LABORATORY INVESTIGATION

# Pharmacokinetic Study of Paclitaxel Concentration after Drug-Eluting Balloon Angioplasty in the Iliac Artery of Healthy and Atherosclerotic Rabbit Models

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## ABSTRACT

**Purpose:** To assess whether the presence of an atherosclerotic lesion may alter the deposition kinetics of paclitaxel on the arterial wall after drug-eluting balloon (DEB) angioplasty, as well as paclitaxel concentrations in serum and in the recovered balloons.

**Materials and Methods:** Three New Zealand White rabbit models were created: an atheroma group (arterial mechanical injury and hyperlipidic diet; group A), a prelesional group (fat arterial infiltration, hyperlipidic diet; group B), and a control healthy group (group C). Forty-five animals underwent DEB angioplasty in the iliac artery. Arteries and serum samples were analyzed by liquid chromatography/tandem mass spectrometry at 1, 24, 48, 72, and 96 hours (arteries) and at 1, 6, 12, and 24 hours (serum). Recovered balloons were analyzed by UV chromatography. Histologic and statistical analyses were also performed.

**Results:** Group A showed significantly higher arterial paclitaxel concentrations in the first hour after DEB angioplasty (632.05 ng/mg ± 125.75 in group A vs 179.55 ng/mg ± 45.64 and 168.54 ng/mg ± 83.48 in groups B and C, respectively; $P < .05$). Paclitaxel was undetectable in serum at 24 hours in all groups, but the amount was significantly higher ($P < .05$) in group B at 1, 6, and 12 hours. The paclitaxel amount in navigated balloons from group A was significantly lower than in other groups ($P < .05$).

**Conclusions:** Paclitaxel concentration in an atherosclerotic lesion model immediately after DEB angioplasty is nearly fourfold higher than in a healthy artery. Paclitaxel remains in the bloodstream longer when a universal state of fat arterial infiltration is achieved. These findings could have clinical implications, as studies testing commercial drug-eluting devices on healthy animals may be underestimating paclitaxel arterial uptake.

## ABBREVIATIONS

DEB = drug-eluting balloon, DES = drug-eluting stent, HDL = high-density lipoprotein, LDL = low-density lipoprotein, TC = total cholesterol, TG = triglycerides

Drug-eluting stents and balloons have been developed to minimize intimal hyperplasia restenosis after angioplasty. They are used to deliver high concentrations of rapamycin, everolimus, or paclitaxel to the injured regions to inhibit vascular smooth muscle cell migration and proliferation, maintaining a patent lumen (1–4). Paclitaxel is considered the drug of choice in peripheral arteries. It interferes with the cell cycle predominantly at mitosis, disrupting microtubule dynamics by binding to α-tubulin, resulting in the arrest of cells in the M phase of the cell cycle, leading to apoptosis (5). When delivered to the artery, paclitaxel causes cell cycle arrest of its smooth muscle and inhibits neointimal hyperplasia in experimental animals and humans (2,6,7).

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Figure E1 is available online at *www.jvir.org*.



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Drug-eluting balloons (DEBs) have been developed to overcome the limitations of drug-eluting stents (DESs). However, a meta-analysis that compared the outcomes of DEB and DES use in the treatment of coronary artery lesions showed similarity in safety and clinical efficacy (8). When paclitaxel-coated balloon angioplasty was compared to uncoated balloon angioplasty in patients with femoropopliteal arterial disease, the former was superior to the latter in antistenotic efficacy (9–11). There are a lot of preclinical studies related to DESs but very few about DEBs, and most of them were developed in healthy experimental animals, with the exception of the study by Tzafriri et al (12), in which paclitaxel distribution was analyzed ex vivo in healthy and atherosclerotic aortas from rabbits and humans.

Experimental and clinical studies have described the accumulation, pharmacokinetics, and elution process of paclitaxel. Because of the strong affinity of paclitaxel for tubulin, paclitaxel is not homogenously distributed throughout the thickness of the arterial wall (1,13); consequently, this binding probably determines the diffusion and elution of the drug. Arteries do not have a homogenous structure, and the amount of muscular or elastic tissue differs depending on the anatomic territory. Finally, paclitaxel is a highly lipophilic compound that will bind more easily to a diseased atheromatous artery than to a healthy one, creating a different drug uptake by the diseased vessel (12,14,15).

It is likely that atheromatous plaques with associated disruption of the arterial wall architecture alter the elution kinetics of paclitaxel. In the present study, we compared paclitaxel elution kinetics among three rabbit models: normal iliac artery, arteriosclerotic artery, and fat-infiltrated artery.

## MATERIALS AND METHODS

### Phase I: Development of Animal Models

Fifty-seven male New Zealand White rabbits weighing 4–5 kg (age 7–8 mo) were randomly divided into three groups. The care and use of animals was in compliance with local animal welfare laws, guidelines, and policies. Our protocol was approved by the institutional review board ethics committee.

Three different models were created based on literature review (16,17): group A animals had atheroma lesion in the left iliac artery and hyperlipidemia, group B animals had a prelesional stage of fatty artery infiltration and hyperlipidemia, and group C was a healthy control group. The study design is summarized in **Figure 1**.

In animals from group A, an arterial injury was inflicted to the iliac arteries by using an angioplasty balloon before a 6-week hyperlipidic diet. Transcarotid catheterization was performed by using carotid artery cutdown and a 4-F introducer sheath (Micropuncture Introducer Set; Cook, Bloomington, Indiana). We obtained an aortoiliac arteriogram, and common iliac artery angioplasty was performed by using a 3-mm × 25-mm angioplasty balloon (Pantera; Biotronik, Berlin, Germany) inflated for 30 seconds at 7 atm three times. Postangioplasty iliac arteriograms were obtained in all animals (**Fig E1**, available online at *www.jvir.org*). The carotid artery was occluded, and animals were given

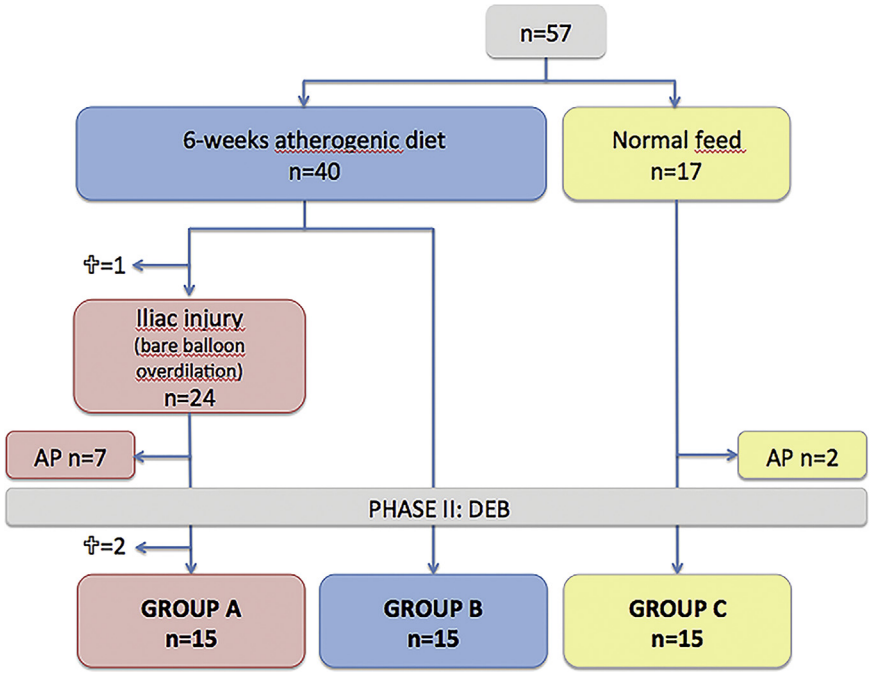


**Figure 1.** Study design. AP = animals for anatomopathologic study. (†Deceased animals.)