Local Drug Delivery for Restenosis and Thrombosis — Progress?

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ABSTRACT: Platelet activation, inflammation, recoll, tissue hyperplasia and remodeling are pivotal pathophysiologic factors in acute myocardial ischemia and restenosis development after angioplasty. Even after the rising use of stents, the tremendous amount of resulting tissue hyperplasia remains a therapeutic problem.

It has been suggested that short duration of effective drug levels and poor efficiency of systemic drug administration account for the failure of therapy in clinical trials. A rational effective therapy for angina and restenosis should therefore be locally administered at the site of vascular obliteration. Special local drug delivery devices could be used to administer sufficient drug amounts at the site that needs to be treated.

Local drug delivery systems using modified balloon systems, stent systems or newly designed catheters have been developed. In experimental studies, different effects can be demonstrated by using endoluminal and adventitial substance delivery. Endoluminal application usually resulted in <1% effective drug delivery in the arterial wall and short lasting deposition. Adventitial deposition led to higher mural concentrations; the drug was detectable for up to 21 days. In media, the maximum is still comparable to the maximum obtained after systemic application. Experimental studies indicate positive therapeutic effects in restenosis models. Feasibility has been proven in clinical studies of unstable angina with anticoagulants or antithrombotics. Further preclinical and preliminary clinical studies are needed to clarify regional drug distribution, regional wash-out, adverse effects and evaluation of long-term therapeutic effects. Recent developments in catheter techniques might enable effective local drug application in angina and restenosis prophylaxis with a reduction in systemic adverse effects. (Supported by DFG Go 739/1-1).

J INVASIVE CARDIOL 1998;10:528–532

Key words: restenosis, thrombosis, angioplasty

Angioplasty is limited by a restenosis rate of approximately 30–60%. The pivotal pathophysiologic facts are triggered immediately after angioplasty and result in excessive tissue hyperplasia especially after stenting.1–9,17–20 Agents that may be promising in preventing restenosis are those that interfere with inflammation, proliferation and matrix production. Therefore, restenosis appears to be a disease that can be targeted with local drug delivery. This therapeutic approach might overcome the crucial paradox: a number of drugs effectively suppress cellular activity and matrix production in vitro and in animal experiments, but fail to show therapeutic effectiveness when given systemically in patients.4 Consequently, much effort was
made to achieve high local concentration of drugs by means of catheter associated techniques. As restenosis is a focal event, a local drug delivery system which allows delivery of highly concentrated agents is potentially needed. Local drug application should be performed immediately before or after the therapeutic angioplasty procedure with the above mentioned drugs.

Devices For Local Drug Delivery (Figure 1)

**Diffusion systems.** Balloon devices result in close contact with the vessel wall and enable transmural diffusion. This method is fairly atraumatic at comparatively low pressures. However, the drug may be lost into side branches. Another common representative is the double balloon. Coated balloons, such as hydrogel balloons, prevent disappearance of the perfusion substance while the catheter is placed in the artery. A promising method is the coated stent, which is currently under investigation in the clinical environment. It ensures a prolonged contact of substance or radioactivity at the site where the catheter or stent associated injury is induced. Dosage and long-term effects are pivotal factors with these systems.

**Pressure driven devices.** The drug is driven transmurally by pressure into the arterial wall. The best known model is the porous balloon, several modifications of which have been described. Drug delivery will be determined by pressure, pore size and the contact with the artery. It is therefore asso-

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**Figure 1. Local drug delivery devices.**
associated with severe pressure damage to the arterial wall by small pores with an increasing wash-out effect by increasing pore size if inflation pressures above 4 atm are used. Efficiency has been measured with various indicators resulting in better uptake with lipophil drugs. This illuminates the importance of pharmacologic aspects of local drug delivery.

**Miscellaneous devices.** One exciting concept is the iontophoretic balloon, a modified balloon which incorporates cathode and anode. This device is only useful for applying polarized substances by electrical forces.

Another device is the needle-injection catheter, which consists of a flexible polyethylene catheter with preshaped circumferential injection needles. The needles penetrate the arterial wall and target the perivascular area for local drug deposition. This results in a local drug level several times higher than can be achieved by any other device or by systemic application. Current investigations reveal that significant systemic waste has to be considered with this device from the first hour after injection. Furthermore, the pivotal role of the adventitia, a somewhat neglected vascular component, has been documented in several studies. Therefore, this layer is preferentially accessible with the needle-injection-catheter. However, technical refinements of this system are necessary if adverse effects due to additional trauma are to be avoided.

Other devices include the infiltratory, which is a balloon catheter that features protruding infusion channels that penetrate the arterial wall, and the coated or radioactive stent, which is being investigated in the clinical environment. It ensures a prolonged contact of substance or radioactivity at the site where catheter or stent associated injury is induced. Dosage and long-term effects are pivotal factors to consider with these systems. A subgroup of intravascular radiation devices uses radiation emitting wires. Thus problems arising with dosage “leaks” in between un-homogenous deployed stent struts are avoided.

**Photodynamic Therapy (PDT).** A unique approach offers photodynamic therapy. Experimental studies in large animals show that PDT is strikingly effective at suppressing vascular tissue hyperplasia after angioplasty using special isotropic light application devices (Figures 2 and 3).

**DISCUSSION**

Recent data indicate that restenosis prevention strategies should be applied soon after percutaneous intervention. A local strategy is particularly promising in restenosis because the site of delivery is accessible immediately following angioplasty and the
pathophysiological process is limited to the lesion treated. To date, several devices designed to achieve local drug delivery in arteries have been investigated, but none of them have been able to show high local drug delivery efficiency. The major problem seems to be achieving sufficient drug concentration in the arterial wall without leakage, side-effects or toxicity.

Many local drug delivery devices are available. A perfect intravascular device must meet several criteria. It should be capable of delivering a high and measurable quantity of drug into the arterial wall with minimal loss. Delivery should be atraumatic and cause no complications, such as ischemia.

Systemic load has to be calculated with every endoluminal approaching device and even with trans-arterial injection using devices like the needle injection device. Therefore, approaches like gentechique have to calculate and prove that there are no significant adverse systemic effects. Currently, two therapeutic strategies are unique: intravascular radiation and intravascular photodynamic therapy. Radiation has shown efficiency in experimental and first clinical applications. However, decades of experience with radiation reveal that adverse effects are due to complex three-dimensional dosage and fibrosis occurring up to several years later.

Photodynamic therapy with local intravascular sensitiser application and subsequent light amplification has been evaluated and showed efficiency with several photosensitizers. Systemic side-effects are usually inconsequential because the dyes are modified endogenous substrates and toxic only at the site of amplifications. Clinical efficiency will be tested in projected trials.

REFERENCES

GARY ROUBIN: This is great work. The progress in this area has been slow, but every year we learn a little bit more about using local drug delivery to achieve our goals. I think it is only a matter of time before we have coated stents that contain agents that will help us prevent intimal proliferation, but we have to continue on this mission. In a clinical sense, we have tested very few agents out of hundreds of potential agents that could do this work for us. Therefore, I think that we are still at the stage of developing good methods to transport these agents to the vessel wall. Next, we have to set about the task of testing the myriad agents.

GERALD DORROS: When I consider the subject of restenosis, I think that we are fighting a war; each time we fight the war, we use a larger armamenture and each side gets worse. Now we have deep tissue injury. If you look at Elazar Edelman's work, one thing is peculiar. In a normal scenario, the body easily prevents tissue from migrating from one side to another. We, however, are trying to ablate, to fight, and to destroy the tissue that is responding in the normal way of the body. Why aren't we trying to restore the normal barriers that separate one tissue from another as opposed to trying to destroy the normal body response? There is some work that is being done regarding this idea. And it seems to me that if they are correct by restoring the normal barriers that exist by stimulating tissue growth, as even Jacque Perrone talked about, by taking ulcerated plaque and injuring the endothelialization. After that occurred, you did not get intimal proliferation. Why are we not looking at ways of restoring the normal barriers as opposed to trying to destroy the tissue response which is going to continue as long as we have a stent in place?

PETER GONSCHIOR: I think the problem is a target problem. Again, nobody wants to get into the adventitia. It just happens in some cases. If you destroy tissue, you have to do it selectively. You must do it in a controlled way, and if you want to stimulate something in order to seal something that might be a very good approach you must be sure that you do not overdose your wound healing or your stimulating response.

GERALD DORROS: If you can preferentially reestablish the lining that separates the tissues, you are not going to have smooth muscle migrating and have multi-potential cells causing endothelialization or intimal proliferation or restenosis. I question why we are spending so much time and effort fighting the body's normal responses and why we are not investigating ways to stimulate the normal body response to restore normal barriers between tissue layers.

PETER GONSCHIOR: If you are able to seal the area, then it's a potential therapeutic response. In our experimental set-up, we could clearly demonstrate that there is excessive wound healing if you get a deep injury; that is what we are trying to target. That's the problem. We have increased proliferation and excessive inflammation; that was the reason for us to use an antiproliferative and antiphlegistic approach.