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

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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.1–3 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, Viner4 also employed the sacral route, using procaine in normal saline, Ringer’s solution, or “liquid petrolatum.” Evans5 reported using procaine hydrochloride. In attempts to relieve sciatica and low back pain, patients improved: 68%。“mechanical stretching” of nerve roots, he found that the volume of injectate (100 ml or more with and without local anaesthetic) was the most important factor. Sciatica was relieved completely in 24 patients and “considerable benefit” occurred in six. In these uncontrolled trials, the nature of the pathological process and the duration of pain relief were not specified.

**Articular steroid injection—the harbinger of intraspinal therapy**

Compound E (cortisone) was discovered in 1936.6 In 1950 Hench et al7 reported that it produced transient improvement of “rheumatoid arthritis, rheumatic fever, and certain other conditions.” Then Hollander8 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.9–10 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**

<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>
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<tbody>
<tr>
<td>Lievre et al11</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>Brown et al12</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>
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<td>1960</td>
<td>239</td>
<td>Sciatica</td>
<td>Epidural</td>
<td>Methylprednisolone acetate</td>
<td>Retrospective</td>
<td>100 at 8 w</td>
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<tr>
<td>Goebert et al13</td>
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<td>Hydrocortisone</td>
<td>Retrospective</td>
<td>66 at 12–130 w</td>
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<td>Gardner et al14</td>
<td>1961</td>
<td>75</td>
<td>Sciatica</td>
<td>Intrathecal</td>
<td>Methylprednisolone acetate</td>
<td>Retrospective</td>
<td>83 at 124 w</td>
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<tr>
<td>Sehgal15</td>
<td>1962</td>
<td>100</td>
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<td>Intrathecal</td>
<td>Methylprednisolone acetate</td>
<td>Retrospective</td>
<td>60 at 1–44 w</td>
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<td>1972</td>
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<td>Methylprednisolone acetate</td>
<td>Prospective</td>
<td>90 at 2–104 w</td>
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<tr>
<td>El-khoury et al17</td>
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<td>116</td>
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<td>Epidural</td>
<td>Betamethasone</td>
<td>Prospective</td>
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<td>Rosen et al18</td>
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<td>Methylprednisolone acetate</td>
<td>Prospective</td>
<td>98 at several h</td>
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<tr>
<td>Power et al19</td>
<td>1992</td>
<td>16</td>
<td>Sciatica</td>
<td>Epidural</td>
<td>Methylprednisolone acetate</td>
<td>Prospective</td>
<td>25 at 1–32 w</td>
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<td>Bowman et al20</td>
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<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”.

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In 1952 Robecci and Capra reported using "periradicular" hydrocortisone to treat lumbar disk herniation. They speculated that their patient’s "lumbago and sciatica" were produced by "inflammation." Caudal epidural hydrocortisone therapy gained wide popularity after Lievre et al. reported improvement in five of 20 patients; there were no controls and outcome was not defined past 3 weeks (table 1). For 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 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. Goebert et al. reported relief of radicular pain in 72% of 352 patients with sciatica treated with 30 ml volumes of 1% procaine hydrochloride and 125 mg hydrocortisone by caudal epidural injection adjacent to the involved nerve root. They used no controls and outcome was not defined past 12 weeks.

MODERN HISTORY: INTRATHECAL, EPIDURAL, AND NERVE ROOT THERAPIES

Origins of intrathecal steroid therapy

Gardner et al. first tried epidural injections of 30 ml 1% procaine and 125 mg hydrocortisone in 239 patients with sciatica, half with failed back surgery. Because of 57% failure, they used an intrathecal mixture of 80 mg MPA and 40 mg procaine in 75 subjects with sciatica of undefined aetiology. Forty five (60%) had "...relief of sciatica for periods of more than 4 months" (table 1). Details of outcome were undefined; there were no controls and no animal experiments were cited.

Later, they reported intrathecal MPA therapy to 100 patients with arachnoiditis after iophendylate (Pantopaque) myelography; 60% had pain relief for up to 24 months (table 1). Only 33 had myelographic proof of cicatrix, outcome data were not provided, and there were no controls. The routine practice of injecting MPA at myelography was summarised in two critical reviews. By 1963, Sehgal et al. had treated more than 1000 patients with intrathecal MPA for 19 different conditions ranging from failed back surgery to histamine cephalgia, pseudotumour cerebri, and Guillain-Barré syndrome. Duration of improvement was not stated, neurological signs and outcome were not described, and there were no controls.

Intrathecal steroids for multiple sclerosis

In 1953, Kamen and Erdman reported treating a patient with relapsing-remitting multiple sclerosis using both intrathecal hydrocortisone and intramuscular adrenocorticotropic hormone (ACTH). Numerous neurological signs cleared during a stay in hospital and 6 week follow up. Boines reported 75%–80% “excellent or good” results with intrathecal MPA in 42 patients between 1961 and 1963. In these trials and follow up of 12–52 weeks, no outcome evaluations, controls, or follow up plan were provided.

Goldstein et al. reported that intrathecal MPA reduced spinal fluid γ-globulin in multiple sclerosis, but they warned that “the effect on the clinical course remains to be established.” In a prospective study of intrathecal MPA in 20 patients, Van Buskirk et al. reported no effect on the frequency of exacerbations; improvement in spasticity was "largely of a subjective nature." In 1970 Goldstein et al. reported on 38 patients treated with 4–8 intrathecal MPA infusions and followed up for 2–8 years. Neurological examinations disclosed some initial improvement but this persisted in only 16. In a prospective study of 23 patients with multiple sclerosis given 83 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 Snoek 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. 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. 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 sulfate, MPA, aminocaproic acid, and a microfibrillar 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.

**Systematic steroid treatment for back and radicular symptoms**

Oral steroid medication for pain of presumed spinal inflammatory origin is a very popular nostrum, usually a tapering dose over 2–3 weeks. We have been unable to find any reports.

### 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(s); ref</th>
<th>Controls</th>
<th>Placebo or sham injection</th>
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<tbody>
<tr>
<td><strong>With steroid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sciatica improved (%) * (n=219)</td>
<td>Sciatica improved (%) * (n=249)</td>
<td></td>
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<tr>
<td></td>
<td>24 h–3 w</td>
<td>8–120 w</td>
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<tr>
<td>Dikke 1973&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Double blind, randomised</td>
<td>35</td>
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<td>Snoek 1977&lt;sup&gt;41&lt;/sup&gt;</td>
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<td>Randomised</td>
<td>19</td>
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<td>Cuckler 1985&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Double blind, randomised</td>
<td>22</td>
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<tr>
<td>Carette 1997&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Double blind, randomised</td>
<td>77</td>
</tr>
<tr>
<td>Fukusaki M† 1998&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Randomised</td>
<td>20</td>
</tr>
<tr>
<td>Fukusaki M† 1998&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Randomised</td>
<td>19</td>
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<tr>
<td>Average improvement</td>
<td></td>
<td>37</td>
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</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).
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, foraminar arthrosis, facet disorders, spinal stenosis, and failed back surgery.45 53 61 62 The concept that inflammation is the target lesion of these conditions is based on two assumptions: (a) direct pressure on nerve roots or ischemia from compression produces local inflammation; (b) free fragments of nucleus pulposus release inflammatory phospholipase A2.55 56 63 These were reviewed in detail by Haddox64 who wrote, “Surgeons . . .state that the nerve root that is causing the problem is easily identifiable by its edematous inflammatory character.” But a review of the literature refutes that assertion. In 160 random necropsy examinations, Lindblom and Rexed65 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 deformation). The most frequent 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 Rexed66 reported small nerve fibers. “Surgeons . . .state that the nerve root that is . . .could in fact cause permanent functional and/or degenerative changes.” Transectory 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.67

In addition to chemical injury to nociceptor nerve fibers, the hypertonicity of the injectate mixtures may have an independent mischievous effect. The normal osmolality 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), etc.
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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.72 73 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 formication (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, 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.” Lieve 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.21 25 Intrathecal MPA for arachnoiditis produced pleocytosis as high as 3000/mm3 with protein concentrations up to 250 mg/dl, correlated with dosage.2 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.37 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).38 39 Other complications were brain damage, spinal cord lesions,40 and dense widespread pachymeningitis.41 The therapeutic trial by Nelson et al was foreshortened because of adhesive 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.44 46

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.47 49 Another report of 18 case histories concluded that radiographic arachnoiditis can occur from only one MPA injection shortly preceding myelography.50 A subsequent publication concluded that three of 15 such patients (20%) later developed clinical signs and symptoms of arachnoiditis.51 Despite these reports, several authors continue to recommend intrathecal steroid therapy.52 55

Adverse reactions from epidural steroids: 1989–94

Beginning in 1989 in Australia, there were numerous claims of adverse reactions to epidural steroid therapy.56 Case histories suggested diagnoses of encephalopathy (three), myelopathy (three), cauda equina syndrome (two), sciatica (one), chemical meningitis (one), and cerebrovascular accident (one).57 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 prescribe 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.58 59 60 Chan and Leung60 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.61 62
Delayed septicaemia followed epidural MPA in another.97 98

DANGEROUS ANATOMICAL PASSAGES DURING EPIDURAL INJCTIONS

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.75 94 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 60 70-80 94-105

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, foraminal injection, and nerve block. Radicular or spinal cord damage may be permanent sequelae. In cervical epidural procedures and trigger point blocks, the vertebral artery can be accidently punctured leading to medullary infarct.114 Retinal damage from MPA arterial micro-emboli 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, mening-othy after epidural injection into the segmental vessels on nerve roots.104

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. Extrafascicular nerve injections of MPA or its vehicle produced histological lesions in sciatic nerve.124 Direct sciatic nerve injections of MPA and other steroid formulations produced intrafascicular 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 . . . depotesteroid preparations do not produce spinal cord damage when injected neuraxially."
Cicala et al[^20] 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[^20] 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 “...epidural application, 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[^105] 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-picolinium 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 (MPA) produced by Pharmacia and Upjohn, Kalamaazoo, MI, USA. Included with the steroid is an alcohol and non-ionic detergent polyethylene glycol, and myristyl-γ-picolinium chloride, an antibacterial agent. In 1990, the manufacturer substituted benzyl alcohol for myristyl-γ-picolinium chloride, which is effective against gram positive bacteria but not gram negative *Salmonella typhimurium*. Benzyl alcohol is effective against both types, which are sometimes found in epidural abscesses. In 1991, benzyl alcohol was removed from the 1 ml vials and was replaced by myristyl-γ-picolinium chloride as in the original formulation. This change followed complaints that both polyethylene glycol and benzyl alcohol are potential neurotoxins. Therefore, only the multiple dose vials now contain benzyl alcohol.

Triamcinolone diacetate, often used for epidural therapy, also contains PEG and benzyl alcohol. Because of reports of neurotoxicity from polyethylene glycol and benzyl alcohol, some physicians have begun to use betamethasone sodium phosphate. But this formulation does contain the preservative benzalkonium chloride, which is also potentially toxic.

From its first introduction the manufacturer of MPA advised against diluting or mixing it with other solutions because of “possible physical incompatibilities.” This caveat is generally ignored; MPA is often mixed with local anaesthetic or contrast agent at the time of injection. Local anaesthetics themselves can produce both transient and permanent neurological injuries and these risks are potentially additive.

An adverse reaction warning about intrathecal injections was first published in the *Physicians’ Desk Reference* in 1979: “Arachnoiditis has been reported following intrathecal administration.” The 1980 statement was, “Depo-Medrol Is Not Recommended For Intrathecal Administration.” In 1989, a stronger warning under “CONTRAINDICATIONS” stated that “DEPO-MEDROL Aqueous Suspension is contraindicated for intrathecal administration. This formulation of methylprednisolone acetate has been associated with severe medical events when administered by this route.” The most recent caveat in 1989 was: “Adverse Reactions Reported with the Following Routes of Administration: Intrathecal/epidural: Arachnoiditis, Meningitis, Paraparesis/paraplegia, Sensory Disturbances, Bowel/Bladder Dysfunction, Headache, Seizures.” But now in 2000 there is no warning in the *Physicians’ Desk Reference* that epidural therapy with MPA is contraindicated. Potential risks led the manufacturer of betamethasone sodium phosphate (Celestone®) to warn in 1991, “Under no circumstances do we recommend that Celestone Chronodose (Australian trademark) be administered by epidural injection.”

### 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>(epidural therapy only 94)</td>
<td>109</td>
</tr>
<tr>
<td>(other injection sites with pathophysiological correlations 15)</td>
<td>94</td>
</tr>
</tbody>
</table>

- **94 patients who received epidural therapy:**
  - Total patients who received epidural injections: 94
  - Scanty reports not analysed: 46
  - Detailed classifiable DERs: 48
  - Epidural therapeutic attempts in 48 patients: 58
  - Accidental intrathecal injections: 10

- **15 injections into non-epidural sites: DERs of neurological significance:**
  - Intentional intrathecal: 4
  - Paraspinal nerve blocks: 3
  - Spinal facet blocks: 3
  - Intraoperative discotomy: 1
  - Nasal surgery: 2
  - Optic globe injection: 1
  - Peripheral nerve injection: 1

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[^20]: Cicala et al. 1989
[^105]: McLain. 1989
[^132]: Benzyl alcohol is effective against gram positive bacteria but not gram negative *Salmonella typhimurium*. Benzyl alcohol is effective against both types, which are sometimes found in epidural abscesses. In 1991, benzyl alcohol was removed from the 1 ml vials and was replaced by myristyl-γ-picolinium chloride as in the original formulation. This change followed complaints that both polyethylene glycol and benzyl alcohol are potential neurotoxins. Therefore, only the multiple dose vials now contain benzyl alcohol.

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**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-
ance (three), ventriculitis (two), and allergic reaction (two).38

A review of DERs filed between 1992 and 1996 is summarised in tables 3–5. Table 3 lists all uses of MPA derived from 680 FDA drug experience reports (DERs) in which 109 (16%) contained neurologically pertinent data. This table also shows that of 94 epidural steroid therapy reports, about half were insufficiently detailed for further analysis, a well known deficiency in volunteer reporting. The neurological database used here is derived from 48 DERs listing 58 spinal injections and 15 into other regions. Among the spinal injection reports (table 3) there were 10 accidental subarachnoid space punctures and four intentional intrathecal treatments. These resulted in arachnoiditis with high spinal fluid protein (three), paraplegia at T-10 with MRI intensities (one), and “isolated motor deficit” not clearly defined (one). Table 4 lists the various signs, symptoms, and syndromes of a predominantly inflammatory nature, also affirmed by these spinal fluid and imaging studies. Table 5 lists the clinical diagnoses that led to epidural steroid injection. Low back pain is the most common. Complications not listed in tabular form are: paraspinal nerve blocks and spinal facet blocks that resulted in chemical meningitis (four), postsurgical nasal injections of MPA that produced amynbopia due to arterial 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.

### 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>“Dural tear,” 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>Event followed third epidural injection, patient recovered, 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* (methylprednisolone acetate (Depo-Medrol sterile aqueous suspension—Pharmacia and Upjohn))

<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/paraparesis (6)</td>
</tr>
<tr>
<td>Sciatica (9)</td>
<td>Chills/fever (6)</td>
<td>Axasia (2)</td>
<td>Organic mental syndrome (6)</td>
</tr>
<tr>
<td>Spinal stenosis (3)</td>
<td>Nausea/vomiting (5)</td>
<td>Aphasia (1)</td>
<td>Cauda equina syndrome (2)</td>
</tr>
<tr>
<td>Failed back syndrome (2)</td>
<td>Photophobia (3)</td>
<td>Dyssarthis (1)</td>
<td>Pseudotumour cerebri (1)</td>
</tr>
<tr>
<td>Spondylolysis (2)</td>
<td>Pareasthesiae legs (3)</td>
<td>Moon facies (1)</td>
<td>Increased CSF pressure (1)</td>
</tr>
<tr>
<td>Coccydynia (1)</td>
<td>Urinary retention (3)</td>
<td></td>
<td>Discits (1)</td>
</tr>
<tr>
<td>Unknown (7)</td>
<td>Parasthesia head (2)</td>
<td></td>
<td>Tereplegia (1)</td>
</tr>
<tr>
<td></td>
<td>Leg and back cramps (2)</td>
<td></td>
<td>Arachnoiditis (1)</td>
</tr>
<tr>
<td></td>
<td>Urinary/rectal incontinence (2)</td>
<td></td>
<td>Infectious meningitis (1)</td>
</tr>
<tr>
<td></td>
<td>Convulsion (1)</td>
<td></td>
<td>Demyelinating disease (1)</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>

*www.jnp.com
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are most like the human.78 Do the presently model whose meninges and spinal structures logical techniques. Just as important is an testing the steroid compound(s) acutely and ously, the experimental plan should include evoke arachnoiditis/pachymeningitis? Obvi-
ously, the experimental plan should include testing the steroid compound(s) acutely and chronically using both physiological and histo-
logical techniques. Just as important is an exhaustive testing of each component in the injectate mixture. The cogent question of whether steroids affect the lesions produced by experimental primate back surgery is obtain-
able but is now unanswered.

In a recent treatise on chronic pain, Justins151 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 under-
standing” of intraspinal steroid use for back and radicular pain is careful animal experimen-
tation to ascertain safety. More extensive stud-
ies 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

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-
konium chloride—can be neurotoxic when injected intrathecally. Further research may disclose that the steroid formulations and mix-
tures themselves may be neurotoxic because of high osmolalities. (4) Epidural steroid infusion may result in increased pain, early or late. There may also be serious complications of arachnoiditis, spinal infection, or permanent neurological deficits. (5) Patients should be informed that there is no evidence that epidural steroid injections provide permanent relief of pain. Serious permanent complications to the spinal cord, nerve roots, or peripheral nerves are a rare but certain risk.

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 expediting the epidemiology of FDA data. Our deep gratitude to Patrick A Wilson, MD who determined osmolalities of formulations and to Scott T Sampson, MBA, RPh who researched this subject in the pharmacology literature. Much appreciation to Crawford MacKend, MIEEE 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 Patri-
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