Paclitaxel-coated Angioplasty Catheters for Local Drug Delivery

a report by

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Percutaneous transluminal angioplasty (PTA) and percutaneous transluminal coronary angioplasty (PTCA) are established, proven methods for re-opening stenotic or occluded arteries in a minimally invasive way. The balloon is placed in the stenotic segment of the artery and then expanded until the lumen reaches its original diameter. To this end, very high pressure (up to 15 bar) is applied, which unavoidably causes vessel wall injury. Hyperproliferation resulting in lumen narrowing is the natural reaction to this injury.

A single short contact of tissue with a small dose of paclitaxel has been shown to efficaciously inhibit local cell proliferation. Paclitaxel is a natural compound found in the bark of Pacific yew trees. It binds to tubulin and thus inhibits the regular separation of chromosomes in dividing cells. It belongs to the group of cytostatic agents. Antiproliferative taxanes such as paclitaxel seem to be suitable due to their high lipophilicity and tight binding to various cell constituents, resulting in effective local retention at the site of delivery. Paclitaxel as a hydrophobic compound possesses preferential tissue binding. Two recently published papers documented effective convection and diffusion mechanisms of paclitaxel into the arterial wall from the lumen. In addition, competitive binding – for example by albumin and other plasma proteins – was identified as the main reason for diminished paclitaxel accumulation. Plasma concentrations of paclitaxel in the general circulation sufficient to inhibit restenosis would probably reach toxic levels. The coating of angioplasty balloons with paclitaxel allows for arterial uptake not hindered by protein binding due to the direct exposure of the drug to the luminal surface and short-lasting high local concentrations.

Adhesion of paclitaxel to the balloon surface is of great importance for successful coating delivery. The coating must adhere to the balloon during its passage through the introductory sheath or guiding catheter in the bloodstream, as well as during its passage through tortuous and sometimes calcified arteries. Upon inflating the balloon, the coating must be immediately released to the vessel wall. Ultravist® 370 is added to the coating in order to facilitate the release of paclitaxel from the balloon surface and enhance the solubility of paclitaxel in aqueous media.

Even if the highest dose was applied, histology revealed complete healing and endothelialisation four to five weeks after balloon dilatation and stent implantation.

Non-clinical Studies

The efficacy of paclitaxel locally administered by implanted drug-eluting stents (DES) in inhibiting restenosis following coronary angioplasty has been proved in animal experiments and clinical trials. Unlike DES, the drug is released from coated balloons upon contact within seconds to a minute. Studies have investigated the effectiveness of short exposure times of the drug on the tissue. Cell culture experiments provided the first hint that short exposure times may be sufficient to achieve persistent effects. The exposure of cells for three minutes was sufficient to inhibit cell proliferation for the following 12 days without impairing cell survival. In vivo studies of coronary overstretch in the porcine model showed that the paclitaxel-coated balloons effectively inhibited neointimal proliferation at all dose levels tested. Doses between 2.5 and 10µg paclitaxel/mm² balloon surface were equally effective. No difference was found between a 10-second and the standard 60-second inflation time. Efficacy compares favourably with the best-known DES on the market.

Experience with DES – although different because of the sustained drug supply – indicate the risk of delayed healing of the vessel wall after dilatation. Delayed healing, particularly delayed endothelialisation and coverage of the stent struts by endothelial cells, increases the risk of late thrombosis, which may result in vessel occlusion and myocardial infarction. Theoretically, paclitaxel administration to a coronary vessel may cause damage to the myocardial tissue supplied by this artery, whereas effects after further dilution and recirculation can be excluded because of the low dose. The risk of delayed healing and local damage to the treated vessel and myocardium has been assessed in various studies of coronary overstretch in the pig model. The effect of paclitaxel-coated balloons on the prevention of restenosis has been studied in pigs after implantation of the paclitaxel-coated balloons. No differences in the acute tolerance of coated and conventional non-coated balloon catheters were found during the interventional procedures. No signs of delayed thrombotic events possibly caused by delayed healing could be detected. Even if the highest dose was applied, histology revealed complete healing and endothelialisation four to five weeks after...
balloon dilatation and stent implantation. In order to obtain the clinical benefit of restenosis inhibition, it is important that the coating is not lost or washed off during catheter use. Potential areas of loss include passage through the introductory sheath, use with the guiding catheter while on its way to the stenotic lesion and contact with flowing blood and tortuous vessels before the balloon is expanded and pressed against the vessel wall. The transfer of the drug from the balloon surface to the vessel wall during balloon inflation has been investigated and found to be sufficient.6 The pharmacokinetics and biotransformation of paclitaxel reaching the general circulation are well-known from clinical use.

A single local administration of the drug must be sufficient to inhibit the excessive long-lasting hyperproliferation of tissue due to the vessel injury that can accompany angioplasty. To test its effectiveness, the coated catheter was tested directly against the state-of-the-art DES in the established porcine model of coronary overstretch.7

In Vivo Trials

Paclitaxel on Balloon Catheters – Comparison with Drug-eluting Stents

The purpose of the study7 was to compare the efficacy of intracoronary paclitaxel dissolved in the contrast medium and paclitaxel-coated balloons with the sirolimus-releasing Cypher® stent. Efficacy was tested in 22 pigs. Each pig received two coronary stents applying slight overstretch. The animals were treated by: uncoated balloons, bare stents, plain contrast medium Ultravist®, which comprised the control group; the same treatment but with paclitaxel in Ultravist; paclitaxel-coated balloons (about 3µg/mm²) with pre-mounted bare stents plus Ultravist; or sirolimus-eluting stents plus Ultravist. Inflation time of balloons was always one minute. Stenosis was assessed four weeks later by angiography and histomorphometry. Angiography indicated pronounced stenosis in the control group and minimal stenosis in the group treated with the paclitaxel-coated balloon. Histomorphometry confirmed the efficacy of the three routes of drug delivery with the effect being most impressive for the coated balloons (p<0.01 versus all other groups) (see Figure 1).

Paclitaxel on Balloon Catheters – Assessment of Shorter Contact Time and Higher Doses

Applying the same stenting overstretch methods used in previous studies, 60- and 10-second inflation times (approximate contact time to the vessel wall), 5µg paclitaxel/mm² balloon surface and the use of two coated balloons at the same site, one immediately after the other (two times 5µg paclitaxel/mm²), were compared with coronary stenting without drug administration (control).8 Quantitative evaluation of coronary angiograms taken four weeks after the treatment and histomorphometry revealed strong stenosis within the control segments (no drug) and an almost complete inhibition of neointimal proliferation in the arteries in which the paclitaxel-coated balloons were used (independent of the balloon inflation time).

Pharmacokinetics

Coating Release and Uptake During Vessel Dilatation

The balloon was coated with approximately 3µg paclitaxel/mm² expanded balloon surface. Studies6 in pigs showed that <10% of the dose was lost when the balloon was inserted into the vessel, left unexpanded for one minute and retracted through the guiding catheter. Approximately 40–60 minutes after angioplasty with the paclitaxel-coated balloon, about 10% of the dose was recovered from the arterial wall of the treated segment. An average 15% of the paclitaxel was found in the tissue if a stent was inserted prior to balloon use (see Table 1). The concentration of paclitaxel in the vessel wall decreased with an initial half-life of one to two hours when paclitaxel dissolved in Ultravist was injected into pig coronary arteries.3

Toxicology

Taxol® (Bristol-Myers Squibb) was approved in 1993 in The Netherlands (RGV 16265) for the treatment of certain cancers. The intended use in patients is a local single administration of an immediately bioavailable dose (no sustained release as with coated stents). The maximum dose is recommended in patients is up to 11.5mg paclitaxel per treated vessel site (large balloons, peripheral vessel). For tumour therapy, paclitaxel is recommended at a dose of 175mg/m². As the side effects of systemic paclitaxel therapy are due to the same mechanism as the antineoplastic effect and the presence of cremophor, which is responsible for the allergic-type reactions, cremophor is not used for balloon coating. Systemic effects of paclitaxel at 20mg/m² body surface area or lower are not expected.

Studies Addressing Arterial Healing and the Risk of Local Thrombi

Whereas the risk of systemic adverse effects is negligible due to the small dose administered by the coated balloon catheters, local tolerance has to be determined. The most relevant risk due to antiproliferative agents is delayed healing of the vessel injury, increasing the risk of thrombotic occlusion.

In the above-mentioned animal studies, vessel injury was caused by overdilatation. Furthermore, stents were implanted, which adds thrombogenic metal surface to the unprotected subintimal tissue. During one study, four balloons (uncoated, 1.3 or 2.5µg paclitaxel/mm²) were applied in coronary and peripheral arteries of 22 pigs.4 No delayed deaths potentially indicating thrombotic events were observed. Two pigs did not recover from the intervention and died four and 14 hours after treatment.
Table 1: Paclitaxel Content and Drug Transfer to the Vessel Wall After Coronary Artery Dilatation

<table>
<thead>
<tr>
<th>Balloon Catheter</th>
<th>Use</th>
<th>Dose Recovered on the Balloon Following PCTA or Stent Implantation (%)</th>
<th>Dose in the Vessel Wall 40-60 Minutes after PCTA or Stent Implantation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel-coated 3.0–20 or 3.5–20mm</td>
<td>PICA with coated balloon</td>
<td>7.9±2.6 (n=4)</td>
<td>8.7±1.9 (n=4)</td>
</tr>
<tr>
<td>Paclitaxel-coated 3.5–20 or 3.5–20mm</td>
<td>Stent + post-dilatation with coated balloon</td>
<td>11.0±4.3 (n=4)</td>
<td>15.6±4.13 (n=4)</td>
</tr>
<tr>
<td>Paclitaxel-coated 3.0–20 or 3.5–20mm with stent</td>
<td>Pre-mounted stent on coated balloon</td>
<td>6.1±1.8 (n=4)</td>
<td>17.3±8.5 (n=4)</td>
</tr>
</tbody>
</table>

Angio-plasty alone with paclitaxel-coated balloon coating. Paclitaxel = solvent that is ace tone and excipient. UltraStent implantation with non-coated balloon catheter and post-dilatation with paclitaxel-coated balloon and stent implantation with coated balloon catheter. PICA = percutaneous transluminal coronary angioplasty. Mean ± standard deviation.

due to a perforation of a vessel and a spasmus in an artery, respectively. Histology five weeks after the intervention revealed complete coverage of stent struts by the endothelium and no signs of thrombus deposition.

In a further study,7 stent implantation in 11 pigs was performed using balloons carrying about 3µg paclitaxel/mm² (one balloon per animal). In this study, none of the pigs died and, again, histology four weeks after the intervention showed endothelial cells covering all stent struts.

Clinical Studies

The principle of local drug delivery with paclitaxel-coated balloons has already been tested in prospective clinical trials. Scheller et al.10 enrolled 52 patients with in-stent restenosis of a coronary artery in a randomised, double-blind, multicentre trial to compare the effects of a paclitaxel-coated angioplasty balloon (3µg/mm² balloon surface) with those of an uncoated angioplasty balloon. The primary end-point was angiographic late lumen loss (LLL). Secondary end-points included binary restenosis and major adverse cardiac events.

Multivessel disease was present in 80% of patients in both groups. Quantitative coronary angiography revealed no differences in baseline parameters. At six-month angiography, LLL was 0.74±0.86mm in the uncoated balloon group versus 0.03±0.48mm in the drug-coated balloon group (p=0.002). The rate of binary restenosis was 43.5% (10/23) in the uncoated balloon group versus 4.5% (1/22) in the drug-coated balloon group (p=0.002). The major adverse cardiac event rate after 12 months was 31% (8/26) with the uncoated balloon versus 4% (1/26) with the drug-coated balloon (p=0.01). This difference was primarily due to the need for target lesion revascularisation in the uncoated balloon group (6/26 versus 0/26; p=0.02).

Two alternative approaches — paclitaxel either coated on angioplasty balloons or dissolved in contrast agent — were investigated by Tepe et al. In a blinded multicentre trial, 154 patients with stenosis or occlusion of a femoropopliteal artery were randomised to treatment by paclitaxel either coated on standard balloon catheters or admixed to the contrast agent, or control treatment (balloon angioplasty without paclitaxel). The primary end-point was LLL at six months, which was documented by control angiography analysed by an independent blinded core laboratory. The data have not been published until now, but reports suggest a clear benefit of drug-coated balloons compared with uncoated balloons.

Based on positive data in animal trials, which have been followed by prospective randomised trials in different vessel areas, drug-coated balloons may be a new, safe, effective and easy-to-use tool for the prevention of restenosis, and may change the treatment paradigms of atherosclerotic patients.

Conclusions

The non-clinical studies indicate that balloon catheters applied for PCTA are suitable for delivering paclitaxel coated on the surface of the balloons to the vessel wall. In spite of a single administration of the immediately bioavailable drug, neointimal hyperplasia — a major reason for restenosis following angioplasty — is efficaciously inhibited. The efficacy of the balloon coating compares favourably with DES, but does not require stent implantation. The achievable effect has been observed at a varied coating range from approximately 1.3µg to 10µg paclitaxel/mm² balloon surface without signs of toxicity.7

After local administration to well-perfused arteries, paclitaxel is rapidly washed out. Twenty-four hours after administration, tissue levels approach the detection limit of the method, indicating that tissue concentration declined to <5% of the initial levels.8 No signs of toxicity could be observed either in functional tests or by histological examination.

The paclitaxel dose applied on a single balloon is significantly lower than 5% of the paclitaxel dose approved for Taxol (≈11.5mg versus approximately 300mg), and the poorly tolerated excipient cremophor contained in Taxol is not used for the coating of balloons.

Non-clinical studies indicate that paclitaxel-coated balloon catheters may be safely used to inhibit neointimal proliferation induced by balloon angioplasty. Thus, they may enhance the efficacy of this important method by preventing early restenosis of the dilated vessel lumen. A broad range of doses (1.3–10µg/mm²) has been found to be safe and efficacious in inhibiting restenosis.