).

After killing the rabbits at the end of the experiment all the implanted capsules were found to be intact, no damage of them could be detected. In the control group, macroscopically, enlargement of the medullar cavity with thin cortical area was seen in the tibia at the site of infection. In the central part of the samples a yellowish-white substance was found, which proved to be necrotic tissue full of granulocytes and degrading cells on the histological preparations. The surrounding cortical bone was widened and showed only some signs of reparation with an irrelevant restructuring of the neighboring trabecular bone. Slight reparation, formation of fibrotic tissue and scar, chronic inflammatory signs were seen in the intertrabecular spaces. In the animals treated with Tazocin-containing PMMA capsules, the tibia did not show macroscopic enlargement, only at the localization of the capsules. Microscopically, intact haemopoetic tissue of the bone marrow was found in the medullar cavity. Signs of only minimal chronic inflammation were seen in the surrounding trabecular and cortical bone tissue with small fibrosis, the width of the cortical area was normal. As result of the evaluation histological healing was achieved in 7 animals, initiation of the reparative phase was observed histologically in 3 cases and no reparative signs were detected in 2 rabbits. The composite histological osteomyelitis score in the control group, in which only surgical debridement was performed without antibiotic inplantation was 6.8±0.5. In rabbits treated with local tazocin-containing PMMA capsules, this score was significantly smaller, only 3.7±0.4 (p=0.002).

Summary of Novel Results

We have developed a novel antibiotic carrier, which can be filled with any original antibiotic chosen on the basis of the sensitivity of the respective microorganism. The antibiotics can reach bactericidic concentrations in the infected area after penetrating through the wall of these carriers. The material used for the production of these carriers is PMMA, which has been used in bone surgery for a long time. However, we did not intend to apply this in its usual form (intraoperative prepared spacers), but created capsules after its polymerization with the help of a self-developed pressing machine and filled these with different antibiotics.

1. We have provided *in vitro* evidence that clindamycin is able to penetrate through PMMA sheets (0.2-0.8 mm) both from low and high concentration solutions after 4-5 days. The speed and extent of penetration was dependent on the antibiotic concentration.
2. However, there was no significant difference between antibiotic penetration in cases of different wall diameters.
3. We produced specific antibiotic carrier PMMA capsules with different wall diameters with the help of a self-designed and created pressing machine made of bacelite and aluminium. These capsules were filled with several antibiotics which were examined in further *in vitro* and *in vivo* studies.
4. We have demonstrated *in vitro* that all the 6 chosen antibiotics are able to penetrate through the wall of these capsules in more than 100 times higher concentration than the MIC values of the *Micrococcus luteus* ATCC 9341 test stain.
5. Further *in vitro* comparative studies revealed that there was a significantly greater release from PMMA capsules than beads containing the same amount of antibiotics.
6. We have provided *in vivo* data showing that inplantation of Tazocin-containing PMMA capsules in the experimental rabbit tibia osteomyelitis model results in physical, radiological and histological healing.
7. In this *in vivo* model we have shown with microbiological assessments that locally administered Tazocin does not get into the systemic circulation.

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