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Analgesic and Neurotoxic Effects of Intrathecal Corticosteroids in Rats

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Background: **Despite the widespread use of epidurally administered corticosteroids in the treatment of sciatica and the failure of animal studies to demonstrate neurotoxicity from epidermally administered corticosteroids, controversy remains regarding the mechanism of action as well as the safety of this treatment. The goal of this study was to determine whether spinally administered corticosteroids have any analgesic effects, and whether repeated intrathecal administration causes any neuronal damage to the spinal cord.**

Methods: **Chronic lumbar intrathecal catheters were implanted in rats. Formalin testing was carried out 1 h after the intrathecal administration of 400 μg methylprednisolone sodium succinate, 48 h after intrathecal administration of triamcinolone diacetate 250 μg, or 24 h after the last of a series of four injections of triamcinolone diacetate 250 μg given at 5-day intervals. Histologic sections of multiple levels of spinal cord from the animals receiving repeat intrathecal steroid injections were compared to those from animals that received intrathecal saline at the same intervals.**

Results: **The animals receiving repeated intrathecal triamcinolone diacetate demonstrated mild, statistically significant reduction of pain behavior (hindlimb flinching) during the second but not the first phase of the formalin test when compared to controls. No analgesic effects were demonstrated after methylprednisolone sodium succinate or a single injection of triamcinolone diacetate. Animals that received methylprednisolone sodium succinate demonstrated transient segmental allodynia. No behavioral or neurologic abnormalities were seen in any other group. Some histologic evidence neuronal damage (the presence of argyrophilic neurons was seen in the chronically implanted animals in areas of the cord adjacent to the spinal catheters, but there was no difference in incidence of these changes between the steroid and control groups.**

Conclusions: **Intrathecal steroid injections have no analgesic effect and do not suppress spinal sensitization when administered acutely. After chronic administration, there is a mild effect on nociceptor-driven spinal sensitization (phase 2 of the formalin test), but no analgesic effect on an acute noxious stimulus (phase 1 of the formalin test). Repeated intrathecal administration of triamcinolone diacetate (0.8 mg/kg) is not associated with spinal neurotoxic effects during the time period studied. (Key words: Anesthetic techniques: spinal. Toxicity, spinal cord: corticosteroids.)**

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Mechanism of Action of Epidurally Administered Corticosteroids

EPIDURAL steroid injections are frequently used in the management of radiculopathy caused by lumbar disc disease. It is commonly assumed that the mechanism of action of neuraxially administered corticosteroids involves a reduction in the inflammation and edema of the injured or irritated root.[1–3] Recently, however, there has been considerable interest in the role of prostaglandins in mediating various forms of spinal sensitization,[4] and it is conceivable that corticosteroids may influence pain perception because of their effect on spinal prostaglandin production. First, noxious stimulation evokes the release of prostaglandins from the spinal cord.[5–7] Second, prostaglandins have been shown to enhance neurotransmitter release from primary afferent neurons.[8] Third, spinal administration of nonsteroidal antiinflammatory drugs block the second, or sensitization-dependent phase of the formalin test at doses 100–300 times smaller than those associated with systemic analgesic effects.[9] Similarly, small doses of spinally administered nonsteroidal antiinflammatory drugs reduce the acute hyperalgesic behavior evoked by spinally administered N-methyl-D-aspartic acid and substance P.[10] Corticosteroids are capable of reducing production of prostaglandins by inhibiting phospholipase A_2,[11] leading to speculation

that at least part of the beneficial effect of these agents in radiculopathy might be to limit or reduce sensitization of dorsal horn neurons by noxious inputs arising from the injured nerve root.

Potential Neurotoxicity of Epidurally Administered Corticosteroids

Despite the extremely low incidence of reported complications from epidural steroid injections, there has been recent speculation that the neuraxial administration of long-acting preparations that are suspended in a propylene glycol suspension are inherently unsafe.[12] Two previous histologic studies of the effects of epidurally administered steroid suspensions on the spinal cord and meninges have failed to demonstrate neurologic damage or inflammation.[13,14] However, there is continued concern that accidental intrathecal injection may be hazardous, particularly in light of a case report of sclerosing pachymeningitis after multiple intrathecal methylprednisolone acetate injections in a patient with multiple sclerosis[15] and of conus medullaris syndrome in a patient receiving frequent intrathecal methylprednisolone acetate injections for chronic sciatica.[16]

The purpose of this study was twofold. First, we sought to determine whether intrathecal corticosteroids, administered both acutely and chronically, provide analgesia in the rat formalin test, which measures both the acute analgesic effect of a drug (phase 1) and the ability of a drug to modify the appearance of spinally mediated hyperalgesia (phase 2). Second, we sought to determine whether chronic intrathecal administration of a corticosteroid suspension would produce behavioral or histologic evidence of neurologic damage in rats.

Materials and Methods

The following studies were carried out under a protocol approved by the Institutional Animal Care Committee of the University of California, San Diego. Male Sprague-Dawley rats weighing 250–350 g were used for these studies.

Animal Preparation

Animals were implanted with chronic lumbar intrathecal catheters introduced via an incision in the atlantooccipital membrane under halothane anesthesia as previously described by Yaksh and Rudy.[17] Animals showing neurologic deficits after implantation were excluded. All testing was begun 5–7 days after intrathecal implantation.

Neurobehavioral Testing

Animals were tested before and after treatment using placing/stepping response (when the dorsum of the hindpaw is placed against the table edge the animal lifts the paw and places it on the table surface), righting reflex, and observation of posture and gait. Animals were examined for urine staining of the fur over the lower abdomen as evidence of incontinence.

Formalin Test

The formalin test was carried out as previously described.[18] In brief, the animals were individually allowed to breathe 3% halothane until immobile. Animals were quickly removed from the anesthesia and given a subcutaneous injection of 50 μl 5% formalin into the dorsum of the right hindpaw using a 30-G needle. They were then placed in a clear plexiglass chamber for observation. Coordinated spontaneous movement was typically noted less than 30 s after injection. Animals routinely displayed a flinching, withdrawal movement of the injected hindpaw. The number of flinches per minute were then recorded 1 and 5 min after recovery from the anesthetic and at 5-min intervals thereafter for 1 h. The animals were then killed with an overdose of barbiturate.

Experimental Paradigms

A series of discrete studies was carried out to assess the effects of intrathecal corticosteroids on first and second phase formalin test behavior. All intrathecal drugs were administered in 10 μl volumes, followed by 10 μl normal saline. Administration was done with a micrometer driven injection device.

Controls

In six animals, 20 μl normal saline was injected intrathecallly four times, 5 days apart (group 1A). Phase 1 and 2 means from this group were used as controls for animals given triamcinolone diacetate chronically (group 4). Normal saline 20 μl was injected intrathecally 1 h before formalin testing in five animals (group 1B). Phase 1 and phase 2 means from this group were used as controls for the animals given methylprednisolone sodium succinate or triamcinolone diacetate acutely (groups 2 and 3). Twenty-four hours after the fourth injection, animals underwent formalin testing.

Neurobehavioral testing was carried out before each injection, 1 h after each injection and 10 min before formalin injection.

Acute Methylprednisolone Sodium Succinate

Methylprednisolone sodium succinate (Solu-Medrol, Upjohn, Kalamazoo, MI) 400 μg dissolved in normal saline was injected intrathecally 60 min before formalin injection in four animals (group 2). Neurobehavioral testing was carried out 10 min before formalin injection.

Acute Triamcinolone Diacetate

Triamcinolone diacetate (25 mg/ml, Aristocort Intralesional, Fujisawa, Deerfield, IL) 250 μg (10 μl) was injected, undiluted, intrathecally 24 h before formalin testing in six animals (group 3). This dose is roughly equivalent on a per-kilogram basis to the 50 mg dose commonly injected epidurally in human patients. Neurobehavioral testing was carried out 10 min before formalin injection.

Chronic Triamcinolone Diacetate

Triamcinolone diacetate (25 mg/ml, Aristocort Intralesional, Fujisawa) 250 μg was injected intrathecally four times, undiluted, 5 days apart in six animals (group 4). Twenty-four hours after the fourth injection, animals underwent formalin testing. Neurobehavioral testing was carried out before each injection, 1 h after each injection and 10 min before formalin injection.

Histopathologic Studies

After 21 days all animals in group 1A and 4 were anesthetized with an overdose of pentobarbital and transcardially perfused with 100 ml saline followed by 150 ml 4% paraformaldehyde. To avoid the development of *post mortem* artificial neuronal changes all precautions for the fixation process and handling of the material[19] were observed and the spinal cords were removed from the vertebral column 24 h after perfusion fixation. Twenty frozen transverse sections 20 μm thick were taken from each of the following blocks of spinal cord: C2–C5, T1–T10, and L1–S2. These sections were prepared and impregnated by the suppressive Nauta method. This technique has been described in detail elsewhere.[20] In brief, the selective neuronal impregnability of affected neurons is used as a response to a variety of pathologic condition such as transient central nervous system or spinal cord ischemia as well as traumatic central nervous system and spinal cord injury.[20–22]

Five representative sections from each spinal level mentioned above were coded in each animal and then subjected to a systematic examination for the presence of argyrophilic neurons. Scores were tabulated and analysis prepared by an observer blinded to the behavioral outcome and duration of occlusion.

For electron microscopy the tissue samples from the same spinal levels as above were taken and postfixed in 1% buffered OsO_4; semithin sections were stained with toluidine blue and ultrathin sections were stained with uranyl acetate followed by lead citrate. We avoided using glutaraldehyde because of nonspecific mitochondrial costaining in silver impregnated sections.[22]

Data Analysis

The total number of flinches was determined for all of the phase 1 (1 and 5 min) and phase 2 (10–60 min) observations for each animal, and these data were compared by one-way analysis of variance (StatView II, Abacus Concepts, Berkeley, CA). *Post hoc* comparisons were done with Scheffé's F test.

Statistical analysis of neuropathologic scoring was carried out with analysis of variance using multiple means analysis followed by the Tukey-Kramer test. A P value of < 0.05 was considered significant. Data were expressed as mean ± SD.

Results

Behavioral Testing

There were no abnormalities in righting response, placing or stepping, gait or posture at any time among the control or triamcinolone diacetate treated animals. Likewise, no urine staining of the abdomen, a sign of bladder dysfunction, was noted at any time. Among the methylprednisolone sodium succinate treated animals, the following behavioral abnormality was observed. In all four animals, beginning 5–10 min after steroid injection, the animals stopped their normal grooming and exploring behavior and remained in one corner of their cage. Touching the fur in the low thoracic, lumbar or sacral areas was met by vocalizing and, occasionally, aggressive behavior (attempted biting). Stroking the fur of the upper thoracic, cervical regions or the head evoked no such response. This response was mild in two animals and quite pronounced in the other two. That behavior resolved in 20–40 min, before formalin injection. This response was interpreted as mechanical allodynia. Because of this untoward response, no more animals received this drug.

Table 1. Mean Total Number of Flinches (± SEM) for Phase 1 (1 and 5 min) and Phase 2 (10–60 min) for Each of the Treatment Groups

Group	N	Treatment	Mean Phase 1	Mean Phase 2
1A	6	Saline control, chronic	16.7 ± 2.7	165.3 ± 4.5
1B	5	Saline control, acute	20.8 ± 4.5	180.2 ± 9.7
1C	11	Combined controls	18.5 ± 2.6	172.1 ± 5.6
2	4	Methylprednisolone Na succinate	12.3 ± 2.9	158.0 ± 45.2
3	5	Triamcinolone diacetate, 48 hr	23.8 ± 7.1	164.0 ± 19.8
4	6	Triamcinolone diacetate, 21 days	26.2 ± 4.5	135.2 ± 16.0*

* Significantly different from group 1C ($P < 0.05$).

Formalin Testing

Means for the total number of flinches for each group are shown in table 1. The two control groups were very similar in their phase 1 and 2 responses (table 1 and fig. 1). Therefore, these groups were combined and used as controls for all of the experimental paradigms.

Although the phase 1 mean value for the methylprednisolone group was somewhat lower than controls, there were no significant differences among phase 1 data (see table 1).

The phase 2 mean value for animals receiving triamcinolone diacetate chronically (group 4) was significantly lower than that for the combined controls (group 1C) ($P < 0.05$), but did not achieve statistical significance when compared to the chronic control group (group 1A) alone ($P = 0.06$). The phase 2 means for groups 2 and 3 were not significantly different from controls. As can be seen from figures 2, 3, and 4, there was a modest reduction in phase 2 flinching activity in the chronic triamcinolone diacetate group 30–50 min after injection, but not at earlier or later times, as compared to the combined control, but there was no difference from control for the other two steroid groups.

Histopathologic Analysis

Saline-treated Animals. Using silver impregnation techniques, occasional somatodendritic argyrophilia typically affecting A-motor neurons or medium-sized interneurons was found in control animals (group 1A). However, the majority of the neuronal pools displayed normal structure with fully preserved nucleus and nu-

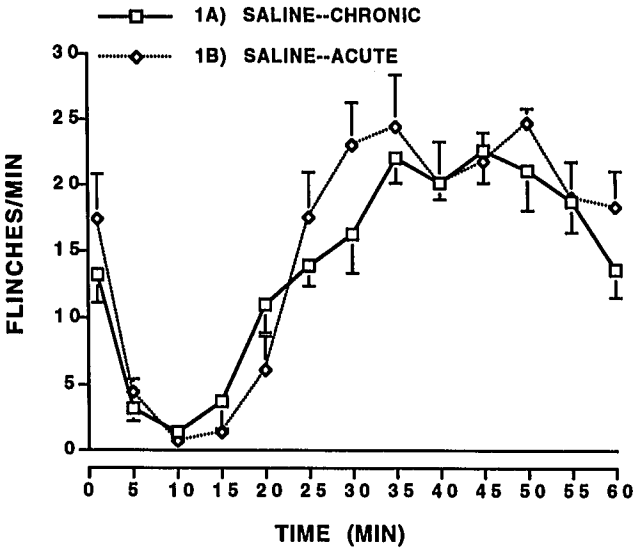

Fig. 1. Mean number of flinches per minute plotted as a function of time after injection of formalin for the two control groups (groups 1A and 1B).

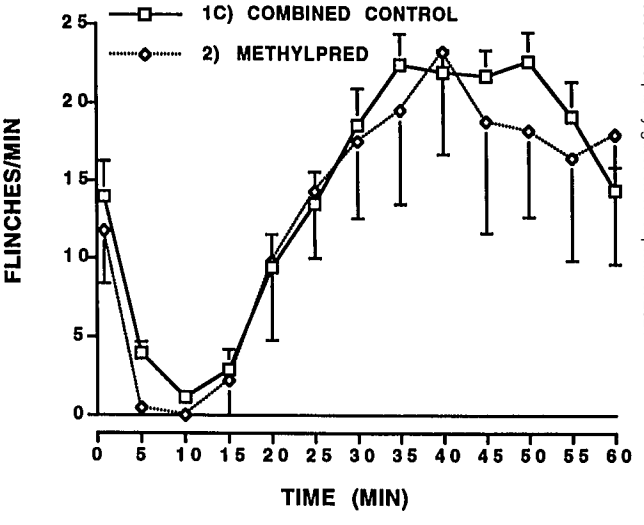

Fig. 2. Mean number of flinches per minute plotted as a function of time after injection of formalin for the combined control group (group 1C) and the group that received methylprednisolone sodium succinate 400 μl intrathecally 1 h before formalin injection (group 2).

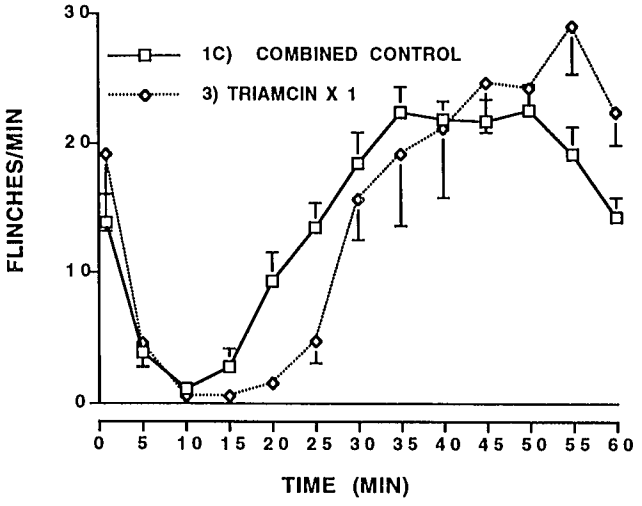

Fig. 3. Mean number of flinches per minute plotted as a function of time after injection of formalin for the combined control group (group 1C) and the group that received triamcinolone diacetate 250 μg 48 h before formalin injection (group 3).

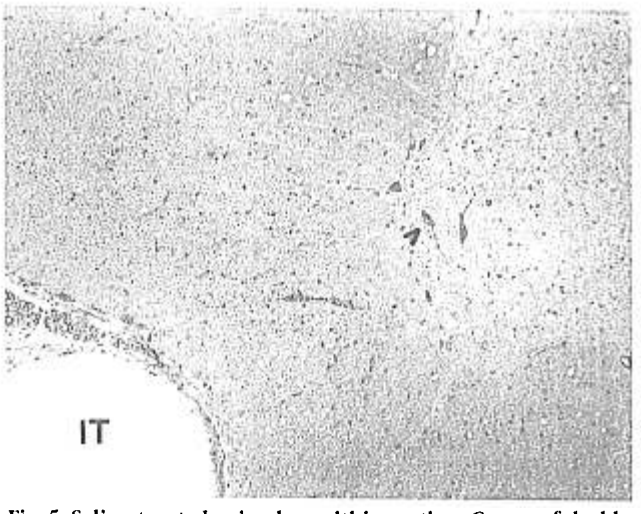

Fig. 5. Saline-treated animal, semithin section. Group of darkly stained neurons (arrow) localized close to the catheter-caused white matter compression (× 12). Intrathecal—intrathecal catheter.

cleolus. In semithin sections stained with toluidine blue, comparable neuronal changes were detected. Dark type of neuronal degeneration with nuclear condensation was seen in close vicinity to normally appearing neurons. The majority of dark neurons were localized in the ipsilateral side to the side of catheter localization i.e. the areas showing direct tissue compression due to catheter implantation (fig. 5). In some sections edematic changes expressed as a dissociation of vascular wall from surrounding tissue was seen (fig. 6).

Triamcinolone-treated Animals. In the chronically treated steroid group (group 4), comparable histo-

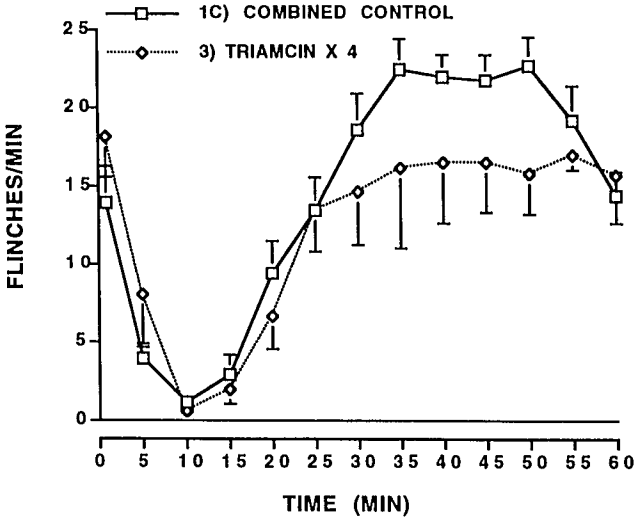

Fig. 4. Mean number of flinches per minute plotted as a function of time after injection of formalin for the combined control group (group 1C) and the group that received triamcinolone diacetate four times, at 5-day intervals, before formalin injection (group 4).

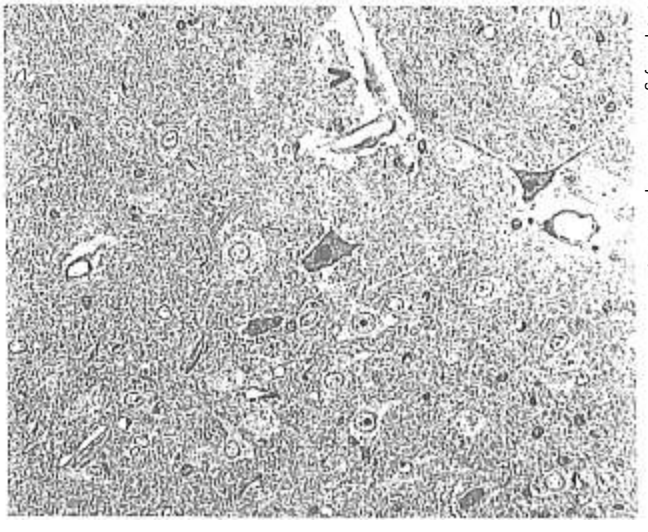

Fig. 6. Saline-treated animal, semithin section. Perivascular edema (arrow) is present as are several normally appearing, medium-sized interneurons localized in laminae VII (× 80).

pathologic changes to those seen in saline treated animals were detected. Occasional appearance of argyrophilic-dark neurons was seen in the vicinity of catheter-caused compression. However, the majority of neurons as well as the neuropil displayed normal structure (fig. 7). Statistical analysis showed no significant differences in the number of dark neurons between saline treated and drug treated animals in any spinal level examined (table 2).

Electron-microscopic analysis revealed changes which corresponded with the findings based on the silver impregnation technique and toluidine stained semithin sections. The majority of neurons survived without any noticeable changes. The profiles of rough endoplasmic reticulum baset and ribosomes with normally appearing mitochondria were detected. In some of these neurons occasional vacuolization of the cytoplasm was seen. Darkly stained neurons seen on semithin sections were characterized by the occurrence of intracytoplasmic dark granules and filament masses forming intracytoplasmic dark accumulation. A qualitatively similar ultrastructural picture was seen in both experimental groups.

Discussion

Formalin Testing

The subcutaneous injection of formalin produces intense nociceptor activity resulting in a brief (<5 min) period of flinching[23] and increased firing of wide-dynamic-range neurons.[24] During this period of acute nociceptor and wide-dynamic-range activity, a series of events occurs that leads to sensitization of dorsal horn neurons to the ongoing low level of discharge from nociceptive afferent neurons. After a period of about 10 min, flinching behavior[23] and wide-dynamic-range activity[24] begins again as a result of the increased neuronal sensitivity. This sensitization is initiated by release of excitatory amino acids, predominately glutamate, with subsequent activation of the N-methyl-D-aspartic acid receptor, resulting in calcium ion influx. The increased intracellular calcium ion then leads to several intracellular events that result in an increased responsiveness to subsequent afferent stimuli. One of these events is the activation of phospholipase A_2, which leads to the release of intracellular arachidonic acid and the formation of prostaglandins.[9,25] The resultant spinal cord accumulation of prostaglandins is thought to contribute to the hyperalgesic state.

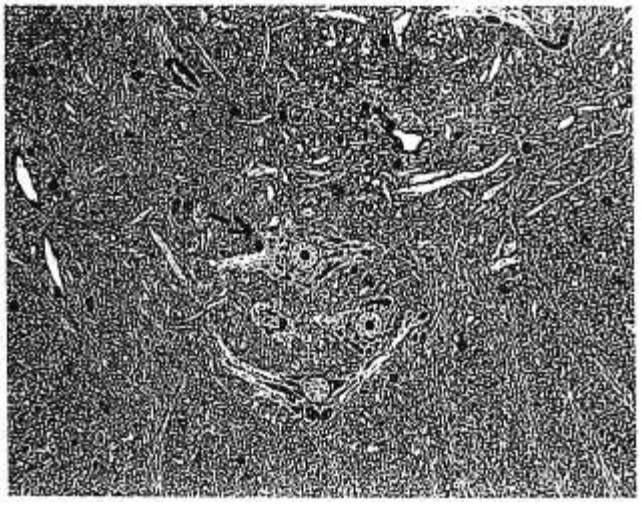

Fig. 7. Triamcinolone-treated animal, semithin section. Group of normally appearing A motor neurons with fully preserved nucleus and nucleolus are present (arrow) (× 120).

Table 2. Mean Number of Dark Neurons (± SD) at Each Spinal Level Examined Histologically

	C2–C5	T1–T10	L1–S2
Control group	2.1 ± 2.2	5.8 ± 3.6	5.4 ± 4.7
Treatment group	2.5 ± 2.5	6.1 ± 4.0	4.8 ± 3.7

After a single administration, it appears that neither soluble corticosteroids nor insoluble suspensions such as triamcinolone diacetate are capable of blocking either the first or the second phase of the formalin test. Repeated doses of steroid suspension, administered over a 3-week period, have no effect on phase 1 and produce only a slight reduction in phase 2, which is questionable in terms of statistical significance. The relative inability of intrathecal corticosteroids to block spinal sensitization is somewhat surprising, since spinally administered nonsteroidal antiinflammatory drugs, which also block prostaglandin production, are moderately effective.[9] On the other hand, Coderre[4] showed that other agents that inhibit phospholipase A2, such as quinacrine, are ineffective in blocking phase 2 of the formalin test. These results reinforce the theory that the beneficial effects of epidural steroid injections result from effects of the drug on the injured nerve root. Such effects may include reduction of inflammation and edema of the affected nerve roots[1–3] or possibly suppression of ectopic discharge from the injured nerve segment.[26] Because levels of spinal prostaglandins were

not assessed, it is possible that doses employed were not adequate to reduce prostaglandin production. The dose used was selected because it is roughly equivalent, in milligrams per kilogram, to doses used epidurally in humans. It would appear, therefore, that the often dramatic improvement seen in patients with radiculopathy after epidural steroid injections is not due to an action upon dorsal horn sensory systems.

Neurotoxicity Studies

The preparation chosen for neurotoxicity studies, triamcinolone diacetate, contains the triamcinolone diacetate suspension (25 mg/ml), polyethylene glycol 3%, polysorbate 80 0.2% and benzyl alcohol 0.9%. Of these substances, only polyethylene glycol has been suggested to be neurotoxic. The majority of statements concerning the neurotoxic potential of this substance have been published by Nelson,[12] who states that it is likely to cause damage if it gains access to the subarachnoid space. However, two of the studies he cites as evidence for polyethylene glycol's neurotoxicity used 80–100% solutions of propylene glycol,[27,28] as opposed to the 3% polyethylene glycol found in most steroid suspensions, and the third study tested still other alcohols and detergents.[29] None of the studies he cited actually evaluated the neurotoxic potential of polyethylene glycol. Other steroid agents, including methylprednisolone acetate, that contain polyethylene glycol, were tested for peripheral nerve neurotoxicity by Mackinnon *et al.*[30] and were found to cause nerve damage only when injected intrafascicularly. Our study failed to show any evidence of neurotoxic potential by the steroid preparation tested. Although we cannot rule out the possibility that a larger number of animals might reveal some neurologic sequelae, the lack of adverse effect in this study is reassuring. The dose was fairly large (about 1 mg/kg) and was repeated multiple times in each animal. Rats have a comparatively small subarachnoid space compared to humans, so that injected substances will not be diluted appreciably.

It may be argued that the duration of our study was not long enough interval to reveal complications such as arachnoiditis, which can be delayed in onset. However, by 21 days after the initial injection, it seems likely that some changes would be evident if any animals were developing arachnoiditis. Cicala *et al.*[14] reported that animals receiving epidural injections of normal saline containing talc had marked epidural infiltration by macrophages 4 and 10 days after injection. Moreover, previous studies with the rodent intrathecal model have shown it to be particularly sensitive to the development of inflammatory reactions[31] and to the evolution of signs of motor dysfunction caused by spinally delivered drugs.[32–34] The failure to see any adverse effects in this model provides additional evidence for a lack of direct toxicity.

We are not advocating the intentional intrathecal injection of steroids for radiculopathy, particularly since previous studies have demonstrated relatively little added benefit compared to epidural injections.[35] However, the data from this study, coupled with the low incidence of reported complications in humans after intrathecal triamcinolone diacetate or methylprednisolone acetate, provides reassurance that accidental intrathecal injection of these substances during attempted epidural injection has a low potential to cause harm. Although there have been reports of neurologic complications after intrathecal steroid injections in patients with multiple sclerosis,[15,36] it is conceivable that such problems are related to their disease process rather than to their treatment. Other series of patients with multiple sclerosis treated with intrathecal steroids have not encountered such problems.[37,§] Reports of neurologic dysfunction in patients treated with intrathecal steroid injections for sciatica are even less common. A case of conus medullaris syndrome was reported in a patient treated with intrathecal and epidural methylprednisolone acetate,[16] but this patient received 14 intrathecal injections over an 18-month period.

In conclusion, this study indicates that there is little evidence that neuraxial steroid injections have an effect on the development of nociception-induced spinal sensitization. Earlier speculation that epidural steroid injections act by reducing inflammation or stabilizing axonal membranes of affected nerve roots remains a more plausible theory. It also provides additional evidence that commercially available deposteroid preparations do not produce spinal cord damage when injected neuraxially.

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