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TRANSLATIONAL

Impact of Paclitaxel Dose on Tissue Pharmacokinetics and Vascular Healing

A Comparative Drug-Coated Balloon Study in the Familial Hypercholesterolemic Swine Model of Superficial Femoral In-Stent Restenosis

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ABSTRACT

OBJECTIVES This study sought to compare the effect of paclitaxel-coated balloon (PCB) concentration on tissue levels and vascular healing using 3 different PCB technologies (In.Pact Pacific = 3 μg/mm^2, Lutonix = 2 μg/mm^2 and Ranger = 2 μg/mm^2) in the experimental setting.

BACKGROUND The optimal therapeutic dose for PCB use has not been determined yet.

METHODS Paclitaxel tissue levels were measured up to 60 days following PCB inflation (Ranger and In.Pact Pacific) in the superficial femoral artery of healthy swine (18 swine, 36 vessels). The familial hypercholesterolemic swine model of superficial femoral artery in-stent restenosis (6 swine, 24 vessels) was used in the efficacy study. Two weeks following bare-metal stent implantation, each in-stent restenosis site was randomly treated with a PCB or an uncoated control balloon (Sterling). Quantitative vascular analysis and histology evaluation was performed 28 days following PCB treatment.

RESULTS All PCB technologies displayed comparable paclitaxel tissue levels 4 h following balloon inflation. At 28 days, all PCB had achieved therapeutic tissue levels; however, the In.Pact PCB resulted in higher tissue concentrations than did the other PCB groups at all time points. Neointimal inhibition by histology was decreased in all PCB groups compared with the control group, with a greater decrease in the In.Pact group. However, the neointima was more mature and contained less peri-strut fibrin deposits in both 2-μg/mm^2 PCB groups.

CONCLUSIONS Compared with the clinically established PCB dose, lower-dose PCB technologies achieve lower long-term tissue levels but comparable degrees of neointimal inhibition and fewer fibrin deposits. The impact of these findings in restenosis reduction and clinical outcomes needs to be further investigated. (J Am Coll Cardiol Intv 2015;8:1115–23)

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ABBREVIATIONS AND ACRONYMS

ANOVA = analysis of variance

PCB = paclitaxel coated balloon

QVA = quantitative vascular analysis

Early clinical trials demonstrated the clinical efficacy of a paclitaxel-coated balloon (PCB) in the femoropopliteal arterial territory (1-3). The original coating formulation used in these studies (iopromide as a carrier at a dose of 3 μg/mm^2) was highly crystalline, achieved high tissue levels over time, and produced a high number of coating particles following balloon inflation (4-7). Newer generation PCB technologies have reduced both paclitaxel concentration and coating crystallinity aiming to decrease vascular toxicity and the production of coating microparticles. However, although the pharmacokinetic profiles and clinical efficacies of these first-generation technologies are well documented (1,8,9), the biological effects of these technological changes on clinical performance are still unknown. Recent studies suggest that not only efficient tissue transfer, but also sustained drug retention play a critical role in the clinical efficacy of PCB technologies (5,7,10). Therefore, understanding the impact of reducing paclitaxel dose on vascular healing is critical for the successful development of future local drug delivery technologies. In this study, we aimed to study the biological effect of paclitaxel concentration and coating type on drug tissue levels and neointimal inhibition using several experimental methodologies.

METHODS

PACLITAXEL-COATED BALLOON DESCRIPTION. The following PCB technologies were used in this study: 1) Ranger (2 μg/mm^2; Boston Scientific, Marlborough, Massachusetts); 2) In.Pact (3 μg/mm^2; Medtronic, Dublin, Ireland); and 3) Lutonix (2 μg/mm^2; BARD, Tempe, Arizona). Each treatment device uses different coating techniques and excipients. The Ranger PCB employs an acetyl tributyl citrate as the excipient. The In.Pact PCB uses urea as the excipient. The Lutonix PCB uses a non-polymer-based polysorbate/sorbitol as the excipient. The control device used was an uncoated balloon (Sterling, Boston Scientific). All balloons used in all the studies were 5 to 6 × 40 mm. The self-expanding stents used in the efficacy study were 5 to 6 × 20 mm (EverFlex, eve3 Endovascular, Plymouth, Minnesota).

IN VITRO COATING PARTICULATE FORMATION STUDY. Coating characterization (n = 3 per group) was performed using an in vitro coating particulate testing bench top model. Phosphate-buffered saline (pH 7.4) at 37°C was circulated at 150 ml/min through a glass iliofemoral model using a contralateral approach. An in-line 47-mm diameter black polycarbonate filter (5.0-μm pore size) was used to collect downstream particulate. Each PCB (6.0 × 40 mm) was inserted into individual 5.5-mm inner diameter Tecothane tubes (Lubrizol Advanced Materials, Inc., Cleveland Ohio) through a new introducer sheath, tracked (2 min), and inflated per their nominal label for 45 s. After deflation, the devices were withdrawn from the model and the sheath was flushed with 20 ml of media. Filters were collected, dried, and then imaged (25×) using a Clemex Vision Particle Analyzer (Longueuil, Quebec, Canada) with Leica DM4000M microscope (Leica Microsystems, Buffalo Grove, Illinois). All particles were highlighted with green color for better visualization. The particulate images were further analyzed for the size and number (Vision PE, version 5.0 software, Clemex); the size of a particle was estimated by converting the number of neighboring pixels with similar color associated with a particle to an equivalent diameter. The average number of particulates above 300 μm in size was plotted to illustrate the different levels of systemic particles for the devices.

PHARMACOKINETIC STUDY IN FEMORAL ARTERIES. Arterial paclitaxel concentrations were determined following PCB delivery (Ranger or In.Pact) in the femoral territory of swine. The results were compared with well-established historical data published for the Lutonix PCB technology (11). Arterial tissue concentrations of paclitaxel were measured at 4 h and 1, 7, 21, 45, and 60 days. A total of 3 animals per time point (18 animals) were included and received PCB delivery in every femoral artery (36 vessels). At sacrifice, individual arteries were harvested, homogenized, extracted, and quantified by mass spectrometer for arterial paclitaxel concentration.

HYPERCHOLESTEROLEMIC SWINE MODEL. A total of 6 familial hypercholesterolemic swine obtained from the University of Wisconsin, Department of Animal Sciences were used in this study. The genotypic and clinical features of this model have been already published (12,13). For this study, animals were maintained on a low-grade cholesterol pig chow in order to increase the cholesterol levels and to accelerate the disease process. In this study, younger animals were used (~8 months) as based on previous studies demonstrated the accelerated progression of neointimal proliferation following vascular injury despite the absence of significant atherosclerotic burden at this age (14,15).

IN-STENT RESTENOSIS MODEL AND TREATMENT. Figure 1 describes the study design. The study was approved by the Institutional Animal Care and Use