From Systemic Shotgun to Site-Specific Nanoparticle-Targeted Delivery

A New Paradigm for Drug Delivery

Ian J. Sarembock

Since the introduction of percutaneous techniques for the relief of symptomatic obstructive atherosclerotic coronary artery disease in the late 1970s, the major Achilles heel was restenosis. After nearly 3 decades of study, the cellular and molecular biology of this complex response to injury is now far better understood and includes the role of thrombosis, cellular proliferation, inflammation, matrix production, and elastic recoil. Some 15 years ago there was enthusiastic interest in the concept of “site specific” or “direct delivery” of antiproliferative or anticoagulant therapies. Edelman et al reported on the inhibition of SMC proliferation after vascular injury by surgical placement of heparin-impregnated polymer matrix in the periadventitial tissue of rat carotid arteries. At that time a catheter-based porous balloon catheter became available for “site specific” delivery but failed to be effective in limiting restenosis in an atherosclerotic rabbit femoral artery injury model. Although labeled heparin could be demonstrated to be present in the injured vessel wall, retention time of the drug and potential additional injury created by a jet effect of the porous balloon catheter were cited as potential explanations for the lack of efficacy. Subsequently, the concept of local delivery remained dormant and a multitude of clinical trials using systemically administered pharmacological agents to reduce or prevent restenosis demonstrated no benefit.

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In the late 1980s and early 1990s, coronary stents, providing the necessary scaffolding to prevent elastic recoil become the new standard for the percutaneous treatment of obstructive coronary disease. Nevertheless, in-stent restenosis remained the major limitation of coronary stenting, with the predominant mechanism being intimal hyperplasia. Despite an improved understanding and identification of patient-specific, lesion-specific, and procedure-specific factors, in-stent restenosis remained a challenge despite newer therapies including intravascular brachytherapy. Subsequently the concept of local drug delivery using the surface area of the stent was proposed and investigated, allowing for drug application at the specific injury site with minimal systemic release or toxicity of drug. Since the introduction of drug-eluting stents (DES) into clinical practice in 2002, this approach has transformed the practice of interventional cardiology by dramatically reducing in-stent restenosis and the need for repeat revascularization. Although animal models have in general predicted the response to DES in humans with a near absence or minimal intimal hyperplasia, what is characteristically different is the temporal response to healing which is substantially delayed in humans. This has been painfully borne out by reports of late stent thrombosis, again highlighting the need for verification of proof of efficacy (“to help”) with the risk-benefit relationship (“do no harm”) for specific new technologies and therapies. Although there remains an incomplete understanding of the etiology of late stent thrombosis, discontinuation of dual antiplatelet therapy, in particular clopidogrel use, appears to be the most important risk factor. These unanticipated and potentially catastrophic adverse outcomes continue to remind us of the need to pursue improved and safer alternatives to the presently available therapies. Newer stent platforms, bio-compatible and bioabsorbable polymer alternatives, and new drugs and drug combinations are being developed as we strive toward safer DES.

In this issue of Arteriosclerosis, Thrombosis and Vascular Biology, Joner et al report that site specific targeting of nanoparticle prednisolone reduced in-stent restenosis in a rabbit model of established atheroma. Using the rationale that the present generation of DES are hampered by local drug toxicity and polymer-induced inflammation with resultant delayed healing, the investigators use a novel strategy of prednisolone phosphate encapsulated in pegylated 3,5-dipentadecyclobenzamidine hydrochloride (TRX-20) liposomes which specifically bind to chondroitin sulfate proteoglycans (CPSGs) which are differentially expressed in the subendothelial matrix and exposed after vascular injury. CPSGs are not expressed in vascular endothelial cells. This strategy has previously been shown to have high affinity for injury sites and can be delivered at doses far lower than systemic delivery of free prednisolone phosphate, thereby minimizing the risk of systemic side effects. Once localized to sites of vascular injury, the cationic lipid component of TRX-20 is endocytosed by cellular mechanisms resulting in direct intracellular drug release. Using a well accepted rabbit model of experimental atherosclerosis and exemplary experimental design and techniques, the authors performed a proof of concept study to demonstrate that nanoparticle-laden drug can be site-directed...
to areas of vascular injury and showed that therapeutic concentrations of prednisolone phosphate were achieved at approximately 100-fold higher concentration in stented compared to nonstented arteries after a single injection at 1 mg/kg. This resulted in a significant 24% to 27% reduction in intimal area within the stent with a 40% reduction in neointimal macrophages and an approximately 60% reduction in inflammatory score. Importantly, reendothelialization was not retarded and was not different between the experimental groups, with no signs of systemic toxicity. Of note, empty liposomes did induce an inflammatory response despite attempts to minimize opsonization by modification of the nanoparticles with polyethylene glycol (PEG). The ability to minimize this phenomenon will need further refinement.21 Macrophages were localized to the adventitia, suggesting that opsonin-tagged empty liposomes accumulated via transport through the vasa vasorum rather than transmural trafficking from the luminal surface. In contrast, steroid-loaded liposomes were deposited in the neointima. The explanation for this observation and its potential implications require further investigation.

Although this study used glucocorticoids as a primary antiinflammatory strategy with a secondary suppression of neointimal growth, advances in the cellular and molecular biology of atherosclerosis and vascular injury responses, provide promising new therapeutic opportunity for more specific, potent, and efficacious molecular targeting. The rapid growth of nanotechnology and the potential dual use of nanoparticles for both molecular imaging and site-directed delivery of therapeutic agents offers great promise for individualizing therapeutics for vascular disease.22 Previous reports in a rabbit model of atherosclerosis and vascular injury demonstrate that intravenous fumagillin-loaded nanoparticles targeted to αvβ3-integrin epitopes on the vasa-vasorum of arteries resulted in marked inhibition of plaque angiogenesis in cholesterol-fed atherosclerotic rabbits.23 Using a novel cremophor-free albumin-stabilized nanoparticle formulation of paclitaxel, Kolodgie et al reported sustained suppression of neointimal thickening with nearly complete reendothelialization after only 2 doses of systemically administered drug in a rabbit iliac stent model.24 With this relatively wide therapeutic index, and repeat dosing as necessary, optimization of neointimal suppression with a normal healing response appears attainable. This new paradigm for drug delivery thus represents a unique opportunity to improve efficacy and minimize adverse effects as first described by the father of medicine, Hippocrates, “As to diseases, make a habit of two things—to help, or at least do no harm.”

Taken together, it is fair to conclude that the future is bright and the journey has begun, so let us continue to strive for safer and more effective therapies for the control of vascular disease in our patients.

Disclosures

None.

References

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