Dexamethasone: Effects on neointimal hyperplasia and vessel integrity

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The clinical success of balloon angioplasty is limited by restenosis, which occurs in up to 50% of patients. Lumen compromise and restenosis are caused by acute elastic recoil and late constrictive remodeling and to a lesser degree by neointimal hyperplasia [1,2]. The application of bare metal stents (BMS) has revolutionized percutaneous coronary interventions by reducing the rate of clinical complications and the need for target vessel revascularization. Although BMS mechanically prevent the decrease of total vessel area caused by constrictive remodeling, in-stent restenosis still reduces the clinical success rate of BMS substantially. In contrast to restenosis after balloon angioplasty, after stent implantation restenosis is caused exclusively by ingrowth of a thickened neointima as the result of increased migration and proliferation of vascular smooth muscle cells (SMC) [3,4]. The invasion of inflammatory blood cells with the concomitant release of cytokines and growth factors positively correlates with the degree of in-stent stenosis [5]. In addition to the cellular component of the stent neointima, the accumulation of extracellular matrix (ECM) components such as proteoglycans and collagens has been recognized to be a key factor, since the ECM determines SMC phenotype, thrombogenic properties, and volume expansion [6,7].

Since in-stent restenosis is determined by the extent of neointimal hyperplasia, the application of anti-proliferative, anti-migratory, or anti-inflammatory drugs locally at the target lesion has become an attractive possibility to further enhance the long-term patency of stented vessels. Indeed, the introduction of drug-eluting stents (DES) has been clinically very successful. Sirolimus (rapamycin) and paclitaxel have been approved for clinical use in DES. Both drugs strongly inhibit SMC proliferation and migration [8,9]. After local application by DES, both drugs have proven superior to BMS with respect to reduction of in-stent stenosis and associated clinical complications such as myocardial infarction or the need of target vessel revascularization (for review see [10]). The impressive clinical benefits of sirolimus and paclitaxel DES have stimulated research on other pharmacologically active compounds that interfere with processes that regulate restenosis. Among these agents is the glucocorticoid dexamethasone, which is also in the focus of an elegant study by Pires et al. appearing in this issue of Cardiovascular Research [11].

Dexamethasone has been in clinical use for more than 40 years and is among the most potent anti-inflammatory and immunosuppressive glucocorticoids with only minimal mineralocorticoid effects. However, the long-term, systemic use of glucocorticoids causes serious side effects such as osteoporosis, immunosuppression, hypertension, and disturbance of glucose and lipid metabolism (iatrogenic Cushing’s syndrome). These serious side effects make local application a very attractive treatment option for glucocorticoids. Glucocorticoids affect the gene expression profile of target cells by binding to cytosolic glucocorticoid receptors, which dimerize and translocate into the nucleus. Among the many target genes of glucocorticoids are annexin-1 (lipocortin-1) and the inhibitor of nuclear factor kappa B (I-κBα). The expression of annexin-1 is upregulated, thereby inhibiting phospholipase A2 and in turn suppressing prostaglandin synthesis. I-κBα is induced by glucocorticoids as well, thereby inhibiting the NFκB-mediated effects of cytokines on expression of pro-inflammatory factors such as cyclooxygenase-2, cytokines, and adhesion molecules. Furthermore, proliferation of fibroblasts, SMC,
and macrophages is inhibited by glucocorticoids. Overall, glucocorticoids are considered as anti-inflammatory, immunosuppressive, and anti-proliferative agents, which places them among the disease-modifying drugs in the treatment of chronic inflammatory diseases such as asthma and rheumatoid arthritis. Since atherosclerosis involves inflammatory events and inflammation occurs in response to stent implantation, dexamethasone appears to be a promising candidate drug for DES.

Dexamethasone-eluting stents have been used in three clinical trials. The STRIDE trial by Liu et al. reported low restenosis rate (13%) after implantation of dexamethasone-eluting stents [12]. The lowest restenosis rate was observed in patients with unstable angina. In contrast, two clinical trials by Hoffmann et al. revealed no benefit of dexamethasone-eluting stents in a patient collective that included high-risk patients such as diabetics [13]. As in clinical studies, animal models of stent restenosis revealed conflicting results with regard to efficiency of dexamethasone in preventing neointimal hyperplasia. Therefore, it seems necessary to investigate the potential of dexamethasone for use in DES in more detail and to define the dosage and the type of lesions that might be treated successfully with dexamethasone.

In this issue, Pires et al. investigated the effect of dexamethasone application in a murine model of intimal hyperplasia [11]. Neointimal hyperplasia was induced in the femoral artery of mice by placing a non-constricting cuff around the adventitial layer of the neointima. This model was originally described by Moroi et al., who demonstrated the development of concentric neointimal thickening within 2–3 weeks [14]. The neointima that develops underneath the cuff is composed mainly of SMC and ECM and mimics key features of the fibroproliferative neointima that develops within stented arteries. However, in contrast to human atherosclerosis the inflammatory reaction is weak in this model. Recently the same group refined this model and developed a ‘drug-eluting cuff’ composed of poly(--caprolactone) polymer matrix that allows the testing of candidate compounds suitable for DES [15]. In the current study, cuffs containing 1%, 5%, and 20% dexamethasone strongly reduced neointimal thickening. The changes were shown to be dose dependent and maximal at 5% and 20% and to involve a loss of SM-actin-positive SMC, increased apoptosis, and decreased collagen accumulation. The medial layer of the femoral arteries was also affected and characterized by decreased medial area, increased SMC apoptosis, and internal elastic lamina (IEL) fragmentation. Apoptosis and IEL fragmentation were most pronounced at 20% dexamethasone but this concentration did not increase the inhibition of neointimal hyperplasia compared to 5% dexamethasone cuffs. These results point towards a steep dose-response relationship with respect to inhibition of neointimal hyperplasia by dexamethasone and a narrow therapeutic window because of medial atrophy.

The observations could have clinical relevance since the dose of dexamethasone released by the clinically used dexamethasone-eluting stents was well within the range tested here. However, the finding of medial atrophy and IEL fragmentation in response to dexamethasone suggests that the safety margin of local application of dexamethasone to arterial vessels is narrow. Several questions remain with respect to the mechanisms and signaling pathways underlying the effects of dexamethasone on apoptosis, IEL fragmentation, and collagen synthesis. Furthermore, since the periadventitial delivery of dexamethasone is specific to the model used by Pires et al., it will be of interest whether the effects of dexamethasone after intraluminal application by DES are similar. The intraluminal delivery of stents causes damage to the endothelial layer, which increases the risk of target lesion thrombosis. Therefore, the use of a model of dexamethasone-eluting DES is also necessary to analyze the effect of dexamethasone on reendothelialization. Furthermore, it must be determined whether the disturbance of vessel integrity caused by dexamethasone occurs in human arteries after deploying dexamethasone DES and whether such consequences would cause stent malapposition or stent thrombosis.

Although efficacy and safety need to be determined clinically, preclinical testing of candidate drugs in well-defined animal models is necessary to gain insight into the basic biological responses to candidate compounds [16]. An important aspect of the current paper is the model used, which enables screening of candidate drugs for DES and the establishment of dose–response relationships with respect to both therapeutic and harmful effects on the vessel wall. The results from drug testing using the drug-eluting cuff model could help to quickly and cost-effectively establish the dose range of candidate drugs with reasonable potential for DES that can subsequently be tested in an animal model of actual DES implantation such as the porcine coronary artery model.

References


