**REVIEW**

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.1,2 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, Viner1 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 “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.4,5

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

Compound E (cortisone) was discovered in 1936.6,7 In 1950 Hench et al8 reported that it produced transient improvement of “rheumatoid arthritis, rheumatic fever, and certain other conditions.” Then Hollander9 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.10–18

**Transient therapeutic response**

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>Lievre53</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>Brown50</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>Goebert49</td>
<td>1960</td>
<td>239</td>
<td>Sciatica</td>
<td>Epidural</td>
<td>Hydrocortisone</td>
<td>Retrospective</td>
<td>100 at 8 w</td>
</tr>
<tr>
<td>Goebert43</td>
<td>1961</td>
<td>113</td>
<td>Sciatica</td>
<td>Epidural</td>
<td>Hydrocortisone</td>
<td>Retrospective</td>
<td>83 at 12+ w</td>
</tr>
<tr>
<td>Gardner46</td>
<td>1961</td>
<td>75</td>
<td>Sciatica</td>
<td>Intrathecal</td>
<td>Methylprednisolone acetate</td>
<td>Retrospective</td>
<td>60 at 1–34+ w</td>
</tr>
<tr>
<td>Sehgal37</td>
<td>1962</td>
<td>100</td>
<td>Sciatica</td>
<td>Intrathecal</td>
<td>Methylprednisolone acetate</td>
<td>Retrospective</td>
<td>90 at 9–104 w</td>
</tr>
<tr>
<td>Winnie48</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-khoury39</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>Rosen44</td>
<td>1988</td>
<td>40</td>
<td>Sciatica, LBP</td>
<td>Epidural</td>
<td>Methylprednisolone acetate</td>
<td>Retrospective</td>
<td>25 at 1–32 w</td>
</tr>
<tr>
<td>Power45</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>Bowman46</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”.

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Epidural pressure injections combined with steroid therapy: a transition

In 1952 Robecchi 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 Lieve 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 cortisol 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.44 showed that “extra-
dural injection of methyl prednisolone (80 mg) is no more effective than a placebo injection in relieving chronic symptoms due to myelo-
graphically demonstrable lumbar disc hernia-
tion” (table 2).

A randomised unblinded study of 63 pa-
tients with sciatica by Klenerman et al.39 re-
ported 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 injec-
tions of normal saline or local anaesthetic. In
the double blind trial of 36 patients with lum-
bar radicular pain by Cuckler et al.,50 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 signifi-
cant difference was observed between the con-
trol and experimental patients.”

Carette et al. provided the most definitive
well controlled study of epidural MPA therapy
doing disc related sciatica. Using careful follow up
neurological examinations and exacting statisti-
cal methods, they concluded: “Thus, we
found that epidural corticosteroid injections do
not afford long term advantages over place-
bo . . . (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 place-
bo groups.43, 44 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
Emmons47 claimed a need for less postopera-
tive analgesia as well as a 37%-40% decrease in
postoperative stay. With the patients blinded,
Layne and Bilsky45 compared intraoperative
MPA to saline irrigation. In another study,
McNeill et al.48 compared intraoperative MPA,
placebo, morphine, and morphine-MPA mix-
ture. Both groups concluded that this applica-
tion of MPA was useless. No comparable dou-
ble blind prospective research has been pub-
lished.

Recently, small volume perineural epidural
injection into the anterior epidural space has
been advocated.46-51 Different techniques using
various steroids, local anaesthetic, epiduo-
gram 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 com-
pared with isotonic saline.52 Both groups
reported 80% “good” plus “fair” results. Marks
et al.53 evaluated lumbar facet joint injection of
20 mg MPA and local anaesthetic. They con-
cluded, “In the absence of a control group
we cannot quantify the placebo effect and can-
not, therefore, draw any conclusions regarding
the validity of these procedures as diagnostic
tests . . .”

Epidural “morphine nerve paste” at discectomy
Needham45 reported “painless lumbar surgery”
using a thick paste composed of morphine sul-
fate, MPA, aminocaproic acid, and a microfi-
brillary haemostatic powder applied intraop-
eratively to the epidural space. No animal
experimental or human clinical data were pro-
vided. This was further investigated by Hurl-
bert et al.54 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 sig-
ificantly 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(s)/ref.</th>
<th>Controls</th>
<th>Placebo or sham injection</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>With steroid</td>
<td>Placebo or sham injection</td>
</tr>
<tr>
<td></td>
<td>Sciatica improved (%)* (n=219)</td>
<td>Sciatica improved (%)* (n=249)</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>24 h–3 w</td>
</tr>
<tr>
<td>Dilke 1973†††</td>
<td>Double blind, randomised</td>
<td>35</td>
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<td></td>
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<tr>
<td>Kleneman 1984‡‡‡</td>
<td>Randomised</td>
<td>19</td>
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<tr>
<td>Cuckler 1985‡‡‡</td>
<td>Double blind, randomised</td>
<td>22</td>
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<tr>
<td>Carette 1997‡‡‡</td>
<td>Double blind, randomised</td>
<td>77</td>
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<tr>
<td>Snoek 1977‡‡‡</td>
<td>Double blind, randomised</td>
<td>27</td>
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<tr>
<td>Cuckler 1985‡‡‡</td>
<td>Double blind, randomised</td>
<td>20</td>
</tr>
<tr>
<td>Fukusaki Mr 1998‡‡‡</td>
<td>Randomised</td>
<td>19</td>
</tr>
<tr>
<td>Average improvement</td>
<td></td>
<td>35</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).
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 intracerebrally with hydrocortisone and described histological reduction of talar induced arachnoiditis. Feldman and Behar also reported treating talar 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.

Posпеч et al. produced epidual 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 sarring 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 artheros, facet disorders, spinal stenosis, and failed back surgery.47 48 49 50 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 A2.51 52 53 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 edematous 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 deformation). 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 Gibbs, who wrote concerning the thousands of nerve roots he has inspected at disc surgery, “There is . . . the 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 capillary dilatation, leucocyte infiltration, and oedema deep in the arachnoid membrane. We have discovered no necropsy reports that support the 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.42 43 Johansson et al. applied MPA to the plantar nerve in rats. Within 60 minutes they discovered a blockade of unmyelinated nociceptive C fibres that was 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.” Transitory amelioration of symptoms can also be explained by chemical blockade or destruction of C fibre axons and nerve terminals produced by polyethylene glycol and benzyol alcohol contained in several steroid formulations.73

In addition to chemical injury to nociceptor nerve fibres, 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),
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 paraesthesia, 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, opisthotonus, unconsciousness, and incontinence of urine and faeces followed the injection of 120 cc 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. 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 . . . . with the approval of a hospital ethics, accreditation or credentialling committee . . . . for radicular pain . . . . part of a properly constituted research protocol aimed at determining the efficacy of the epidural injection of steroids.”

**MENINGITIS AND EPIDURAL ABSCESSES 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.29

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.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 49 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.110

Retinal damage from MPA arterial microemboli has followed accidental injection of MPA into arteries or collaterals supplying ton- silar 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.204

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, meningitis from the irritant 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.79 117 118 On rare occasions, a needle puncture can accidently 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 ambylophia 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).115-119 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 al22 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 Riester58 reported that rabbits injected intrathecally with 10 mg hydrocortisone developed transient severe major motor seizures. In cats with talc 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 al118 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 nerves.123 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.27 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 in 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-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 methylprednisolone-picolinium chloride, which is effective against gram positive bacteria but not against gram negative *Serratia marcescens*. 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)

| Total incidents reported (approved and “off label” use) | 680 |
| (epidural therapy only 94) | 109 |
| (other injection sites with pathophysiological correlations 15) | |
| 94 patients who received epidural therapy: | |
| Total patients who received epidural injections | 94 |
| Scanty reports not analyzed | 48 |
| Detailed clasuslable 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 discectomy | 1 |
| Nasal surgery | 2 |
| Optic globe injection | 1 |
| Peripheral nerve injection | 1 |

For 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-
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 given</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>

Polys=Polymorphonuclear leucocytes; lymphs=lymphocytes.

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>Clinical condition after epidural injections of 40–200 mg doses</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low back pain</td>
<td></td>
<td>Headache (15)</td>
<td>Sensory loss (6)</td>
<td>Aseptic meningitis (8)</td>
</tr>
<tr>
<td>Herniated disc (14)</td>
<td></td>
<td>Sciatica (7)</td>
<td>Leg weakness (6)</td>
<td>Paraplegia/paraparesis (6)</td>
</tr>
<tr>
<td>Sciatica (9)</td>
<td></td>
<td>Chills/fever (6)</td>
<td>Ateaxia (2)</td>
<td>Organic mental syndrome (6)</td>
</tr>
<tr>
<td>Spinal stenosis (3)</td>
<td></td>
<td>Nausea/vomiting (5)</td>
<td>Aphasias (1)</td>
<td>Cauda equina syndrome (2)</td>
</tr>
<tr>
<td>Failed back syndrome (2)</td>
<td></td>
<td>Photophobia (3)</td>
<td>Dysarthria (1)</td>
<td>Pseudotumour cerebri (1)</td>
</tr>
<tr>
<td>Spondylitis (2)</td>
<td></td>
<td>Paraesthesiae legs (3)</td>
<td>Moon facies (1)</td>
<td>Discitis (1)</td>
</tr>
<tr>
<td>Coccydynia (1)</td>
<td></td>
<td>Urinary retention (3)</td>
<td></td>
<td>Tereplegia (1)</td>
</tr>
<tr>
<td>Unknown (7)</td>
<td></td>
<td>Paraesthesia head (2)</td>
<td></td>
<td>Arachnoiditis (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leg and back cramps (2)</td>
<td></td>
<td>Infectious meningitis (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinary/faecal incontinence (2)</td>
<td></td>
<td>Demyelinating disease (1)</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/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 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 amblyopia 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.
event reporting even though there is no decline in usage.106

The most often quoted article concerning underreporting of complications is the Rhode Island regional study.105 The physicians who were polled reported 27,000 adverse drug reactions of all of the drugs that they used (adjusted to 36,000 by including non-respondents). This was compared with only 55 reports (11 from physicians) sent to the United States FDA. From these data, it can be estimated that only 0.15%-0.2% of adverse drug reactions will be reported to the FDA. For every reported complication there are probably 400–600 unreported cases! Less than 1% of adverse reports are ever reported in the literature. We must conclude that adverse drug reactions of intraspinal steroid therapy submitted to the FDA (and especially individual case reports in the literature) comprise only the “tip of the tip of the iceberg.”

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.105 Reported animal studies are inadequate to deal either with therapeutic efficacy or specific measures of complications. We think that problems of this magnitude merit carefully planned animal research using a model whose meninges and spinal structures are most like the human.106 Do the presently used formulations ameliorate or actually provoke arachnoiditis/pachymeningitis? Obviously, the experimental plan should include testing the steroid compound(s) acutely and chronically using both physiological and histological 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 obtainable but is now unanswered.

In a recent treatise on chronic pain, Justins107 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

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 benzalkonium chloride—can be neurotoxic when injected intrathecally. Further research may disclose that the steroid formulations and mixtures 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 Sampselle, MBA, RPh who researched this subject in the pharmacology literature. Much appreciation to Crawford MacKeand, MIEE 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 Patricia Patterson, Mrs Roberta Reprini, and Mrs Joan Smith.


7 Mason HL, Myers CS, Kendall EC. Chemical studies of the suprarenal cortex II. The definition of a substance which possesses the qualitative action of cortin; its conversion into a diketone closely related to androstenedione. J Biol Chem 1936;116:267–78.


