

Epinephrine Increases the Neurotoxic Potential of Intrathecally Administered Lidocaine in the Rat

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Background: Epinephrine is commonly added to lidocaine solutions to increase the duration of spinal anesthesia. Despite this common usage, the effect of epinephrine on the neurotoxic potential of this anesthetic is not known. The current experiments investigated whether adding epinephrine increases functional impairment or histologic damage induced by spinal administration of lidocaine in the rat.

Methods: Eighty rats were divided into four groups to receive an intrathecal injection of normal saline containing either 5% lidocaine, 5% lidocaine with 0.2 mg/ml of epinephrine, 0.2 mg/ml of epinephrine, or normal saline alone. Animals were assessed for persistent sensory impairment using the tail-flick test administered 4 and 7 days after infusion. Animals were then killed, and the spinal cord and nerve roots were prepared for neuropathologic evaluation.

Results: Rats given 5% lidocaine developed persistent sensory impairment and histologic damage, and the addition of epinephrine resulted in a further significant increase in injury. Sensory function in animals given epinephrine without anesthetic was similar to baseline and did not differ from saline. Histologic changes in animals treated with epinephrine alone did not differ significantly from saline controls.

Conclusions: The neurotoxicity of intrathecally administered lidocaine is increased by the addition of epinephrine. When making clinical recommendations for maximum safe intrathecal dose of this anesthetic, one may need to consider whether the solution contains epinephrine.

EPINEPHRINE is commonly added to lidocaine solutions to enhance the intensity and prolong the duration of spinal anesthesia. Despite this common practice, the effect of epinephrine on the neurotoxic potential of intrathecally administered lidocaine is not known. This information has become critically important as continued reports of neurologic deficits appear to define a narrow therapeutic index for spinal lidocaine.

Concern that neurotoxic damage can occur with clinically relevant concentrations of lidocaine began a decade ago with reports of cauda equina syndrome after continuous spinal anesthesia.¹ Reports of deficits follow-

ing repetitive injection after a failed spinal² and after subarachnoid injection of a dose intended for epidural administration³ reinforced concern that injury could occur if high doses of lidocaine are administered intrathecally. Subsequent reports documented cases in which similar deficits were associated with administration of lidocaine at doses recommended for single-injection spinal anesthesia.^{4,5} Although the mechanism of injury has yet to be established, anesthetic neurotoxicity remains the most likely etiology.⁶ If correct, the threshold for toxicity with spinal lidocaine lies close to the upper end of the clinical dose range, making it essential to understand factors that modify risk. In several cases, lidocaine was coadministered with epinephrine.^{1,3,5}

Although an association of epinephrine with clinical deficits may be readily explained on the basis of frequent usage, there are reasons to be concerned that adding epinephrine to an anesthetic solution might increase risk of neurotoxicity: (1) epinephrine produces a reduction in absorption of intrathecal lidocaine,^{7,8} effectively increasing anesthetic exposure; (2) reducing blood flow may promote ischemia, which has been postulated to be an etiologic factor in anesthetic-induced injury⁹; (3) coadministration of epinephrine is known to potentiate axonal degeneration induced by intrafascicular injection of local anesthetic¹⁰; (4) there is some suggestion that adding epinephrine increases the incidence of nerve injury after brachial plexus block¹¹; and (5) commercially available solutions of epinephrine contain bisulfite, a preservative previously associated with neurologic deficits.^{12,13} Accordingly, the present experiments sought to determine whether epinephrine potentiates functional impairment or histologic damage induced by intrathecally administered lidocaine.

Materials and Methods

The study was approved by the Committee on Animal Research of the University of California, San Francisco. All experiments were conducted on male Sprague-Dawley rats (weight, 200–250 g).

Surgical Procedure

Animals were anesthetized by intraperitoneal injection of methohexital (40–60 mg/kg), and catheters were introduced into the subarachnoid space using previously described modifications^{14,15} of the method of Yaksh and Rudy¹⁶: 32-gauge polyurethane catheters (Micor, Allison

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Park, PA) were passed through a slit in the atlanto-occipital membrane and advanced 11 cm to lie with their tip caudal to the conus medullaris. Rats were allowed to recover for 24 h before the study began.

Measurement of Sensory Function

To assess sensory function, the tail-flick test was performed at the proximal, middle, and distal portions of the tail, as previously described.^{14,15} To prevent tissue damage, the heat stimulus was terminated if no response occurred by 8 s (cutoff). Anesthesia in the perineum, hind limbs, or trunk was defined as the absence of a vocal response and withdrawal to skin clamp.

Experimental Protocol

Rats were divided into four groups to receive a 1-h intrathecal infusion (1 μ l/min) of one of four test solutions. Group L (n = 20) received 5% lidocaine in saline; group LE (n = 20) received 5% lidocaine with epinephrine (0.2 mg/ml) in saline; group E (n = 20) received epinephrine (0.2 mg/ml) in saline; and group S (n = 20) received saline.

All solutions were prepared immediately before injection. The lidocaine solutions were prepared by dissolving crystalline lidocaine hydrochloride (Sigma Chemical, St. Louis, MO) in preservative-free normal saline (Abbott Laboratories, North Chicago, IL). The epinephrine solutions were prepared by adding the appropriate volume of a 1:1000 epinephrine solution (Abbott Laboratories) to the lidocaine solution or preservative-free normal saline.

Rats were placed in a horizontal acrylic restraint, and baseline tail-flick latency was assessed immediately before infusion. Infusions were administered at a rate of 1 μ l/min for 1 h using a mechanical infusion pump. A segment of calibrated polyethylene tubing was inserted between the syringe and the intrathecal catheter, and the infusion was monitored by observing the movement of a small air bubble within the tubing. During infusion of the test solution, tail-flick latency was assessed every 10 min until the animal failed to respond to the heat stimulus. The extent of anesthesia level was determined by a skin clamp applied progressively cephalad until a response was elicited. Animals were evaluated for persistent elevation in tail-flick latency 4 and 7 days after infusion.

Tissue Preparation

Animals were killed by injection of an overdose of pentobarbital 7 days after infusion. They were perfused intracardially with a phosphate-buffered glutaraldehyde-paraformaldehyde fixative. The spinal cord and nerve roots were dissected, immersed in the same glutaraldehyde solution used for perfusion fixation, and embedded in glycol methacrylate. The embedded tissue was sectioned at 6 mm rostral and 12 mm caudal to the conus

Table 1. Nerve Injury Scoring System

| Score | Category | Description |
|-------|----------|-------------------------------------------------------------------|
| 0 | Normal | No edema; no injured nerve fibers |
| 1 | Mild | Edema; little or no nerve fiber degeneration or demyelination |
| 2 | Moderate | Less than 50% of nerve fibers with degeneration and demyelination |
| 3 | Severe | More than 50% of nerve fibers with degeneration and demyelination |

medullaris, using a JB-4 microtome (1- μ m transverse sections; Energy Beam Sciences, Agawam, MA). The tissue was treated with 4% osmium tetroxide and stained with toluidine blue. Histopathologic evaluation was performed using light microscopy by a neuropathologist blinded to the intrathecal solution received and to the results of sensory testing.

Data Analysis

Functional Assessment. Tail-flick latencies at the proximal, middle, and distal portions of the tail were averaged to give a mean tail-flick latency. The extent of anesthesia during infusions was scored on a scale of 1–5, where 1 = tail, 2 = perineum, 3 = hind limb, 4 = lower trunk, and 5 = upper trunk. To assess the effect of drugs infused on sensory function, average tail-flick latencies were converted to percent maximal possible effect, calculated as [(tail-flick latency – baseline)/(cutoff – baseline)] \times 100.

Histologic Analysis. Specimens obtained 6 mm rostral to the conus were used for qualitative examination of the spinal cord. Specimens obtained 12 mm caudal to the conus were used for quantitative analysis of nerve injury. There were approximately 25 fascicles per cross-section, and each was assigned an injury score of 0–3, where 0 = normal, 1 = mild, 2 = moderate, and 3 = severe (table 1). The injury score for each animal was then calculated as the average score of all fascicles present in the cross-section.

Statistics. To ensure that the four groups were equivalent before administration of the test solutions, baseline tail-flick latencies were compared using one-way analysis of variance. To assess the effect of infusion, baseline latencies for the control (saline) group were compared with their respective values obtained 4 and 7 days after infusion using repeated-measures analysis of variance. To determine the effect of the test solutions, the percent maximal effect data for tail flick for all groups were compared using a two-way analysis of variance with repeated measures over time (day 4 and day 7), with comparisons of all pairs performed with the Tukey Kramer test. The effect of epinephrine on block height was tested by ordinal logistic regression. Nerve injury severity for lidocaine *versus* lidocaine with epinephrine, lidocaine *versus* saline, and epinephrine *versus* saline was evaluated using the Mann-Whitney U test with

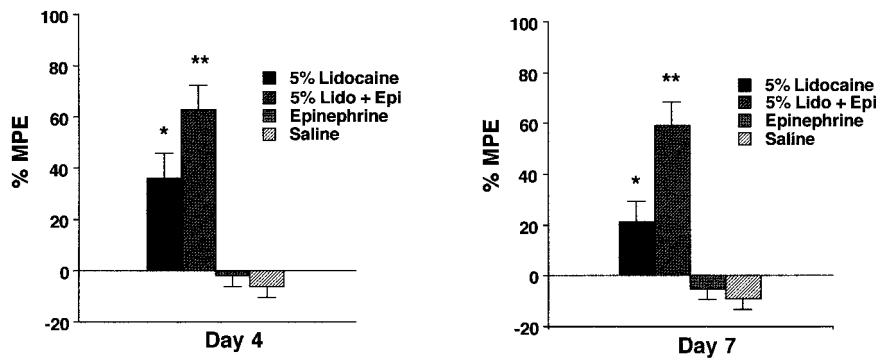


Fig. 1. Sensory function 4 and 7 days after intrathecal administration of 5% lidocaine, 5% lidocaine with epinephrine (0.2 mg/ml; Lido + Epi), epinephrine (0.2 mg/ml), or saline. Tail-flick latency values were calculated as the average of latencies for the proximal, middle, and distal portions of the tail and are expressed as percent maximum possible effect (MPE): $[(\text{tail-flick latency} - \text{baseline}) / (\text{cutoff} - \text{baseline})] \times 100$. Data represent mean \pm SD. * $P < 0.05$ versus epinephrine or saline. ** $P < 0.05$ versus all other groups.

Dunn correction for multiple comparisons. Analyses were performed with GB-Stat (Dynamic Microsystems, Silver Spring, MD). For all comparisons, $P < 0.05$ was considered significant.

Results

One animal given 5% lidocaine (group L) failed to develop perineal anesthesia during infusion and was excluded from data analysis. At necropsy, this catheter was noted to be extradural. During infusion, the level of sensory block ranged from the perineum to the upper trunk and was significantly higher in animals given lidocaine with epinephrine than in those given lidocaine alone.

Neurologic Function

There was no significant difference in baseline tail-flick latencies for the four groups. Assessment of sensory function on days 4 and 7 in saline-treated animals were similar to baseline. Tail-flick latencies (percent maximal effect) in animals treated with lidocaine and lidocaine plus epinephrine differed significantly from latencies in epinephrine- and saline-treated animals (fig. 1). The tail-flick latencies for animals given lidocaine with epinephrine were significantly greater than the latencies of animals receiving lidocaine alone. Sensory function in epinephrine- and saline-treated animals did not differ.

Histopathologic Findings

Sections obtained from animals treated with lidocaine, lidocaine with epinephrine, and epinephrine demonstrated moderate to severe injury in 32, 46, and 3% of fascicles, respectively. Those obtained from saline-treated animals revealed moderate injury in less than 0.5% of fascicles and no severe injury. The nerve injury scores for lidocaine with epinephrine were significantly greater than for lidocaine alone, and both differed significantly from saline or epinephrine. However, there was no significant difference between epinephrine and saline (fig. 2).

Qualitative light microscopic examination revealed focal damage of spinal posterior column in four animals in

group L and one animal in group LE; however, there was no apparent spinal cord injury in the remaining animals, nor in any of the those in the epinephrine- or saline-treated groups.

Discussion

The current experiments demonstrated that adding epinephrine significantly increases sensory impairment and morphologic damage induced by intrathecal lidocaine. However, although epinephrine affected lidocaine-induced injury, we found no significant functional or morphologic effect of epinephrine administered in the absence of anesthetic. The latter finding is consistent with previous results in the literature¹⁷ but must be interpreted cautiously. First, animals might have had minor functional impairment that went undetected by observation and limited sensory testing. Second, the incidence of moderate to severe fascicle injury with epinephrine was slightly higher than with saline. It is there-

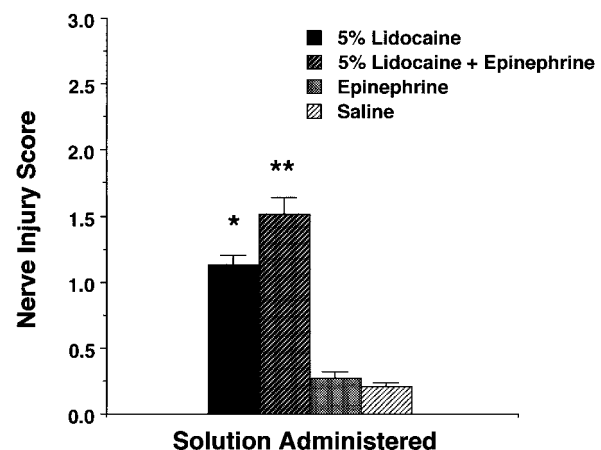


Fig. 2. Nerve injury score for sections obtained 12 mm caudal to the conus medullaris 7 days after an intrathecal infusion of 5% lidocaine in saline, 5% lidocaine with epinephrine, epinephrine, or normal saline. Nerve injury scores were based on all fascicles present in each cross-section. Each fascicle was assigned an injury score of 0–3, where 0 = normal, 1 = mild, 2 = moderate, and 3 = severe. The injury score for each cross-section was calculated as the average score of all fascicles in the section. Data reflect the mean \pm SD. * $P < 0.05$ versus epinephrine or saline. ** $P < 0.05$ versus all other groups.

fore possible that failure to detect a significant difference reflects lack of statistical power. Finally, morphologic changes were assessed only by light microscopic examination, and epinephrine might have an effect detectable by more sensitive methods. However, the clinical significance of such findings, if present, would be insignificant compared with the major sensory deficits and histologic damage produced by lidocaine and the profound potentiation of injury by the addition of epinephrine.

Four of the animals in the lidocaine group had focal damage in the posterior column compared with one animal in the group that received lidocaine with epinephrine, an observation inconsistent with the functional and quantitative histologic data. However, this difference was not statistically significant and may reflect the limited examination of the spinal cord, which was confined to a single evaluation at one level.

That epinephrine alone had no demonstrable effect may provide insight into the mechanism of its potentiation. Although such findings do not exclude epinephrine impacting directly on neural tissue, they are more consistent with an indirect effect perhaps mediated by epinephrine-induced vasoconstriction. Specifically, whereas vasoconstriction *per se* might be well tolerated, a reduction in blood flow could delay absorption of lidocaine, increasing anesthetic exposure and hence toxicity. Although controversy exists, the available laboratory and clinical data provide some support for this concept. Experimentally, subarachnoid epinephrine has been shown to produce regional dural vasoconstriction¹⁸ while not affecting spinal cord blood flow.^{8,18} However, when administered with lidocaine, epinephrine attenuates both spinal cord and dural hyperemia induced by subarachnoid anesthetic.¹⁹ Epinephrine has also been shown to prolong spinal block in dogs²⁰ and primates,²¹ although this may result, in part, from an antinociceptive effect derived from the α -adrenergic agonism of epinephrine.²² The impact of epinephrine on lidocaine uptake has been inconsistent, as some laboratory studies report significant reductions by epinephrine⁹ while others do not.^{20,21} Perhaps most pertinent, data from clinical investigations demonstrate the expected reduction in peak plasma lidocaine concentrations⁷ as well as a delay in recovery from spinal anesthesia.^{7,23-26}

Surprisingly, in contrast to these data and despite its clinical use to prolong sensory block, some studies have not found epinephrine to extend the duration of a lidocaine spinal anesthetic.^{27,28} Two factors appear to account for these conflicting results. First, there is wide interpatient variability, which would promote a type II error, a concept supported by data from a crossover study in volunteers.²⁵ Second, prolongation by epinephrine tends to preferentially occur at the lower segments of the neuraxis, and some studies have focused attention on thoracic dermatomes. For example, Spivey²⁸ reported negative results but only examined the effect of epinephrine on two-segment regression. Although a

study by Chambers *et al.*²⁷ is often quoted for its negative findings, this interpretation is based on their data for two- and four-segment regression and duration of T12 sensory block. However, in the same study, Chambers *et al.* reported statistically significant differences with respect to complete resolution of sensory impairment and recovery of motor function. In fact, the investigators never concluded that epinephrine lacked effect, but rather that there was no "clinically useful prolongation of spinal anesthesia." This circumstance contrasts sharply with enhancement of lidocaine neurotoxicity, where the effect of epinephrine would be greatest for those neural elements most susceptible to injury.

Recommendations regarding the amount of epinephrine to be used for spinal anesthesia generally vary between 0.2 and 0.5 mg (0.2–0.5 ml of 1:1000 epinephrine).²⁹ However, although there are no data regarding practice patterns, it is likely that the majority of clinicians use a dose between 0.2 and 0.3 mg with lidocaine administered as a 2.5% solution. Thus, when expressed as a concentration, the epinephrine administered in the current studies (0.2 mg/ml) likely exceeds that used by most clinicians. This difference might potentially impact the ability to extrapolate from the present data. However, it is the subarachnoid concentration that determines effect, and the subarachnoid concentration of epinephrine relative to that of lidocaine after injection is determined exclusively by the ratio of their respective doses in the administered solution. When considered on this basis, the amount of epinephrine used in the present studies (0.2 mg/50 mg lidocaine) is at the low to mid region of the clinical dose range. Moreover, the available data suggest that higher doses of epinephrine are needed with lidocaine to provide a clinically useful effect for most surgical procedures. For example, the most recent study examining the effect of epinephrine on duration of lidocaine spinal anesthesia compared 0.2, 0.4, and 0.6 mg, and only the 0.6-mg dose prolonged the time to two-segment regression.²⁴ As previously noted, this finding is consistent with those in the literature demonstrating that lower doses of epinephrine are only effective at prolonging lidocaine spinal anesthesia at more caudal segments.^{25,27,28}

Although adequate data concerning nerve blood flow of the cauda equina are lacking, the results of the current study suggest that ischemia is unlikely to play an important role with respect to epinephrine's enhancement of lidocaine neurotoxicity. However, these results may not be applicable to peripherally injected anesthetic.^{10,11} In contrast to spinal administration, epinephrine and lidocaine both reduce peripheral-nerve blood flow, and the combination appears to be synergistic.³⁰ It therefore remains to be determined whether such reduction is sufficient to induce ischemic injury or to contribute to anesthetic neurotoxicity.

The current studies used a commercially available so-

lution of epinephrine containing the preservative sodium bisulfite. This was chosen to model anesthetic practice and thereby assess the clinical impact of using epinephrine with lidocaine for spinal anesthesia. Furthermore, it would have been difficult to conduct these experiments without an antioxidant because epinephrine is unstable in solution, undergoing rapid decomposition to adrenochrome. Nonetheless, we cannot rule out the possibility that potentiation of injury was caused by bisulfite, a preservative previously implicated in neurologic injury^{12,13} and with documented toxicity in some experimental models.³¹⁻³³ However, despite these concerns, we believe it is unlikely that bisulfite contributed to recent deficits with spinal anesthesia or to the enhanced toxicity we observed. First, previous clinical deficits were associated with possible intrathecal administration of intended epidural doses of chloroprocaine.^{12,13} In addition to the much larger volume injected, the anesthetic solution contained 0.2% sodium bisulfite, which was not diluted before administration. In contrast, when epinephrine is used with lidocaine for spinal anesthesia, the final concentration of bisulfite is substantially lower because the epinephrine is added to a larger volume of (preservative-free) anesthetic. Second, the concentration of bisulfite used in earlier toxicity studies were generally an order of magnitude greater than we administered and, despite these high concentrations, evidence for bisulfite toxicity was inconclusive.^{34,35} Third, autopsy examinations after long-term intrathecal infusion of bisulfite-containing solutions for cancer pain fail to reveal neuropathologic findings suggestive of toxicity.^{36,37} Finally, we found no significant functional or morphologic effect of the epinephrine solution alone. Again, this does not eliminate the possibility that bisulfite potentiates lidocaine-induced damage, but it does make it far less likely.

The present findings perhaps shed some light on the etiology and significance of transient neurologic symptoms after spinal anesthesia. After a 1993 report of four patients with pain, dysesthesia, or both after spinal anesthesia with lidocaine,³⁸ numerous case reports³⁹⁻⁴² and clinical studies⁴³⁻⁴⁹ documented that these symptoms commonly follow lidocaine spinal anesthesia but are relatively rare with other anesthetics. There has been speculation and considerable concern that transient neurologic symptoms and neurologic deficits after spinal anesthesia represent opposite points on a single spectrum of toxicity. However, in contrast to the enhancement of injury we observed, data from a clinical trial⁴⁷ and a large-scale epidemiologic study⁴⁹ indicate that epinephrine has no effect on the incidence of transient neurologic symptoms after lidocaine spinal anesthesia. This discrepancy between our results and the clinical data argues against a common mechanism. At a minimum, the inconsistency indicates that the presence of transient neurologic symptoms is not an appropriate

surrogate marker for major toxicity and, conversely, raises doubt that transient neurologic symptoms can be effectively investigated using existing animal models of neurotoxicity.

In conclusion, our results suggest that the neurotoxicity of intrathecal lidocaine is enhanced by the coadministration of epinephrine. The mechanism of this enhanced toxicity remains to be established, but it is perhaps related to an effect of vasoconstriction on anesthetic exposure. Although extrapolation to clinical practice must be made with caution, recommendations for maximum safe intrathecal dose of lidocaine may need to consider whether the solution contains a vasoconstrictor. However, considering the already narrow therapeutic index of spinal lidocaine and the existence of viable alternatives to lidocaine with epinephrine (e.g., bupivacaine), the present findings call further into question the practice of using a vasoconstrictor to prolong lidocaine spinal anesthesia.

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