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Drug-eluting bioabsorbable stents – An in vitro study

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Abstract

The aim of this study was to investigate the drug elution properties of novel drug-eluting bioabsorbable stents in vitro with four different drugs: dexamethasone, indomethacin, simvastatin and ciprofloxacin. Braided stents of poly-lactic acid (96L/4D) fibers were coated with a solution containing the appropriate bioabsorbable polymer and drug, with acetone as the solvent. Two different drug concentrations for both non-sterile and gamma sterilized stents were used for dexamethasone and indomethacin. For ciprofloxacin and simvastatin, only one drug dose was used. The stents were placed in sodium–phosphate-buffered saline in a shaking incubator (pH 7.4, +37 °C) and the eluted drug was measured periodically using an ultraviolet spectrometer. The drugs were hydrophobic to different degrees, as demonstrated by their various speeds of elution. In general, the higher the drug load in the stent, the faster the drug elution and the more hydrophilic the elution profile. In the cases of dexamethasone, indomethacin and ciprofloxacin, the sterilization decreased the drug elution rate slightly and the elution started earlier. However, in the case of ciprofloxacin, the gamma sterilization increased the drug elution rate slightly. Sustained elution was achieved for all four drugs. It was also evident that both the concentration and the hydrophility of the drug had a great influence on the drug elution profile. Gamma sterilization modified the drug elution profiles of dexamethasone, indomethacin and simvastatin, but had little effect on the drug elution profile of ciprofloxacin compared to three other drugs.

Keywords: Stent; Bioabsorbable; Drug elution; In vitro; Coating

1. Introduction

Stents have been successfully used in various applications, e.g. vascular surgery, urology and gastrointestinal tract surgery [1–4]. But as well as the good results, several complications have been reported with the use of stents, e.g. irritative symptoms, encrustation of the stent and infections in urology [4–6], and restenosis and inflammatory response in vascular applications [1,7]. To enhance the performance of the stents by preventing such problems, various pharmacological agents and their local elution from the stent coatings have been studied [1,6]. Bioabsorbable stents that elute the pharmacological agent(s) from the stent material or from the stent coating, or both, have also been investigated [3,8,9]. The bioabsorbable material used in this study has been studied and used in medical applications before. Biocompatibility testing has shown the material to be safe to use in vivo [10].

Dexamethasone has been studied as an anti-inflammatory and smooth muscle cell anti-proliferative drug eluted locally from the stents [9,11–14]. The delivery of dexamethasone from a poly-L-lactide coating on a tantalum wire-coil stent has been studied. The duration of sustained elution is about 1 week, according to in vitro testing. The in vivo results of a porcine coronary injury model, however, were not promising as restenosis still existed [12]. The elution of dexamethasone from a bioabsorbable polymeric coating of a knitted tantalum stent has also been investigated. The coating closed the stent

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mesh like a mantle, so that the drug load was comparatively high. According to in vitro studies, the total drug elution lasted up to 40 days. In vivo results in canine femoral arteries have also been promising, showing less intimal hyperplasia compared to noncoated stents [13]. Other studies have investigated commercial BiodivYsio-stents coated with phosphorylcholine and dexamethasone [11,15,16]. The in vitro results showed that the total drug elution lasted only about 1 day [11]. In a clinical pilot test the dexamethasone had not reduced restenosis at 6 months follow-up. This study was made without a control group [15]. The 12 month follow-up of another clinical study showed significantly lower restenosis rates compared to the control group [16]. Bioabsorbable 96L/4D-PLA stents with a dexamethasone-eluting P(D,L)LA coating have also been studied in an animal model. Common iliac arteries of pigs were stented and the animals were sacrificed after 1 month. The dexamethasone-eluting bioabsorbable stents reduced intimal hyperplasia compared to a plain bioabsorbable stent [9].

The effect of simvastatin on vascular smooth muscle cell (VSMC) proliferation and neointimal formation has been investigated. Simvastatin appeared to have a potential influence on VSMC proliferation in vitro and prevented neointimal formation in vivo after vascular injury [17]. Statin-eluting stents have been studied previously, but the results have not been promising [9,18].

Ciprofloxacin has effectively been used to treat urinary tract infections [19]. Adsorption of orally administrated ciprofloxacin onto ureteral stents and its antibiotic effect have been reported [20]. Therefore ciprofloxacin could be an effective drug to reduce infections caused by stents when eluted locally from the stent. However, no reports about ciprofloxacin-releasing stents have been published.

Indomethacin is a nonsteroidal anti-inflammatory drug that has an effect on the immune response [21]. The drug could also be used to prevent inflammation caused by stents by eluting it locally from the stent. However, no reports of studies about indomethacin-eluting stents have been published either.

The effect of gamma irradiation on drug elution from bioabsorbable polymer has been investigated. Commonly sterilization done by gamma irradiation causes the drug to elute more quickly, especially at the beginning of the drug elution [22–25].

The purpose of this investigation was to focus on the following aspects:

(1) Evaluation of the in vitro drug elution profiles of a novel bioabsorbable stent with selected drugs.
(2) Improvement of the dexamethasone elution profile compared to already reported studies.
(3) Study of the possibilities of sustained elution of simvastatin, ciprofloxacin and indomethacin.
(4) Investigation of the effect of drug load and gamma irradiation on drug elution profiles.

2. Materials and methods

Four different drugs – dexamethasone, indomethacin (Orion Pharma Oyj., Finland), simvastatin (GEA Pharmaceutic Fabrik, Denmark) and ciprofloxacin (Dinxing Kangle Pharmaceutical Factory, China) – were used in this study, with three simultaneous samples being used for each group. The medical-grade polymer used for manufacturing the fibers was a 96L/4D-copolymer of L-lactide and D-lactide (96L/4D PLA, inherent viscosity, i.v. 7.6 dl g^{-1} (chloroform, +25 °C), Purac Biochem bv., Gorinchem, Netherlands). The medical-grade polymers used for coating of stents were racemic 50L/50D copolymer of L-lactide and D-lactide (P(D,L)LA, i.v. 1.6 dl g^{-1}, Boehring Ingelheim, Ingelheim, Germany) and poly-ε-caprolactone (PCL, i.v. 0.7 dl g^{-1}, Birmingham Polymers, Inc., Birmingham, AL, USA). The ratio of different copolymers is represented by the molar ratio of the monomers prior to polymerization.

The stent fiber was manufactured by extrusion with a single screw extruder (Extrudex, Mühlacker, Germany). The extrusion was followed by a drawing process to create the fibrillated monofilament. The extrusion and drawing parameters are shown in Fig. 1.

The final diameter of the fiber was 0.2 mm. The fibers were braided over a 6.0 mm diameter mandrel with a Pick Master, 16 spindle braiding machine (J.B. Hyde & Co. Ltd., Sheshire, England) using a half load diamond braiding pattern. The braids were heat-treated in appropriate temperature to stabilize the structure. Finally the braid was cut to mesh stents of 30 mm in length (Fig. 2).

For the stent coatings, appropriate concentrations of polymer–drug solutions were prepared by weighting the materials in test tubes and by adding acetone at room temperature. Two different drug concentrations were used for dexamethasone- and indomethacin-coated stents. The stents were placed on the mandrel and immersed in the polymer–drug solutions. The stents were dried in fume chamber for 24 h and the coating procedure was then repeated to obtain thick enough coating. After another 24 h of drying in a fume chamber, the stents were kept in a vacuum chamber for 48 h to thoroughly evaporate the acetone. A scanning electron icroscopy (SEM) image of the fiber after drawing and an optical microscope image of the fiber after coating are shown in Fig. 3.

The stents were weighed with a Mettler AT 261 Deltarange FACT (Mettler-Toledo AG, Greifensee, Switzerland) before and after the coating procedures to measure the drug content and to weigh the coating of the stents. The loaded drug was calculated from the weight of the

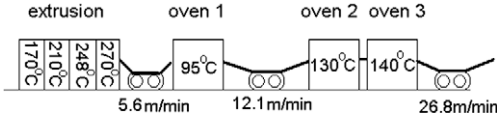

Fig. 1. The extrusion and drawing parameters for the stent fiber.