Subject: arachnoiditis

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Epidural Steroid Injections and the Lumbar Spine

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The following represents text, originally published on the Internet, which has been edited by the Burton Report® with further emphasis by M.Feehan with the permission of Dr. Burton. This material is being presented because it is important and accurate. Richard Koontz is to be complimented on his concern and his efforts.

Since the withdrawal of oil-based myelography **Depo-Medrol** and **Depo-Medrone** have become the principal cause of clinically significant adhesive arachnoiditis in the Western world.

Depo-MedrolÒ (and other similar suspensions) are being administered epidurally as routine off-label and ill-advised, treatments for back pain. The rationale given for the use of these suspensions is that their main ingredient, **methylprednisolon**e, is an anti-inflammatory agent. Although basically true in concept suspensions of synthetic glucocorticoids are effective anti-inflammatory agents but **they also contain preservatives such as polyethylene glycol, known better as a anti-freeze in car cooling systems**. Other preservatives include alcohol. **Both ethylene glycol and alcohol are well-recognized toxic agents** if introduced into the sub-arachnoid space. **Wood (1980 *1)** studied the effects of injections of methylprednisolone acetate into rat sciatic nerves. **Nerves treated with either the steroid or its vehicle showed damage, including collagen (scar) formation and demyelination**.

The manufacturers Depo-MedrolÒ **(Upjohn Pharmaceutical Co., Kalamazoo, Michigan, U.S.A.) stated in 1981 that "we would advise against the epidural/ extradural routes of administration because of possible adverse reactions"**. However, this specific recommendation was withdrawn from the data sheet in 1997.

Kenalog (triamcinolone suspension) is another steroid used in epidural injections. **This drug is "not recommended for administration via the epidural route" according to the data sheet provided by its manufacturers, Bristol Myers Squibb (Wallingford, Connecticut, U.S.A.)** As with any "off-label" use of a drug or device their application is dependent upon the individual doctor's discretion and clinical judgment. It is the individual physician who then takes personal responsibility for this. In both the U.S. and England epidural steroid injection (ESI) in the treatment of back pain is practiced extensively and by a variety of clinicians including general practitioners, anesthesiologists, radiologists and specially trained physiotherapists. The current associated literature on **Depo-MedrolÒ states that it is contraindicated for intrathecal administration and that it contains benzyl alcohol, which is potentially toxic when administered locally to neural tissue.**

Most patients who have had adverse effects from the epidural suspensions say they would not have allowed the injection if they had been provided with informed consent and had known that these drugs were not licensed for this particular application. **Nelson (1988*2) has maintained that "the epidural space is not wholly separate from the subdural and/ or subarachnoid space" and that the spaces are "not only contiguous, but continuous".** He concluded that epidural delivery of drugs may not guarantee that

the substance will remain isolated in the epidural space alone and cites **a 2.5% risk of inadvertent drug injection directly into the subarachnoid space.**

The Mackinnon studies on rats (1982*3) showed that a variety of injectable steroids may damage peripheral nerves if injected intraneurally. **The National Health and Medical Research Council of Australia (NHMRC) report (4) from 1994** indicated that **the risk of dural puncture is, on average, "at least 5%"**. These authors also warn, **"particular care must be taken if attempting an epidural injection in patients previously treated by spinal surgery"** because complete local obliteration of the epidural space occurs following surgery and in such cases an attempted epidural injection carries a very high risk of direct entry into the subarachnoid space.

It appears that few of the health care professionals who perform ESI have any awareness of this fact. **Byrod and Olmarker (1995*5) found evidence that the potential barrier properties of the dura/ arachnoid "seem less than effective" in preventing substances in the epidural space from reaching the subarachnoid space**. Several other authors have questioned the basic efficacy of epidural steroid injections (ESI) in treating disc herniation, lumbar stenoses and "failed back surgery syndromes". **Rosen et al (6) concluded in 1988, "overall results were poor", with only approximately 50% of patients receive temporary relief, while long-term relief occurred in less than 25% of patients.**

Anderson and Mosdal (1987*7) found that epidural steroid injection was "useless" in patients with long-standing complaints and previous surgeries. This conclusion was also supported by the study by **Cuckler et al (1985*8)**, which failed to demonstrate ESI efficacy, with the authors also raising **the issue of published reports of "serious complications"**. More recently, in 1997, **Carette et al (9)** studied patients with herniated discs and found that **epidural steroid "offers no significant functional benefit, nor does it reduce the need for surgery**," although there may be short-term improvement in pain and sensory deficit. **Ringsdal et al (1997*10) proposed that "future correctly designed studies are necessary to clarify whether the injection should be a supplement to the established treatment of low back pain and sciatica," as they found that previous studies showed conflicting results.**

The NHMRC report suggests that ESI are of greater use when sciatica is present because this implies a substantial inflammatory component (especially if acute) but are less use if neurologic deficit is present. The Agency for Health Care Policy and Research of the U.S. Government (AHCPR) Clinical Practice Guideline clearly states that **"Epidural injections are invasive and pose rare but serious potential risks. There was no evidence that epidural steroids are effective in treating acute radiculopathy."** These papers demonstrate that there remains a question about the benefit of ESI, which at best tends to be temporary (less than 6 months) which must be of limited use in patients with long-term problems.

Epidural anesthetics are another group of drugs implicated in causing arachnoiditis. (see below). **Vandermeulen (1997*11) includes arachnoiditis as a "mishap"… "solely due to … epidural anesthesia". Haisa et al (1995*12)** state that lumbar adhesive arachnoiditis should be considered for differential diagnosis of back and leg pain after epidural anesthesia. Furthermore, epidural anesthesia may cause subarachnoid cysts or cavities, which are also recognized complications of arachnoiditis. (see below) If the epidural space is already compromised by disc herniation, stenosis or epidural fibrosis, the risk is greater. **Yuen et al (1995*13) state that neurological. complications " may be more severe in the presence of spinal stenosis". Rocco et al (1997*14) in a study of pressure gradients in the epidural space, concluded that as resistance to inflow of fluid was significantly higher in the diseased epidural space, "spread of anesthetics might be difficult to predict".**

In 1955, Hurst conducted studies on monkeys **(15)**, which demonstrated that a wide range of chemicals, when introduced into the CSF, produced an immediate pathological response, which "proceeds steadily to its termination". The early stages are asymptomatic, but after a latent period, the clinical picture is then one of "severe and progressive signs and symptoms". This is similar to the picture in arachnoiditis, and therefore all short-term studies (which make up the majority of the evidence concerning safety of ESI) will fail to address the issue of arachnoiditis, which tends to occur after an indeterminate interval following exposure.

PRESERVATIVES IN SPINAL INJECTIONS

In 1975, Kelly et al wrote a paper describing the neuropathological effects of the intrathecal introduction of water. They concluded that infusing distilled water intrathecally could cause distinctive lesions of spinal roots and cord. It follows therefore, that if a substance as inert as water can cause damage, that more complex preparations are also likely to carry some risk given the pristine and fragile environment of the subarachnoid space.

As early as 1954, **Moore** advised that local anesthetic administered epidurally should be free of preservatives in case of inadvertent subarachnoid entry of the drug. **Malinovsky suggested that "neurotoxicity can result from decrease in neuronal blood supply, elicited by high concentrations of the solutions, long duration exposure to local anesthetics, and the use of adjuvants"**. Other authors suggest that arachnoiditis reactions can occur simply from the vasoconstrictive component of an anesthetic, while others have noted that even minor contaminants or preservative agents can be responsible for this condition. It needs to be stressed that any drug preparation injected into the spinal column, may contain preservatives such as benzyl alcohol, polyethylene glycol, and chlorobutanol (a derivative of chloroform). All of these substances carry a risk of neurotoxic effect. Another preservative known to cause reaction is sodium bisulfate, which may trigger a severe autoimmune (allergic) reaction if the patient is susceptible (and studies on the general population in regard to this have never been performed). Burm believes that epidural anesthesia results from the interaction of local anesthetics with nerve structures within the subarachnoid space, which they reach by indirect uptake via systemic and epidural fat absorption. Because of this epidural doses need to be much higher than spinal doses.

The transmission of this information to patients is almost non-existent in the world today. This means that informed consent is also non-existent. Many physicians feel that it would be confusing to the patient to be given a detailed breakdown of relative risks and potential adverse effects. This disrespectful attitude is, sadly, all too common. **In addition, because adhesive arachnoiditis continues to be viewed by the medical profession as a rare pathologic entity they incorrectly believe that it does warrant mentioning.** As with all therapeutic techniques, it is essential that the potential benefit be weighed against the potential risk. **If this is not communicated informed consent does not exist.** Part of the problem has been the universal under-reporting of adverse effects, so that clinicians may not even have access to accurate information to pass on to the patient. O'Connor et al summed up the situation by stating that the "abnormalities of the epidural and subarachnoid spaces in such patients"(i.e. with chronic spinal arachnoiditis) … gives rise to "unpredictable and potentially dangerous results" following drug injection into these spaces. >

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Publication Commentary:
Arch Neurol 1988 Jul;45(7):804-806
Dangers from methylprednisolone acetate therapy by intraspinal injection.
Nelson DA Section of Neurology in Medicine, Medical Center of Delaware, Wilmington.
Clinical trials with methylprednisolone acetate (Depo-MedrolÒ) administered intrathecally first began in 1960, in an attempt to treat both disc disease and multiple sclerosis. After a few reports of positive results, there then began an outpouring of contradictory data, which continued to 1988. During this time span, researchers who initially ventured the opinion of improvement began to publish serious warnings regarding the many complications observed. For ten years prior to the intraspinal use of suspensions containing methylprednisolone acetate, basic scientists in anesthesiology and neurochemistry had published the following facts:
1. Methylprednisolone acetate suspension's content of polyethylene glycol raises the risks of using it near the central nervous system.
2. Deleterious effects follow the use of glycols when they are placed into or near the neuraxis.
3. Methylprednisolone acetate suspension contains approximately 30 mg of polyethylene glycol per milliliter.
When that glycol, which is both alcohol and detergent, is injected intraspinally, sterile meningitis, arachnoiditis, or pachymeningitis occur. It was also recognized since the 1960s that the epidural space was neuroanatomically not wholly separate from the subdural and/or subarachnoid space. Many thousands of arachnoid villi subtend all the membranes from the intrathecal space, and many of these end in the large epidural veins (Batson's Venous Plexus). Therefore, the various spaces and membranes are not only contiguous, but continuous. It follows that an injection of methylprednisolone acetate into the epidural space does not guarantee that it will remain isolated there. Finally, the inadvertency of injections by the epidural route occurs with the following frequency:
40% of injections can be inadvertently made into interspinous ligaments, and
2.5% (or more) into the subarachnoid space

Spine 1993 Feb;18(2):278-286
Intraspinal therapy using methylprednisolone acetate. Twenty-three years of clinical controversy.
Nelson DA Section of Neurology, Medical Center of Delaware, Wilmington.
The intraspinal use of methylprednisolone acetate (Depo-Medrol®) began in 1960, followed 10 years later by reports of complications. In 1960, methylprednisolone acetate was first injected by the epidural route to treat low-back syndromes. Then in 1961, the intrathecal route was more widely used to treat arachnoiditis and multiple sclerosis. Epidural therapy again came into general use in 1980 for the treatment of the "Failed Back Surgery Syndrome" because intrathecal therapy was virtually abandoned after 10 years of spirited scientific controversy. Epidural steroid therapy is now employed extensively, and while there exist many reports to its efficacy in treating in treating chronic pain problems there have also been reports of important complications. This review was prompted both by manufacturer warnings, as well as by an ongoing controversy in different countries throughout the world. The paucity of meaningful scientific data regarding intrathecal and epidural steroid therapy from 1960 to 1993 is pointed out.

Clin Orthop 1988 Mar;228:270-272
A retrospective analysis of the efficacy of epidural steroid injections.
Rosen CD, Kahanovitz N, Bernstein R, Viola K

Hospital for Joint Diseases Orthopaedic Institute, New York, New York 10003.
Forty patients were studied retrospectively to evaluate the effect of epidural steroid injections on low back pain and sciatica characteristic of spinal stenosis or a herniated lumbar disc. All but one of these patients had radicular symptoms. The average age was 55 years, and the average follow-up time was eight months. All patients were injected by the same anesthesiologist with 2 cc of Depomedrol-40. Thirty-six patients received either one, two, or three injections. Four patients received either four or five injections. The overall results were poor, with about 60% of patients reporting varying degrees of relief from leg and back pain immediately after injection. However, at follow- up examination, only 24% were asymptomatic; 40% reported no change in preinjection numbness, weakness, or pain; and approximately 35% had varying degrees of relief with no consistent pattern. Of those who had complete relief, there was no correlation between relief of pain, age, or number of injections. From this study, it appears that approximately 50% of patients with radicular symptoms may receive temporary relief with steroid injection. However, long-term relief occurs in less than 25% of patients.>

Surg Neurol 1983;19:393-4
Letters To The Editor: Complications From Depo-MedrolÒ
Dear Sir:
From the initial observation upon the peripheral nerves of rabbits, and of the retina, optic nerve, brain, spinal cord, and intrathecal nerve roots of rats, it appears that both Depo-Medrol® and its sterile vehicle, polyethylene glycol 4000, can immediately result in the dissolution of myelin and may cause manifestations of loss of neural function. The two agents appear to act immediately and most intensely in the experimental arrival at the site of contact of the agents upon the nervous tissue, although alterations are found in more remote parts as well. Because of these findings it may be worthwhile to avoid the use of Depo-Medrol® in and about any nervous elements, including the optic nerve and dorsal nerve roots until the matter is resolved. This applies only to Depo-Medrol® and not to Solu-Medrol® which does not appear to possess this action. These findings, thus far, are compatible with several case reports describing adverse clinical reactions following the use of injections of Depo-Medrol® in or about nervous tissue. The author would appreciate learning from readers of instances of neural damage possibly related to the injection of Depo-Medrol® into the cerebrospinal fluid (CSF), extradurally or into and around peripheral nerves. Roy Selby LaCrosse Wisconsin.

Reply: Dr Selby's letter was submitted to the Upjohn Company. A summary of their letter has been prepared by us. They state that intrathecal administration of Depo-Medrol® may be associated with a number of undesirable side effects. Accordingly they have placed a "warning" in the Depo-Medrol®---"Depo-Medrol is not recommended for intrathecal administration".

In the ISIS (International Spinal Injection Society, www.spinalinjection.com newsletter of July 1998 Richard Derby MD wrote: **"any substance injected into the epidural space near a prior dural puncture site will inevitably find its way into the subarachnoid space. It would be inappropriate to risk bathing a segment of the spinal cord in ethylene glycol, or any depo-corticosteroid solution.** In the same July 1998 newsletter Richard Derby MD also wrote: "There are several preparations commonly used during epidural injection procedures that are potentially neurotoxic in nature and are a likely contributing factor to observe chronic arachnoiditis when inadvertently injected into the subarachnoid space. On the other, Celestone Soluspan® has been shown in animals to be "relatively innocuous" when the clinical equivalent human dose of 12mg is injected within the subarachnoid space."

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