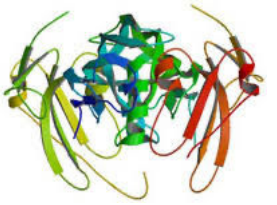

Doses of Drugs in Devices
Medical Device Technology
Material Matters, 2009

David Williams

Recent experiences with active molecules in spinal fusion devices points to the need to be cautious with dosing regimes and the use of products in off-label situations.

Recombinant bone morphogenetic protein

The headline of a recent report in the *Wall Street Journal* stated "[Medical Device Company x] product faces a US inquiry."[1] Two aspects of this story deserve attention. The product is a device that promotes bone growth in spinal fusion. It utilizes recombinant bone morphogenetic protein [2] (rhBMP-2) contained within a sponge of bovine Type 1 collagen that is enclosed within a cage, typically a metallic titanium cage. The BMP is reconstituted by dissolving it in water at the time of surgery and soaking the collagen sponge in the solution. The first issue is whether the product is performing as safely in patients as anticipated. The second is whether the product is being used in a significant way in off-label use and whether the company knew about and actively promoted this off-label use.

The first of these concerns is the center of the controversy of drug-device combinations: What is the safe and effective dose of a biologically active molecule when used in combination with, and released from, a medical device? The company received United States (US) Food and Drug Administration (FDA) approval for the use of this product in anterior lumbar spinal fusion in 2002; the technique obviated the need for the associated surgical intervention to acquire autologous bone from the hip. According to the *Wall Street Journal*, sales of this product have amounted to more than US$3 billion since 2002. Recently the company has been investigating the use of variations of the product elsewhere in the body and it received FDA approval for its use in the treatment of acute open fractures on the leg and in certain oral and maxillofacial procedures.

In October 2006, FDA granted approval through an Investigational Device Exemption for the company to conduct a clinical trial on the use of the product in the cervical spine. The product was similar to that used in the lumbar spine, but with a polyetheretherketone cage, which was discussed recently in this column.[2]

Clinical complications

However, in July of 2008, FDA issued a warning about the potential problems of using recombinant human bone morphogenetic protein in the cervical spine.[3] It had received approximately 38 reports of complications during the past four years associated with swelling of neck and throat tissue, which resulted in compression of the airway or neurological structures in the neck. There were reports of difficulty with swallowing, breathing and speaking. The warning commented on the anatomical proximity of the cervical spine to

airway structures that could contribute to the seriousness of the events and the need for emergency medical intervention. Most complications occurred up to 14 days after surgery. Treatments included respiratory support with intubation, anti-inflammatory medication, tracheotomy and further surgery to drain the affected site. FDA notes that neither the mechanism(s) of action with these complications nor the characteristics of those patients at increased risk have been identified. It also notes that rhBMPs are contraindicated for all uses in patients who are skeletally immature or pregnant, and in those with a known hypersensitivity to the specific rhBMP or bovine Type 1 collagen. The premarket approval was given specifically for fusion of the lumbar spine in skeletally mature patients with degenerative disc disease at one level from Lumbar 2 to Sacral 1 vertebrae.

At a recent spine conference in the US, as reported in *The Spine Journal*, Jarosz et al. discussed the clinical problem.[4] In a retrospective review of cases where the product, in a variety of forms and apparently with a variety of doses of the rhBMP2, had been used in the cervical spine, 58 patients received treatment and were followed for up to two years. Twenty of the patients had complications, especially where the protein was used in “uncontained anterior placement,” with a higher incidence of complications when the rhBMP2 was used “in higher doses;” the complications being associated with “an enhanced inflammatory response". The *Wall Street Journal* makes it clear that clinicians are entitled to use medical devices in any way they see fit, including using them in off-label situations. It is equally clear that the manufacturers must not promote this off- label use and, in particular, should not offer inducements to doctors to undertake these practices. There has already been much speculation about the role of the company in these cases, including some litigation and a US Department of Justice investigation. No comment is made about this here, apart from noting the increasingly belligerent stance taken by some newspapers against medical device companies. The real issues here are the impact that these situations have on the already difficult balance between introducing innovative technologies that could ultimately benefit hundreds of thousands of patients and the potential risk to those patients.

Lessons for drug-device combinations

I have written about drug-device combinations in this column several times over the years and have commented on the potential and the risks. Fundamental to our concerns must be the disparity between the pharmacokinetics and bioavailability of drugs released from devices over a period of time compared with those characteristics associated with more conventional delivery modes such as ingestion or injection. There should be no assumption that the mechanisms of action, distribution and metabolism will be the same when a highly potent molecule is released from a collagen sponge into local sensitive tissue, as when it is instilled into the body in some other way. Our awareness should be heightened when the molecule is prepared by recombinant methods and when the drug pathway and any associated inflammatory responses involve highly sensitive and crucial tissues such as the spinal cord and the airways. It is a matter of historical record that medical device companies will de-emphasize the potential significant activity of a molecule that they wish to incorporate into a device. They do this by insisting, usually correctly, that the molecule serves in an ancillary role and that the product is regulated as a device, or possibly a combination product, and not as a drug. However, they then promote the product once regulatory approval has been obtained as if it is better than all other products on the market because of these “special properties.”

I am a strong supporter of the introduction of new concepts and materials into medical device technology, but the details must be right, and preferably as soon as possible. It is clear in this case that the optimal dose of the rhBMP2 has not been identified for all potential applications and it would seem that too much is being left to chance. Even when there is no evidence of culpability or malpractice, it is our responsibility to do as much as possible to optimize innovative products early on and resist the temptation to move too fast on the basis of too little evidence. This does us no good in the long term and possibly denies patients the benefits of the technology when things go unnecessarily wrong.

References

1. *Wall Street Journal*, 20 November 2008.
2. D.F. Williams, "Polyetheretherketone For Long-Term Implantable Devices," *Medical Device Technology*, **19**, 1, 8–11(2008).
3. FDA Public Health Notification: Life-threatening Complications Associated with Recombinant Human Bone Morphogenetic Protein in Cervical Spine Fusion Issued: 1 July 2008, www.fda.gov/cdrh/safety/070108-rhbmp.html
4. T. Jarosz et al., "Complications of BMP Use in Cervical Spine Surgery," *The Spine Journal*, **8**, 5, S23-24 (2008).