MINIREVIEW

Pharmaceutical Aspects of Drug Eluting Stents

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ABSTRACT: This review focuses on the pharmaceutical aspects of the development of drug eluting stents. It discusses the different processes that can be used to obtain a controlled release of a drug from the stent as well as the coatings therefore applied. Results obtained for stents already available on the market or in a far stage of development are discussed. In a final part possible future research areas as well as expected new evolutions in the design of drug eluting stents are presented. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:5047–5060, 2008
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INTRODUCTION

Cardiovascular diseases are still one of the major causes of death in the western world. The most known and the most frequent heart diseases are caused by atherosclerosis, a process of vessel wall degradation and calcification, leading to narrowing and/or occlusion of the blood vessels.

The pathophysiology of atherosclerosis can be divided in different processes. The first step is the adhesion of blood platelets and leucocytes to the endothelial wall. This is probably due to initial lesions caused by physical effects. In a second step macrophages migrate to and accumulate in the vascular wall, followed by the development of foam cells, which finally cause a chronically vascular inflammation, followed by the activation and migration of smooth muscle cells.[1]

At the end a so-called atheromata is formed consisting, next to foam and smooth muscle cells, of dead cells, extra cellular fat, cholesterol, calcium, and collagen. In the atheromata a necrotic core of foam cells, dead cells and fat is formed, surrounded by a fibrotic cap of smooth muscle cells, proteoglycans, collagen, and calcium. The presence of these lesions eventually leads to narrowing of the artery. This reduces the transport of oxygen and blood to the heart, leading to ischemia and angina pectoris. In case of a disruption of the lesion it can also lead to thrombosis and occlusion of the diseased vessel.[1–3]

To threat atherosclerosis, three main approaches exist: drug therapy, bypass chirurgy, and balloon angioplasty with or without the implantation of a stent.[4] This review will focus on the use of stents with balloon angioplasty. Balloon angioplasty was introduced in 1979 and became the main therapy in cardiology. Still this procedure results in a high risk of restenosis, due to the balloon-induced endothelial injury. Restenosis is primarily characterized by neointimal proliferation and elastic recoil of the vascular wall.[5,6]

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From 1990, metallic scaffolds or stents were implanted at the lesion site in order to prevent restenosis.[7] Even if the implantation prevented the elastic recoil of the vascular wall, the injury caused by the implantation of the stent resulted in neointimal proliferation and in-stent restenosis.[8,9]

The logical step was to combine the stent implantation with the use of drugs, to inhibit one of the multiple processes promoting restenosis. Systemic administration was not successful due to the low tissue druglevels at the target site, that is, the lesion at the vascular wall.[5] This lead to the idea of developing drug eluting stents. These stents can be considered as local drug delivery systems, resulting in higher tissue levels at the target site, minimizing the risk of systemic toxicity, and allowing a controlled drug release.[10]

This review will threat the pharmaceutical aspects of drug eluting stents. It will be focused on the different types of coatings, the way they are applied and their influence on the physical and chemical properties of the drug eluting stents leading to differences in the drug release profiles.

DRUGS

In this first part a short overview is given of the different drugs used in drug eluting stents. The majority of them are still under investigation.

General

Four classes of drugs inhibiting one or more biochemical pathways leading to restenosis, are candidate drugs to be used in drug eluting stents: anti-inflammatory, antithrombogenic, antiproliferative, and immunosuppressive drugs. Also some research is conducted using antibodies blocking specific receptors as active compounds.

Paclitaxel

Paclitaxel is an immunosuppressive and antiproliferative agent, very common as component of chemotherapy in cancer treatment. Paclitaxel is a potent antimicrotubule agent that reversibly binds to microtubules and promotes the formation of extremely stable and nonfunctional microtubule bundles. As a result paclitaxel inhibits the proliferation of the cells by blocking them in the G_1 or M-phase of the cell cycle. In addition it also inhibits the cells locomotion, shape changes, intracellular transport and secretory functions. Paclitaxel is also able to inhibit the proliferation and the migration of smooth muscle cells, one of the major steps in the development of atherosclerosis and restenosis. More information about the pharmacology of paclitaxel in the prevention of restenosis can be found in references.[8,11,12] Its biological properties and activities made that paclitaxel is used as the active component in several commercially available drug eluting stents, for example, TAXUS™ Express²™. Multiple clinical trials were conducted and showed the safety and efficacy of the TAXUS™ stent. The different clinical trials were recently reviewed by Kamath et al.[13]

A new Paclitaxel eluting stent, that recently came on the market in Germany, is the Coroflex™ Please stent. The 1-year clinical follow-up of the so-called PECOPS I trial has recently been published.[14] The clinical endpoints of the PECOPS I study comprised death, myocardial infarction, premature target lesion revascularization and the combined event rate (MACE) after 6, 12, and 36 months. As an example the MACE rate was 13.5% in the treated population, which is within the range of TAXUS II and IV. In the latter studies a paclitaxel-eluting coronary artery stent for treatment of comparable lesions in patients with single vessel disease (58.4% multivessel in PECOPS I) was evaluated. The SIRTAX study enrolled 59.1% with multivessel disease compared to 58.4% in the PECOPS I study and 51.7% with acute coronary syndrome. The 9 months MACE rate in the SIRTAX study was 10.8%, which is in between the 6 and 12 months MACE rates of PECOPS I. The authors could conclude that the results after 1 year are in line with the results obtained in the TAXUS II, the TAXUS IV and the SIRTAX clinical trial, all evaluating the use of paclitaxel eluting stents.

Rapamycin

Rapamycin, also called sirolimus, is a macrocyclic antibiotic with potent immunosuppressive properties. It acts as a pro-drug that binds to specific cytosolic proteins (FK-506 binding protein-12), which blocks the cell proliferation.[8]

It has been reported that rapamycin is able to inhibit several phases of the restenosis cascade, such as inflammation, neointimal hyperplasia