Drug-eluting Balloon Analysis

Alexander Ruebben, Juergen Boeing and Norbert Weiss

Aachen Resonance GmbH

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The Elutax© is a rapid exchange percutaneous transluminal coronary angioplasty (PTCA) catheter. There are two versions: one for standard-size coronary and small peripheral vessels (Elutax 2nd Generation) and one for small coronary vessels (Elutax SV).

The Aachen Resonance® Elutax drug-eluting balloon family was developed especially for coronary arteries and venous bypass as well as for small vessels in peripheral and supra-aortic regions. The balloon is coated with 2.0µg paclitaxel/mm^2. The Aachen Resonance Elutax drug-eluting balloon is intended for the treatment of atherosclerotic lesions, e.g. stenoses, recanalised occlusions and restenosis in naïve or previously treated vessels (for example stent, percutaneous transluminal angiography [PTA] or percutaneous transluminal coronary angiography [PTCA]). The paclitaxel is released by contact with the vessel wall intima during balloon inflation. The balloon inflation should be performed for at least 30 seconds to ensure a sufficient drug release (95%). Longer inflation or multiple dilatations are possible to optimise immediate PTA or PTCA results.

Successful implementation of local arterial drug delivery requires intramural distribution of drug. The physicochemical properties of the applied compound, which govern its transport and tissue binding, become as important as the mode of delivery. Hydrophilic compounds distribute freely but are cleared rapidly. Hydrophobic drugs, insoluble in aqueous solutions, bind to fixed tissue elements, potentially prolonging tissue residence and biological effect. Paclitaxel is such a hydrophobic compound, with proven excellent therapeutic potential against proliferative vascular disease.[1]

We hypothesised that the favourable pre-clinical data with this compound may derive especially from preferential tissue binding as a result of unique physicochemical properties. These data suggest that paclitaxel interacts with vessel wall elements as it moves under the forces of diffusion and convection and can establish substantial partitioning and spatial gradients across the tissue. The complexity of paclitaxel pharmacokinetics requires in-depth investigation if this drug is to reach its full clinical potential in proliferative vascular diseases.

Unlike other antiproliferative agents, paclitaxel also has several properties that make it a good candidate for local drug therapy of excessive arterial smooth-muscle-cell (SMC) proliferation in restenosis after balloon angioplasty or stent implantation; thus far, these properties have been tested *in vitro*, in animal models and in clinical studies.

First, the highly lipophilic character of paclitaxel promotes rapid cellular uptake by enabling it to easily pass through the hydrophobic barrier of cell membranes. This uptake is probably due to passive diffusion; no active transport mechanism is known. Second, the unique mode of action supports a long-lasting antiproliferative action even after a brief, single-dose application at low concentrations, as previously shown in tumour cells. An antiproliferative effect of paclitaxel on vascular cells has been shown *in vitro* in rat vascular SMCs (VSMCs) as well as *in vivo* in the rat carotid artery injury model. Paclitaxel was found to interfere with VSMC proliferation and migration at nanomolar levels *in vitro* and to prevent neointimal VSMC accumulation in the carotid artery *in vivo*.

Paclitaxel shows dose-dependent growth inhibition of human SMCs with levels from 1.0 to 10.0µmol/litre. Remarkable unspecific cell toxicity was seen only at very high concentrations (100.0µmol/litre paclitaxel). Even short-term treatment with 0.1–10.0µmol/litre paclitaxel for one, 12 or 24 hours, as well as continuous treatment for eight days, leads to typical alterations of cell morphology. A major effect of paclitaxel is microtubule stabilisation. The alterations of the cytoskeleton caused by paclitaxel are responsible for reduced proliferation, signal transduction and migration.[2] However, a dose-dependent, significant growth inhibition of endothelial cells at high concentrations is also described (0.01–1.0µmol/litre). At low doses of paclitaxel (<0.1µmol), growth of human endothelial cell (EC) monocultures was less inhibited than human SMC growth, whereas high doses of paclitaxel (0.1–10.0µmol/litre) exerted similar effects in both human ECs and human SMCs.

Paclitaxel is considered to be suitable for the treatment of vascular disease because of its high molecular weight and lipophilic characteristics. However, the pharmacokinetics of paclitaxel in the vessel wall are still not known. In order to understand the therapeutic dose and to avoid overdosing, the aim of this study is to evaluate the paclitaxel tissue concentration over time.

The literature and our own results were based on paclitaxel concentrations measured after one hour, six, 12, 24 and 48 hours. The

Figure 3: Paclitaxel Tissue Concentration

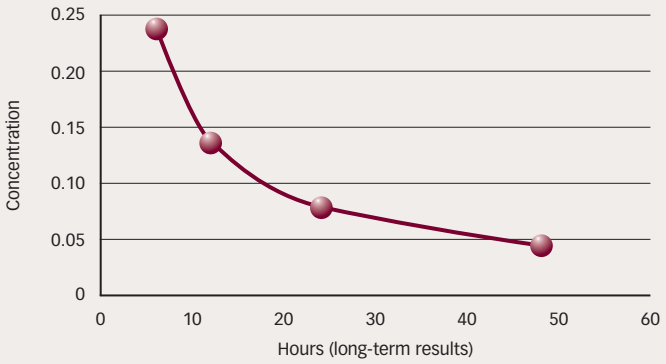


Figure 4: Master Curve

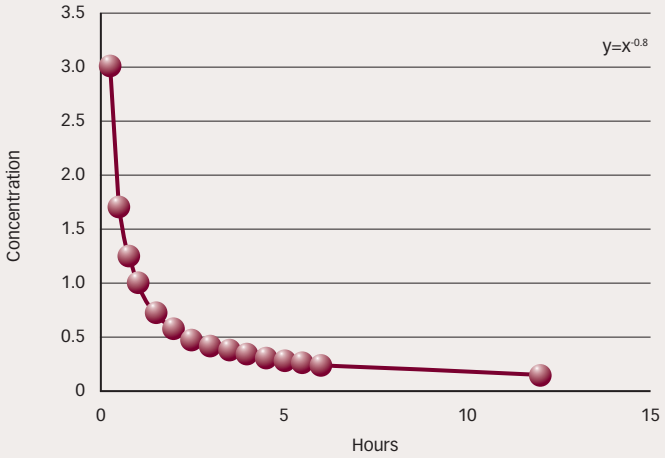
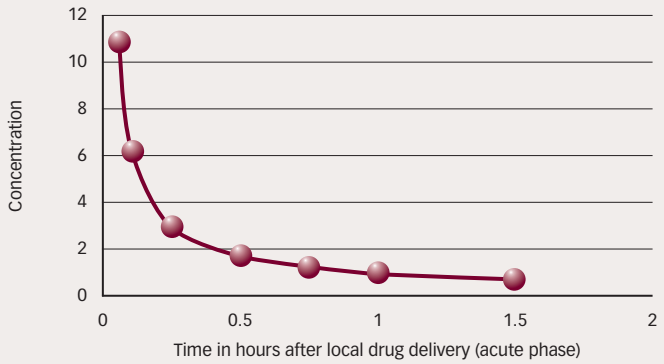


Table 2: Calculated Normalised Paclitaxel Levels Over 48 Hours

Time in Hours	Normalised Paclitaxel Level (Concentration)
0.05	10.98
0.10	6.30
0.25	3.03
0.50	1.70
0.75	1.25
1.00	1.00
1.50	0.72
2.00	0.57
2.50	0.48
3.00	0.42
3.50	0.37
4.00	0.33
4.50	0.30
5.00	0.28
5.50	0.26
6.00	0.24
12.00	0.14
24.00	0.08
48.00	0.045
240.00	0.012
720.00	0.005

Figure 5: Paclitaxel Tissue Concentration



Gutenberg–Richter law for earthquake sizes, Pareto's law of income distribution, structural self-similarity of fractals and scaling laws in biological systems. Research on the origins of power law relationships and efforts to observe and validate them in the real world is an active topic in many fields of science, including physics, computer science, geophysics and more.

Estimating the Exponent n from Empirical Data

There are many ways of estimating the value of the scaling exponent n for a power law tail, but not all of them yield unbiased and consistent answers. The most reliable techniques are often based on the method of maximum likelihood. Alternative methods are often based on making a linear regression on either the log–log probability, the log–log cumulative distribution function or on log-binned data, but these approaches may be problematic as they can lead to highly biased estimates of the scaling exponent. The curve in *Figure 4* can be calculated. In order to calculate the values, once we have one single time-dependent tissue value we can use the following equation (see *Table 2*):

$$y = x^{-0.8}$$

x = time in hours; y = paclitaxel level (concentration) in tissue

Once we have identified an appropriate function describing the tissue behaviour, we can extrapolate the curve for the values, which were unknown until now (see *Figure 5*).

What Can We Do with this Curve and Values?

This curve and values mean:

- no need for further animal trials to measure the time-dependent paclitaxel tissue level (concentration) for a prolonged time;
- there is the possibility of analysing and evaluating data from different products;
- paclitaxel tissue level (concentration) calculation of the first few minutes after drug delivery is possible;
- establishing criteria to decrease prolonged toxicity is possible;
- calculating needed time for safe endothelisation is possible; and
- minimised toxicity when using long and large balloons is possible. ■

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