The Relevance of Paclitaxel Dose and Coating for Efficacy and Safety

Renu Virmani, MD
CVPath Institute, Inc.
Gaithersburg, Maryland, USA
Speaker's name: Renu Virmani, MD

I have the following potential conflicts of interest to report:

Consultant: 480 Biomedical, Abbott Vascular, Medtronic, and W.L. Gore.

Employment in industry: No


Owner of a healthcare company: No

Stockholder of a healthcare company: No
Requirements For DCB

• Must deliver large quantities of the drug within seconds
• Must distribute within the media in the first few days
• Therapeutic drug levels must be maintained for at least several weeks
• Must allow rapid healing as compared to DES
• No need for long-term anticoagulation
• Light microscopy must show biologic effects at 28-days at least
**Drug coated balloon devices** (Peripheral artery)

<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Coating</th>
<th>Drug dose (µg/mm²)</th>
<th>CE mark*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advance 18 PTX™</td>
<td>Cook Medical, Bloomington, IN, USA</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Cotavance*</td>
<td>Bayer Schering Pharma AG, Berlin, Germany</td>
<td>Paclitaxel–iopromide</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Freeway™</td>
<td>Eurocor, Bonn, Germany</td>
<td>Paclitaxel–shellac</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>IN.PACT™ Admiral, Amphilon, Pacific</td>
<td>Medtronic Vascular, Santa Clara, CA, USA</td>
<td>Paclitaxel–urea</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Lutonix DCB® (Moxy)</td>
<td>BARD, Murray Hill, NJ, USA</td>
<td>Paclitaxel–polysorbate/sorbitol</td>
<td>2.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Legflow*</td>
<td>Cardionovum, Warsaw, Poland</td>
<td>Paclitaxel–shellac</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Passeo-18 Lux®</td>
<td>Biotronik, Bülach, Switzerland</td>
<td>Paclitaxel–butyryl-tri-hexyl citrate</td>
<td>3.0 (No → Yes)</td>
<td></td>
</tr>
<tr>
<td>Stellarex*</td>
<td>Covidien, Mansfield, MA, USA</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>No → Yes</td>
</tr>
</tbody>
</table>

*Lutonix DCB® and IN.PACT™ are currently approved by the FDA for clinical use in USA.*

The effect of nonstop incubation with 1.0 μmol/L paclitaxel on haSMC morphology.

Paclitaxel-treated cultures, cell numbers are reduced. haSMCs are smaller and discoid with a loss of tail.

### How is DCB Different from DES

<table>
<thead>
<tr>
<th>Parameters that distinguish DCB from DES</th>
<th>DES</th>
<th>DCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug concentration on the device</td>
<td>Low 5-10 μg/mm</td>
<td>Very High 2-3 μg/mm² (≒20-30 μg/mm)</td>
</tr>
<tr>
<td>Drug transfer at the time of deployment</td>
<td>Slow</td>
<td>Rapid, all at once</td>
</tr>
<tr>
<td>Reservoir of drug</td>
<td>Polymer</td>
<td>No (excipient important)</td>
</tr>
<tr>
<td>Drug retention in tissues</td>
<td>Short term</td>
<td>Need a drug which binds to cell membranes and is easily transferable to adjacent cells</td>
</tr>
<tr>
<td>Diffusion</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>Lipophilic</td>
<td>yes</td>
<td>Even better</td>
</tr>
<tr>
<td>Active ingredient</td>
<td>Not necessary</td>
<td>Should be active immediately</td>
</tr>
</tbody>
</table>

![Graph showing primary patency over years with DES labeled as 67.6% Zilver PTX and Optimal PTA + BMS labeled as 45.5%]

![Images of DES, PTX Coated, and DCB]
Histologic Parameters for Evaluation of DCB Safety/Efficacy

• Key parameters include:
  – Endothelial Loss
  – Fibrin/Platelets
  – Inflammation
  – Injury
  – Medial Smooth Muscle Cell Loss
  – Matrix Replacement:
    • Proteoglycan
    • Collagen
  – Adventitial Fibrosis
Drug deliver of DEB

Unpublished Data; Pharmakokinetic and Histologic Response to a Paclitaxel Eluting Balloon (Sponsor: Kaneka Corporation) in 2009

Coating Integrity is Variable

Braun (Sequent)

MDT/Invatec (Admiral)

PTX in coating after aqueous exposure

Lutonix Catheter
PTX Adherence to Balloon: iopromide versus urea coating

- **p=0.002**
- **through a blood-filled hemostatic valve and guiding catheter and 1min in stirred blood**
- ***not released during expansion in a coronary artery***

Paclitaxel uptake in the Arterial Wall

Paclitaxel uptake in arterial wall 15-25 minutes
Post stent implantation (n= 6 arteries each)

Lutonix, 2 μg/mm² deployed in Swine Femoral Artery model at 1x

Vascular, downstream, and pharmacokinetic responses to treatment with a low dose drug-coated balloon in a swine femoral artery model

Vascular changes following Lutonix DCB treatment in Porcine Iliac arteries

<table>
<thead>
<tr>
<th>1x dose</th>
<th>28-days</th>
<th>90-days</th>
<th>180-days</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;E</td>
<td><img src="image1" alt="H&amp;E 28-days" /></td>
<td><img src="image2" alt="H&amp;E 90-days" /></td>
<td><img src="image3" alt="H&amp;E 180-days" /></td>
</tr>
<tr>
<td>Actin</td>
<td><img src="image4" alt="Actin 28-days" /></td>
<td><img src="image5" alt="Actin 90-days" /></td>
<td><img src="image6" alt="Actin 180-days" /></td>
</tr>
<tr>
<td>Movat</td>
<td><img src="image7" alt="Movat 28-days" /></td>
<td><img src="image8" alt="Movat 90-days" /></td>
<td><img src="image9" alt="Movat 180-days" /></td>
</tr>
<tr>
<td>Masson</td>
<td><img src="image10" alt="Masson 28-days" /></td>
<td><img src="image11" alt="Masson 90-days" /></td>
<td><img src="image12" alt="Masson 180-days" /></td>
</tr>
</tbody>
</table>

IN.PACT Drug Eluting Balloon: Medtronic

Drug in Tissue
Paclitaxel concentrations post-treatment support long-term efficacy*

- Detectable levels of drug up to 180 days in both arms (therapy dose and safety margin)
- At 320 no quantifiable drug is identified in the targeted tissue area

*Medtronic data on file
Preclinical Response
Histomorphometry of Treated Porcine Arteries*

- Very mild neointimal / medial inflammation resolved by 180 days
- SMC loss at indicating pharmacological activity of paclitaxel

*Medtronic data on file
Dose-dependent Changes in Iliofemoral Arteries Following SeQuent DEB treatment at 14 days

Controls 1X Inflation 4X Inflations 6X Inflations

X6 inflations

Crystalline material Fibrin Inflammation

Plasma

200 μm 200 μm

500 μm
Vascular Changes in Downstream Skeletal Muscle

(None of physiological significance observed for Moxy DCB at any time)

1x Dose

28 Days

90 Days

(None observed for 1x dose at 180 days)

4x Dose

28 Days

90 Days

180 Days
Safety Profile

All about Balancing Safety, Efficacy and Biologic Response

Not all balloons are created equal

- More Efficacy: Less neointima, Absence of restenosis, No, early or late thrombosis
- More Safety: Rapid Vascular Healing, Good Re-Endothelialization, No distal Emboli

- Less Drug Load: Use of Carrier/Excipient, Drug Retention, Repeat Inflations
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Renu Virmani, MD
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Gaithersburg, Maryland, USA