

An Important Step Forward in the Safe Use of Epidural Steroid Injections

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DURING the past decade, there has been a rapid increase in the use of epidural steroid injections (ESIs) for the treatment of spinal pain. The annual number of epidural injections performed on Medicare beneficiaries has approximately doubled since 2000; in 2012 alone, there were more than 2 million claims submitted to Medicare for ESIs.¹ Because many of the conditions treated by ESI are common in the elderly, the number of injections is likely to increase as the U.S. population ages; however, this is unquestionably also dependent on whether Medicare and other payers continue to reimburse for the procedure.

Although rare, ESI can be associated with catastrophic, even fatal, neurological complications including stroke and paralysis.* These injuries are thought to occur by a variety of mechanisms.*² Injection of particulate steroids into the vertebral artery and its branches during transforaminal, cervical ESIs can cause embolic stroke. Injection into the radiculomedullary arteries that supply the spinal cord during transforaminal, high lumbar, or thoracic ESI can lead to embolic infarction of the spinal cord. In addition, direct needle-associated injury to the spinal cord during ESI has been reported, and it has been postulated that contact between the ESI needle and the vascular supply of the spinal cord may lead to ischemic injury of the cord.

The true incidence of these catastrophic neurological complications is unknown due to the lack of the large prospective studies that would provide accurate numerator (all adverse events) and denominator (total epidural injections performed) data. A query of the U.S. Food and Drug Administration's (FDA's) Adverse Events Reporting System covering November 1, 1997 through April 23, 2014,



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placed on all injectable corticosteroids regarding the risk of neurological complications including spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. The new label reminded clinicians that the FDA had not evaluate the safety and effectiveness of the epidural injections of steroids and, as such, this use was “off-label.”*

A second step that the FDA took was to convene a meeting of the Anesthetic and Analgesic Advisory Committee during November 2014 to discuss whether additional regulatory measures or changes to the label were needed. The Committee heard 2 days of presentations from the FDA, outside experts, professional societies, and patients, and there was extensive discussion regarding the risks and benefits of procedure. At the conclusion of the meeting, the Committee voted on the question of whether there are any clinical situations for which a *contraindication* should be added to

identified 90 cases of serious neurological adverse events associated with ESIs.* However, interpreting these data is challenging as the Adverse Events Reporting System relies on spontaneous reports by healthcare providers and patients, and it is unclear what proportion of all adverse events it is likely to detect. What is clear is that when these complications do occur they can be devastating.

The risk of adverse neurological events, particularly those occurring in association with transforaminal injection of particulate steroid formulations, was brought to the attention of the FDA in 2009.* This prompted the FDA to investigate the issue and to subsequently take a number of steps in attempt to mitigate these risks including changing the product labeling for corticosteroids when used for ESI. Last April, the FDA required that a Class Warning be

Image: J. P. Rathmell.

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Accepted for publication January 15, 2015. From the Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, and Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (B.T.B.); and Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts (G.J.B.).

* Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM422692.pdf>. Accessed January 5, 2015.

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the labeling of corticosteroids regarding their injection in the epidural space. The vote was 15 in favor and 7 against (with one abstention), with all those voting in the affirmative supporting a contraindication against cervical transforaminal injection of steroids. Whether the Advisory Committee's recommendations will result in further changes to the labeling of steroids has not been announced.

In addition to the measures taken to examine and change the labeling of corticosteroids, the FDA has also sought to address the issue of neurological complications by convening and facilitating a Working Group of experts under the auspices of the FDA Safe Use Initiative to develop practice suggestions to improve the safety of the procedure. According to the FDA, the Safe Use Initiative is designed "to create and facilitate public and private collaborations within the healthcare community ... to reduce preventable harm by identifying specific, preventable medication risks and developing, implementing, and evaluating cross-sector interventions with partners who are committed to safe medication use."[†] This process is separate from the regulatory arm of the FDA, and the FDA neither endorses nor mandates the suggestions produced by these initiatives. The Working Group on the safe use of ESIs was cochaired by James Rathmell, M.D., and Honorio Benzon, M.D., and included a range of experts drawn from a number of stakeholder specialties. The Group achieved consensus on 17 suggestions to guide practice in the performance of ESI to minimize the risk of neurological complications. The consensus statement summarizing these suggestions is published in this month's issue of *ANESTHESIOLOGY*.³ Remarkably, 13 specialty and professional organizations, representing the full spectrum of clinicians that perform epidural injections, were signatories to the statement.

Interestingly, both the process of this Working Group and its practice suggestions are not without controversy. In a recently published article, "Epidural steroid injections safety recommendations by the Multi-Society Pain Workgroup: more regulations without evidence or clarification,"⁴ Manchikanti and coauthors reject many of the suggestions generated by the Working Group, stating "none of the recommendations provided by Multi-Society Pain Workgroup seem to have been based on evidence." We would argue that the absence of level-1 (highest quality) outcome data that could explicitly guide minimization of risk associated with ESI does not diminish the value of expert guidance to inform clinical practice. In the absence of high-quality evidence, safe clinical practices need to be defined by reports of complications, what is understood about the pathophysiology of the complications, and the common sense of a broadly represented group of experts. In our opinion, the Multidisciplinary Working Group has synthesized these components into a series of reasonable best practices that, if embraced by practitioners, should achieve the goal of maximally limiting

the rare catastrophic complications of this very commonly performed procedure.

Although the Working Group's consensus statement is an important step forward for pain medicine, it is essential that as a field we perform the studies that will better elucidate the risks of ESI, to further refine the Group's suggestions. We must define how risk is influenced by patient (*e.g.*, prior spinal surgery) and technical (transforaminal *vs.* interlaminar, particulate *vs.* nonparticulate, spinal level, *etc.*) factors. We need to also understand the effect on risk of the background and training of the clinicians performing the procedure, particularly as many practitioners performing ESIs have not completed a formal pain fellowship.

Perhaps most critically, our field needs to better define the efficacy of ESIs. Two recent well-designed and appropriately implemented randomized control clinical trials—one focused on lumbar spinal stenosis and the other on cervical radicular pain—failed to demonstrate a significant ESI-associated improvement in their primary endpoints.^{5,6} In response, some have suggested that there may be subgroups of patients with these conditions that benefit from ESI. But for many, perhaps even for the majority of patients, we do not understand the pathophysiology of their pain and thus have difficulty predicting for a given patient whether ESI will confer benefit. Data do suggest that ESI may be more efficacious in the setting of acute, severe radicular pain associated with lumbar disc herniation, providing a modest, short-term reduction in pain,^{7,8} though the natural history of this condition is such that the pain will generally resolve over a period of weeks. It remains to be elucidated whether the decrease in pain, which will likely get better on its own, is worth the risk of these rare complications. Resolving the issue of the relative risk and benefit of ESI is complicated by the fact that alternative treatments (opioids, surgery, or neuropathic pain medications) have a relatively high number needed to treat and are also associated with significant risks.

This consensus statement generated by the Working Group is an important step in advancing the safe use of ESI. Of course, a variety of issues were not addressed by the Working Group's suggestions. For example, we wonder about the degree to which a provider's training might influence their usage of "best practices" and thus risk to their patients. Should performance of ESI, as well as other pain-related interventions, be restricted to practitioners with formal pain medicine training (*i.e.*, an Accreditation Council for Graduate Medical Education accredited fellowship) or to those working directly under individuals with that or other appropriate (*e.g.*, neurosurgical) training? Certainly, a great challenge for the field of pain medicine is to better define the appropriate use of ESI. Clinicians and patients need to be able to carefully consider the procedure's risks and benefits in deciding whether the balance of these factors is favorable given a patient's clinical condition, values, and preferences. To enable this kind of deliberation and facilitate appropriate use, a deeper understanding of the risks and benefits is urgently needed.

[†] Available at: <http://www.fda.gov/Drugs/DrugSafety/SafeUseInitiative/default.htm>. Accessed January 5, 2015.

Acknowledgments

Brian T. Bateman was a committee member of the Food and Drug Administration (Silver Spring, Maryland) Anesthetic and Analgesic Advisory Committee and participated in the meeting described in the editorial. He is supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (Bethesda, Maryland) (grant no. K08HD075831).

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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