Notes from the Editor Emeritus

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Say goodbye to post-op pain medications?

When I read the efficacy and safety data from clinical trials introducing a new single dose, non-opioid local anesthesia, I was excited. Bupivacaine liposome injectable suspension represents an old drug that has been reformulated with novel liposomal technology. The trade name for this drug is Exparel®, available through Pacira Pharmaceuticals. It is touted as the only single-dose analgesic that provides up to 72 hours of post-op analgesia; the technology used to reformulate bupivacaine is known as Depo Foam (the product delivery platform). This multivesicular liposomal technology can encapsulate a drug without altering its molecular structure. The drug is then released slowly over a desired period of time. The pharmacokinetic profile supplied by the company is impressive. It demonstrates plasma levels of bupivacaine persisting for up to 96 hours after administration. Keep in mind that any systemic levels of bupivacaine following the local administration cannot be correlated to local efficacy. It is important to remember that the rate of systemic absorption of any local anesthetic is dependent upon the route of administration, the method of administration, and the vascularity of the administration site. Local anesthetics for scalp use generally do not have the persistence in efficacy as elsewhere in the body. The scalp is vascular and local anesthesia may be carried off quickly with a resultant short-lived duration. I believe that there is a pressing need for a longer acting local anesthetic for our specialty.

Now back to Exparel. Could this new local anesthetic be the answer? We offer an elective procedure that can present challenges in the management of post-surgical pain. Even with the current FUE techniques, pain can be an issue. A physician has to be astute enough to separate the drug seekers from those with true post-op surgical pain. Then there are issues of dosing narcotics based on body weight, the route of administration, and the rare allergic reaction. It certainly has been my experience that most individuals allergic to "codeine-derived" products are simply describing an episode of severe nausea. Could all of these concerns simply vanish with a single, novel local anesthetic? No more prescriptions, no more nausea, no more calls. Now granted, I am glad to hear back from my patients on their status, but I don't get particularly excited when they report nausea, post-op vomiting, or the ineffectiveness of my post-operative pain regimen. And yes, the issue of driving while under the influence of opioids must be addressed as well. A long-acting effective local anesthetic would negate all of these concerns.

In pivotal Phase II trials, Exparel was administered using a standard anal block procedure prior to hemorrhoidectomy. The perianal tissue was infiltrated in a fan-like fashion. One hundred and eighty-nine subjects participated in the trial; half were given placebo and the other half Exparel. While the results were quite impressive, my thoughts kept wandering to the unfortunate group of subjects who received placebo after a hemorrhoidectomy. Back to the Phase II trials, the findings showed almost a 50% decrease in opioid consumption. There was a significant increase in time to the first opioid use among subjects receiving Exparel. Most importantly, three times more Exparel patients were opioid free at 72 hours. The placebo group did not fare as well. Without going into a lot of detail, let's just say this was an impressive study demonstrating the effectiveness of this long-acting liposomal bupivacaine. Bupivacaine is not without its concerns. While there was no QTC prolongation and no cardiac events in this study, these possibilities certainly linger in the back of my mind. The company points out there are no significant interactions of this with epinephrine, corticosteroids, antibiotics, or non-steroidal anti-inflammatory or oral opioids.

Armed with all the available information on this newly approved drug, I planned my course of action. I elected to use Exparel in every single patient that underwent transplantation in our clinic. Prior to the initial strip removal, Exparel was used in initial cases as the only local anesthetic. The drug cost is a factor at approximately $200 per surgery case, but probably well worth it if it becomes the panacea we are looking for. Exparel is supplied in a ready-to-use aggregate suspension or it can be diluted with normal saline to accommodate administration for a large area, such as the scalp. I elected to dilute it in a ratio of 50/50 with normal saline. I did not receive this suggested dilution from the sales representative or an article…I was just guessing here. This provided exactly 40ml of anesthesia from a 20ml vial. I also did not administer Exparel with a 25 gauge needle as recommended and instead opted for a 30 gauge needle. The Exparel was stored in a refrigerator prior to use and prior to dilution with saline. Once diluted, it was kept at room temperature for the remainder of the case. My initial impression was, "This stuff really hurts." Nearly all of my patients tolerated this local anesthesia poorly. Well, would it make sense to use Lidocaine prior to administration of Exparel? You can't! Non-bupivacaine-based local anesthesia, such as lidocaine, causes an immediate release of bupivacaine from Exparel. The injection of Exparel may follow the administration of lidocaine after a delay of 20 minutes or more. Some of my colleagues (not the makers of Exparel) have expressed concerns about the administration of bupivacaine after lidocaine since the receptor sites are already blocked at that time and the patient may not experience the long-acting effects of bupivacaine. At this point, something had to give. Patients simply could not tolerate Exparel at the beginning of the procedure.

After operating on a dozen or so patients, I decided to alter my protocol and administer Exparel at the end of the procedure; at least an hour after the last dose of lidocaine had been given. The result was more impressive. It still hurt, but less. Thus, I believe that when this novel local anesthetic is given at the conclusion of procedure, it does reduce the need for opioids, just as any commercially available Marcaine® or Naropin® would do. I have been performing administration of local anesthesia to the donor site at the end of procedures for my entire career and believe

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it is helpful. Is Exparel better than generic bupivacaine in the above setting? Maybe.

The unanswered question is, "How much longer is the pain relief patients actually experience?" I have no doubt this product is wonderful for hemorrhoidectomy patients and other post-operative surgical procedures. I'm just not convinced it is significantly better than the existing bupivacaine when used in the manner described above. It definitely works. It definitely hurts. To determine how much better will take years to sort out, new dilutional ratios, several thousand patients, and the input of ISHRS physicians.

This editorial was not meant in any way to be a review of Exparel. There are other issues you need to read about concerning this drug. Be careful in patients with hepatic disease, because it is metabolized by the liver. I do, however, encourage you to try Exparel as the potential is there. Google it on the Internet, contact the representative, ask about pricing, and give it a whirl.

The author has no past, present, or future consulting agreement with Pacira Pharmaceuticals, manufacturer of Exparel.◆