Not All DCBs Are Created Equal

ENDURACOAT™ TECHNOLOGY

Spectranetics' proprietary EnduraCoat™ Technology limits drug loss during transit and facilitates efficient drug delivery with a

low-dosage density of

$2\ \mu g/mm^2$

Michael Joner, MD, is CEO of CVPath Institute Inc., in Gaithersburg, Maryland. He has disclosed that the CVPath Institute received research grant support from Covidien. Dr. Joner may be reached at (301) 208-3570, ext 113; mjoner@cvpath.org.

Clinicians want to have an effective drug-coated balloon (DCB) that is flexible and has good trackability and pushability to be delivered to the lesion. In addition, particulate embolization and loss of drug in transition are important factors that should be minimized. Arterial healing also plays a key role because in some patients, it may be necessary to shorten dual-antiplatelet therapy. If the same level of efficacy can be delivered with less drug, that would certainly be helpful, but this needs to be proven.

Not all DCBs are created equal. In general, paclitaxel-coated balloons offer the greatest efficacy so far, and there seems to be agreement that balloons with excipient coating technology offer greater efficacy. Within this group, however, there is tremendous variability with respect to efficacy in drug transfer, drug loss, and particulate.

The crystallinity of the coating plays a very important role in paclitaxel-coated balloons and the uniformity of drug coating. The higher the crystallinity, the greater the drug uptake for DCBs. Small- to medium-sized paclitaxel crystals stick to the injured vessel surface and continuously release paclitaxel over time into the underlying tissue.

With regard to how the coating technology affects durability, many factors are involved, such as the drying process, coating on a folded versus an inflated balloon, crystallinity, ultrastructure, etc.

To improve restenosis rates, the drug should remain resident in the tissue for at least 3 months, and the most important factors that seem to improve or worsen drug residency in the tissue are the level of crystallinity and the degree of injury. ■

89.5%
primary patency at 12 months*

80.3%
primary patency at 24 months*

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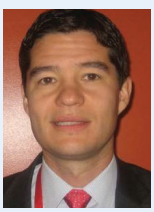

Juan F. Granada, MD, FACC, is with the Skirball Center for Innovation for the Cardiovascular Research Foundation in Orangeburg, New York. He has disclosed that this organization has worked with most drug-coated balloon manufacturers. Dr. Granada may be reached at jgranada@crf.org.

Drug-coated balloons (DCBs) essentially function via the passive transfer of paclitaxel into the vessel wall by means of a carrier that helps the transportation of paclitaxel from the surface of the balloon to the vessel wall. Then, the paclitaxel particles that adhere to the vessel wall are responsible for the drug-tissue concentrations over time.

One challenge in the effectiveness of this approach is that although some of the drug goes into the vessel, there is an important degree of drug loss into the bloodstream. At present, the potential biological effect of the drug lost downstream is unknown. However, an important attribute for DCB technologies is having a consistent dose—that is, a coating that is stable on introduction into the human body that provides a precise percentage of transfer into the vessel wall and achieves a long-term pharmacokinetic profile to prevent restenosis.

FORMULATIONS AND COATING CHARACTERISTICS

Not all DCBs are created equal. The final formulation on the surface of the balloon depends on many factors—not just the paclitaxel, but the way it is combined with the carriers, as well as processed to be put on the coating. Similarly, not all paclitaxel coatings are the same. Some are more soluble than others, and some are more crystalline. All of these important differences in coating characteristics provide specific pharmacokinetic and efficacy profiles in patients.

I believe coating characteristics are the most important aspect of DCBs. One big difference between DCBs and drug-eluting stents is that in the latter, the medication is encapsulated inside of a polymer, and its release is precisely titrated over time. In drug-eluting stents, the biological

effect relies on the principle of drug release that is known and predictable via the polymeric surface. The pharmacokinetics in DCBs depend on two things: (1) a proper amount of drug transfer at the time of balloon inflation, and (2) an appropriate distribution and retention of the drug over time. Characterization of the coated surface is essential in helping us determine which types of DCBs have the attributes that achieve the desired clinical effects.

The first DCB concepts were created with a combination of iopromide, which is a contrast agent, and paclitaxel. Iopromide was intended to help carry the drug into the vessel wall. But, we very quickly found out that although this combination produced a highly crystalline coating that was extremely effective in transferring the drug into the vessel surface, the coating was also brittle and fragile.

Industry has since attempted to balance the crystallinity such that the tissue penetration levels can be maintained over time while decreasing the potential for embolization and improving the consistency of the coating. I believe that a certain degree of crystallinity is important in achieving a biological effect. There are absolutely differences in drug residency between the different DCBs, and the pharmacokinetic profiles of clinically available devices also appear to be different. But, acute transfer is more important than long-term drug retention.

MEETING ANATOMY- AND LESION-SPECIFIC CHALLENGES

We now have a significant amount of clinical data gathered regarding local drug delivery technologies in both the coronary and peripheral vasculatures. For polymer-based coronary drug-eluting stent applications, industry typically designed technologies to maintain drug presence in the tissue for anywhere from 45 to 60 days; this is a curve that is reproduced for paclitaxel-based technologies in the peripheral territory. However, due to the unique biological differences encountered in each setting, we must be careful in designing peripheral vascular technologies based on knowledge gathered in the coronary field. I would still estimate that anywhere between 45 and 60 days of residency time—but perhaps longer—would be needed for a paclitaxel-coated balloon to work in the peripheral space.

At the experimental level, the absence of plaque, atherosclerosis, and calcium is the best-case scenario. It is difficult to extrapolate those lessons into the human clinical arena.

Although most research has been performed for above-the-knee arterial disease in claudicants, I believe there is even more of a need and role for DCBs in below-the-knee disease in patients with critical limb ischemia. The unmet clinical need is even higher, and the clinical impact would be greater for below-the-knee disease, in which the options are currently limited. However, this a very different vascular territory: the disease behavior is very aggressive; there is often significant calcium; and there is a large burden of disease. Usually, these vessels are as small as coronary arteries, but they are much longer and slower in blood flow. Critical limb ischemia is a unique clinical scenario with a very different biological makeup, so, similar to the caution we must take in applying our coronary understanding in the periphery, we must be careful in extrapolating the knowledge we have obtained in the superficial femoral artery into below-the-knee therapy.

Accordingly, the technical approach will also be anatomy-specific. There may be more need for vessel preparation with ancillary devices, such as atherectomy and others, and the balloons used will likely need to be simultaneously longer and smaller in diameter. There is a significant potential for DCB use in below-the-knee disease, but it must be approached with the right technology and formulation. There is the potential risk of distal embolization, which is compounded in the presence of limited vessel runoff and tissue loss, so we must be careful in evaluating each technology with regard to the specific challenges of the below-the-knee vascular territory.

At present, this application requires significant clinical evaluation, but these are a few of the important considerations for companies developing these technologies. Efforts must be focused on addressing drug dosing, coating stability, and transfer efficiency in this challenging environment. ■