



November 6, 2014

Randall P. Flick MD, MPH
Chair, Anesthetic and Analgesic Drug Products Advisory Committee
c/o Stephanie L. Begansky, PharmD
Designated Federal Officer
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, WO31-2417
Silver Spring, MD 20993-0002

Dear Dr. Flick and Committee:

The American Academy of Pain Medicine and the American Society of Anesthesiologists appreciate the opportunity to comment on the safety and efficacy of epidural steroid injections. We would like to specifically address the FDA's April 23, 2014 Drug Safety Communication, which stated:

“The U.S. Food and Drug Administration (FDA) is warning that injection of corticosteroids into the epidural space of the spine may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death. The injections are given to treat neck and back pain, and radiating pain in the arms and legs. We are requiring the addition of a Warning to the drug labels of injectable corticosteroids to describe these risks. Patients should discuss the benefits and risks of epidural corticosteroid injections with their health care professionals, along with the benefits and risks associated with other possible treatments.”

While we appreciate the FDA's intent to improve safety of patient care, we and other professional organizations dedicated to the safe and effective relief of pain are extremely concerned that this statement may create an unintended and unjustified barrier to patient access to safe and effective treatment. We disagree with the FDA warning statement for several reasons. First, the FDA warning fails to differentiate the intended “epidural space” injection from the rare, unintended injection into other structures whose injury is associated with the reported adverse effects. Any unintended injection into critical structures such as the spinal cord may cause serious adverse effects. In this context, it is not the injected drug *per se* that is responsible for the reported complications. Second, the FDA warning fails to differentiate particulate and non-

particulate formulations of steroids. All of the rare adverse effects reported in the references cited by the FDA are related to particulate formulations of steroids. None of these complications have been linked to non-particulate formulations of steroids. Thus, not all “injectable corticosteroids” have these risks. Third, the FDA warning fails to differentiate interlaminar and transforaminal routes of corticosteroid administration. None of the references cited in the FDA’s Warning are relevant to interlaminar lumbar epidural steroid injections or caudal epidural steroid injections.

It is important to recognize that all of the references cited to support the warning are limited to isolated retrospective case reports in which unrecognized confounding factors may well be present. None of the cited references qualify as Level I evidence. This absence of Level I evidence of risk contrasts with the large number of injections performed annually.¹ In fact, no serious neurological complications have ever been reported in any prospective study of epidural steroid injections, regardless of technique, medication, or anatomical segment injected. A recent study of a multi-institutional cohort of over 16,000 consecutive epidural steroid injection procedures at all spine segments did not find any major complications.^{2,3,4} In contrast, alternative treatments for spine pathology have significantly higher rates of serious complications. There are 14,800 opioid related deaths and 16,500 NSAID-related deaths annually in the United States.^{5,6} More than 103,000 individuals are hospitalized annually in the United States for NSAID-related serious GI complications in patients with rheumatoid arthritis and osteoarthritis.⁶ Spinal surgery has a much higher incidence of complications than any type of epidural injection, regardless of the steroid formulation utilized.⁷ Thus, it appears that the FDA relied on weak evidence to issue a warning that may create unnecessary fear and limit patient access to a safe and effective treatment.

In addition to its well-established safety record, the efficacy of epidural steroid injections has also been supported by robust evidence of reducing and eliminating pain, improving function, decreasing reliance on opioids, and eliminating the need for surgery for many patients. For example, a double blind randomized controlled trial (RCT) demonstrated that only 29% of patients who were treated with transforaminal injection of betamethasone and bupivacaine required surgery during the 13-28 month follow-up period compared with 66% of those who received transforaminal injection of bupivacaine alone ($P < 0.004$).⁸ Another RCT found that after an average follow-up period of 1.4 years, patients receiving transforaminal steroid injection had an 84% success rate compared to only 48% for the group receiving deep lumbar paraspinal muscle injection with saline ($P < 0.005$).⁹ A third RCT found that a significantly greater proportion of patients treated with transforaminal injection of steroid (54%) achieved relief of pain than did patients treated with transforaminal injection of local anesthetic (7%) or transforaminal injection of saline (19%), intramuscular steroids (21%), or intramuscular saline (13%).¹⁰ Relief of pain was accompanied by significant improvements in function and disability, and reductions in use of other health care. Furthermore, an RCT showed dexamethasone (a non-particulate steroid) was equivalent to triamcinolone (a particulate steroid), with over 70% of subjects that received an epidural steroid injection experiencing at least 50% pain relief and avoiding surgery through the study’s 6-month follow-up period.³ Moreover, recent systematic reviews^{11,12,13,14} with meta-analyses of large numbers of research subjects have concluded that up to 70% of patients achieve 50% pain relief for 1-2 months; 30% achieve complete pain relief.¹² For patients with disc herniations, up to 70% may achieve 50% pain relief for six months.³ Pain

relief is accompanied by functional recovery and reduced reliance on other health care resources.^{3,12,13,14}

Collectively these studies have unequivocally established the safety and efficacy of epidural steroid injections for specific indications in patients with back pain and radicular pain. Thus, the FDA warning is inaccurate at best and misleading at worst. It is inconsistent with the facts established by extensive research findings. As a multidisciplinary society representing a large number of specialists in pain medicine and a recognized leader in patient safety, AAPM is extremely concerned that the FDA warning may yield unintended consequences and lead to unfounded fear among patients, unnecessary utilization of inferior alternatives, and worse outcomes with higher costs. We strongly recommend that the FDA warning be retracted and replaced with one that accurately represents the risks and benefits associated with epidural steroid injections.

Respectfully yours,

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