Intraspinal steroids: history, efficacy, accidentality, and controversy with review of United States Food and Drug Administration reports

D A Nelson, W M Landau

This review, covering a timespan of almost a century, attempts to answer five pressing questions:
1. Are intraspinal steroid therapies effective for back pain or radicular syndromes?
2. Do epidural injections remain confined to the epidural space?
3. Are presently prescribed steroid formulations neurotoxic?
4. What are the risks of epidural steroid injection?
5. What information should be given to patients in obtaining informed consent for these procedures?

Efficacy of intraspinal therapy

REMOTE HISTORY

Early cocaine and "pressure injections"
In 1901 there were reports of cocaine injection via the sacral hiatus for sciatica. De Pasquier and Leri used lumbar intrathecal injections containing 5 mg cocaine that produced "toxic cocaine accidents ... to the bulbar and cerebral centers." They attempted without success to prevent flow of cocaine intracranially "by the use of a band of rubber gently tightened around the neck." Then they tried sacral epidural injections and claimed success. In 1925, Viner also employed the sacral route, using procaine in normal saline, Ringer’s solution, or “liquid petrolatum.” Evans reported these procedures?

Articular steroid injection—the harbinger of intraspinal therapy
Compound E (cortisone) was discovered in 1936. In 1950 Hench et al reported that it produced transient improvement of “rheumatoid arthritis, rheumatic fever, and certain other conditions.” Then Hollander reported the intra-articular effects of a longer acting steroid, Compound F (hydrocortisone), warning that “... it should be emphasised that its action is non-specific and palliative but not curative.” The reduction of synovial membrane inflammation was confirmed histologically; however, the anti-inflammatory and immunosuppressive mechanisms are still under investigation.

Transient therapeutic response is modified by route of injection, dosage, and by how rapidly a particular crystalline steroid is phagocytosed by synovial cells. Soon after the discovery of cortisone, steroid injection became a popular treatment for many other conditions.

Table 1 Representative uncontrolled intraspinal steroid investigations 1953–98. Intraspinal steroids for sciatica and low back pain in 798 subjects: 36 week average follow up

<table>
<thead>
<tr>
<th>First author (ref)</th>
<th>Date</th>
<th>n</th>
<th>Diagnosis</th>
<th>Route</th>
<th>Steroid</th>
<th>Type of study</th>
<th>Patients with pain relief (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lievre18</td>
<td>1953</td>
<td>20</td>
<td>Sciatica</td>
<td>Epidural</td>
<td>Hydrocortisone</td>
<td>Retrospective</td>
<td>25 at 3 w</td>
</tr>
<tr>
<td>Brown21</td>
<td>1960</td>
<td>20</td>
<td>Sciatica, LBP</td>
<td>Epidural</td>
<td>Prednisone, hydrocortisone</td>
<td>Retrospective</td>
<td>100 at 52 w</td>
</tr>
<tr>
<td>Goebert22</td>
<td>1960</td>
<td>230</td>
<td>Sciatica</td>
<td>Epidural</td>
<td>Methylprednisolone acetate</td>
<td>Retrospective</td>
<td>100 at 8 w</td>
</tr>
<tr>
<td>Goebert23</td>
<td>1961</td>
<td>113</td>
<td>Sciatica</td>
<td>Epidural</td>
<td>Hydrocortisone</td>
<td>Retrospective</td>
<td>66 at 12–130 w</td>
</tr>
<tr>
<td>Gardner24</td>
<td>1961</td>
<td>75</td>
<td>Sciatica</td>
<td>Intrathecal</td>
<td>Methylprednisolone acetate</td>
<td>Retrospective</td>
<td>83 at 12+ w</td>
</tr>
<tr>
<td>Sehgal25</td>
<td>1962</td>
<td>100</td>
<td>Sciatica</td>
<td>Intrathecal</td>
<td>Methylprednisolone acetate</td>
<td>Retrospective</td>
<td>60 at 1–44 w</td>
</tr>
<tr>
<td>Winnie26</td>
<td>1972</td>
<td>10</td>
<td>Sciatica</td>
<td>Epidural</td>
<td>Methylprednisolone acetate</td>
<td>Prospective</td>
<td>90 at 2–104 w</td>
</tr>
<tr>
<td>El-khoury27</td>
<td>1988</td>
<td>116</td>
<td>LBP</td>
<td>Epidural</td>
<td>Betamethasone</td>
<td>Prospective</td>
<td>98 at several h</td>
</tr>
<tr>
<td>Rosen28</td>
<td>1988</td>
<td>40</td>
<td>Sciatica, LBP</td>
<td>Epidural</td>
<td>Methylprednisolone acetate</td>
<td>Prospective</td>
<td>25 at 1–32 w</td>
</tr>
<tr>
<td>Power29</td>
<td>1992</td>
<td>16</td>
<td>Sciatica</td>
<td>Epidural</td>
<td>Methylprednisolone acetate</td>
<td>Prospective</td>
<td>6 at 1 w</td>
</tr>
<tr>
<td>Bowman30</td>
<td>1993</td>
<td>35</td>
<td>Sciatica, LBP</td>
<td>Epidural</td>
<td>Methylprednisolone acetate</td>
<td>Retrospective</td>
<td>43 at 12 w</td>
</tr>
</tbody>
</table>

LBP=Low back pain.
†Definition of "pain relief"=excellent+good+moderate+"not severe".  

www.jnnp.com
Epidural pressure injections combined with steroid therapy: a transition

In 1952 Robecci and Capra reported using "periradicular" hydrocortisone to treat lumbago and sciatica. Few low back pain or sciatica, Brown used "pressure caudal anaesthesia" with various 50–70 ml solutions of lidocaine hydrochloride, normal saline, and steroid. Of 38 cases treated with local anaesthetic and saline alone, 32 improved "substantially" compared with 100% success in 28 patients. Hydrocortisone therapy gained wide popularity after Lievre et al. reported success in 28 when hydrocortisone, prednisone, or methylprednisolone acetate (MPA) was added to the injectate. The aetiology of pain was usually undefined and there were neither therapeutic controls nor structured follow up. Robecci and Capra in 1952 described in two critical reviews. By 1963, Sehgal et al. had treated more than 1000 patients with intrathecal injections of MPA for 46 acute exacerbations (follow up averaged 22 months). Nelson et al. reported only slight Kurtzke scale improvement in four patients. No patient improved directly after injection as had been previously reported. We have discovered no controlled studies of intrathecal steroid for multiple sclerosis.

"Classic" epidural techniques (table 1)

The transition back again from intrathecal to epidural therapy for sciatica began in 1972 with the claim by Winnie et al. that their successful small volume injections proved that "the anti-inflammatory action of the steroid (MPA) itself" was the therapeutic mechanism. Twenty patients with disc herniation were treated, half by intrathecal and half by epidural therapy using 80 mg (2 ml) MPA. Nine in the first group and 10 in the second experienced complete pain relief with follow up periods of about 2 years during which 1–4 additional injections were needed. There were no neurological examination data, no evidence that sciatica resulted from inflammation, and no controls (table 1). Concerning safety, the prior animal experimentation that they cited applied to cortisone and hydrocortisone, not to MPA.

With the rationale that inflammation from disc rupture should be most prominent at the onset of symptoms, Power et al. in 1992 reported acute MPA injection in 16 patients with recently extruded disc fragments. Fifteen required surgery in 7 days, and one within 12 weeks (table 1). The authors explained that their project was aborted "partly due to the strict entry criteria and partly because we felt it was unethical to continue the study in view of overwhelming (poor) results."

Dilke et al. studied 99 patients with sciatica from disc disease, 71 of whom were assessed for pain control (table 2). Thirty five received 80 mg epidural MPA in 10 ml normal saline and 36 had interspinous (not epidural) injection of 1 ml normal saline. An unspecified number received a repeat dose of steroid. The study design was flawed because both the site and content of injectate differed for the two groups. After 2 weeks, pain relief (defined subjectively and by consumption of opiates) was relieved in 46% of treated patients and 11% of
controls. After 3 months, pain was “not severe or none” in 98% of treated and 82% of controls. No significant changes in neurological signs occurred in either group. The first well controlled double blind investigation of disc rupture by Snook et al. showed that “extra-dural injection of methyl prednisolone (80 mg) is no more effective than a placebo injection in relieving chronic symptoms due to myelographically demonstrable lumbar disc herniation” (table 2).

A randomised unblinded study of 63 patients with sciatica by Klenerman et al. reported that 79% of patients in the treatment and 73% of the placebo group obtained pain relief. “Dry needling” into the lumbar inter-spinous ligament was performed in one third of controls and the others received epidural injections of normal saline or local anaesthetic. In the double blind trial of 36 patients with lumbar radicular pain by Cuckler et al., 32% had pain relief at 24 hours and only 26% between 52–120 weeks. Placebo injections resulted in only 15% long term improvement. These authors concluded that “No statistically significant difference was observed between the control and experimental patients.”

Carette et al. provided the most definitive well controlled study of epidural MPA therapy for disc related sciatica. Using careful follow up neurological examinations and exacting statistical methods, they concluded: “Thus, we found that epidural corticosteroid injections do not afford long term advantages over placebo...there was no significant functional benefit, nor does it reduce the need for surgery.” Two studies of spinal stenosis treated with MPA demonstrated that pseudoclaudication improved only slightly in both steroid and placebo groups. 45 46 Table 1 demonstrates that in uncontrolled reports, about 68% of patients with sciatica were improved by epidural steroid injection, but in controlled studies, the patients who received steroid infusions did not do significantly better than the placebo and sham groups (table 2).

Specific nerve root therapy by the epidural route: recent techniques
In a study of intraoperative epidural placement of aqueous MPA on an exposed nerve root and using retrospective “controls,” Davis and Emmons claimed a need for less postoperative analgesia as well as a 37%-40% decrease in postoperative stay. With the patients blinded, Lavyne and Bilsky compared intraoperative MPA to saline irrigation. In another study, McNeill et al. compared intraoperative MPA, placebo, morphine, and morphine–MPA mixture. Both groups concluded that this application of MPA was useless. No comparable double blind prospective research has been published.

Recently, small volume perineural epidural injection into the anterior epidural space has been advocated. 45–51 Different techniques using various steroids, local anaesthetic, epidurogram guidance, and hyaluronidase produced mixed results in uncontrolled studies of 169 patients. In a prospective double blind trial of 49 subjects with lumbar sciatica, low volume injections of 10 mg triamcinolone were compared with isotonic saline. 52 Both groups reported 80% “good” plus “fair” results. Marks et al. evaluated lumbar facet joint injection of 20 mg MPA and local anaesthetic. They concluded, “In the absence of a control group we cannot quantify the placebo effect and cannot, therefore, draw any conclusions regarding the validity of these procedures as diagnostic tests...”

Epidural “morphine nerve paste” at discectomy
Needham reported “painless lumbar surgery” using a thick paste composed of morphine sulphate, MPA, amincaproic acid, and a microbrillary haemostatic powder applied intraoperatively to the epidural space. No animal experimental or human clinical data were provided. This was further investigated by Hurlbert et al. in a prospective randomised double blind study of 60 patients using a placebo paste. The authors found lower consumption of narcotic in the hospital with “...better pain control immediately postoperatively and significantly better health perception.” After 1 year, neurological examinations and MRI studies showed no differences of postoperative scar in subjects treated with paste and controls.

Table 2 Controlled intraspinal steroid investigations of pain from disc disease and spinal stenosis 1973–98. Prospective studies of 468 subjects comparing methylprednisolone acetate (Depo-Medrol sterile aqueous suspension) with placebo and sham injections

<table>
<thead>
<tr>
<th>First author(yr; ref)</th>
<th>Controls</th>
<th>With steroid</th>
<th>Placebo or sham injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sciatica improved (%) (n=219)</td>
<td>Sciatica improved (%) (n=249)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 h–3 w</td>
<td>8–120 w</td>
</tr>
<tr>
<td>Dilk 1973**</td>
<td>Double blind, randomised</td>
<td>35</td>
<td>46 at 2 w</td>
</tr>
<tr>
<td>Snook 1977†</td>
<td>Double blind, randomised</td>
<td>27</td>
<td>26 at 48 h</td>
</tr>
<tr>
<td>Klennerman 1984‡</td>
<td>Randomised</td>
<td>19</td>
<td>79 at 2 w</td>
</tr>
<tr>
<td>Cuckler 1985§</td>
<td>Double blind, randomised</td>
<td>22</td>
<td>32 at 24 h</td>
</tr>
<tr>
<td>Carette 1997**</td>
<td>Double blind, randomised</td>
<td>77</td>
<td>33 at 3 w</td>
</tr>
<tr>
<td>Cuckler 1985§</td>
<td>Double blind, randomised</td>
<td>20</td>
<td>25 at 24 h</td>
</tr>
<tr>
<td>Fukusumi M† 1998‡</td>
<td>Randomised</td>
<td>19</td>
<td>16 at 4 w</td>
</tr>
<tr>
<td>Average improvement</td>
<td></td>
<td>37</td>
<td>41</td>
</tr>
</tbody>
</table>

*Patient evaluation scales of pain relief “relieved, none, not severe, mild, intermediate, severe” (using questionnaire or visual analogue).
†Results recorded in walking distance (m).
‡Results recorded in walking distance (m).
§Results recorded in walking distance (m).

435
www.jnnp.com
that justify this practice. Bannwarth et al. demonstrated that oral prednisolone crosses the blood-brain barrier; CSF concentration equilibrates to plasma concentration in about 6 hours. A careful double blind study of a 7 day course of intramuscular dexamethasone for patients with “common symptoms of prolapsed disc” was definitively negative.37

ANIMAL RESEARCH TO INVESTIGATE EFFICACY
Oppenheimer and Riester injected rabbits intracisternally with hydrocortisone and described histological reduction of tale induced arachnoiditis. Feldman and Behar also reported treating tale arachnoiditis in cats with intrathecal hydrocortisone. Serial sections of spinal cord and brain showed a reduction of the reticulum network around the particles and decreased spinal fluid pleocytosis.

Pospiech et al produced epidural scars by laminectomies at three different levels in 30 dogs, thus yielding 90 operative segments for study of various substances that might reduce cicatrix. They applied 10 mg liquid triamcinolone to 18 of these segments that were examined histologically. Significant scarring was demonstrated in seven of 12 segments examined between 1 week and 3 months compared with 12 of 13 in the control (laminectomy only) group. Heavy cicatrix was found in only one of six steroid treated segments examined at 6 months and in four of five controls.

Exploring the inflammatory theory
Epidural steroid therapy is most often prescribed for low back pain, foraminal arthrosis, facet disorders, spinal stenosis, and failed back surgery.50 51 52 The concept that inflammation is the target lesion of these conditions is based on two assumptions: (a) direct pressure on nerve roots or ischaemia from compression produces local inflammation; (b) free fragments of nucleus pulposus release inflammatory phospholipase A2.53 54 55 These were reviewed in detail by Haddox who wrote, “Surgeons . . .state that the nerve root that is causing the problem is easily identifiable by its oedematous inflammatory character.” But a review of the literature refutes that assertion. In 160 random necropsy examinations, Lindblom and Rexed found 60 nerve root compressions. Forty four nerve root segments were examined histologically by serial section (specimens selected from 17 cases with the most severe macroscopic deformations). The most common findings were atrophic pressure effects sometimes with increased connective tissue, with “diffuse degenerations mixed with regenerative processes . . .especially in the ventral root fibers.” No cellular infiltrates were found except for some red blood cells in one ventral root. Lindahl and Rexed reported small nerve biopsies of “the dorsal part of the nerve root” of 10 patients operated on for sciatica from herniated disc. They identified no pathology in five, degenerated fibres and dural thickening from pressure effects in three, “cell infiltrates here and there” in one, and “excessive cell infiltration . . .with a preponderance of the mononuclear type” in only one. The inflammation theory is further questioned by Gibbs67 who wrote concerning the thousands of nerve roots he has inspected at disc surgery, “There is . . .a normal vascularisation of the dura covering the nerve root, but it would be rare, if ever, to observe an increase in the blood supply even under the magnification that we so frequently use. The nerve roots of the cauda equina (intrathecal) are frequently swollen by passive congestion because the drainage to the extradural veins is blocked . . .from the herniated nucleus. Passive congestion alone does not constitute inflammation.” Bogduk summarised, “Authors . . .have argued by inference that this (inflammation) must be the pathology they treat with epidural steroids. However, no clinical studies have demonstrated how inflammatory radiculopathies are distinguished from noninflammatory radiculopathies before treatment with epidural steroids.” In summary, there are no consistent operative descriptions of nerve roots showing inflammatory theory.

Reasonable explanations for transient improvement
Two controlled studies of epidural steroid reported that sciatica signs and symptoms were more improved after 12 weeks of follow up than shortly after injection when the steroid effect is most efficacious (table 2).40 41 This is unexpected because the duration of action of intrathecal and epidural MPA does not exceed 2 weeks measured by CSF cortisol and suppression of plasma corticoid.12 13 Johansson et al applied MPA to the plantar nerve in rats. Within 60 minutes they discovered a blockade of unmyelinated nociceptive C fibres that cleared when the compound was removed. The authors warn that a longer duration exposure of nerve “. . .could in fact cause permanent functional and/or degenerative changes.” Transtity amelioration of symptoms can also be explained by chemical blockade or destruction of C fibre axons and nerve terminals produced by polyethylene glycol and benzyl alcohol contained in several steroid formulations.77

In addition to chemical injury to nociceptor nerve fibres, the hypertonicity of the injectate mixtures may have an independent mischievous effect. The normal osmolarity in the epidural space is about 293 mOsmol/kg H₂O (CSF 301, plasma 285). Merck’s commercially premixed formulation (1 ml) (often used but not recommended by the manufacturer for epidural steroid therapy) contains dexamethasone sodium phosphate (4 mg) and lidocaine hydrochloride (10 mg), along with “inactive ingredients” citric acid anhydrous (10 mg), creatinine (8 mg), sodium bisulphite (0.5 mg), disodium edetate (0.5 mg), and sodium hydroxide to adjust pH. The pH is 6.5–6.9 and the osmolality is 398 mOsmol/kg H₂O. Before performing a selective perineural nerve block, clinicians often compose their own bedside formulation such as 1 ml each of: bupivacaine (0.75%), methylprednisolone acetate (80 mg),
and iopamidol contrast (61%). The osmolality of this combination is 601–605 mOsmol/kg H2O. We suspect that both the function and structure of unmyelinated and even small myelinated nerve fibres may be impaired by prolonged immersion in such media.

Another explanation lies in placebo power coupled with “tincture of time.” Placebos result in significant relief of pain in 35%-40% of patients regardless of the aetiology. A 1998 prospective study of spinal stenosis treatment by Fukusaki et al found no advantage of epidural MPA over local anaesthetic. They stated that “It seems that other factors might have led to patient improvement including placebo effect or perhaps the volume of the injectant itself produced a spinal canal dilating effect.” In a recent article, Vroomen et al concluded that 87% of patients with sciatica not treated with steroid therapy showed improvement after 12 weeks with or without complete bed rest.

Risks

Complications during clinical trials: A chronology

Adverse reactions from epidural pressure injections and steroids: 1930–60

During pressure therapy with high volume epidural saline and procaine, some of Evans’ patients complained of “...abnormal sensations or paraesthesiae, such as formation (and) found it difficult to control a desire to shout or scream.” In one experiment, when 30 ml saline was injected epidurally, the subarachnoid pressure at L4-L5 rose to 320 mm H2O, ...cyanosis, opisthotonos, unconsciousness, and incontinence of urine and faeces followed the injection of 120 ccm of 2 percent solution of novocain; consciousness returned within half hour ...and recovery was complete.” Lievre et al described a “pain reaction crisis” in a patient treated with epidural hydrocortisone for arachnoiditis. During pressure injections of isotonic saline and lidocaine hydrochloride, four of Brown’s patients had “a mild tetanic episode.” Possible explanations include spinal cord compression or injection into the epidural venous plexus.

Adverse reactions from intrathecal steroids: 1956–91

In 1956, Deveux et al reported that 12 intrathecal injections of hydrocortisone over a 96 day period produced a subarachnoid block at T3-T7 requiring laminectomy. Accidental subarachnoid injections of hydrocortisone and betamethasone mixed with local anaesthetic produced transient sensory levels in several patients. Intrathecal MPA for arachnoiditis produced pleocytosis as high as 3000/mm3 with protein concentrations up to 250 mg/dl, correlated with dosage. The authors asserted that these changes were “...a result of mechanical rather than chemical irritation.” However, later investigations proved the mechanism to be chemical meningitis. Generalised convulsions during intraspinal steroid therapy are probably due to this irritative effect.

Intrathecal MPA therapy for multiple sclerosis produced transient urinary incontinence in two of 20 patients. In two subsequent reports of 61 patients, complications included constrictive arachnoiditis in the thoracic or lumbar area (three), aseptic meningitis (two), subarachnoid haemorrhage (one), and neurogenic bladder (one). Other complications were brain damage, spinal cord lesions, and dense widespread pachymeningitis. The therapeutic trial by Nelson et al was foreshortened because of adverse arachnoiditis in two patients and almost fatal chemical meningitis in another. Since 1961, in six uncontrolled studies of intrathecal MPA for multiple sclerosis, 16 of 131 patients had complications.

Between 1976 and 1978, studies by two neuroradiology groups described about 90% incidence of radiographic arachnoiditis in patients who received MPA intrathecally during myelography to prevent contrast induced arachnoiditis. Another report of 18 case histories concluded that radiographic arachnoiditis can occur from only one MPA injection shortly preceding myelography. A subsequent publication concluded that three of 15 such patients (20%) later developed clinical signs and symptoms of arachnoiditis. Despite these reports, several authors continue to recommend intrathecal steroid therapy.

Adverse reactions from epidural steroids: 1989–94

Beginning in 1989 in Australia, there were numerous claims of adverse reactions to epidural steroid therapy. Case histories suggested diagnoses of encephalopathy (three), myelopathy (three), cauda equina syndrome (two), sciatica (one), chemical meningitis (one), and cerebrovascular accident (one). In 1991, The Health Care Committee of the National Health and Medical Research Council was appointed to investigate complications of epidural steroid therapy. The panel concluded that “In view of the absence of definitive evidence for or against the efficacy of epidurally administered corticosteroid preparations (the Council) can neither endorse nor proscribe the epidural use.” In view of the potential hazards (epidural therapy should be administered) only with fully informed consent...only with the approval of a hospital ethics, accreditation or credentialling committee...only for radicular pain...as part of a properly constituted research protocol aimed at determining the efficacy of the epidural injection of steroids.”

Meningitis and epidural abscess after intraspinal steroids

Epidural abscess after MPA therapy has resulted in tetraplegia and death. Chan and Leung reported tetraparesis with complete epidural block at C3 from epidural granulation tissue and abscess after a lumbar epidural injection of triamcinolone acetonide for low back pain and sciatica. Steroid activation of latent infection probably explains cryptococcal and tuberculous meningitis in two patients given intrathecal MPA.
Delayed septicaemia followed epidural MPA in another.97,99

DANGEROUS ANATOMICAL PASSAGES DURING EPIDURAL INJECTIONS

Accidental subarachnoid injections

Inaccurate placement of epidural needles into veins, ligaments, and the subarachnoid space occurs in 25%-52% of epidural procedures by the caudal approach and in 30% by the lumbar approach.97,98 Accidental intrathecal injection occurs during epidural therapy in about 5%-6% of procedures; it is now generally agreed that accidental intrathecal injections are dangerous.40,45,70,80,94,109

Intravascular complications

The arterial supply of the spinal cord and roots below T2 is from aortic segmental vessels that enter through spinal foramina.106 These arteries are vulnerable to laceration or intravascular injection during epidural therapy, foramen injection, and nerve block. Radicular or spinal cord damage may be permanent sequellae. In cervical epidural procedures and trigger point blocks, the vertebral artery can be accidentally punctured leading to medullary infarct.106

Retinal damage from MPA arterial microemboli has followed accidental injection of MPA into arteries or collaterals supplying tonsillar fossa, sphenopalatine ganglion, ethmoid sinus, nasal septum, and also into a chalazion.107–109 The emboli evidently travel antegrade or retrograde into retinal arteries; a similar mechanism may explain acute myelopathy after epidural injection into the segmental vessels on nerve roots.104

Other vulnerable structures

Root sleeves contain representative layers of pia, arachnoid, and dura that terminate on the dorsal root ganglia in or near neural foramina where the dura continues as epineurium.110,111 After facet joint or epidural injections, meningismus from the irritating effects of steroid formulations and complications from infectious meningitis have been reported.80,111 Immediate reinserterion of inaccurately placed needles can result in subarachnoid injections through false passages.76,113,114 On rare occasions, a needle puncture can accidentally transect a nerve root.79 Because the subarachnoid space extends into root cuffs, the chance of accidental injection is increased when Tarlov cysts are present.

OPHTHALMOLOGICAL COMPLICATIONS FROM EPIDURAL STEROID THERAPY

Recently reported in five articles115–119 were eight case studies of retinal venous haemorrhage and amblyopia after epidural injection of various steroid formulations (usually MPA) and local anaesthetic for treatment of low back pain and sciatica. The common pathophysiological agent was a volume of injectate that exceeded 40 ml (10-20 ml epidural injections have been reported significantly to increase intracranial pressure).115,118 The authors concluded that the visual loss is produced by increased spinal fluid pressure in the optic sheath subarachnoid space that increases retinal venous pressure.118,119 This concept is supported by the experiments of Usbiaga et al118 who studied 24 patients placed in the lateral decubitus position before spinal anaesthesia. They measured subarachnoid pressure at L4-L5 and epidural pressure at L3-L4. After injecting 10-20 ml normal saline into the epidural space they measured pressure changes for 10 minutes. Clinical symptoms included dizziness, nausea, frontal headache, contraction of back muscles, and tachypnoea. Epidural pressures increased to 650 mm H2O whereas subarachnoid pressures reached 850 mm. For reasons unknown, subarachnoid pressures were always higher.

NEUROTOXICITY OF FORMULATIONS: ANIMAL RESEARCH

Oppenheimer and Riester18 reported that rabbits injected intrathecally with 10 mg hydrocortisone developed transient severe major motor seizures. In cats with t alc induced arachnoiditis, Feldman found that cisternal injection of hydrocortisone induced a CSF pleocytosis of 150 white blood cells/mm3 increased from baseline levels of 20 white blood cells/mm3; these reactions subsided with repeated injections.121 In later experiments, “synchronous rhythmic spikes” and “generalised epileptic seizures” followed infusions of 1.5 mg hydrocortisone sodium succinate into the hippocampus, posterior hypothalamus, and midbrain reticular formation.122

Eldervik et al123 studied macaque monkeys after intrathecal injection of the myelographic contrast agent iocarmate, MPA alone, and contrast agent mixed with MPA. After 12 weeks, all three groups showed myelographical and histological arachnoiditis. Extravascular nerve injections of MPA or its vehicle produced histological lesions in sciatic nerve.123 Direct sciatic nerve injections of MPA and other steroid formulations produced infrasacicular damage in rats.125 Microscopically noted immediate demyelination followed the application of MPA or polyethylene glycol 4000 to peripheral nerve, retina, optic nerve, brain, spinal cord or intrathecal nerve roots of rabbits and rats.126 Concentrations of more than 20% polyethylene glycol produced acute slowing of nerve transmission in rabbits.127 The authors reported no immediate effect from the 3% polyethylene glycol used in commercial formulations but they did not look for prolonged physiological or histological sequelae.

Abram et al28 injected MPA and triamcinolone directly into the subarachnoid space in rats. Measuring flinches/minute of the injected paw, they found no analgesia after a single injection. But after four intrathecal injections over 20 days, there was measurable decrease of nociceptor afferent sensitivity. The authors stated that “Although we cannot rule out the possibility that a larger number of animals might disclose some neurological sequelae, the lack of adverse effect in this study is reassuring.” They concluded that their study “provides evidence that ... deposteroid preparations do not produce spinal cord damage when injected neuraxially.”
Cicala et al. reported that epidural MPA produced no histological damage in 12 rabbits examined 4 and 10 days after injection. They warned that their series was small and that interspecies differences might qualify results. In the pig, Byrod et al. demonstrated rapid venous transport from the epidural space to spinal nerve roots and spinal nerves. Evans blue labelled albumin travelled from the epidural space to intraneural veins within 1 minute. They speculated that “...epidurally applied substances, such as local anaesthetic drugs or epidurally injected corticosteroids, may have a rapid, direct transport route to the axons of the spinal nerve roots.”

In sheep, intrathecal betamethasone acetate (11.4–91.2 mg) produced arachnoiditis. But no pathological changes were produced by 5.7 mg (the usual epidural dose in humans is 5.7–11.4 mg). An editorial comment by McLain warned that “The possibility remains that there is a cumulative effect to benzalkonium chloride exposure (the bacteriostatic preservative in the betamethasone formulation) that is not apparent in this experimental design...”

Three studies of rabbit optic globe injections disclosed that the vehicles contained in commercial MPA, betamethasone sodium phosphate, dexamethasone sodium phosphate, and dexamethasone acetate produced retinal damage. The vehicles of MPA and betamethasone sodium phosphate when injected alone produced “remarkable retinal degeneration and preretinal membrane formation or cataracts.” In addition, abnormal evoked potentials and electroretinograms followed intravitreal injection of myristyl-γ-picolinum chloride, the preservative in MPA. Because the retina is derived from evagination of the fetal forebrain, this research may well apply to CNS neurotoxicity.

COMPONENTS OF STEROID FORMULATIONS

The compound most often injected is methylprednisolone acetate (Methylprednisolone sodium phosphate when injected alone produced “remarkable retinal degeneration and preretinal membrane formation or cataracts.” In addition, abnormal evoked potentials and electroretinograms followed intravitreal injection of myristyl-γ-picolinum chloride, the preservative in MPA. Because the retina is derived from evagination of the fetal forebrain, this research may well apply to CNS neurotoxicity.

**Table 3** FDA drug experience reports (DERs) on 109 patients (1992–6). Review of epidural injections using methylprednisolone acetate (Depo-Medrol)

<table>
<thead>
<tr>
<th>Total incidents reported (approved and “off label” use)</th>
<th>680</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients of neurological interest</td>
<td>109</td>
</tr>
<tr>
<td>(epidural therapy only 94)</td>
<td></td>
</tr>
<tr>
<td>(other injection sites with pathophysiological correlations 15)</td>
<td></td>
</tr>
<tr>
<td>94 patients who received epidural therapy:</td>
<td></td>
</tr>
<tr>
<td>Total patients who received epidural injections</td>
<td>94</td>
</tr>
<tr>
<td>Scanty reports not analyzed</td>
<td>46</td>
</tr>
<tr>
<td>Detailed classifiable DERs</td>
<td>48</td>
</tr>
<tr>
<td>Epidural therapeutic attempts in 48 patients</td>
<td>58</td>
</tr>
<tr>
<td>Accidental intrathecal injections</td>
<td>10</td>
</tr>
</tbody>
</table>

15 injections into non-epidural sites: DERs of neurological significance:

| Intentional intrathecal                                   | 4   |
| Paraspinous nerve blocks                                   | 3   |
| Spinal facet blocks                                        | 3   |
| Intraoperative discectomy                                 | 1   |
| Nasal surgery                                              | 2   |
| Optic globe injection                                     | 1   |
| Peripheral nerve injection                                | 1   |

Food and drug administration (FDA) drug experience reports (DERs)

The DERs of 57 patients treated with intrathecal MPA between 1965 and 1983 included these complications: aseptic meningitis (24), thoracolumbar arachnoiditis (12), myelopathy and cauda equina syndrome (11), prolonged spinal puncture headache (seven), bacterial meningitis (four), epidural abscess (three), generalised seizures (three), electrolyte imbal-
Polys=Polymorphonuclear leucocytes; lymphs=lymphocytes.

Table 4 Spinal fluid and imaging findings reported with adverse reactions from epidural injections. Methylprednisolone acetate (40 mg–200 mg (Depo-Medrol sterile aqueous suspension—Pharmacia and Upjohn))

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Protein (mg/dl)</th>
<th>Glucose (mg/dl)</th>
<th>White cells (mm³)</th>
<th>Cultures</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arachnoiditis from chemical meningitis</td>
<td>302</td>
<td>41</td>
<td>1300 polys</td>
<td>Negative</td>
<td>MRI intensities in meninges, recovery after steroid therapy</td>
</tr>
<tr>
<td>Chemical meningitis</td>
<td>775</td>
<td>48</td>
<td>8000 polys</td>
<td>Negative</td>
<td>&quot;Dural tear,&quot; recovery after prophylactic antibiotics</td>
</tr>
<tr>
<td>Chemical meningitis</td>
<td>420</td>
<td>89</td>
<td>8400 (type unknown)</td>
<td>Negative</td>
<td>Brain abscess, recovery after prophylactic antibiotics given</td>
</tr>
<tr>
<td>Meningitis, unknown aetiology</td>
<td>400</td>
<td>50</td>
<td>1700 lymphs</td>
<td>Unknown</td>
<td>Treated for TBC meningitis 6 weeks after epidural therapy</td>
</tr>
</tbody>
</table>

Table 5 Adverse reactions after epidural steroid therapy given to 48 patients reported to FDA 1992–6*

<table>
<thead>
<tr>
<th>Indications</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low back pain (17)</td>
<td>Headache (15)</td>
<td>Sensory loss (6)</td>
<td>Aseptic meningitis (8)</td>
</tr>
<tr>
<td>Herniated disc (14)</td>
<td>Sciatica (7)</td>
<td>Leg weakness (6)</td>
<td>Paraplegia/paresis (6)</td>
</tr>
<tr>
<td>Sciatica (9)</td>
<td>Chills/fever (6)</td>
<td>Aphasias (1)</td>
<td>Cauda equina syndrome (2)</td>
</tr>
<tr>
<td>Spinal stenosis (3)</td>
<td>Nausea/vomiting (5)</td>
<td>Dysarthria (1)</td>
<td>Pseudotumour cerebri (1)</td>
</tr>
<tr>
<td>Failed back syndrome (2)</td>
<td>Photophobia (3)</td>
<td>Moon facies (1)</td>
<td>Increased CSF pressure (1)</td>
</tr>
<tr>
<td>Spondylitis (2)</td>
<td>Paraesthesiae legs (3)</td>
<td></td>
<td>Discits (1)</td>
</tr>
<tr>
<td>Coccydynia (1)</td>
<td>Urinary retention (3)</td>
<td></td>
<td>Terraplegia (1)</td>
</tr>
<tr>
<td>Unknown (7)</td>
<td>Paraesthesia head (2)</td>
<td></td>
<td>Arachnoiditis (1)</td>
</tr>
<tr>
<td></td>
<td>Leg and back cramps (2)</td>
<td></td>
<td>Infectious meningitis (1)</td>
</tr>
<tr>
<td></td>
<td>Urinary/faecal incontinence (2)</td>
<td></td>
<td>Dermolyeinating disease (1)</td>
</tr>
<tr>
<td></td>
<td>Convulsion (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sexual impotence (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Visual blurring/scotomas (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somnolence (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EPIDEMIOLOGICAL CORRELATES OF FDA DATABASE

General FDA epidemiological principles establish that (1) neither incidence nor frequency of complications can be calculated from DERs; (2) trends alone can be detected; (3) adverse events are grossly under-reported. Computation of the true prevalence of adverse drug reactions is dependent on complete reporting of complications, number of patients using a drug, and number of doses. (Incidence=adverse reactions/fixed interval (that is, 1 year, etc). Frequency=adverse reactions/occasions of use.) There are no reliable data concerning these numerators or denominators; FDA reviews can only detect trends over time. Furthermore, after the 2nd year of marketing any drug, there is an unexplained precipitous decrease of adverse reactions due to arteriole microemboli (two), vertebral artery injection resulting in a fatal medullary and thalamic infarction (one), intrathecal injection causing upper cervical cord and lower brain stem fatal infarction (one), bilateral permanent leg paresis after intraoperative epidural application of MPA (one), detached retina with permanent blindness after optic globe injection (one), and paralysis of the hand and chronic pain after local tendon injection.
Epidural steroids are most like the human. The presently model whose meninges and spinal structures merit carefully planned animal research using a tions. We think that problems of this magnitude are inadequate to deal either with therapeu-... 

The five questions posed at the beginning of this review can be answered with reasonable evidence based certitude: (1) Intraspinal steroid therapy is not effective therapy for back pain or radicular syndromes because steroid formulations, placebos, and sham injections have similar outcomes. (2) When injected, epidural medications may not remain confined to the epidural space and some inaccuracies of placement approach 40%. (3) The additives of steroid formulations—polyethylene glycol, benzyl alcohol, and benzal-... 

Qualities and quantities of animal experimentation In a heterogeneous group of patients, surgical failures of lumbar discectomy by laminectomy and laminotomy (even in the most skillful hands) are 7% after the 1st year, 20% after 5 years, and 40% after 10 years with an unknown decrement thereafter. Reported animal studies are inadequate to deal either with therapeutic efficacy or specific measures of complicat... 

In a recent treatise on chronic pain, Justin151 concluded that “In the future we may see more specific treatments based on an improved understanding of the specific pathophysiology of different pain syndromes but for the moment there are no ‘magic bullets.’” The necessary first step toward “improved understanding” of intraspinal steroid use for back and radicular pain is careful animal experimentation to ascertain safety. More extensive studies of direct blocking and possible destructive effects upon nociceptive fibers are essential. Further aggressive clinical and pathological studies must take into account the well known factor of improvement over time and the placebo effect.

Conclusions

Sincere thanks to Richard G Berry, MD who expounded the neuroanatomy of the intraspinal spaces. Robert W Frelick, MD was of much assistance in organizing the tables and in explaining the epidemiology of FDA data. Our deep gratitude to Patrick A Wilson, MD who determined osmolarities of formulations and to Scott T Sampson, MBA, RPh who researched this subject in the pharmacology literature. Much appreciation to Crawford MacKeand, MBE who translated the early Italian and French literature to disclose the arcane history of this subject. Expert computerised and manual literature reviews were provided by medical librarians Mrs Christine Chastain-Warheit, Mrs Ann Gallagher, Ms Sharon Gannett, Ms Ellen M Justice, Mrs Patrici... 

www.jmp.com

Snoek W, Weber H, Jorgensen B. Double blind evaluation of
et al.

Davis R, Emmons SE. Benefits of epidural methylpred-
et al.

Goldstein NP, McKenzie BF, McGuckin WF, et al.


Power RA, Taylor GJ, Fyfe IS. Lumbar epidural injection of
et al.

Sehgal AD, Gardner WJ, Dohn DF. Pantopaque “arach-
et al.


Yin Y. Personal communication, April 1999.

Bogduk N. Spine update epidural steroids. Spine 1995;20:

Burn JM, Langdon L. Duration of action of epidural methyl


Ryley MG, Kingley GH, Gibson T, et al. Outpatient lum-


Gibbs M. Personal communication, April 1999.

Bousfield K. Lumbar and cephalic epidural corticosteroid injec-
et al.


Spaccarelli K. Lumbar and cephalic epidural corticosteroid injec-
et al.

Yin Y. Personal communication, April 1999.

Bogduk N. Spine update epidural steroids. Spine 1995;20:

Burn JM, Langdon L. Duration of action of epidural methyl


Ryley MG, Kingley GH, Gibson T, et al. Outpatient lum-


Gibbs M. Personal communication, April 1999.

Bogduk N. Spine update epidural steroids. Spine 1995;20:

Burn JM, Langdon L. Duration of action of epidural methyl


Ryley MG, Kingley GH, Gibson T, et al. Outpatient lum-


Gibbs M. Personal communication, April 1999.

Bogduk N. Spine update epidural steroids. Spine 1995;20:

Burn JM, Langdon L. Duration of action of epidural methyl


Ryley MG, Kingley GH, Gibson T, et al. Outpatient lum-


Gibbs M. Personal communication, April 1999.

Bogduk N. Spine update epidural steroids. Spine 1995;20:

Burn JM, Langdon L. Duration of action of epidural methyl


Ryley MG, Kingley GH, Gibson T, et al. Outpatient lum-


Gibbs M. Personal communication, April 1999.

Bogduk N. Spine update epidural steroids. Spine 1995;20:

Burn JM, Langdon L. Duration of action of epidural methyl


Ryley MG, Kingley GH, Gibson T, et al. Outpatient lum-


Gibbs M. Personal communication, April 1999.

Bogduk N. Spine update epidural steroids. Spine 1995;20:

Burn JM, Langdon L. Duration of action of epidural methyl


Ryley MG, Kingley GH, Gibson T, et al. Outpatient lum-


Gibbs M. Personal communication, April 1999.

Bogduk N. Spine update epidural steroids. Spine 1995;20:

Burn JM, Langdon L. Duration of action of epidural methyl


Ryley MG, Kingley GH, Gibson T, et al. Outpatient lum-


Gibbs M. Personal communication, April 1999.

Bogduk N. Spine update epidural steroids. Spine 1995;20:

Burn JM, Langdon L. Duration of action of epidural methyl


Ryley MG, Kingley GH, Gibson T, et al. Outpatient lum-


Gibbs M. Personal communication, April 1999.
Epidural steroids


