

American Society of  
Anesthesiologists® 



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Randall P. Flick M.D., M.P.H.  
Chair  
Anesthetic and Analgesic Drug Products Advisory Committee  
c/o Stephanie L. Begansky, Pharm.D.  
Designated Federal Officer  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, M.D. 20993

Dear Dr. Flick and Members of the Committee:

The American Society of Anesthesiologists, American Society of Regional Anesthesia and Pain Medicine, American Academy of Pain Medicine, and International Spine Intervention Society appreciate the opportunity to provide comments in advance of the Anesthetic and Analgesic Drug Products Advisory Committee meeting on epidural steroid injections. In particular, our comments will 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.

We are extremely concerned that the FDA *Warning* fails to differentiate between the risks and benefits of transforaminal and interlaminar routes of administration, and particulate and non-particulate formulations of steroids. The resulting message inaccurately groups all epidural steroid injections into one broad warning, but the critical distinctions between the routes of administration and formulations of steroids represent the difference between safe and effective use of epidural steroid injections and unsafe use associated with catastrophic injuries. **We strongly recommend that the *Warning* be retracted and replaced with one that accurately represents the risks associated with epidural steroid injections used to manage painful spinal conditions.**

In particular, we agree with the FDA that there are well-documented, rare complications that may occur when particulate steroid medications are injected into critical arteries that supply the brain or spinal cord using the transforaminal approach of delivery, regardless of whether those injections are conducted in the cervical, thoracic, or lumbar spinal regions. However, the FDA has overgeneralized and

misinterpreted this information as being applicable to all routes of epidural medication delivery and to all glucocorticoid medications. The evidence does not support that conclusion. There are no case reports published in the world literature that document patients being paralyzed or gravely injured when injections of non-particulate steroids are performed using a transforaminal route. For interlaminar lumbar injections and for caudal epidural steroid injections, the evidence fails to establish a causal relationship between injections of steroidal medications and the development of paralysis or death.

The references cited by the FDA only support a *Warning* which applies to particulate steroids administered via a transforaminal approach. The FDA's *Warning* contains 17 references, none of which pertain to interlaminar lumbar epidural steroid injections or caudal epidural steroid injections. Furthermore, none of the 17 references qualify as Level I medical evidence, but rather are limited to isolated case reports, which cannot be considered an accurate appraisal of the robust evidence that should be used to substantiate a claim or bolster any argument being made on behalf of patient safety.

The FDA's references 1-6 do not pertain to lumbar interlaminar or caudal epidural steroid injections and are exclusively concerned with transforaminal injections of particulate steroid medication using a cervical or lumbar approach. The references cite case reports of injury after transforaminal injections, including a complication of transforaminal epidural injections in which "particulate" steroids were unintentionally injected into a radicular type artery, leading to an embolic process that likely resulted in infarction of vital structures.

References 7-12 also do not pertain to lumbar interlaminar epidural steroid injections or caudal epidural steroid injections. These references provide isolated reports of injury associated with cervical and thoracic injections, including transforaminal injections and interlaminar procedures as well as cervical facet joint blocks. None of these studies involve a prospective evaluation of either efficacy or safety, including the incidence of complications.

Finally, references 13-17 do not address lumbar interlaminar or caudal epidural steroid injections. Rather, reference 17 is the only review article cited by the FDA and actually lauds the relative safety of neuraxial (spinal and epidural) block techniques. In that paper, Tony Wildsmith and colleagues concluded that, "The data are reassuring and suggest that CNB (central neuraxial block) has a low incidence of complications, many of which resolve within six months." Furthermore, in a recent large retrospective review of epidural steroid injection complications, McGrath and colleagues [1] identified no major complications including those relevant to this FDA warning.

Caudal and interlaminar epidural steroid injections are among the most often performed interventional pain medicine technique in the United States [2]. Epidural steroid injections are effective in well-selected patients providing a short-term (<6 month) benefit [3]. The use of interlaminar epidural steroid injections for the treatment of radicular pain is supported by good evidence of analgesic effectiveness [4-8]. In a recently published review, Pinto and colleagues [9] concluded that high quality evidence, using the GRADE classification system [10], exists supporting the use of epidural steroid injections to reduce pain and disability related to radicular leg pain thereby providing level 1 evidence of effectiveness. The meta-analysis of these high quality randomized controlled studies showed a significant reduction in pain and disability scores for 3 months following caudal and interlaminar epidural steroid injections [9].

In summary, we believe that the 17 references selected by the FDA to support the *Warning* do not address or in any way support a safety concern related to epidural steroid injections when administered by the interlaminar or caudal approach and underscore the need for the FDA to retract and revise the *Warning*. We strongly support providing patients with accurate information so they can make informed decisions about their treatment. Because of the omissions outlined above, we believe that the FDA's *Warning* has led many physicians and patients to incorrectly conclude that all epidural steroid injections carry grave risks. When epidural injections are performed correctly (correct technique, correct medications, and correct setting) for appropriate indications, they are safe and can provide improved quality of life and function. Removal or curtailing these procedures would lead to more patients seeking surgical or unsafe medical therapies with potentially (much) greater risks.

We are working diligently with other pain medicine specialty societies and the FDA Safe Use Initiative to provide safety information that will be useful for all physicians and for any patient seeking non-surgical interventional pain management. Our hope is that the FDA will provide an opportunity for this group of thought leaders to complete their work and publish their findings. At that time, the FDA and stakeholders should convene a meeting to discuss these findings and reach a consensus that will enhance the experience of the patient with sub-acute or chronic spinal pain while providing a framework for making safety recommendations that is based on evidence and not on partial or inaccurate information.

Respectfully yours,

J.P. Abenstein, M.S.E.E., M.D.  
President  
American Society of Anesthesiologists

Joseph M. Neal, M.D.  
President  
American Society of Regional Anesthesia and Pain Medicine

Sean Mackey, M.D., Ph.D.  
President  
American Academy of Pain Medicine

Jeffrey Summers, M.D.  
President  
International Spine Intervention Society

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