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DRUG DELIVERY THROUGH DRUG ELUTING STENTS -A REVIEW

Pharmacology

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ABSTRACT

Drug eluting stents were first developed in an attempt to prevent or address the issue of restenosis. Drug eluting stents consists of three parts namely, a stent platform, a coating of polymer that binds the drug to the stent and releases the drug and the stent itself .
The basic mechanism of drug delivery from a drug eluting scaffold involves encapsulating a drug in a polymer that either allows the drug to diffuse outward from it or that undergoes degradation in order to release the drug directly. For long term effects, non -biodegradable stents are the most commonly used stents. There are a wide variety of stents available and they are used for different purposes and procedures in the field of medicine. Vascular and biliary stents, expandable coronary stents and there are also simple plastic stents which is used to allow the flow of urine between kidney and the bladder. Drugs such as dexamethasone, betamethasone, heparin, hirudin, tocopherol, angiopeptin are delivered via stents.

KEYWORDS

Drug delivery, drug eluting stents

INTRODUCTION:

Stent is a metal or a plastic tube which is inserted into the lumen of an anatomic vessel or a duct to keep the passage open during which the procedure is done. The term 'stenting' is used to refer to the procedure which involves the placement of these stents. Drug eluting stents consists of three parts namely,a stent platform,a coating of polymer that binds the drug to the stent and releases the drug and finally,the stent itself[11].

The first procedure to treat blocked coronary arteries was coronary artery bypass graft surgery (CABG), in which a section of vein or artery from anywhere else in the body is used to bypass the diseased segment of coronary artery.

In 1977, Andreas Grüntzig introduced percutaneous transluminal coronary angioplasty (PTCA), also called as balloon angioplasty, in which a catheter tube was introduced through a peripheral artery and a balloon was expanded to dilate the narrowed segment of the artery [4]. As equipment and techniques improved, the use of PTCA rapidly increased, and by the mid-1980s, PTCA and CABG were being performed at equivalent rates worldwide[5].

Balloon angioplasty was generally effective and safe, but restenosis was frequent, occurring in about 30–40% of cases, usually within the first year after the dilation process. In about 3% of balloon angioplasty cases, failure of the dilation and acute or threatened closure of the coronary artery (often because of dissection) prompted emergency CABGs [6].

Dotter and Melvin Judkins had suggested using prosthetic devices inside arteries in the leg to maintain blood flow after dilation as early as 1964[7].In 1986, Duel and Sigwart implanted the first coronary stent in a human trials in the 1990s showed the superiority of stent placement over the balloon angioplasty. Restenosis was reduced because the stent acted as a scaffold to hold open the dilated segment of artery; acute closure of the coronary artery (and the requirement for emergency CABG) was reduced, because the stent repaired dissections of arterial wall.

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Coronary stents:

Coronary stents are made of metal and will consist of three parts, an inflated balloon with a drug coated stent, a stent delivery catheter and a location marker. Coronary stents are used during an angioplasty procedure. It is also called as a percutaneous coronary intervention. Coronary stents are most commonly placed inside a coronary artery. Inside these coronary arteries, three types of stents can be placed. It can either be a drug eluting stent, bio absorbable stent or a dual therapy stent or it can also be a covered stent.

Vascular stents:

Vascular stents are placed as a part of a peripheral stent angioplasty. Common sites which are treated with peripheral artery stents include carotid, femoral and iliac arteries. Because of the compressive and the mechanical forces which are applied at this point, the stents which are associated with these regions must be flexible. Materials like nitinol are used for these locations.

Ureteral stents:

Ureteral stents are used to ensure the patency of a ureter which may be compromised. This is usually done as a temporary measure to prevent damage to a blocked kidney until the kidney stone which is causing the blockage can be removed.

Oesophageal stents:

Oesophageal stents are generally made of metal. Oesophageal stents are important tools for palliative treatment of inoperable oesophageal malignancies [1].Oesophageal stent is a flexible mesh and is about 2cm wide. These stents are used to allow the free movement of food from the oral cavity to the stomach via the oesophagus.

Biliary stents:

Biliary stents provide the drainage of bile juice from the bile ducts, pancreas and the gall bladder to the duodenum in conditions such as ascending cholangitis due to the obstruction of the passage way by the gall stones [2].It is usually made up of plastic or metal.

Prostatic stents:

These stents are placed from the bladder through the penile urethra and prostatic urethra to allow the drainage of a bladder through the penis. This is sometimes required in benign prostatic hypertrophy. Prostatic stents are generally made up of plastic.

Duodenal stents:

An alternative to a stomach bypass operation is the insertion of a stent, which holds the sides of the duodenum open in the same way that a stent might relieve a blocked bile duct. The aim of putting in a stent is to allow food and other substances to pass through the stomach and reduce nausea and vomiting. Usually made up of metal or plastic.

Recent Advances in Stents:

Glaucoma drainage stents are a recent advancement awaiting approval in several countries. These stents are used to reduce the intraocular pressure by providing a drainage channel. Some of the other types of stents are colon stents, duodenal stents and pancreatic stents. Different types of stents are constantly being developed.

Drug eluting stents:

A drug eluting stent is a metal or a ceramic tube which is placed in a blocked artery to block Cell proliferation by slowly releasing drugs into the blood circulation. Drugs such as glucocorticoids (dexamethasone and betamethasone), heparin, hirudin, tocopherol, angiopeptin are delivered via stents.

A drug-eluting stent (DES) is a peripheral or coronary scaffold placed into narrowed, diseased peripheral or coronary arteries that slowly releases a drug to block cell proliferation. Drug-eluting stents in current clinical use were approved by the FDA after clinical trials showed they were statistically superior to bare-metal stents for the treatment of native coronary artery narrowing, having lower rates of major adverse cardiac events[3].

By 1999, stents were used in 84% of percutaneous coronary interventions [8].Early difficulties with coronary stents included a risk of early thrombosis which was resulting in the occlusion of the stent[9].Coating stainless steel stents with other substances such as platinum or gold did not eliminate this problem.

High-pressure balloon expansion of the stent to ensure its full apposition to the arterial wall, combined with drug therapy using aspirin and another inhibitor of platelet aggregation nearly eliminated this risk of early stent thrombosis. Though it occurred less frequently than with balloon angioplasty or other techniques, stents nonetheless remained vulnerable to restenosis, caused almost exclusively by the neointimal tissue growth.

To address this issue, developers of drug-eluting stents used the devices themselves as a tool for delivering medication directly to the arterial wall. While initial efforts were unsuccessful, the release (elution) of drugs with certain specific physicochemical properties from the stent was shown in 2001 to achieve high concentrations of the drug locally, directly at the target lesion, with minimal systemic side effects.

As currently used in clinical practice, "drug-eluting" stents refers to metal stents that elute a drug designed to limit the growth of neointimal scar tissue, thus reducing the likelihood of stent restenosis. The first successful trials were of sirolimus-eluting stents.

A clinical trial in 2002 led to approval of the sirolimus-eluting Cypher stent in Europe in 2002. After a larger pivotal trial (one designed for the purpose of achieving FDA approval), published in 2003, the device received FDA approval and was released in the U.S. in 2003.Soon thereafter, a series of trials of paclitaxel-eluting stents led to FDA approval of the Taxus stent in 2004.

The first resorbable stent tested in humans was developed by the Igaki Medical Planning Company in Japan and was constructed from poly-L-lactic acid (a form of polylactic acid); they published their initial results in 2000. The German company, Biotronik, developed a magnesium absorbable stent and published clinical results in 2007.

The first company to bring a bioresorbable stent to market was Abbott Vascular which received a European marketing approval in September 2012; the second was Elixir which received its CE mark in May 2013[10].

Dexamethasone eluting stents is one of the first generation of drug eluting stents for local drug delivery to prevent restenosis. Other glucocorticoids including betamethasone are also delivered via stents to prevent restenosis.

Drug eluting stents were first developed in an attempt to prevent or address the issue of restenosis. Restenosis is the closure of a peripheral or coronary artery following a trauma to that artery[10]. The basic mechanism of drug delivery from a drug eluting scaffold involves encapsulating a drug in a polymer that either allows the drug to diffuse outward from it or that undergoes degradation in order to release the drug directly.

Polymers can be subdivided into bioerodable and nonbioerodable categories.

The bioerodable polymers can be further subdivided into either bulk or surface erosion[17]. For long term effects,non bioerodable stents are the most commonly used stents.

There are various drugs that are delivered through stents and they can be used to prevent restenosis. These drugs fall under four major categories[12].They are anti-neoplastics, immunosuppressive, migration inhibitors and enhanced healing factors[13].

Anti-neoplastics :
Sirolimus is undergoing research as CYPHER. Tacrolimus, everolimus, leflunomide, M-prednisolone, cyclosporin are all examples of anti neoplastic drugs delivered through stents[14]. Anti-proliferative compounds include paclitaxel, QP-2, actinomycin, statins and many others. Paclitaxel was originally used to inhibit tumor growth by assembling microtubules that prevent cells from dividing. It has also recently been observed to attenuate neointimal growth [18].

Immunosupressives :
Taxol, actinomycin, methotrexate, angiopeptin are delivered through stents[15].Immunosupressives are generally used to prevent the immune rejection of allogenic organ transplants. The general mechanism of action of most of these drugs is to stop cell cycle progression by inhibiting DNA synthesis. Everolimus, sirolimus, tacrolimus (FK-506), ABT-578, interferon, dexamethasone, and cyclosporine all fall into this category. The sirolimus derived compounds appear especially promising in their ability to reduce intimal thickening[19].

Migration Inhibitors :
Batimistat,probucol are examples of migration inhibitors[15].

These compounds are aimed at preventing endothelial cell migration to the inside of the stent. Once smooth muscle cells migrate to the luminal side of the stent, they can produce extracellular matrix and begin to occlude blood flow. Therefore, inhibiting their migration can have great therapeutic applications for preventing in stent restenosis. Examples of these compounds are batimastat and halofuginone. Batimastat, for example, is a potent inhibitor of matrix metalloproteinase enzymes. It can prevent the matrix degradation that is necessary for cells to free themselves to move. If the cells cannot move, they cannot invade the stent area[20].

Enhanced Healing Factors :
VEGF is an example of an enhanced healing factor[16].Vascular endothelial growth factor (VEGF) promotes healing of the vasculature. In the context of stents, this would heal the implantation site and reduce platelet sequestration due to injury related chemotaxis. Nitrous oxide donor compounds may also replicate this effect. Healing of the vessel wall seems to be the gentlest approach to preventing ISR, but healing factors are still in the early stages of development for this application[21].

The release of the drugs from the stents is principally based upon the process of diffusion[22].Most of the drug eluting stents will operate through the principle of diffusion with the exception of a few stents undergoing clinical trials like CYPHER and TAXUS.

The Cypher drug eluting stent manufactured by Cordis, a Johnson and Johnson company, utilized the drug Sirolimus to combat restenosis. The Cypher stent comes in a variety of lengths and diameters. These range from 8 to 33 mm in length and 2.5 to 3.5 mm in diameter. These coronary stents are constructed out of 316L stainless steel (low-magnetic, low-carbon) and are coated with a mixture of two polymers, parylene C, and the Sirolimus drug. The two non-erodible polymers (polyethylene-co-vinyl acetate (PEVA) and poly n-butyl methacrylate (PBMA)) are combined in a 67/33 percent ratio respectively and then applied to a parylene C coated stent.

A drug free coat of PBMA is also applied to the stent surface to control drug release[23].RAVEL and SIRIUS were two clinical trials which were conducted to test the efficacy of the CYPHER system[24]. Following up on the success of the Sirolimus-eluting Cypher stent manufactured by Cordis, Scientific designed their own drug-eluting stent in hopes of creating some competition in the drug-eluting stent in hope of taking some of Cordis's monopoly.

The Boston Scientific stent, called Taxus, utilizes the drug Paclitaxel. Paclitaxel is in a class of drugs called taxanes. Its main uses are to prevent the growth of cancer cells in the body, treat metastatic breast cancer, metastatic ovarian cancer, and Kaposi's Sarcoma[26].

Paclitaxel works by promoting the assembly of microtubules and stabilizes them by preventing depolymerization. This stability results in an inhibition of the reorganization of the microtubule network during the cell mitotic process – thus preventing the accumulation of anti-inflammatory cells at the site of the injury. The Taxus stent comes in lengths of eight to 28 mm and diameters of 2.5 to 3.75mm.

The stent is constructed out of 316L stainless steel and is coated with the Translute polymer [poly(styrene-b-isobutylene-b-styrene)]. This polymer functions similarly to the PEVA/PBMA copolymer used in the CYPHER stent. This polymer is also notable for its excellent vascular compatibility, which is extremely important in a system designed for long-term implementation.

The pharmacokinetics of the paclitaxel release are slightly different from the CYPHER stent: Burst release in the first 48 hours[27].

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