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Methylprednisolone Acetate Does Not Cause Inflammatory Changes in the Epidural Space

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Few studies have examined the possible adverse effects that epidural injection of depot corticosteroid preparations may have on meningeal membranes and nervous tissue. Thirty-six healthy adult white rabbits received 0.3 ml/kg epidural injections of either lactated Ringer's solution (negative control group), 1% lidocaine containing methylprednisolone acetate (study group), or normal saline containing talc (positive control group). Animals were killed either 4 or 10 days after injection and stained sections of the spinal cord and meningeal membranes were examined by light microscopy. In all animals that received either lactated Ringer's solution or lidocaine with methylprednisolone acetate, microscopic examination of specimens taken from the L5-L6 interspace revealed no white cell infiltrates and no fibroblastic activity. All animals that received epidural injections of normal saline containing talc had marked infiltration of tissue macrophages in the epidural space. There was no thickening of the meningeal membranes or nerve roots in any animal. The complete lack of inflammatory changes and meningeal thickening demonstrated in this pilot study helps to confirm the safety of methylprednisolone acetate when injected into the epidural space. (Key words: Anesthetic techniques: epidural. Complications: epidural inflammation. Hormones, corticosteroid: methylprednisolone acetate.)

INJECTION of depot corticosteroid preparations into the epidural space in an attempt to relieve pain originating in the spine is a common procedure, although some debate continues concerning its efficacy. While much is known about the pharmacology of local anesthetic agents in the epidural space, there is a lack of data concerning any possible inflammatory effects that depot corticosteroid preparations may have on meningeal membranes and nervous tissue.

While clinical experience suggests that side effects of epidural injections of corticosteroids are rare, laboratory evidence has been limited to the study of Delany *et al.*[1] They demonstrated a minimal, self-limited inflammatory reaction when triamcinolone diacetate in vehicle (Aristocort Intralesional, Lederle Laboratories, Wayne, NJ) was injected into the epidural space of cats.[1] The depot corticosteroid preparation most commonly used for epidural injection is methylprednisolone acetate (Depo-Medrol®, Upjohn Company, Kalamazoo, MI, and others) suspended in a solution of preservative-free lidocaine or bupivacaine. Depo-Medrol® contains 28–30 mg/ml of polyethylene glycol, which is an alcohol and nonionic detergent. Polyethylene glycol has been shown to cause necrosis of connective tissue, neurons and muscle, and demyelination of peripheral nerves.[2]

Epidural injection of corticosteroid preparations is generally considered to be a safe procedure, but subarachnoid injection of these agents has been associated with several complications including neuronal damage,[3] adhesive arachnoiditis,[4] meningitis,[5] and permanent paralysis.[6,7] Epidural corticosteroid injection has been anecdotally associated with epidural adhesions.[8] Nelson[2] speculated that epidurally injected corticosteroid compounds probably transude the dura mater and arachnoid membranes *via* the arachnoid villi, and concluded that methylprednisolone acetate should not be administered in the vicinity of any neural tissue.

To our knowledge no animal studies have been performed to assess the possible toxicity of Depo-Medrol® when injected into the epidural space, and no studies have examined the acute (<30 day) period after the epidural injection of corticosteroids. We attempted to determine if Depo-Medrol® mixed with lidocaine provoked any inflammatory effects when injected into the epidural space of rabbits.

Materials and Methods

After permission was obtained from the University of Tennessee Animal Care and Use Committee, 36 healthy adult white rabbits weighing 4.3–6.1 kg were divided into six groups. All animals were anesthetized using ketamine 35 mg/kg with xylazine 4 mg/kg intramuscularly prior to the procedure. Using a 22-G B-bevel needle and the loss of resistance to air technique, an epidural injection was performed at the lumbosacral interspace. After careful aspiration to determine that subarachnoid puncture had not been inadvertently performed, study agents were injected. Groups A and B received epidural injections of *p*H-balanced lactated Ringer's solution, 0.3 ml/kg of body mass to serve as a negative control. Groups C and D received preservative-free 1% lidocaine hydrochloride, 0.3 ml/kg body mass which contained Depo-Medrol 2 mg/kg of body mass. Groups E and F received normal saline, 0.3 ml/kg of body mass which contained talc, 0.1 mg/

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ml, to serve as a positive control. Hind-limb dysfunction was used as an indication of successful injection for those animals in groups C and D.

Animals in groups A, C, and E were killed on day 4 following the procedure, and those in groups B, D, and F were killed on postinjection day 10. During ketamine/xylazine anesthesia, all animals were exsanguinated *via* an abdominal aortic incision after which an en-block excision of the lumbar vertebral column was performed. The vertebral specimens were preserved in 10% formalin for 24 h, and then decalcified for 72 h. Bilateral laminectomies at the L5 and L6 levels were then performed. The lamina and spinous processes were removed, the dura exposed, and the meningeal membranes and nerve roots were examined grossly. Complete cross sections of meningeal membranes, spinal cord, and nerve roots were then made at the L5-L6 level. This level was chosen to avoid any evidence of direct trauma that might have occurred at the injection site (L6-S1). Specimens were processed for light microscopy by embedding in paraffin, sectioning in 4-μg thicknesses, and staining with hematoxylin and eosin. The slides were examined for cellular infiltrates, signs of inflammation, and fibroblastic activity by an experienced histologic anatomist (J.E.), who was blinded as to the agent injected and the time until sacrifice of each animal.

Results

All 12 animals in groups C and D (lidocaine and Depo-Medrol®) had hind-limb dysfunction that lasted 1–3 h after injection. No animal in any group exhibited permanent gait impairment. One animal in group B (lactated Ringer's) died between 2 and 24 h following the procedure, presumably as a consequence of ketamine/xylazine anesthesia.

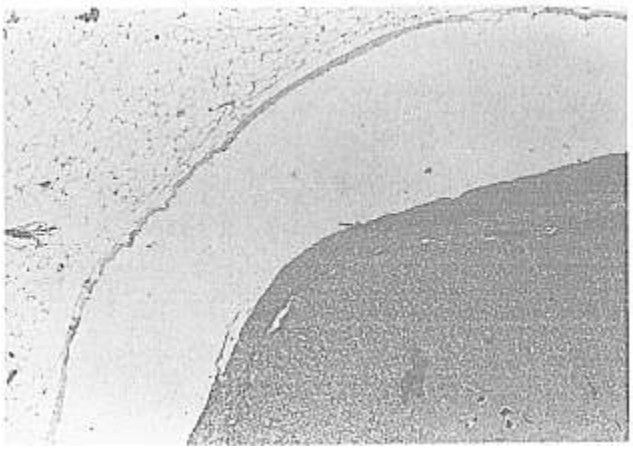

FIG. 1. Photomicrograph of meningeal membranes and spinal cord at the L5-L6 level 10 days after epidural injection of Depo-Medrol®, 0.2 mg/kg in preservative-free lidocaine 1%, 0.3 ml/kg. No white cell infiltrates are present.

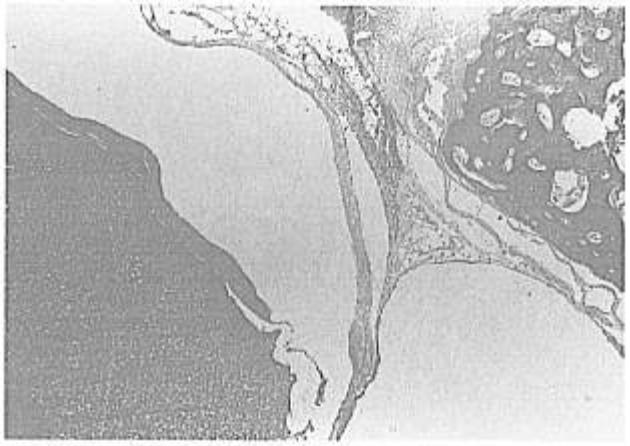

FIG. 2. Photomicrograph of meningeal membranes and spinal cord at the L5-L6 level 10 days after epidural injection of normal saline, 0.3 ml/kg containing talc, 0.1 mg/ml. A large number of tissue macrophages are present in the epidural space.

In all animals killed on day 4 (groups A, C, and E), epidural puncture sites could be identified by a small area of ecchymosis under the interspinous ligament at L6-S1. None of the animals killed on day 10 (groups B, D, and F) had visible evidence of epidural puncture. There was no hematoma formation in any animal.

In all animals that received epidural injections of either lactated Ringer's solution or lidocaine with methylprednisolone acetate, microscopic examination of specimens taken from the L5-L6 interspace revealed no white cell infiltrates and no fibroblastic activity (fig. 1). There was no thickening of the meningeal membranes or nerve roots in any animal. All animals had small areas of red cell deposits perivenously. Since only arterial exsanguination was performed, this was probably secondary to incomplete venous exsanguination.

All animals who received epidural injections of normal saline containing talc had marked infiltration of tissue macrophages in the epidural space (fig. 2). In group E (killed on postinjection day 4), an average of 74 (±23) macrophages per slide were seen in the epidural space. In group F (killed on postinjection day 10), an average of 420 (±113) macrophages per slide were seen in the epidural space. Three of the animals in this group also had smaller numbers of macrophages present in the subdural space. No polymorphonuclear cells or fibroblasts were identified. No measurable thickening of the meningeal membranes was found in any group.

Discussion

There is both laboratory and clinical evidence that the intrathecal (but not epidural) injection of corticosteroids is sometimes associated with complications secondary to neurotoxicity and inflammatory reaction.[2,3,9,10] Many clinical reports on the use of corticosteroids in both the

lumbar and cervical epidural space have emphasized the very low complication rates,[11,12,13] but there have been few laboratory studies to corroborate the clinical impression. Since most patients undergoing the procedure already demonstrate pain and other symptoms secondary to spinal pathology, it is possible that subtle inflammatory effects could be masked clinically by pre-existing symptoms.

Delany *et al.*[1] demonstrated only minimal histological findings (focal mononuclear white cell infiltration of the meningeal membranes) in cats 30 days after the epidural injection of Aristicort Intralesional® (Lederle Laboratories, Wayne, NJ) (triamcinolone diacetate 40 mg/ml with polyethylene glycol: 3%; polysorbate 80: 0.2%; and benzyl alcohol: 0.9%) and 2% lidocaine, which had resolved by 120 days. These findings also occurred in control animals and in those animals injected with 2% lidocaine alone.

Our findings of no white cell infiltrates and no meningeal thickening in animals injected with Depo-Medrol® in lidocaine indicate that there is little, if any, irritation and inflammatory reaction when this agent is injected into the epidural space. However, negative results using sample groups of this size must be interpreted cautiously because of the possibility of a Type II statistical error. Power analysis using a 95% confidence limit for a study group of this size (n = 12) shows that the possibility of the occurrence of inflammation could be as high as 27.2%.[14]

The difference between our results and those of Delany[1] may be secondary to the different corticosteroids or vehicles injected, different time of animal death, different species involved, or because we obtained sections one segment above the injection site to eliminate possible findings caused by the mechanical trauma of injection. The findings of hind-limb dysfunction in animals injected with lidocaine confirms that the injectate spread sufficiently to allow this level to be used to assess any inflammatory effects.

Recent articles in the neurologic literature[2] have argued that depot corticosteroid agents should not be used based on the well-recognized complications that have occurred following the subarachnoid injections of these agents. The complete lack of inflammatory changes and meningeal thickening demonstrated in this pilot study does help to confirm the safety of Depo-Medrol® when injected into the epidural space. The lack of changes in this series certainly does not preclude the possibility of inflammatory reaction in other species or of individual sensitivity to this agent. Further studies using other species, multiple injections, and various combinations of medications are needed to further evaluate possible toxicity of corticosteroid preparations injected into the epidural space.

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