Antibiotic-loaded plaster of Paris implants coated with poly lactide-co-glycolide as a controlled release delivery system for the treatment of bone infections

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Summary. *Plaster of Paris implants containing vancomycin (60 mg/g of carrier) were prepared in order to be used as local delivery system for the treatment of bone infections. The regulation of the release rate was performed by coating the carrier with a polylactide-co-glycolide polymer composed by 10% (w/w) polyglycolic acid and 90% (w/w) racemic poly (D,L-lactic acid). The release of the antibiotic from the biodegradable matrix was evaluated in vitro. From this investigation, it is clear that the drug elution depends on the coating depth. After a burst effect occurring on the first day of the experiment, therapeutic concentrations were measured during one week when uncoated implants were used. The coating allowed decrease of the burst effect and extended efficient release to more than five weeks when the implants were embedded with six layers (162 µm) of PLA₄₅GA₁₀. This delivery system was implanted into the femoral condyle of rabbits. It was shown that the in vivo release was also closely regulated by the coating depth. In all bone tissues (bone marrow and cortical bone) surrounding the pellets, the drug concentration exceeded the Minimum Inhibitory Concentration for the common causative organisms of bone infections (*Staphylococcus aureus*) for at least four weeks without inducing serum toxic levels. Due to its cheapness, facility of use and sterilization, biocompatibility and biodegradability, plaster of Paris coated with PLA₄₅GA₁₀ polymer giving a controlled release of vancomycin appears to be a promising*

sustained release delivery system of antibiotics for the treatment of bone and joint infections.

Résumé. *Des implants de plâtre de Paris chargés de vancomycine (60 mg/g) ont été préparés pour l'administration locale et prolongée d'antibiotique. La libération du principe actif à partir de ces vecteurs biodégradables a été évaluée in vitro et in vivo au niveau osseux. La régulation de la diffusion de l'antibiotique a été réalisée en enrobant les implants d'épaisseurs croissantes de polymère biodégradable (PLA₄₅GA₁₀) composé de 10% (p/p) d'acide glycolique et de 90% (p/p) d'un mélange racémique d'acide lactique (formes D et L). Des expériences menées in vitro, il apparaît que l'élu-tion de la vancomycine dépend de l'épaisseur de l'enrobage de PLA₄₅GA₁₀. Ainsi la libération de l'antibiotique à partir des implants dépourvus d'enrobage s'effectue rapidement dès le premier jour et dure pendant une semaine. L'enrobage permet de réduire cette libération massive du début et de prolonger la libération au-delà de cinq semaines lorsque les implants sont enrobés de six couches (162 µm) de PLA₄₅GA₁₀. Les expériences menées in vivo, après implantation des billes de plâtre dans le condyle fémoral de lapins, confirment l'importance de l'épaisseur de la couche d'enrobage dans la régulation de la diffusion de l'antibiotique. Que ce soit au niveau de la moelle osseuse ou de l'os cortical environnant l'implant, des concentrations thérapeutiques ont été mesurées pendant plus de quatre semaines sans jamais induire de concentrations sériques toxiques. Grâce à son coût réduit, sa facilité d'utilisation et de stérilisation ainsi que son caractère biocompatible et biodégradable, le plâtre de Paris enrobé de*

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PLA₄₅GA₁₀ constitue un vecteur de choix pour le traitement local et prolongé des infections osseuses.

Introduction

Surgical removal of necrotic tissue and the administration of antibiotics are the primary methods for treating chronic osteomyelitis [7, 23]. Necrotic bone provides an appropriate surface for the development of a biofilm [11] and the causative bacteria produce large amounts of extracellular fibrous glycocalyx materials [13]. Therefore, in order to eradicate bacteria, encased in such a biofilm [11] the antibiotic concentration must be many times higher than the minimum inhibitory concentration (MIC).

As it is impractical to deliver antibiotics to a target site in an effective concentration by the intravenous route, it is wise to use methods of local administration. These include isolated perfusion of a limb [17], suction irrigation [16] and the use of an implantable drug pump [18].

Another approach is to mix antibiotics with a carrier material which can then locally release the drug. Non-biodegradable polymethylmethacrylate (PMMA) bone cement and beads have been used extensively for treatment as well as for prophylaxis in bone infection [8].

Because biodegradable carriers obviate the need for surgical removal, they offer a potential advantage [19, 24, 25, 26]. Plaster of Paris (dried calcium sulphate hemihydrate) was selected as an antibiotic carrier as it is inexpensive, easy to use and to sterilize by heating at 121 °C for 24 hours, and is both biocompatible and bioresorbable. It may be impregnated with various antibiotics in order to produce reliable delivery systems [4, 10, 14, 15]. It has been used successfully in the treatment of acute and chronic osteomyelitis [2, 5, 20, 21].

Vancomycin was employed because this antibiotic is highly effective against Gram-positive skin flora including *Staphylococcus aureus*, *Staphylococcus epidermis* (and other coagulase-negative staphylococci), streptococci and corynebacterium, which together constitute about 75% of the bacteria implicated in deep prosthetic infections. It is thermostable at 37 °C and is not inactivated by the heat of polymerization of plaster of Paris, retaining its antimicrobial properties for more than 6 months after incorporation into this

carrier. It is readily released in vitro into the surrounding medium [1, 4, 14].

Aliphatic polyesters of the poly (α -hydroxy acid) type which are derived from metabolites such as lactic acid enantiomers (LA) and glycolic acid (GA), have been used as suture materials, implants and drug delivery systems [1, 3, 9, 12, 22, 24]. Thanks to its adjustable biodegradation, this type of polymer was selected to try to reduce the initial 'burst effect' of drug release from plaster of Paris implants and thus to extend the therapeutic release from one week to more than one month.

The purpose of our study was to investigate, in vitro and in vivo, the release characteristics of vancomycin hydrochloride from plaster of Paris implants coated or not coated with a biodegradable polymer.

Materials and methods

Materials. Plaster of Paris, dried calcium sulphate hemihydrate ($\text{CaSO}_4 \cdot 1/2\text{H}_2\text{O}$), was obtained from Merck, Darmstadt, Germany. Vancomycin hydrochloride (Vancocin[®]CP) was supplied by Eli Lilly, Brussels, Belgium. PLA₄₅GA₁₀ (MW=95,000) composed of 10% (w/w) polyglycolic acid and 90% (w/w) racemic poly (D,L-lactic acid) was purchased from Phusis, Saint-Ismier, France.

Preparation of implants. Plaster of Paris was first sterilized by heating to 121 °C in an oven for 24 hours. Implants were manufactured in a vertical laminar flow bench as previously described [15]. Sterile plaster of Paris (10 g), antibiotic (600 mg) and ultra pure water (6 ml) were mixed together and placed into sterile moulds. After setting and drying at room temperature, the implants were in the form of a cylinder, 6 mm in diameter and 3 mm in length, and were stored in dry and sterile conditions until tested.

Coating of implants. The coating was done on a vertical laminar flow bench by soaking the implants in a 5% (w/v) PLA₄₅GA₁₀ solution of acetone. They were then divided into 4 groups, 3 being given 1, 2, or 6 successive soakings. Thus one group was devoid of coating; 3 other groups, each with an increasing homogeneous thickness of coating (69 μm , 94 μm and 162 μm), were measured in histological slices by a histometric method.

In vitro release. Five antibiotic-loaded implants were weighed, placed in a test tube containing 2 ml phosphate buffered saline (PBS) (0.01 M phosphate buffered saline – NaCl 0.138 M – KCl 0.0027 M) at pH 7.4, and stored at 37 °C. The buffer solution was removed daily and frozen at –20 °C until examined. The implants were washed once with the same fresh buffer, then placed in 2 ml PBS (pH 7.4), and incubated again [14]. These experiments were conducted twice for each type of implant and lasted 3 weeks.

In vivo release. Three groups of 8-month-old skeletally mature New Zealand white rabbits, weighing around 3.5 kg $\pm$ 0.2, (n = 35) were used for the *in vivo* experiments. The plaster of Paris implant loaded with antibiotic was inserted into the femoral condyle. Good positioning was assured by radiographic control (Fig. 1). The animals were killed after 1 hour and 1, 3,

Fig. 1. Radiograph showing the positioning of the plaster of Paris implant in the femoral condyle of rabbit

4, 7, 10, 14, 24 and 28 days after implantation. The femur was then harvested and the implant removed, weighed, ground up and incubated under gentle agitation at room temperature in 5 volumes of PBS pH 7.4 for 2 hours. The antibiotic concentration was measured in the supernatant fluid obtained by centrifugation ($3,000\times g$, 10 min).

After removal of soft tissues and blood from the surface of the bone, and drying, a slice of 7 mm thickness was cut below the cavity of the implant and the antibiotic concentration was measured separately in the cancellous and the cortical bone. After washing each bone sample to remove blood, they were pulverised, weighed and homogenized with 5 volumes of PBS pH 7.4. Following incubation at room temperature for 48 hours under gentle agitation, the supernatant fluids were collected by centrifugation ($3,000\times g$, 10 min) for antibiotic measurement.

Blood samples were taken during the 24 hours after implantation in order to measure the serum concentration of the antibiotic.

Vancomycin assay. Vancomycin was measured by fluorescence polarization immuno-assay (FPIA) using the TDx^R Abbott apparatus. The lowest detected concentration was about 0.5 µg/ml to 1 µg/ml. The antimicrobial activity of the released fluids was also measured using an agar well plate technique as described by Grove and Randall [16] using *Staphylococcus aureus* (ATCC 25923).

Results

In vitro release characteristics. Four types of plaster of Paris implants loaded with vancomycin (60 mg/g) were prepared in aseptic conditions. Cumulative measured vancomycin was release of from the control group devoid of coating, and from the 3 groups coated with 1 (69 µm), 2 (94 µm) and 6 (162 µm) layers of PLA₄₅GA₁₀ respectively (Fig. 2).

Whatever the type of implants, vancomycin retained its antimicrobial effect after incorporation into plaster of Paris and was subsequently released into the surrounding medium at concentrations sufficient to inhibit bacterial growth during 20 days, with the daily release always superior to

Fig. 2. In vitro release profiles of vancomycin from plaster of Paris implants without coating (○) or coated with one (69 µm) (△), two (94 µm) (◇) or six layers (162 µm) (□) of PLA₄₅GA₁₀, in Phosphate Buffer Saline pH 7.4 at 37 °C

50 µg/g of plaster. The antibiotic release was inversely proportional to the thickness of the coating, being faster without coating and slower with 6 layers of polymer.

The release of vancomycin from the uncoated implants used as the control group was characterized by a 'burst effect' with 70% (w/w) of the total recovered amount of drug detected during the first day. The cumulative percentage of antibiotic release from these uncoated implants did not reach 100%. This phenomenon was due to the adsorption of vancomycin by the carrier, corresponding to the amount of drug ($\pm 20\%$ of the initial concentration) which could not be extracted from the beads in our experimental conditions.

The antibiotic in the implants coated with 1 layer (69 µm) of poly(α -hydroxy acid) polymer, was detected in the incubation medium during 26 days, with 25% (w/w) of the initial concentration of drug released during the first 2 days. After 3 weeks of incubation, 40% (w/w) of the initial concentration of vancomycin remained in the implants.

The plaster of Paris pellets coated with 2 layers (94 µm) of biodegradable PLA₄₅GA₁₀ presented a release profile relatively similar to that from the implants coated with only 1 layer of polymer, occurring over 26 days but characterized by an initial release of 8% (w/w). At the end of the experiment, by day 26, only 43.5% (w/w) of the total amount of antibiotic incorporated in the pellets had diffused into the incubation buffer. A daily release of about 60 µg of vancomycin per gram of implant occurred during the first two weeks when the implants coated with 6 layers (162 µm) were incubated in the aqueous medium. During the third week, and for a further 2 weeks, the release profile became

Fig. 3. In vivo release profiles of vancomycin from plaster of Paris implants without coating (○) or coated with two (94 µm) (◇) or six layers (162 µm) (□) of PLA₄₅GA₁₀, inserted into the femoral condyle from rabbits

practically linear with a rate in the range of 215 µg of vancomycin per day per gram of plaster. These dose rates are very interesting, because the local concentration of antibiotic can reach a level higher than the MIC for many of the pathogenic germs without producing dangerous systemic levels. The cumulative amount of vancomycin released after 37 days was only about 10% (w/w) of the initial concentration.

In vivo release characteristics. The *in vivo* study was carried out on plaster of Paris implants loaded with vancomycin (60 mg/g of plaster) devoid of coating or coated with 2 (94 µg) and 6 layers (162 µg) of PLA₄₅GA₁₀.

The rate of release of the antibiotic was established from its residual concentration remaining in the pellet, after varying periods of implantation into the femoral condyles of rabbits (Fig. 3).

One week after implantation, vancomycin had totally disappeared from the uncoated pellets, with

a high release (37% (w/w) of the initial concentration) occurring during the first hour of implantation. Nevertheless, the complete resorption of the implant, monitored by radiographic and histological methods, required 3 weeks. The presence of a biodegradable polymer coating clearly decreased the drug release at the beginning of the experiment, thus allowing an extension of the antimicrobial activity of the pellets from 1 week to more than 4 weeks. When coated with 2 layers (94 µg) of PLA₄₅GA₁₀, therapeutic concentrations were recorded during at least 3 weeks. At the end of the experiment, 8% (w/w) of the initial concentration of vancomycin were always detected in the implanted pellets. By further increasing the thickness of the coating (162 µm), the release occurred over a period more than 4 weeks with 40% (w/w) of the initial concentration remaining in the pellets 1 week after implantation. Whatever the coating thickness, the implants, entirely surrounded by fibrous connective tissue, were morphologically unchanged after 8 weeks of implantation (data not shown).

The results of vancomycin concentrations measured in bone marrow and cortical bone samples from rabbits treated with plaster of Paris pellets, coated or not with PLA₄₅GA₁₀ (2 or 6 layers), are summarized in Table 1. They are presented in terms of antibiotic concentration above or below the MIC. The MIC of vancomycin against *Staphylococcus aureus*, one of the major causative bacteria of osteomyelitis, is around 3 µg/g.

Whatever the type of plaster implant, coated or not with PLA₄₅GA₁₀, penetration of vancomycin occurred into the bone tissues located near the implant. The concentration exceeded the MIC for at least 4 days after implantation of uncoated vancomycin-loaded plaster pellets, and reached respectively 40 µg/g and 20 µg/g in the bone

Table 1. Detection of vancomycin in the bone marrow and cortical bone samples

Time after operation	Uncoated implant		PLA ₄₅ GA ₁₀ coating 2 layers (94 µm)		PLA ₄₅ GA ₁₀ coating 6 layers (162 µm)	
	Bone marrow	Cortical bone	Bone marrow	Cortical bone	Bone marrow	Cortical bone
1 hour	+	+	+	+	+/-	+
1 day	+	+	+	+	+	+/-
4 days	+	+	+	+	-	-
7 days	-	-	+/-	+/-	+	+/-
10 days	ND	ND	+	+	+	+/-
14 days	-	-	+	+	+/-	+/-
21 days	ND	ND	+	+	ND	ND
28 days	ND	ND	ND	ND	+/-	+

+ concentration upper to MIC (> 4 µg/g); +/- concentration near to MIC (from 1.5 µg to 4 µg/g; - not detected; ND not done

marrow and cortical bone samples by 4 days after implantation. The coating of implants allowed a sustained therapeutic release for at least 3 weeks into the 2 types of bone tissues. Nevertheless, the bone concentrations were always slightly lower than those *in vitro*. The maximum concentration of vancomycin detected in cortical bone and in bone marrow slices 10 days after implantation of plaster pellets coated with 2 layers (94 µg) were 2 and 3 times lower respectively. The antibiotic concentrations in the 2 types of bone tissues treated with pellets coated with 6 layers (162 µg) of polymer were always around the MIC value (± 5 µg/g) except at day 7 when 40 µg of vancomycin per gram of cortical bone were detected.

The serum concentration of the glycopeptidic antibiotic reached a peak (0.6 µg/ml) 3 hours after implantation of an uncoated pellet, but remained undetected during the 4 days of the experiment. Vancomycin was never found in the serum when coated plaster of Paris implants were placed into the femurs of rabbits.

Discussion

This study was intended to assess in a controlled setting the possibility of using plaster of Paris as a vehicle for the local administration of vancomycin. We also investigated the variable controlled rate of drug release resulting from coating the implants with a biodegradable polymer. This is composed of 10% (w/w) polyglycolic acid and 90% racemic poly(D,L-lactic acid) [24, 25] and it does not hinder normal osteogenesis.

From the *in vitro* study, it appears that the rate of diffusion of vancomycin was related to the coating of plaster of Paris implants with a polylactide-co-glycolide polymer. Therapeutic concentrations were found during 25 days, with a 'burst effect' occurring over the first 5 days when only 1 layer of PLA₄₅GA₁₀ (69 µg) was applied. The presence of 2 layers of PLA₄₅GA₁₀ (94 µg) decreased the initial release and increased the daily amount of vancomycin released. This related to the impermeability of the PLA₄₅GA₁₀ to vancomycin, resulting from the hydrophobicity of the polymer. The implants covered by 6 layers were characterised by a sustained release of antibiotic throughout the 24 days of the experiment.

These preliminary observations suggest that the antibiotic is released from the polylactide-co-glycolide coating through an interconnecting series of voids and cracks in the polymer, which can be seen on histological examination (data not shown). These could occur as a result of local stresses, and

Fig. 4. Schematic representation of the presence of vancomycin in bone tissues after increasing times of implantation of plaster of Paris pellets coated with zero, two (94 µm) or six (162 µm) layers of PLA₄₅GA₁₀

shrinkage, at the time of vaporisation of the solvent polymer. Thus, the thicker coating may make the diffusion of antibiotic through defects in the matrix less likely, so reducing the daily release of vancomycin.

The results (Table 1) are indicated in a schematic representation (Fig. 4) which shows the presence of vancomycin in bone marrow and cortical bone following progressive stages of femoral implantation of plaster of Paris pellets with 0, 2 and 6 layers of PLA₄₅GA₁₀.

Whether the implants were polymer controlled or not, concentrations of vancomycin exceeding the MIC were found around the implant in all bone tissues. The bone penetration of the antibiotic was closely related to the thickness of the coating. The implants which were not coated produced osseous penetration of the drug in a week; the 2 layers of PLA₄₅GA₁₀ extended the duration of antimicrobial activity to 2 weeks, and 6 layers of PLA₄₅GA₁₀ maintained a therapeutic concentration for 4 weeks with a delay of 1 week.

Parenteral administration of antibiotics for 4–6 weeks is usually recommended for the treatment of chronic osteomyelitis [23]. The results obtained by local antibiotic therapy suggest that simultaneous use of uncoated and coated implants of plaster of Paris would fulfil this condition.

The serum concentration of an antibiotic, which is important when considering systemic side-effects, reached a peak concentration (< toxic levels) 3 hours after implantation of an uncoated implant, but remained at a low level thereafter. When coated implants were used, vancomycin was never found in the serum throughout the duration of the experiment. These data suggest that a high concentration of antibiotic can be obtained at the

bone-implant interface for 1 month with the depot administration of this drug in plaster of Paris implants coated with PLA₄₅GA₁₀. Contrary to other systems, where the release velocity can only be regulated by modifying the initial drug concentration, or the composition of the polymer, the originality of our local delivery system lies in the close control of the drug release by means of the thickness of the coating [12, 26]. Although it is necessary to perform similar experiments using diseased bones, the biocompatibility and biodegradability of the carrier, the low serum concentrations of the drug which reduce the risk of systemic side-effects and its controlled delivery, suggest a potential use of this system for the clinical treatment of bone and joint infections. Its application may be further widened by changing both antibiotic and loading dose, as well as the ratio of PLA and PGA in order to control the drug release and the biodegradability of the carrier. The addition of osteo-inductive agents (bone morphogenetic protein, demineralised bone matrix, marrow cells or cultured chondrocytes) to promote osteogenesis may also be helpful.

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