

November 7, 2014

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Chair

*via Email to [AADPAC@fda.hhs.gov](mailto:AADPAC@fda.hhs.gov)*

Anesthetic and Analgesic Drug Products Advisory Committee  
c/o Stephanie L. Begansky, PharmD  
Designated Federal Officer  
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WO31-2417  
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Dear Dr. Flick and Members of the Committee:

The American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Section on Disorders of the Spine and Peripheral Nerves, American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Section on Pain, American Academy of Pain Medicine, American Academy of Physical Medicine and Rehabilitation, American Association of Neurological Surgeons, American College of Radiology, American Pain Society, American Society of Anesthesiologists, American Society of Regional Anesthesia and Pain Medicine, Congress of Neurological Surgeons, International Spine Intervention Society, North American Neuromodulation Society, North American Spine Society, and Society of Interventional Radiology would like to take this opportunity to comment on the safety and effectiveness of epidural steroid injections. As medical specialty societies representing physicians who perform epidural steroid injections, we are deeply committed to ensuring that patients are safe and that their quality of life is greatly improved with interventional spine care. Our organizations have a strong record of working to eliminate fraudulent, unproven, and inappropriate procedures. At the same time, we are equally committed to assuring that safe and effective treatments are preserved so that patients do not have to unnecessarily suffer or undergo more invasive surgical procedures.

On April 23, 2014, the Food and Drug Administration (FDA) released a Drug Safety Communication warning that injection of steroids into the epidural space of the spine may result in rare but serious neurologic adverse events including stroke, loss of vision, paralysis, and death. We applaud the FDA on their effort to appropriately remind physicians and patients that they should be aware of the side effects and potential complications related to any and all drugs and medications that may be considered for treatment. The risks and benefits of treatments should be openly discussed by physicians, and considered by patients when determining how best to proceed. Unfortunately, the FDA's Drug Safety Communication is also misleading. The statement indicates that the

safety and effectiveness of epidural administration of steroids have not been established. This is clearly not true based on robust literature on this topic.

### **Safety of Epidural Steroid Injections**

While complications with epidural steroid injections (ESIs) have been reported, and are likely underreported, serious complications are limited to isolated case reports. This is despite the large number of injections performed annually.<sup>1</sup> No serious neurological complications have ever been reported in any prospective study of ESIs, regardless of approach or technique used, or anatomical area injected. A recently completed multi-institutional cohort of over 16,000 consecutive ESI procedures at all spine segments also reported no major complications.<sup>2,3,4</sup>

#### *Particulate and Non-Particulate Steroids*

Though rare, neurological complications are catastrophic and include stroke, blindness, paralysis, and death. These adverse events likely result from inadvertent injection of a radicular or vertebral artery that perfuses the spinal cord and brain. In all reported cases, particulate steroids have been used, and the mechanism of injury is presumed to be embolism of these particulates resulting in infarction. Light microscopy studies have demonstrated that the particles in these steroid preparations are either larger than red blood cells or form aggregates larger than red blood cells.<sup>5</sup> Additionally, animal studies have shown central nervous system infarction with intra-arterial injection of particulate steroids.<sup>6</sup>

This is in contrast to dexamethasone, which has particles 5 to 10 times smaller than red blood cells on microscopic evaluation, and is effectively non-particulate in this context. Dexamethasone has been shown to have no adverse sequelae with direct injection into the arterial supply of the neuroaxis in animals.<sup>5,6</sup> Non-particulate steroids have been routinely administered via the transforaminal epidural technical approach without a single report of a serious neurologic adverse event to date. It is logical to conclude that increased utilization of this medication will lead to decreased complication rates associated with these procedures. However, use of dexamethasone has not been universally adopted due to the fact that most published studies demonstrating the effectiveness of transforaminal injection of steroid (TFIS) have utilized particulate steroids. However, recent high quality studies have demonstrated the non-inferiority of dexamethasone to the most commonly injected particulate corticosteroid, triamcinolone acetate,<sup>7,8</sup> which should further increase its utilization. Given that the risk of neurologic injury resulting from embolization of particulate steroid may be eliminated with the use of a non-particulate steroid, dexamethasone should be considered the preferred first-line medication option for TFIS. Particulate steroids could be considered as a second-line agent for lumbar TFIS (lumbar region only) if non-particulate steroids do not result in adequate duration of relief. This recommendation is consistent with the FDA Safe Use Initiative's recommendations for safe injection practices which have been submitted for publication, and which all signatories to this letter support to help minimize risks associated with epidural steroid injections. Based on these data, and further supported by the consensus of experts representing fourteen

different specialty societies, we feel non-particulate steroids should be excluded from any FDA action as they have a robust safety profile.

#### *Comparison to Alternative Treatments for Back Pain*

For further comparison, the rates of serious complications from alternative treatments for spine pathology are significantly higher. There were 14,800 opioid related deaths in the United States in 2008.<sup>9</sup> More than 103,000 individuals are hospitalized annually in the United States for NSAID-related serious GI complications, with 16,500 NSAID-related deaths occurring each year in the United States among patients with rheumatoid arthritis and osteoarthritis.<sup>10</sup> Based on these data, we request that the FDA warning be modified to reflect the extremely low risk involved with lumbar ESI in comparison to significantly higher risks of alternative treatment option such as opioids and NSAIDs.

#### **Effectiveness of Epidural Steroid Injections**

The second area of concern with the FDA statement is the misleading sentiment that the effectiveness of ESIs has not been determined. While there is always room for more research, there is ample evidence demonstrating the effectiveness of ESIs in reducing and eliminating pain, improving function, decreasing reliance on opioids, and eliminating the need for surgery for many patients.<sup>11</sup>

#### *Particulate and Non-Particulate Steroids*

Multiple high quality studies have demonstrated efficacy of ESIs when performed on patients with appropriate indications. A double blind randomized controlled trial (RCT) by Riew *et al* investigated the effect of TFIS on avoidance of surgery for lumbar radicular pain.<sup>12</sup> Only 29% of patients who were treated with transforaminal injection of betamethasone and bupivacaine required surgery during the 13-28 month post-procedure follow-up time period compared with 66% of those who received transforaminal injection of bupivacaine alone ( $P < 0.004$ ). Corroboration of the surgery-sparing effect of lumbar TFIS has been provided in a recent study in which injections were offered to patients with radicular pain who were on a surgical waiting list. A successful outcome, and avoidance of surgery, was achieved in 51/91 (56%, 95% CI  $\pm$  10%) patients.<sup>13</sup> Lumbar TFIS have also been shown to be effective for the treatment of radicular pain that has not responded to surgical intervention. Of 156 patients whose radicular pain was not relieved by surgery, 38 (31%, 95% CI  $\pm$  7%), responded to TFIS and none of these patients required revision surgery.<sup>14</sup> Another RCT found that after an average follow-up period of 1.4 years, the patients receiving TFIS had an 84% success rate compared to only 48% for the group receiving deep lumbar paraspinal muscle injection with saline ( $P < 0.005$ ).<sup>15</sup> The most scientifically rigorous double blind RCT compared the efficacy of TFIS with transforaminal injection of local anesthetic, transforaminal injection of saline, intramuscular steroids, or intramuscular saline for the treatment of lumbar radicular pain.<sup>16</sup> The authors found that success rates for providing at least 50% pain relief from the various control treatments were statistically indistinguishable at 15% (95% CI  $\pm$  7%) while 54% ( $\pm$  18%) of patients who received TFIS achieved a successful outcome both at 1- month and at 12-month follow-up. Collectively these studies have led to recent systematic reviews<sup>17,18</sup> with meta-analyses that have summarized the large volume of research on this topic. Up to 70%

of patients achieve 50% pain relief for 1-2 months; 30% achieve complete pain relief.<sup>18</sup> For patients with disc herniations, up to 70% may achieve 50% pain relief for six months.<sup>7</sup> Pain relief is accompanied by functional recovery and reduced reliance on other health care resources.<sup>7,18,19</sup>

Recent studies have also demonstrated that non-particulate medications are just as effective as particulate preparations. A large retrospective review of over 3600 lumbar transforaminal injections from the Mayo Clinic showed dexamethasone to be non-inferior to particulate preparations.<sup>8</sup> Also a prospective double blind RCT showed dexamethasone was equivalent to triamcinolone, with over 70% of subjects that received an ESI experiencing at least 50% pain relief and avoiding surgery through the study's 6 month follow-up period.<sup>7</sup>

### *Diagnosis/Indications*

Some studies and reviews, however, do report negative results with ESIs. There are multiple potential reasons for this. First while there is a large preponderance of evidence supporting the effectiveness of image-guided ESIs for radicular pain due to disc herniations, ESIs may not be as effective for other pathologies. Unfortunately, a significant number of studies simply study low back or radicular pain without identifying the underlying etiology. These are merely symptoms and not a diagnosis. For perspective, imagine a hypothetical systematic review of prescription medication for the treatment of cough, a symptom. A few studies may show beneficial effects from antibiotics in a group of patients with bacterial pneumonia, a specific diagnosis, whereas pooled data from heterogeneous groups – including viral bronchitis, chemical pneumonitis, asthma, lung cancer, *etc.* – would produce different effects. If these pooled effects showed that many different medications had minimal impact on cough from various sources, it would still be a disservice to abandon prescription antibiotics for pneumonia.

### *Technique/Image Guidance*

Second, when reviewing the literature regarding the effectiveness of ESIs, it is of utmost importance to know what technique was utilized. Multiple studies have demonstrated that non-image guided ESIs have unacceptably high miss rates with as many as 74% of these injections placing medication either outside the epidural space or not reaching the targeted site of pathology within the epidural space.<sup>20</sup> Since placebo controlled studies of intramuscular steroid injections failed to show any benefits,<sup>21,22,23</sup> it should be no surprise that prospective randomized comparisons of image-guided ESIs to intramuscular steroid injections<sup>16,24</sup> and to blind ESIs<sup>25</sup> unanimously favor image-guided ESIs. In a clinically relevant context, studies of non-image guided ESIs show no benefit over sham treatment with a collective number needed to treat of >90.<sup>26,27,28,29,30,31</sup> In stark contrast, a large number of controlled studies of image-guided TFIS for patients with radiculopathy demonstrate robust positive outcomes<sup>16,32,33,34,35,36,37,38,39,40,41</sup> with a number needed to treat of 3.<sup>18</sup>

### *Data Analysis*

While imprecision in diagnosis and inaccuracy in injections are major contributors to poor reported outcomes, negative studies and reviews are also reported for other reasons.

Unfortunately a preponderance of studies have opted to report clinical relevance by comparing group means for a minimum clinically important difference. While appealingly simplistic, this approach is inherently flawed. This method can result in a misinterpretation of the data, and dismisses clinically important information about the treatment effects of spine injections. Comparison between group means assumes a normal Gaussian distribution of pain and disability in response to spinal injections. In the context of ESIs, the clinical result is often bimodal, with some patients who respond and others who do not. Thus, the treatment effects are best-assessed using categorical data to compare proportions of responders to non-responders. A clear example of the utility of this approach is revealed in a study comparing TFIS to placebo.<sup>16</sup> Comparison of group mean data failed to find any difference between treatment groups, but categorical analysis demonstrated both statistically and clinically meaningful differences in favor of TFIS.

It has also been suggested by some that epidural injections of local anesthetic alone are equivalent to epidural injections that include steroid. We reject this claim. When two treatment arms have similar results, the appropriate conclusion is not necessarily that both treatments are equally effective. Just as likely, the treatments may be equally ineffective. For several indications, the latter is more likely. As cited above, multiple high quality, well-designed studies have demonstrated statistically and clinically significant differences favoring ESIs over local anesthetic alone.<sup>12,15,16</sup>

In conclusion it is clear that indication, technique, data analysis, and treatment medication are all vitally important in determining the effectiveness of ESIs. The data collectively show that for appropriate pathologies, image-guided ESIs with non-particulate steroids are an effective and safe treatment, and it would be inappropriate and biased to conclude that all ESIs are ineffective and unsafe.

We appreciate the opportunity to provide these comments and insights for consideration.

Sincerely,

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