

The Effect of Chronic Subarachnoid Bupivacaine Infusion in Dogs

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A functional and histologic examination of the effect of the continuous intrathecal administration of bupivacaine was made in five dogs. After a partial laminectomy at L5, a silicone rubber catheter was inserted into the subarachnoid space and advanced 10 cm cranially. A model 400 Infusaid pump, used for drug delivery, was placed in a subcutaneous pocket between the 13th rib and iliac crest. Drug infusions were individually adjusted and maintained at a concentration such that the animal just exhibited slight gait impairment. Daily bupivacaine doses ranged from 5.7–11.1 mg. Infusions were maintained for a period of 3–16 weeks. Light microscopic examination of spinal cord and roots revealed no abnormalities. A focal mononuclear cell infiltration of the leptomeninges was seen in two drug animals, as well as one catheter control animal. One of the 16-week animals had a residual limp upon drug removal. While we were not able to quantitatively assess the degree of sensory motor dissociation, the results of this study suggest that chronic intrathecal bupivacaine infusion through an implantable pump system may be a short-term alternative to intrathecal morphine in the control of cancer pain. (Key words: Analgesia. Anesthetics, local: bupivacaine. Injections: intrathecal. Pain: intractable.)

AMONG THE LOCAL ANESTHETICS, bupivacaine has the unique property of permitting lower extremity movements during a lumbar epidural sensory block.¹ This sensory-motor dissociation also exists for subarachnoid injections, although this was not achieved for all patients.² This raises the interesting possibility that bupivacaine might be used for chronic pain control at the spinal cord level. At present, morphine is being used intrathecally with implantable pump systems and subarachnoid catheters for patients with chronic pain due to cancer.^{3,4} While initial pain relief is excellent, clinically significant tolerance

does develop in some patients. It would be desirable if, in these cases, an alternative non-opioid drug were available.

With this in mind, chronic epidural bupivacaine was tried in cancer patients.⁵ The combination of bupivacaine with morphine did allow a reduction in the morphine dosage without muscle weakness, but continuous 0.5% bupivacaine alone did not provide relief. It may have been that the 3 ml/day of 0.5% bupivacaine given epidurally, as the authors suggest, was too low a dosage to produce analgesia.⁵ That same dosage given intrathecally, however, may be sufficient to produce pain relief. Subarachnoid administration of a local anesthetic allows a considerable reduction in dosage from that used epidurally, to produce the same analgesic effects.⁶ This is significant for an implantable pump system, since the fixed reservoir capacity requires low daily flow rates to allow a patient to go at least 2–3 weeks between refills.

The main concern with chronic intrathecal bupivacaine at concentrations of 0.5% or less is whether it will prove to be neurotoxic to the spinal cord or roots. Bupivacaine, up to 0.75%, appears to be a safe agent for spinal anesthesia during surgery.⁷ However, there is no way to be certain that it will be non-toxic during long-term continuous infusion, except to test the drug over a period of months in an animal model. This study examines the histologic and neurologic effects of chronic subarachnoid infusion of bupivacaine given for up to 16 weeks in dogs.

Methods and Materials

Eight mongrel dogs (21–28 kg) of either sex were used in this study. These experiments followed the guidelines on the care and use of animals as approved by the American Physiological Society, and was approved by the Institutional Animal Care and Use Committee. The animals were anesthetized with iv sodium pentobarbital (30 mg/kg) and maintained with supplemental doses throughout the surgery. The dog was placed on an operating table with its head slightly elevated to promote lumbar CSF accumulation. The implantation of the spinal catheter and implantable pump were performed under sterile conditions.

The 5th lumbar vertebrae was approximately located using external anatomical landmarks, and an 18 g hypodermic needle was inserted into the muscle above it. An x-ray was then taken to exactly verify the location of the

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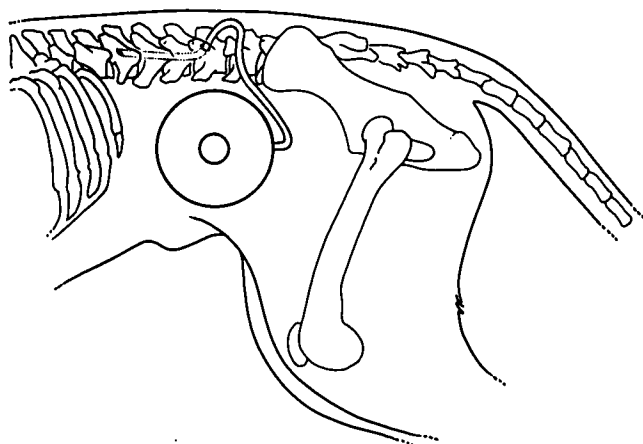


FIG. 1. Diagram of the chronic intrathecal drug delivery system. The catheter is introduced into the subarachnoid space at L5 and advanced to L2. The connected implantable pump is located subcutaneously on the side of the dog.

L5 vertebrae. Using the 18-G needle as the external reference, a 10 cm midline skin incision was made over the spinal column. The muscle overlying the vertebrae was separated by blunt dissection, and the L5 spinal process removed using a bone-cutting forceps. A 5 mm diameter hole was carefully drilled in the L5 lamina, and the epidural fat removed by suction. Using fine forceps and iris scissors, a small slit was made in the dura and arachnoid membranes. Under visual observations, a silicone rubber catheter (.025" ID, .047" OD) was inserted through the slit and advanced 10 cm cranially with the aid of a flexible internal stylet (fig. 1). Small drops of CSF were seen at the external end of the catheter within 1 min of removing the stylet. The catheter was anchored to the L5 vertebrae body, using a silicone rubber butterfly that fitted around the catheter, with cyanoacrylate adhesive.

A skin incision was made laterally between the 13th rib and the iliac crest, and a subcutaneous pocket was created on the animal's side.⁸ A sterile Infusaid Model 400 implantable pump with about 10 cm of catheter attached was inserted into the pocket and sutured to the underlying muscle.^{8,9} The spinal catheter was tunneled subcutaneously to the pump site and the spinal and pump catheters joined together with a titanium connector. The muscle layers above the spinal column were sutured back

together, and all skin incisions closed. The animals were returned to their cages and recovered uneventfully. A total of five dogs had pumps implanted exactly in this way, while a sixth dog had a spinal catheter implanted with no pump attached, to act as a "catheter control." Two other dogs without any spinal surgery were used as "unoperated controls."

The pumps were initially filled with 50 ml of 0.9% sodium chloride injection prior to implantation. The daily flow rate of all the pumps used in this study ranged between 2.5–3.8 ml/day (table 1); although, for each individual pump, the flow rate stayed within $\pm 10\%$ of its value (pre-set by the manufacturer). The flow rate was verified at each refilling (approximately every 10 days) by subtracting the residual volume from the 50 ml that was used to fill and dividing by the number of days between the refill. Access to the pump was attained by inserting a 22-G Huber point needle through the pre-scrubbed skin and into the reservoir septum, while the dog was in the standing position and lightly restrained. At 7–10 days after surgery, the pumps were emptied of their residual 0.9% sodium chloride, the flow rate was calculated, and then the pumps refilled with a solution of 0.25% bupivacaine hydrochloride injection (Marcaine, Breon Labs), an isotonic preservative-free drug solution. Bupivacaine has been shown to be stable within the Infusaid pump.¹⁰

During the weeks of drug infusion, the dogs were evaluated daily with respect to motor ability, sensory response, and overall body function. Motor ability was evaluated by observing any disturbances of locomotion while the animal was walking, including weakness, paresis, or dragging and curling of hind paws. These criteria are similar to those used by Feldman and Covino in evaluating the effect of single local anesthetic injections through implanted lumbar subarachnoid catheters.¹¹ In dogs, it has been demonstrated that local anesthetic blockage of pedal afferents has little effect on normal gait, so that any motor ataxia produced by local anesthetic is probably not an indirect effect of the sensory block.¹² An evaluation of sensory blockage was made by observing the withdrawal response to pinching the toes. The slight motor weakness of these dogs is not a factor in paw-withdrawal. As Feldman and Covino have pointed out, dogs become rapidly conditioned to such testing, and so this qualitative evaluation was only made once every 7–10 days.¹¹ The observation of overall body function consisted of monitoring patterns of urination and defecation, as well as the condition of the stool. Food intake was also monitored.

The daily bupivacaine dosage rate was set based on that amount of drug that just begins to produce disturbance of gait in the hind limbs; specifically, a slight ataxia when the animal is making right-angle turns. Although, clinically, we would not want to use this high a dose, because sensory testing in dogs is very qualitative, it is the

TABLE 1. Continuous Bupivacaine Dosages

| Dog ID | Pump Flow Rate (ml/Day) | Final Bupivacaine Concn. (%) | Final Daily Dosage (mg/Day) | Cumulative Dosage (mg) | Infusion Time (weeks) |
|--------|-------------------------|------------------------------|-----------------------------|------------------------|-----------------------|
| 3 | 3.0 | 0.37 | 11.1 | 197 | 3 |
| 4 | 2.5 | 0.37 | 9.3 | 228 | 4 |
| 8 | 2.5 | 0.37 | 9.3 | 474 | 8 |
| 16a | 2.8 | 0.37 | 10.4 | 1139 | 16 |
| 16b | 3.8 | 0.15 | 5.7 | 737 | 16 |

most reliable way to adjust dose. Because the flow rate of each pump is fixed, dosage is changed by changing the bupivacaine concentration up or down from the original 0.25%. The highest concentration actually used was 0.37%, and the lowest 0.15%. The drug solution was produced by mixing the 0.25% bupivacaine solution with 0.5% bupivacaine (isotonic, preservative-free Marcaine) or 0.9% sodium chloride injection. The final pH of these solutions was between 5.0–6.0.

The end of the initial sodium chloride infusion period was used as the baseline period for all of the evaluations during the drug infusion weeks. At the end of the bupivacaine infusion, the pumps were refilled with sodium chloride, and the animals re-evaluated 1 week later to determine if the drug-induced ataxia had resolved. The dogs were then given an overdose of sodium pentobarbital and perfused intracardially with 0.9% sodium chloride solution, followed by a two-stage aldehyde fixative.¹³ The initial solution of dilute fixative consisted of 2.0 l of 1% paraformaldehyde-1.25% glutaraldehyde in 0.8 M cacodylate buffer (pH 7.2) with 0.05% calcium chloride perfused at room temperature by gravity flow. This was followed by an equal volume of a more concentrated fixative (4% paraformaldehyde-5% glutaraldehyde). During the last stage of perfusion, an additional 5 ml of concentrated fixative was injected through the catheter into the spinal subarachnoid space. The spinal column from T9 to S1 was rapidly removed and placed in fixative. The location of the catheter tip was also verified. It was located closest to the L2 vertebrae, which, at this level, also corresponds to the L2 spinal cord. The next day, the spinal cord and roots were dissected out. The spinal cord was cut into segments and transferred to 10% buffered formalin. The L2 segment and those 8 cm rostral (T12) and 8 cm caudal (L7) were embedded in paraffin, cut into 6 μ sections, and stained with H & E. These slides were evaluated by a neuropathologist (R. Clasen), who was not involved in the study. The dorsal and ventral roots were also sampled at L2, T12, and L7. They were fixed further in the concentrated aldehyde fixative overnight at 4° C, rinsed in buffer, osmicated, dehydrated in ethanol, and embedded in Epon-Araldite. Transverse sections cut at 1 μ were stained in toluidine blue-pyronin B for section analysis. These slides were numerically coded and evaluated (J. Kerns) in a blinded-fashion.

Results

FUNCTIONAL EVALUATION

Dogs in the study received subarachnoid bupivacaine continuously for a period of 3–16 weeks. Table 1 summarizes the dosages given to the animals. The catheter control animal was maintained for the same length of time as the two 16-week animals.

Although the dosage was adjusted so that the animal was just starting to show disturbance of gait in the hind limbs, this level was difficult to maintain precisely. Usually the animals showed no ataxia early in the morning, but later in the day it became noticeable during turning around corners. Therefore, as a compromise, the animals were evaluated during the late morning. No animal showed any weakness in the forelimbs at any time during the study. No animal was ataxic during the initial sodium chloride infusion after implantation.

At the termination of bupivacaine infusion (and the resumption of sodium chloride infusion), all animals, except one, returned to fully normal gait. This one animal, 16b, still showed a slight weakness in one hind leg. The adjustment of a proper dose was especially difficult in this one dog. It was the only animal to show actual curling of the hindpaw, during later times of the day. After an initial 4 weeks at 0.25% bupivacaine, the foot drop in the right hind limb became very pronounced. The concentration was decreased to 0.20% bupivacaine for one week, but the foot drop remained. Concerned that permanent neurologic damage had already occurred in this animal, we switched dog 16b to 0.9% sodium chloride infusion. However, 2 days later, the right hind limb was completely normal. After 1 week of this saline infusion, the animal still had no neurological deficits, and was then returned to 0.15% bupivacaine infusion for 11 weeks. At 0.15%, there was a slight foot drop in the right hind limb. None of the other animals had pronounced foot drop, even at 0.37% bupivacaine.

All of the dogs showed markedly decreased response to toe-pinch of the hind limbs during bupivacaine infusion, as compared to during the initial sodium chloride infusion, and as compared to toe-pinch of the forelimbs. Upon cessation of bupivacaine infusion, all animals returned to their normal hind limb toe-pinch sensitivity.

None of the animals showed any loss of appetite during the drug infusion. There was no difficulty with urination or defecation, nor was there any abnormality in the stool.

HISTOLOGIC EVALUATION

The dorsal and ventral nerve roots of all drug animals were normal at the catheter tip, as well as above (T12 root) and below (L7 root). Figure 2 shows the L2 dorsal (A) and ventral (B) roots of animal 16a. There was no evidence of axonal degeneration, demyelination, edema, or proliferation of mononuclear (arachnoid or lymphocyte) cells. For the animal with the residual deficit, 16b, we examined all of the ventral roots along the catheter track, since there was the possibility that the catheter may have injured one of these roots. However, we were unable to find anything abnormal in these ventral root histologic sections. The catheter control dog also had normal spinal roots.

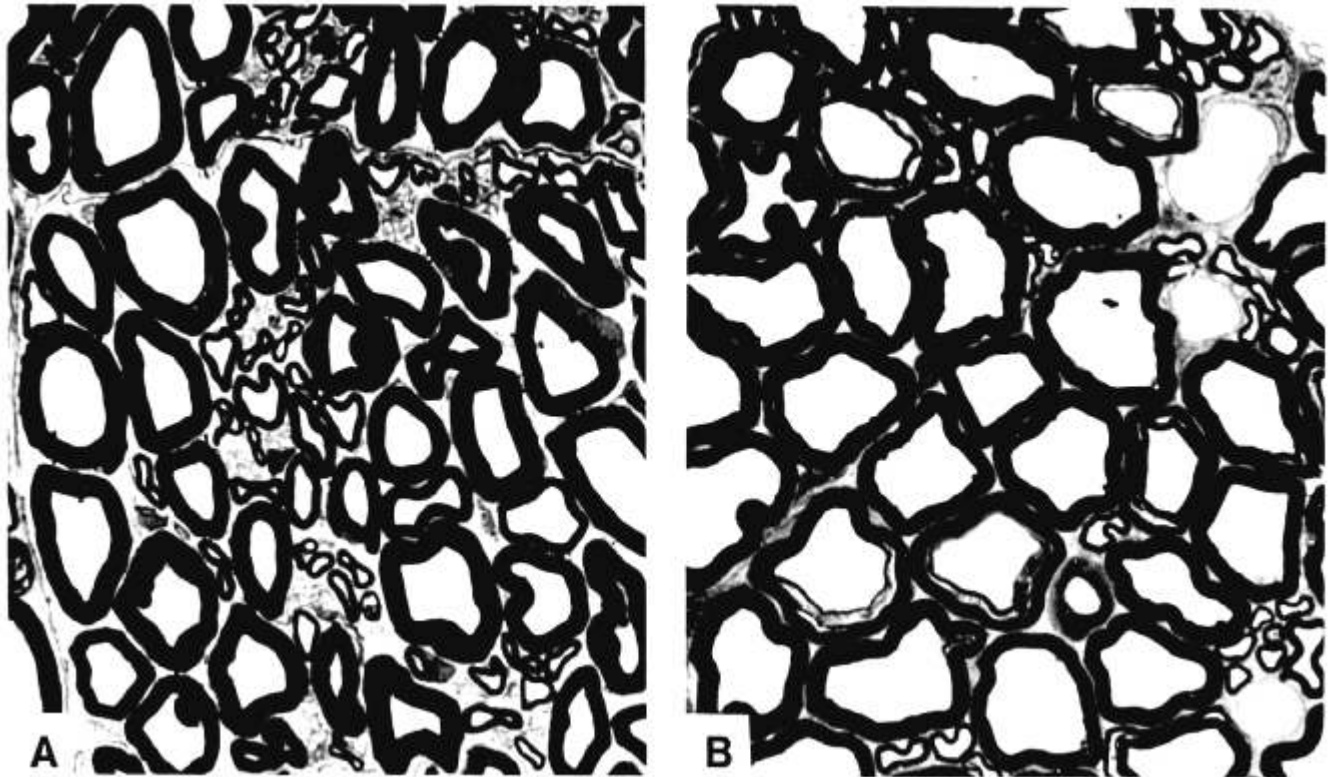


FIG. 2. The dorsal (A) and ventral (B) roots closest to the catheter tip of animal 16a. The axons and endoneurial space have a normal appearance. ($\times 1500$)

The range of normal appearance for transversely sectioned myelinated axons includes a bimodal distribution at the internode, a split myelin sheath at the paranode, and a few smaller profiles at the node of Ranvier. In addition, the dorsal roots contain a large population of non-myelinated axons (C-fibers), visible by oil immersion light microscopy. Since the light microscopic evaluation was negative, the spinal roots were not examined by electron microscopy. Occasional mononuclear cells were seen associated with blood vessels at the leptomeningeal surface of the rootlets, but this could be either a normal occurrence¹⁴ or in conjunction with the response seen in the paraffin sections of spinal cord and described below.

No abnormalities were seen by light microscopy in any of the spinal cord substance of the drug or catheter control animals. There was no cellular damage or vacuolization in the grey matter, nor any pathological changes in the white matter. There were no inflammatory cell infiltrates into the spinal cord substance.

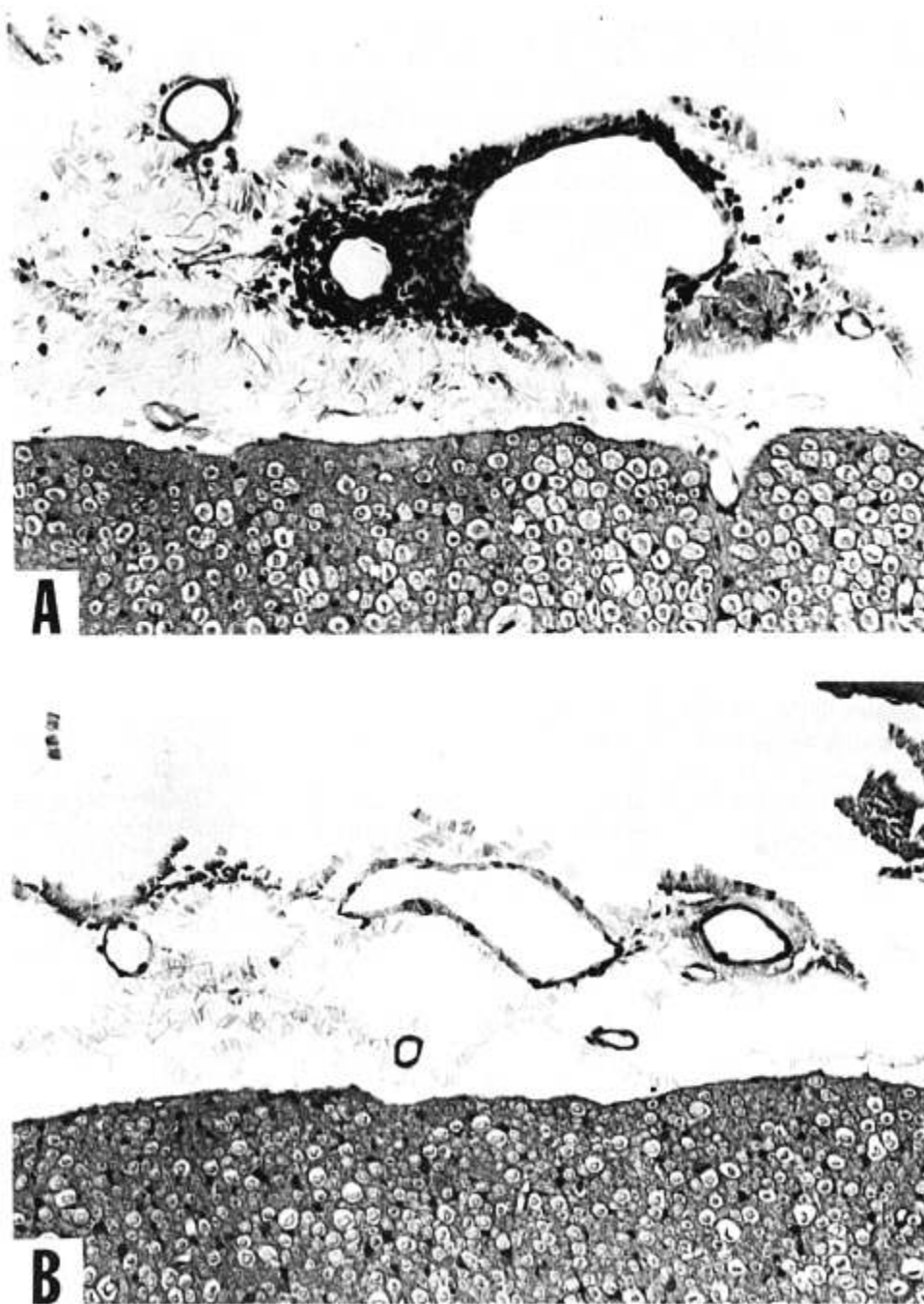
Three of the animals showed a focal infiltration of the leptomeninges by mononuclear cells. This response was most pronounced in animal 4, and ranged from levels T12-L7, but was maximal at L7. Even in this animal, most vessels were unaffected. Animal 16a had mononuclear cell infiltration of the leptomeninges, which was minimal at more cranial levels (T12). Figure 3A shows

an L2 spinal cord section from animal 16a. The catheter control animal also had a perivascular mononuclear cell infiltration, although not as extensive as the two drug animals. Three of the drug animals, 16b, 8, and 3, showed no sign of mononuclear cell infiltration (fig. 3B), nor did the two unoperated control animals.

Discussion

Local anesthetics represent a class of drugs potentially useful for the management of long-standing pain. At the spinal cord level, continuous spinal morphine has been shown to provide considerable relief to large numbers of patients with pain due to cancer, while allowing them to be alert mentally.^{4,15} However, morphine tolerance can develop to a point where even subarachnoid doses of 50 mg a day cannot control the pain. Local anesthetics of the amide type, lidocaine and bupivacaine, are very stable, and, thus, well suited for infusion over a period of weeks in implantable pump systems. Whether tolerance would also develop for the local anesthetics given chronically in humans is hard to predict; however, no increase in bupivacaine dose was needed in our study to maintain the same slight amount of ataxia in dogs. A recent study of epidural catheters in rats indicates that, when tolerance does occur, it may be due to fibrosis around the catheter.¹⁶

FIG. 3. The spinal cord section closest to the catheter tip. Focal infiltration of mononuclear cells with perivascular cuffing can be seen on the outside of the spinal cord of animal 16a (A), but there is no infiltration of the leptomeninges in animal 16b (B). Note the normal appearance of the spinal cord in both animals. ($\times 250$)



The type of pH dependent tachyphylaxis seen in dogs following successive large volume spinal lidocaine injections would not be a problem with the pump infusion where the volume flow rate is only $2 \mu\text{l}/\text{min}$.¹⁷ Also, it is not known if there is a cross-tolerance between bupivacaine and morphine that may be a problem if one is alternating between the two drugs to avoid escalating doses of either.

There were no obvious side effects in the dogs, even after 16 weeks of bupivacaine infusion. There were no

neurological problems, except for the residual weakness in the hind limb of one animal (16b). The adjustment of a proper dose was difficult in this dog, as was described in the "Results" section. The hind limb weakness may have been due to many weeks of reduced muscular activity in that leg, since this animal showed no histological abnormalities in the spinal root or cord. The noticeable ataxia in all animals receiving bupivacaine during the afternoon, compared to the apparently normal gait in the morning, may have been due to the combined effect of

marginal muscle stimulation, plus normal fatigue due to hours of mobility. Changes in spinal CSF bulk flow with activity may also have been a factor in this motor variation.

None of the animals receiving continuous bupivacaine showed any damage to the dorsal or ventral roots, nor was there any pathology within the spinal cord substance. Our study cannot rule out the possibility of more subtle ultrastructural changes; for example, to the axonal cytoskeleton and transport systems. The focal infiltration of the leptomeninges by mononuclear cells seen in some of the animals is puzzling. In the only comparable study, two dogs received repetitive intrathecal lidocaine or tetracaine at 2–7-day intervals for a period of 21–28 days.¹¹ Because they were interested in the possible neural irritation of the implanted chronic catheters, Feldman and Covino killed these animals at 30 days and examined the spinal cords.¹¹ Although no histologic abnormality was seen in the spinal cords, both animals showed a "slight inflammatory arachnoiditis." Whether the mononuclear cell infiltration of the leptomeninges seen in our study is an effect due to the catheter implantation or their extended duration in the subarachnoid space of dogs is not certain. Catheters of this size are routinely used in humans, but human CSF volume is approximately 10 times that of a dog. Table 1 does not reveal any consistent reason why dogs number 4 and 16a showed mononuclear cell infiltration, while dogs 3, 8, and 16b did not. It is possible that, if a large number of catheter-control dogs were implanted, the frequency of this mononuclear cell infiltration would be known. In our study, the only catheter control animal had some infiltration with perivascular cuffing. However, this may be a technical problem with subarachnoid catheters in dogs, since both animals in another study showed a similar effect.¹¹ The intrathecal volume infusion rate of 3 ml/day (2 μ l/min) was not tested by itself for neurotoxicity, since the CSF turnover rate in dogs is about 50 μ l/min. In addition, this same volume flow rate of 3 ml/day has been infused intraventricularly in dogs for up to 105 days without any neurotoxicity.¹⁸

The present study in dogs does not allow us to predict whether the sensory-motor dissociation seen during surgical bupivacaine usage will apply to chronic usage in humans.¹ This is important, since, clinically, we want to produce analgesia with minimal impairment in motor strength. While the bupivacaine dogs showed markedly reduced sensitivity in toe-pinch reflex withdrawal, this does not mean that, in humans, a comparable analgesia, especially to the burning type of chronic pain humans experience, will be attained at a level that doesn't impair motor ability. The primary goal of this study was to choose a reasonable bupivacaine dosage and investigate the toxicity of long-term subarachnoid administration. In our experiments, 3 ml per day of bupivacaine, up to 0.37% concentration, produced no damage to spinal cord or roots, and, therefore, can be considered for short-term,

chronic intrathecal catheter infusion with implantable pump systems, if dosages are maintained below those which produce motor block.

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