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Sustained Local Delivery of Dexamethasone by a Novel Intravascular Eluting Stent to Prevent Restenosis in the Porcine Coronary Injury Model

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Objectives. **This study sought to assess the feasibility, safety and efficacy of sustained intracoronary delivery of dexamethasone by a novel polymer-coated eluting stent.**

Background. **Development of techniques to provide sustained local drug delivery has focused on polymers as matrices for drug incorporation and elution.**

Methods. **A tantalum wire stent was coated with dexamethasone (0.8 mg) suspended in a matrix of either low (~80 kD) or high (~321 kD) molecular weight poly-L-lactic acid (PLLA [0.4 mg]). Uncoated stents, stents coated with PLLA or stents coated with dexamethasone in PLLA were overexpanded by 30% to the normal vessel diameter in the coronary arteries of juvenile farm pigs. Animals were euthanized 28 days later, and neointimal thicknesses were measured. Additional pigs underwent placement of stents coated with high molecular weight PLLA–dexamethasone for assessment of arterial tissue and serum concentrations of dexamethasone at 1 h and 1, 2, 10 and 28 days after stent implantation.**

Results. **In vitro dexamethasone release occurred over the first 6 days. Stents coated with low molecular weight PLLA produced an intense inflammatory neointimal response. Stents utilizing the high molecular weight PLLA were well tolerated within the coronary vessel during the 28-day experiment. However, dexamethasone did not decrease neointimal hyperplasia. Dexamethasone concentrations in the arterial tissue were ~300,000-fold higher than those in the serum 24 h after stent implantation, remaining ~3,000-fold higher at 28 days.**

Conclusions. **The eluting stent utilizing high molecular weight PLLA appeared to be a well tolerated and effective means of providing sustained, site-specific drug delivery to the porcine coronary artery wall for at least 28 days.**

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Local administration of pharmacologic agents directly to the site of coronary intervention has been advocated as a means of concentrating drug in the injured arterial tissue to inhibit restenosis, and several designs of local delivery catheters have been evaluated in patients and animal models (1). However, a consistent limitation of these local delivery techniques appears to be the rapid washout of agents from the arterial wall within hours or even minutes of administration (2–4). Development of techniques to reliably provide sustained local drug delivery has focused on the use of synthetic or biologic polymers as matrices for drug incorporation and elution (5); a configuration that may be particularly useful within the coronary vasculature is that of a polymeric or polymer-coated stent. Given that implantation of conventional stents appears to limit the elastic recoil and adverse remodeling components of the restenotic process, the additional influence of antithrombotic or antiproliferative agents eluted from a delivery stent could theoretically result in a marked synergistic reduction in the extent of lumen renarrowing.

Corticosteroids are potent pharmacologic agents that influence a broad range of cellular activities and may thus be expected to inhibit many of the pathways to restenosis after arterial injury (6). Continuous administration of hydrocortisone or dexamethasone, either systemically or locally from periadventitial polymer matrices, has been shown (7,8) to reduce reactive intimal hyperplasia in rabbit and rat models of arterial injury. However, two clinical trials (9,10) failed to observe a reduction in the incidence of restenosis in humans by systemic administration of methylprednisolone or prednisone for 1 or 7 days, respectively. Corticosteroid therapy was not prolonged further in these trials because of the potential for adverse systemic effects with this class of agents. This discordance between successful results obtained using prolonged corticosteroid delivery in animal models and the lack of benefit with conventional systemic therapy in humans suggest that

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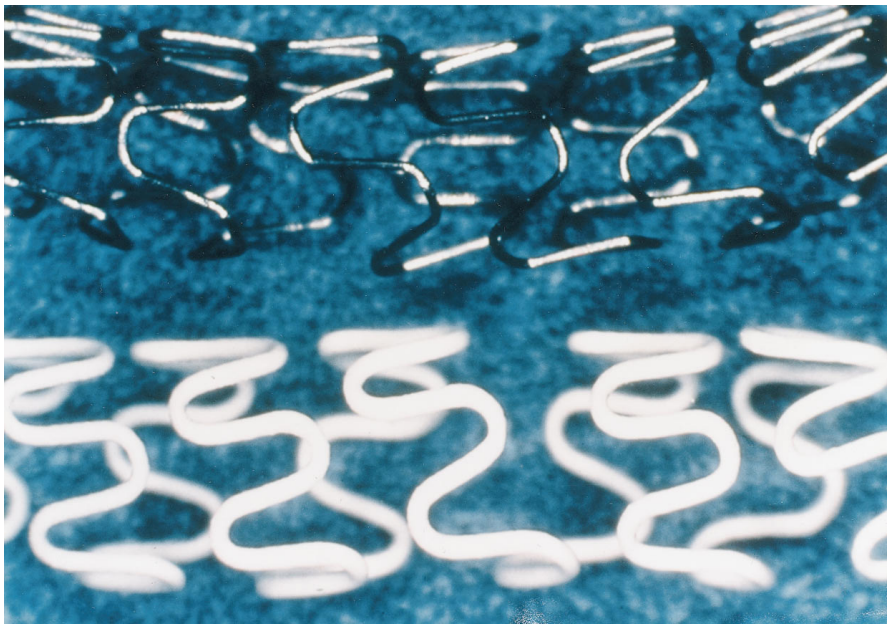

Figure 1. Top, Uncoated control Wiktor tantalum coil wire stent. **Bottom,** Eluting stent coated with high molecular weight poly-L-lactic acid and dexamethasone.

corticosteroids might be useful test agents for local prolonged drug delivery.

The current study was carried out to evaluate the feasibility, safety and efficacy of sustained intracoronary delivery of dexamethasone using a novel polymer-coated eluting stent in the porcine coronary injury model.

Methods

Dexamethasone eluting stent. The dexamethasone eluting stent consisted of a 125-μm diameter tantalum wire configured into a 16-mm long balloon-expandable coil stent (Wiktor, Medtronic, Inc.) and coated with a monolithic matrix of poly-L-lactic acid (PLLA) and dexamethasone base (Upjohn) (Fig. 1). Two different forms of the biodegradable PLLA polymer (Medisorb Technologies International) were evaluated in separate phases of the experiment: a low molecular weight polymer of ~80 kD and a high molecular weight polymer of ~321 kD. A 1% (w/w) solution of PLLA in chloroform was prepared, in which was formed a 2% (w/w) suspension of dexamethasone. This mixture was sprayed onto the stent wires to form the eluting polymer coating by a proprietary technique. The ratio of dexamethasone to PLLA in the coating was 2:1, with ~0.8 mg of dexamethasone and ~0.4 mg of PLLA per stent. The thickness of the polymer layer on the tantalum wire ranged from 14 to 27 μm (mean 20 μm) for stents coated with low molecular weight PLLA and from 11 to 23 μm (mean 16 μm) for stents coated with high molecular weight PLLA. This polymer coating was demonstrated by microscopy to be sufficiently flexible to allow balloon expansion of the coil wire stent without cracking or peeling from the wire. Stents were mounted on commercial angioplasty balloons (Prime, Medtronic, Inc.) and sterilized using a conventional ethylene oxide gas technique.

The kinetics of dexamethasone elution from sterilized polymer-coated stents were characterized in an in vitro system. Stents were placed in glass vials and immersed in 100 ml of phosphate-buffered saline. At time points ranging from 1 to 13 days, dexamethasone concentrations in aliquots of the elution buffer were measured by ultraviolet spectrophotometry (model 8452, Hewlett-Packard) at 244 nm and converted to cumulative elution curves. Chemical stability of the dexamethasone through the coating, drying, sterilization and elution processes was confirmed by comparing high pressure liquid chromatography spectra obtained from dexamethasone samples eluted from stents with those derived from freshly prepared solutions of dexamethasone.

Porcine coronary injury model. All studies were carried out with approval of the Animal Research Committee of the Cleveland Clinic Foundation and conformed to guidelines of the American Association for Accreditation of Laboratory Animal Care.

Normocholesterolemic female juvenile domestic farm pigs weighing 25 to 35 kg were treated with oral aspirin (325 mg) beginning 1 day preoperatively and daily thereafter. General anesthesia was induced with ketamine (22 mg/kg body weight) by intramuscular injection and isoflurane inhalation. Using sterile surgical technique, the right or left carotid artery was cannulated with an 8F hemostatic sheath through a midline cervical incision. Heparin (300 U/kg) was administered through the arterial sheath, and baseline coronary angiography was performed.

The study was performed in two phases: first with stents coated with low molecular weight PLLA and then with stents coated with high molecular weight PLLA. For each phase, pigs were randomly assigned to receive uncoated stents (control group), stents coated with PLLA polymer only (PLLA control group) or stents coated with PLLA and dexamethasone

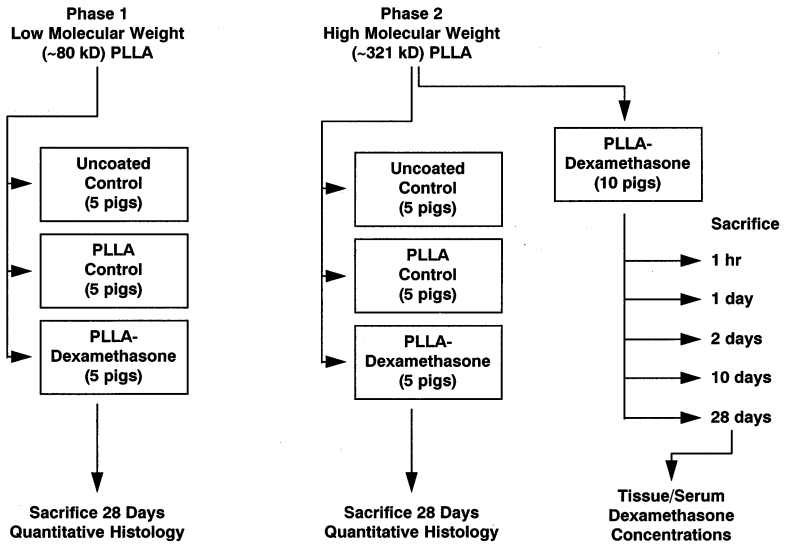

Figure 2. Experimental protocol. PLLA = poly-L-lactic acid.

(PLLA–dexamethasone group) (Fig. 2). One stent was placed within each of the three major epicardial arteries. All coronary segments within a given animal were injured with the same type of stent to avoid the potential confounding influence of drug delivered into the systemic circulation from the stent. Using the known dimensions of the angiographic catheters as a scaling device, suitable vascular segments were chosen to allow placement of 3.0- to 4.0-mm diameter stents intentionally overexpanded by a 1.3:1 ratio to the normal coronary lumen diameter (2.3 to 3.1 mm) to produce the characteristic vascular injury (11). Stents were deployed by a single balloon inflation to 6 atm for 30 s. Angiography was repeated to confirm adequate stent expansion and vessel patency.

The carotid arteriotomy site was ligated and the neck wound closed with layered interrupted sutures. Animals were maintained on a standard laboratory chow diet throughout the study period and received antibiotic prophylaxis with ampicillin (250 mg orally) twice daily.

Histologic analysis of neointimal hyperplasia. Follow-up angiography was performed 28 days after stent implantation under general anesthesia. Pigs were then euthanized by overdose of intravenous pentothal and hearts removed and perfusion fixed at 70 mm Hg for 24 h with 4% neutral buffered formalin. Stented coronary artery segments were located, removed and sectioned at 2-mm intervals perpendicular to the vessel axis using sharp, hardened scissors to divide the tantalum stent wires. Stent wire fragments were carefully removed using a dissecting microscope, and 2-mm arterial segments were embedded in paraffin blocks, sectioned and stained with hematoxylin-eosin and Lawson's elastic-van Gieson. Polymer coatings on the stent wire fragments were evaluated by electron microscopy at Medtronic, Inc.

All coronary segments were qualitatively inspected by an observer (A.M.L.) blinded to treatment regimen for the presence of thrombosis, inflammation or other tissue response and to assess the depth of vascular stent injury by stent wires. The segment demonstrating the most severe degree of lumen stenosis was selected for quantitative morphometric analysis using a computerized digital microscopic planimetry algorithm (Image-1/MetaMorph, Universal Imaging Corporation). Quantitative histologic analysis of stent-injured vessels was performed according to the technique described by Schwartz et al. (11–13). At every stent wire site (typically three to five visible per cross-sectional segment), neointimal thickness overlying the wire was measured along an orthogonal line from the stent wire to the lumen surface. The depth of vessel wall injury by the oversized stent (the stimulus for neointimal formation) at every wire site was also determined and assigned a numeric injury score (0 = internal elastic lamina intact; 1 = internal elastic lamina lacerated; 2 = internal elastic lamina and media lacerated; 3 = external elastic lamina lacerated). A mean neointimal thickness and a mean injury score were calculated for all wire sites within each coronary segment (11–13).

Quantitative assessment of local dexamethasone delivery. In a separate group of 10 pigs, the kinetics of dexamethasone delivery to the arterial wall were assessed (Fig. 2). Overexpanded stents coated with high molecular weight PLLA and dexamethasone were placed in three coronary vessels of each pig, as previously described. At each of five different time points after stent implantation (1 h and 1, 2, 10 or 28 days), two animals underwent measurement of dexamethasone concentrations in the serum and stented vascular tissue. Stented coronary segments were trimmed to exclude periadventitial tissue and arterial tissue proximal or distal to the stent. Each vascular segment was opened longitudinally and the stent removed, with care taken not to dislocate overlying neointimal tissue. Segments were washed with 20 ml of normal saline, blotted dry, weighed, snap-frozen in liquid nitrogen and stored at −70°C. Dexamethasone concentrations in the serum and vascular tissue at the various time points were measured at a commercial reference laboratory (Endocrine Sciences, Calabasas Hills, California).

The "efficiency" of dexamethasone transfer from the eluting stent to the arterial wall was estimated from vascular tissue

concentrations of dexamethasone and in vitro release kinetics data. The vessel wall geometry was simplified with the assumptions of an cylindrical artery with a lumen diameter of 3.75 mm (mean of the 3.5- and 4.0-mm stents used in this phase of the experiment), a length of 16 mm (the length of the implanted stent) and a vessel wall thickness of 1 mm. The density of arterial tissue was assumed to be 1 g/cm^3.

Statistical analysis. Continuous variables are expressed as mean value ± SD. Dexamethasone concentrations in tissue or serum at the various time points were compared by analysis of variance with the Bonferroni adjustment. A p value <0.05 was considered significant.

Differences between treatment groups with regard to the extent of neointimal hyperplasia occurring during the 28 days after stent implantation were assessed as follows. The mean injury score (*stimulus*) and mean neointimal thickness (*response*) may be related by linear regression to calculate a slope and intercept (11–13). A reduction in the neointimal proliferative response to vessel injury due to therapy would result in a decrease in the slope or the intercept of this regression relation, or both. Thus, these slope and intercept values serve as end points for comparing study groups. Linear regression analysis for mean neointimal thickness versus mean injury score was performed using arterial segments obtained from all three study groups (uncoated control stents, PLLA control stents and PLLA–dexamethasone stents). Binary variables G_P and G_D (value 0 or 1) representing implantation of PLLA control or PLLA–dexamethasone stents, respectively, were added to the regression equation to evaluate whether either stent coating produced a statistically significant change in slope or intercept. The following regression equation was used:

$$\text{Mean neointimal thickness} = [\text{Slope} + (\alpha_P \times G_P) + (\alpha_D \times G_D)] \times \text{Mean injury score} + \text{Intercept} + (\beta_P \times G_P) + (\beta_D \times G_D),$$

where α_P and α_D are the coefficients of the slope and β_P and β_D the coefficients of the intercept estimated by multiple regression. A statistically significant effect of either stent coating on the slope of the linear relation between neointimal thickening and injury score was established if the p value for α_P or α_D was <0.05. A significant effect of stent coating on the intercept of the linear relation was established if the p value for β_P or β_D was <0.05.

Among the pigs in phase 1 of the experiment, in which an inflammatory response to the stents coated with low molecular weight PLLA obscured normal vascular wall boundaries and rendered assessment of injury score impossible, quantitative comparison between treatment groups was not performed.

Results

Phase 1: low molecular weight PLLA stents. In vitro elution of dexamethasone from three sample stents coated with low molecular weight (~80 kD) PLLA polymer over 11 days is shown in Figure 3 (top). More than 50% of dexamethasone

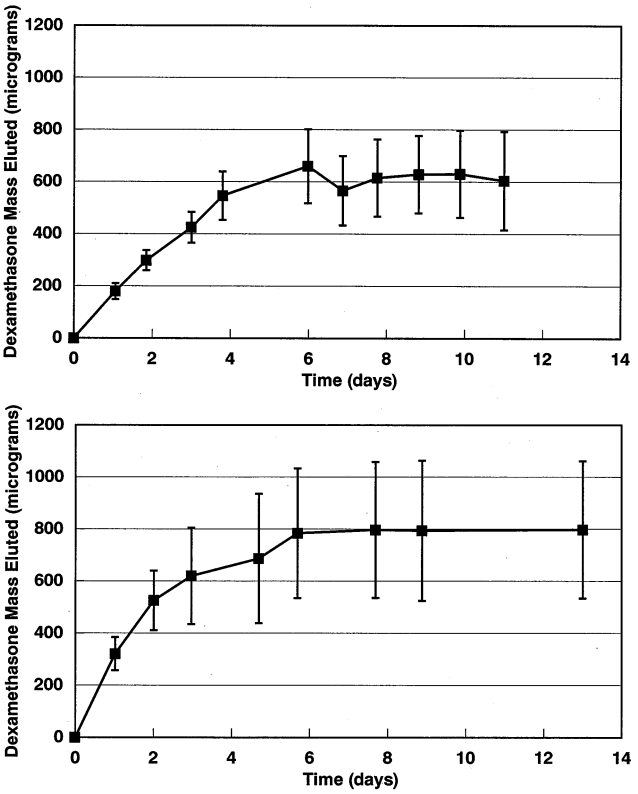

Figure 3. Cumulative (mean ± SD) in vitro dexamethasone elution from poly-L-lactic acid (PLLA)–dexamethasone-coated stents over 12-day period. **Top,** Low molecular weight PLLA (three stents). **Bottom,** High molecular weight PLLA (five stents).

elution occurred within the first 2 to 3 days, with a leveling off of the elution curves after 6 to 7 days.

Fifteen pigs underwent implantation of 44 stents (five animals in each of the three study groups). Four animals died before the scheduled 28-day euthanasia: one with fever and presumed sepsis 9 days postoperatively in the uncoated control stent group, one of stent thrombosis in the PLLA control stent group (2 h postoperatively) and two of stent thrombosis in the PLLA–dexamethasone stent group (2 and 21 days postoperatively). Necropsy studies of animals dying of stent thrombosis demonstrated occlusive or partially occlusive thrombosis in all coronary stents. A total of 32 stented vessels (12 uncoated control, 11 PLLA control, 9 PLLA–dexamethasone) were available for evaluation.

Gross examination of stented coronary segments revealed a thin layer of neointimal tissue overlying uncoated control stent wires. However, in PLLA control stent segments, the vessel lumen was nearly obliterated (Fig. 4), whereas arteries injured with the PLLA–dexamethasone stents exhibited a degree of neointimal thickening that was intermediate between that induced by uncoated control and PLLA control stents. Microscopic examination of the coronary segments injured with uncoated control stents demonstrated a proliferative neointima consisting of a uniform population of spindle-shaped cells in an extracellular matrix. In contrast, a severe cellular inflam-

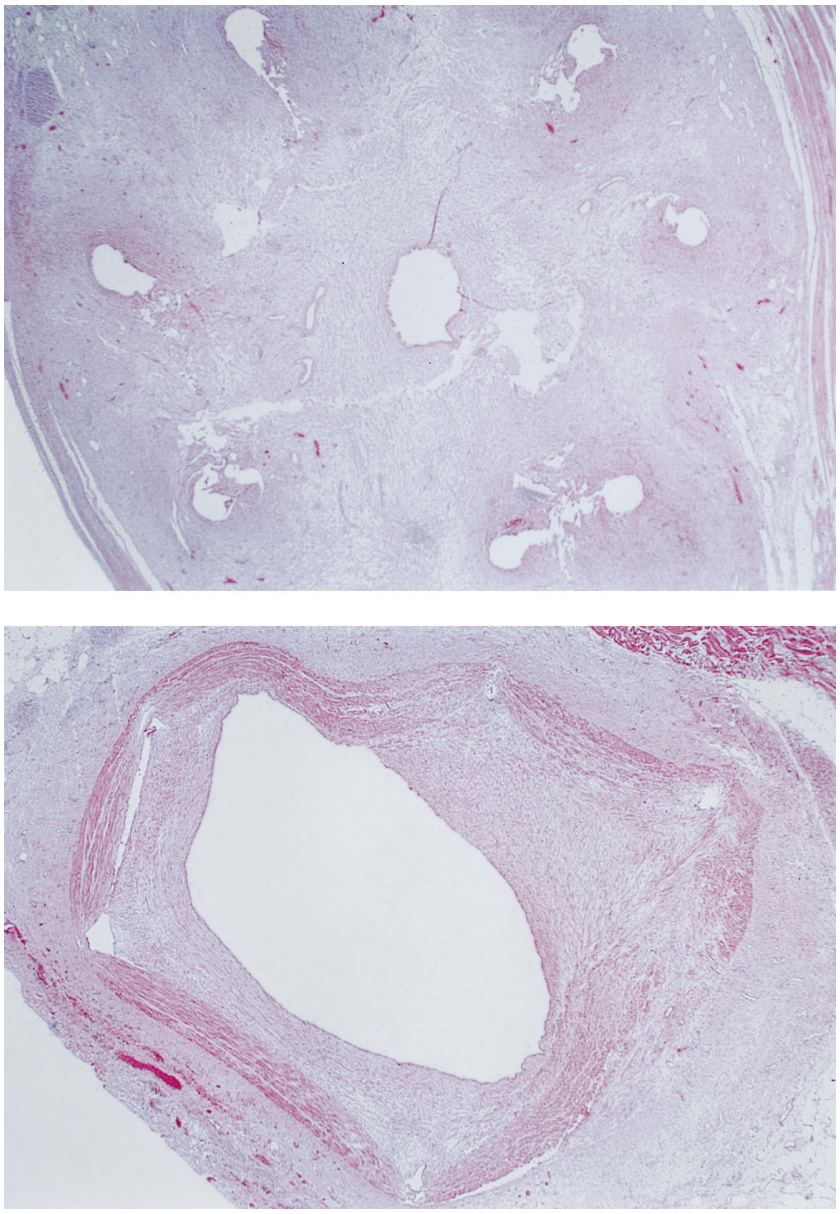

Figure 4. Photomicrographs of arterial cross sections at 28-day euthanasia after injury with low (**top**) and high molecular weight poly-L-lactic acid (PLLA) control stents (**Bottom**). Hematoxylin-eosin stain; ×8, reduced by 35%.

matory response was observed in all arteries in which PLLA stents were deployed, consisting of mononuclear cells, lymphocytes and multinucleated giant cells concentrated at the polymer–tissue interface. Normal vessel architecture was variably destroyed, with lysis of the elastic laminae and severe lumen stenosis.

Phase 2: high molecular weight PLLA stents. In vitro elution curves of dexamethasone from five sample stents coated with high molecular weight (~321 kD) PLLA are shown in Figure 3 (bottom). More than 50% of dexamethasone elution occurred within the initial 1 to 2 days, with a leveling off of the elution curves by 6 days.

Fifteen pigs underwent placement of 45 stents in phase 2 of the study (five animals in each of the three study groups). One animal in the PLLA control group died of excessive stent overexpansion, coronary occlusion and ventricular fibrillation immediately after stent implantation. A total of 42 stented segments (15 uncoated control, 12 PLLA control, 15 PLLA–dexamethasone) in 14 animals surviving to 28-day euthanasia were analyzed.

Electron micrographs of PLLA–dexamethasone stent wire coatings before deployment and at explantation from the porcine coronary vessels are shown in Figure 5. Dexamethasone crystals were visible dispersed within the high molecular weight PLLA matrix before elution. By 28 days after implantation, the dexamethasone crystals had dissolved and were no longer visible, although the polymer matrix appeared largely intact.

All stented vessels were patent, with moderate stenoses by angiography, before 28-day euthanasia. In contrast to the findings with the low molecular weight PLLA stent coatings, vessels injured by stents coated with high molecular weight

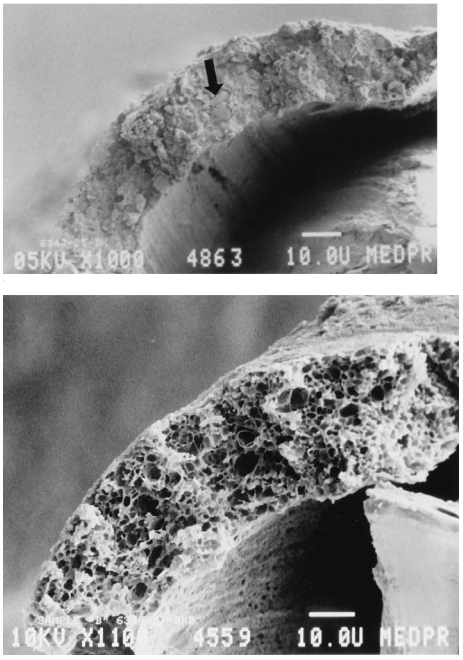

Figure 5. Electron micrographs of high molecular weight poly-L-lactic acid–dexamethasone stent coatings before (**top,** ×1,000 [reduced by 30%]) and 28 days after implantation (**bottom,** ×1,100 [reduced by 30%]) in porcine coronary arteries. Dexamethasone crystals visible before elution (**arrow**) are no longer present after 28 days, although polymer matrix appears largely intact.

PLLA exhibited no evidence of acute or chronic inflammation. Neointimal tissue overlying PLLA control or PLLA–dexamethasone stents was identical in appearance to that forming in response to injury by the uncoated control stents, consisting of smooth muscle cells and extracellular matrix without inflammatory cells (Fig. 4).

Results of the quantitative morphometric analysis are displayed in Figure 6, with mean neointimal thickness as a function of mean injury score. The linear relation between neointimal thickness and injury score was highly significant by linear regression for arterial segments from all three study groups ($R^2 = 0.568$, $p < 0.0001$), and neointimal responses to injury by PLLA control and PLLA–dexamethasone stents were superimposable on uncoated control stent values. The PLLA or PLLA–dexamethasone stent coatings thus produced no significant change in the neointimal hyperplastic response to injury (Table 1).

Figure 6. Quantitative morphometric analysis of relation between mean neointimal thickness and mean injury score at 28-day euthanasia for the second phase of study. There are no differences between study groups. Control = uncoated control stent (n = 15). PLLA = high molecular weight poly-L-lactic acid control stent (n = 12); PLLA-DEX = high molecular weight poly-L-lactic acid–dexamethasone stent (n = 15).

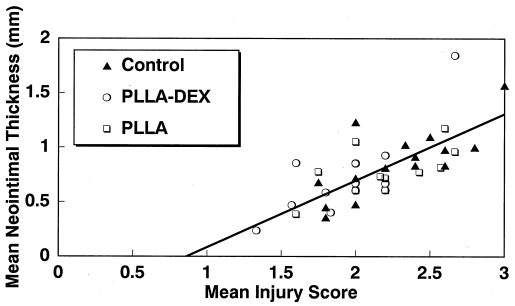

Table 1. Linear Regression Analysis of Morphometric Results for Phase 2 High Molecular Weight Poly-L-Lactic Acid Stents*

	PLLA Control Stents		PLLA–Dex Stents	
	Coeff	p Value	Coeff	p Value
Alpha (slope)	−0.221	0.386	0.262	0.280
Beta (intercept)	0.451	0.433	−0.444	0.389

*Slope = 0.611 mm; intercept = −0.527 mm; $p < 0.0001$; $R^2 = 0.568$.
Coeff = coefficient; Dex = dexamethasone; PLLA = Poly-L-lactic acid.

Quantitative assessment of dexamethasone delivery. Dexamethasone concentrations within arterial tissue (ng/mg wet tissue weight) and serum (ng/μl serum) at the five time points evaluated after implantation of high molecular weight PLLA–dexamethasone stents are displayed in Figure 7. Tissue and serum concentrations were compared by assuming arterial tissue density equal to that of serum. By 1 h after stent deployment, the mean dexamethasone concentration within the adjacent arterial tissue was 250 ± 202 ng/mg, whereas the mean serum dexamethasone concentration was nearly five orders of magnitude lower at 0.00278 ± 0.00106 ng/μl. Tissue concentrations of dexamethasone increased slightly by 1 day (329 ± 285 ng/mg, p = NS vs. 1 h) and decreased thereafter (54.8 ± 45.8 ng/mg at 2 days, p = 0.059 vs. 1 day; 0.850 ± 0.804 ng/mg at 10 days, p = 0.014 vs. 1 day; 0.517 ± 0.581 ng/mg at 28 days, p = 0.014 vs. 1 day). Serum concentrations of dexamethasone progressively declined after 1 h (0.00104 ± 0.001 ng/μl at 1 day, p = 0.174 vs. 1 h; 0.00056 ± 0.00033 ng/μl at 2 days, p = 0.073 vs. 1 h; 0.00040 ± 0.00007 at 10 days, p = 0.054 vs. 1 h; 0.00015 ± 0.00022 ng/μl at 28 days, p = 0.036 vs. 1 h). Even by 28 days after stent implantation, dexamethasone concentrations in the arterial wall remained >3,000-fold higher than those in the serum.

Using the idealized assumptions of cylindrical vessel wall geometry and in vitro elution detailed in the Methods section, it was estimated that 8% and 10% of the total dexamethasone initially contained within the stent coating was present in the arterial wall by 1 and 24 h after implantation, respectively. Moreover, of the estimated 370 μg of dexamethasone that had been eluted from the stent by 24 h, 21% was retained within the arterial wall.

Discussion

A drug-eluting stent consisting of a PLLA polymer over a metal backbone was developed and evaluated using dexamethasone as a test agent in the porcine coronary injury model. Stents coated with the low molecular weight form of this

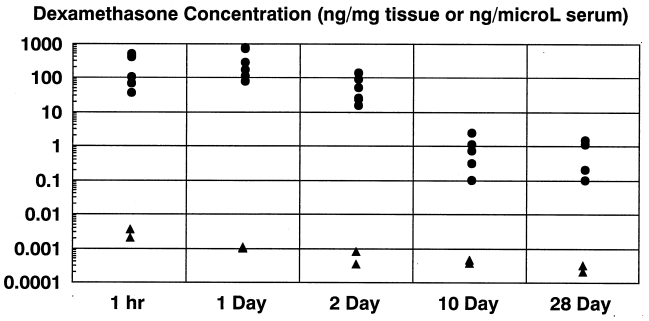

Figure 7. Semilogarithmic plot of dexamethasone concentrations in stented arterial tissue (ng/mg wet tissue weight **[circles]**) and serum (ng/μl serum **[triangles]**) at five time points after implantation of three high molecular weight poly-L-lactic acid–dexamethasone stents in coronary arteries of each pig. At each time point, two serum samples and six stented vascular tissue samples were obtained from two pigs. For comparison, plasma concentrations of dexamethasone 1 h after intravenous administration of a 1-mg dose in humans range from 0.01 to 0.1 ng/μl (24).

biodegradable polymer produced an intense inflammatory neointimal response by 28 days after implantation. However, stents utilizing the high molecular weight form of PLLA appeared to be well tolerated within the coronary vessel during the 28-day experiment, with no evidence of associated cellular inflammation. The concentration of dexamethasone in the arterial tissue treated with the eluting stent was found to be 90,000- to 300,000-fold higher than that in the serum during the first day after stent implantation, remaining 3,000-fold higher even after 28 days. Nevertheless, dexamethasone at the dose administered locally in this experiment did not decrease neointimal hyperplasia in the porcine coronary artery after stent overexpansion injury.

Local drug delivery and residence time. Several investigators have observed that drugs are typically lost from the intramural site rapidly after local administration by delivery catheters. Vascular wall concentrations of labeled heparin, urokinase and hirudin have been documented to decline by as much as 92% within only 30 to 90 min of delivery by hydrogel balloons (14), the Dispatch catheter (3) or iontophoresis (15). Polymeric implants may be useful as vehicles to provide sustained local elution and delivery of therapeutic agents to the arterial wall. Polymers containing heparin (16), antisense oligonucleotides (17) or dexamethasone (8) surgically implanted in a periadventitial position in small-animal models have been demonstrated to reduce reactive neointimal hyperplasia and prolong tissue uptake of drug after experimental arterial injury. However, although useful for providing "proof of concept" of the efficacy of sustained local drug delivery, such periadventitial delivery systems are not practical for human applications after percutaneous coronary revascularization.

Drug-eluting stents. Polymer stents composed of polyethylene terephthalate (18) or PLLA (19) or metal stents coated with polyurethane or the biologic polymer fibrin (20) have been tested for biocompatibility in porcine and canine models, although the usefulness of these designs for drug delivery has not yet been reported. Stents coated with cellulose ester polymer were used to deliver heparin or methotrexate, or both, in the porcine coronary injury model (21), demonstrating apparent biocompatibility over 28 days but no therapeutic effect on reduction of neointimal hyperplasia. Drug delivery to the arterial tissue was not assessed in that study. Lambert et al. (22) utilized a nitinol metal stent coated with a polyurethane to deliver forskolin to the rabbit carotid artery. More than 95% of the forskolin was eluted from the stent coating during the first 24 h after deployment. Arterial wall concentrations of forskolin were demonstrated to increase to 460-fold greater than that in the blood by 4 h after implantation, but local tissue levels declined to 77-fold greater than blood concentrations by 24 h. Acute biologic activity of the forskolin released from the stent was documented by changes in carotid blood flow and prolongation of the time to arterial occlusion after crush injury. Long-term biocompatibility or drug delivery with this stent >24 h was not evaluated.

To our knowledge, the current study is the first to demonstrate the feasibility of local delivery through a percutaneously implanted eluting stent to provide a drug residence time within the injured arterial tissue (≥28 days) that would be relevant for the clinical prevention of restenosis. This delivery stent utilized a monolithic matrix coating of dexamethasone within PLLA. Although PLLA is a biodegradable polymer, hydrolysis in vivo typically occurs over a period of months to years, particularly with the high molecular weight forms (23). Thus, the primary mechanism of dexamethasone release during the 28-day course of this experiment was most likely diffusion of drug through the pores of the polymer. Electron microscopic examination of stent coatings after explantation confirmed that the polymeric matrix was grossly preserved, with disappearance of the dispersed dexamethasone crystals. Although elution studies suggested that nearly all the dexamethasone was released from the high molecular weight PLLA stents within 6 days in vitro, drug delivery appeared to be substantially more prolonged within the coronary artery. Dexamethasone levels were measurable within both arterial tissue and serum for 28 days, although both concentrations fell by two or three orders of magnitude over that time period. Despite the fact that drug release from the stents in vivo was not directly measured in this experiment, it can be inferred from these concentration data and the 2- to 5-h plasma half-life of dexamethasone (24) that elution from these stents may have continued for at least 28 days. Alternatively, the lipophilic properties of the dexamethasone molecule may have prolonged its retention within the arterial tissue, thus exaggerating the apparent duration of delivery from the stent.

On the basis of in vitro elution kinetics and dexamethasone arterial tissue concentrations, it is estimated that 21% of the dexamethasone released from the stent within the first 24 h was delivered to the arterial wall. The remaining dexamethasone either diffused regionally from the coronary artery to the surrounding myocardium or was released into the blood. It is difficult to compare different techniques for local drug delivery assessed in separate studies utilizing agents of varying solubilities or molecular weights. Nevertheless, the extent of drug

transport into the arterial wall by the eluting stent compares quite favorably with the various designs of local delivery balloon catheters, for which transfer efficiencies of 0.01% to 3% are typically reported (3,25–27). The extraordinarily high concentration gradient of dexamethasone between the arterial wall and the blood, ranging from 300,000-fold at 1 day to 3,000-fold at 28 days, suggests that the eluting stent may be particularly useful for achieving local therapeutic tissue concentrations of agents that have systemic toxicity. However, these estimates of dexamethasone transport are subject to two potential limitations: 1) Because a reservoir of delivered dexamethasone within the periadventitial space cannot be ruled out, the removal of periadventitial tissue from the vessels in our experiment could have led to an underestimation of the total quantity of dexamethasone delivered to the vascular tissue. 2) The presence of residual polymeric stent coating on the vessel surface after removal of the stents could not be excluded, despite careful removal of the stent wires and extensive washing of the tissue before analysis; such residual stent coating would have led to an overestimation of drug delivery.

Intravascular biocompatibility. For a polymer to be useful as an intravascular delivery device, compatibility at the blood/tissue interface must be ensured. Previous reports (18,20,28) have in fact suggested that tissue incompatibility may be a major obstacle in the development of polymeric stents for intracoronary drug administration. Variable degrees of accelerated thrombosis and inflammatory responses have been observed with a number of biostable or biodegradable polymers implanted within the porcine coronary vasculature.

The polymer evaluated in the current study (PLLA), has been utilized for orthopedic applications in humans and has generally been found to be biocompatible for at least the first few weeks to months after implantation (29–31). In the first phase of the present study, stents coated with low molecular weight PLLA produced an unequivocal inflammatory reaction within the vascular wall. In contrast, no adverse tissue response was induced over 28 days after implantation of stents coated with high molecular weight PLLA in the second phase of the experiment. Explanations for the observed differences in tissue responses to the two forms of PLLA in this study are speculative but may relate to the prolongation of the biodegradation time with increasing molecular weight (23). It has been suggested (32,33) that the degradation products of PLLA may play a causative role in tissue inflammation, and a slow erosion rate might thus minimize the concentrations of these degradation products. However, under these circumstances, the potential exists for late development of inflammation as the high molecular weight PLLA hydrolyses. Importantly, then, long-term biocompatibility studies with this stent over a period of several months would be required before permanent implantation in humans could be considered.

Corticosteroids for prevention of restenosis. Studies in animal models or with tissue from human coronary lesions have suggested (34,35) that infiltration of monocytes and other inflammatory cells, with release of mitogenic and chemotactic factors, may play a role in the pathogenesis of atherosclerosis and restenosis. Glucocorticoids exert a profound inhibitory effect on these inflammatory processes (6) and may also influence platelet function (36), smooth muscle cell proliferation (7) and collagen synthesis (37). Continuous infusion of hydrocortisone over a 2-week period in rabbits subjected to aortic balloon injury resulted in a significant reduction in neointimal hyperplasia in one study (7). Marked inhibition of neointimal hyperplasia was also achieved in the rat carotid injury model by local delivery of dexamethasone from sustained-release periadventitial polymer matrices (8) or endoluminal nanoparticles (38).

Despite prolonged delivery of dexamethasone to the injured porcine coronary artery by the eluting stent in the current study, neointimal hyperplasia was not reduced by 28 days, although early suppression of neointimal formation, followed by "escape" from inhibition cannot be excluded. The failure of dexamethasone to influence the vascular response to injury in this model may be related to interspecies variability in the pathogenesis of neointimal hyperplasia or differences in the mechanisms of arterial injury. These findings suggest that inflammatory responses, which would have been expected to be suppressed by dexamethasone, may not in fact moderate a key pathway to restenosis, at least in the porcine model of stent arterial injury. Although it is also possible that tissue levels of dexamethasone in the present study may have been inadequate to produce a therapeutic effect, the concentrations of dexamethasone achieved with this eluting stent were comparable to those obtained in previous studies using periadventitial delivery systems. Reductions in neointimal hyperplasia in the rat carotid injury model (8) were demonstrated using periadventitial polymer matrices that produced a concentration of dexamethasone in the arterial wall 14 days after implantation of 0.880 ± 0.220 ng/mg tissue (vs. 0.850 ± 0.804 ng/mg tissue at 10 days after placement of the eluting stents in the current study). Moreover, treatment of injured porcine carotid arteries with periadventitial polymers containing dexamethasone in another study (39) failed to inhibit neointimal hyperplasia, despite arterial wall concentrations of 1.307 ± 0.498 ng/mg tissue 5 days after implantation.

Conclusions. A drug-eluting stent was developed that consists of a tantalum metal wire coated with dexamethasone dispersed within a monolithic matrix of high molecular weight PLLA biodegradable polymer. This stent was demonstrated to be a well tolerated and effective means of providing sustained site-specific drug delivery to the porcine coronary artery wall for 28 days, although longer term biocompatibility of the polymer coating was not assessed. Dexamethasone did not reduce the neointimal hyperplastic response to injury, despite sustained tissue levels of drug. If subsequent studies confirm the biocompatibility of the polymer coating over longer periods of time within the coronary vasculature, this eluting stent may prove to be useful for the prevention of restenosis using other pharmacologic agents.

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