

Comparative Spinal Neurotoxicity of Prilocaine and Lidocaine

Tomomune Kishimoto, M.D.,* Andrew W. Bollen, D.V.M., M.D.,† Kenneth Drasner, M.D.‡

Background: Reports of major and minor sequelae following lidocaine spinal anesthesia have generated interest in an alternative short-acting intrathecal agent. Of the available anesthetics suitable for short-duration spinal anesthesia, prilocaine is perhaps the most promising agent. However, data comparing the neurotoxicity of these agents are lacking. Accordingly, the present experiments investigate whether prilocaine and lidocaine differ with respect to sensory impairment and histologic damage when administered intrathecally in the rat.

Methods: Ninety rats were divided into three groups to receive an intrathecal infusion of 2.5% prilocaine in saline, 2.5% lidocaine in saline, or normal saline. The animals were assessed for persistent sensory impairment 4 days after anesthetic administration using the tail-flick test. Three days later, the animals were killed, and specimens of the spinal cord and nerve roots were obtained for histopathologic examination.

Results: Prilocaine and lidocaine produced equivalent elevations in tail-flick latency that differed significantly from saline. Histologic injury scores with prilocaine were greater than with lidocaine, but this difference did not reach statistical significance.

Conclusions: The propensity for persistent functional impairment or morphologic damage with intrathecal prilocaine is at least as great as with lidocaine. Although the substitution of prilocaine for lidocaine may reduce the incidence of transient neurologic symptoms, it is unlikely to reduce the risk of actual neural injury. This discrepancy may indicate that transient neurologic symptoms and neurologic deficits after spinal anesthesia are not mediated by the same mechanism.

RECENT reports of permanent neurologic injury have generated concern about the potential neurotoxicity of lidocaine.¹⁻⁵ Adding to this concern has been the recognition that transient neurologic symptoms (TNS), *i.e.*, pain and dysesthesia in the buttocks and lower extremities, commonly follow intrathecal administration of this anesthetic agent.⁶⁻⁹ Although the etiology and significance of these transient symptoms is unknown, and a relation to permanent neurologic injuries such as cauda equina syndrome remains highly speculative, their oc-

currence has reinforced dissatisfaction with intrathecal lidocaine. As a result, many clinicians have abandoned the use of this anesthetic agent for spinal anesthesia. Most have substituted bupivacaine for longer procedures, a reasoned judgment based on its extensive clinical use, its dramatically lower incidence of TNS,⁷⁻¹¹ experimental data indicating less toxicity,^{5,12} and the suggestion of a lower risk of clinical injury.¹³ Moreover, lidocaine is often combined with epinephrine for longer procedures, and recent data from our laboratory indicate that epinephrine potentiates lidocaine-induced sensory impairment.¹⁴

Unfortunately, the selection of a spinal anesthetic agent for shorter surgical procedures is more difficult. Although there are reports of the use of low-dose bupivacaine combined with fentanyl,¹⁵ many practitioners have found the failure rate to be appreciable, particularly for more rostral procedures. Of the other alternatives for short-duration spinal anesthesia, prilocaine is perhaps the most promising agent. Although not approved for intrathecal administration in the United States, prilocaine has had limited use abroad for spinal anesthesia for more than 30 yr.¹⁶ It has a duration of action similar to that of lidocaine¹¹, and recent clinical data suggest that the incidence of TNS with prilocaine is lower than with lidocaine.^{11,17,18} However, data comparing these anesthetic agents with respect to their potential to induce neurologic injury are lacking. Although we are not aware of case reports of neural injury with prilocaine, their absence provides little information, particularly with the limited use of the drug as a spinal anesthetic. Data from large-scale epidemiologic studies would be needed to address this question clinically, but such investigations require many years and thousands of patients. Accordingly, the present experiments investigate whether prilocaine and lidocaine differ with respect to sensory impairment and histologic damage when administered intrathecally in the rat.

Materials and Methods

This study was approved by the Committee on Animal Research of the University of California, San Francisco, California. All experiments were conducted on male Sprague-Dawley rats approximately 7 to 8 weeks of age (weight, 200-250 g).

Surgical Procedure

The animals were anesthetized by intraperitoneal injection of methohexital (40-60 mg/kg), and catheters

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* Research Fellow, † Professor of Pathology, ‡ Professor of Anesthesia.

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Address reprint requests to Dr. Drasner: Department of Anesthesia and Perioperative Care, San Francisco General Hospital, Room 3C-38, San Francisco, California 94110. Address electronic mail to: kdrasner@anesthesia.ucsf.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

were introduced into the subarachnoid space using modifications of the method of Yaksh and Rudy,¹⁹ as previously described^{5,20}: 32-gauge polyurethane catheters (Micor, Allison Park, PA) were passed through a slit in the atlanto-occipital membrane and were advanced 11 cm to lie with the tip caudal to the conus medullaris. The 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 applied at the proximal, mid, and distal portions of the tail, as previously described.^{5,19} Briefly, the test was performed by placing the tail over a slit through which a beam of light from a projection lamp was focused, with latency to movement as the measured end point. Baseline tail flick was assessed using three determinations, one each at the proximal, mid, and distal portions of the tail. To prevent tissue damage, the heat stimulus was terminated if no response occurred by 8 s (cutoff).

Experimental Protocol

Ninety rats were divided into three groups to receive one of three test solutions. Group P (n = 30) received 2.5% prilocaïne in saline, group L (n = 30) received 2.5% lidocaine in saline, and group S (n = 30) received saline. The number of animals studied was based on a power analysis using the variability observed in prior experiments and the ability to detect a 20% difference with β set at 0.2 and α set at 0.05.

All solutions were prepared immediately before injection. The anesthetic solutions were prepared by dissolving crystalline prilocaïne hydrochloride or lidocaine hydrochloride (Sigma Chemical, St. Louis, MO) in preservative-free normal saline (Abbott Laboratories, North Chicago, IL). The measured pH of the prilocaïne, lidocaine, and saline solutions were 4.7, 4.5, and 4.9, respectively.

The 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 using a mechanical infusion pump, a rate that generally produces a block to the perineum or hind limbs. In contrast to most of our prior published studies, lidocaine was administered as a 2.5% solution rather than as a 5% solution and was infused for 2 h rather than for 1 h. We have previously observed that functional impairment and histologic damage is primarily dependent on the total dose administered rather than on the concentration. Thus, to facilitate comparison with our prior publications, we used a longer infusion to compensate for the lower anesthetic concentration.

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. The animals

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 |

were evaluated for sensory impairment by determining tail-flick latency 4 days after infusion.

Tissue Preparation

The animals were killed by injection of an overdose of pentobarbital 7 days after infusion. They underwent perfusion intracardially with a phosphate-buffered glutaraldehyde-paraformaldehyde fixative. The spinal cord and nerve roots were removed, immersed in the same glutaraldehyde solution used for perfusion fixation, and embedded in glycol methacrylate. The embedded tissue was sectioned 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.

Statistical Analysis

Functional Assessment. Tail-flick latencies at the proximal, mid, and distal portions of the tail were averaged to give a mean tail-flick latency. To ensure that the three groups were equivalent prior to administration of the test solutions, raw baseline latencies were compared using one-way analysis of variance. To assess sensory function 4 days postinfusion, tail-flick latencies were converted to percent maximal possible effect, calculated as $([\text{tail-flick latency} - \text{baseline}]/[\text{cutoff} - \text{baseline}]) \times 100$. These data were compared using one-way analysis of variance and the Student-Newman-Keuls test.

Histologic Analysis

Quantitative analysis of nerve injury was determined by examination of one cross-section per animal obtained 12 mm caudal to the conus medullaris. 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 this cross-section. The data for the three groups were compared using the Kruskal-Wallis and Dunn tests. Analyses were performed with GB-STAT (Dynamic Microsystems, Silver Spring, MD). For all comparisons, $P < 0.05$ was considered significant.

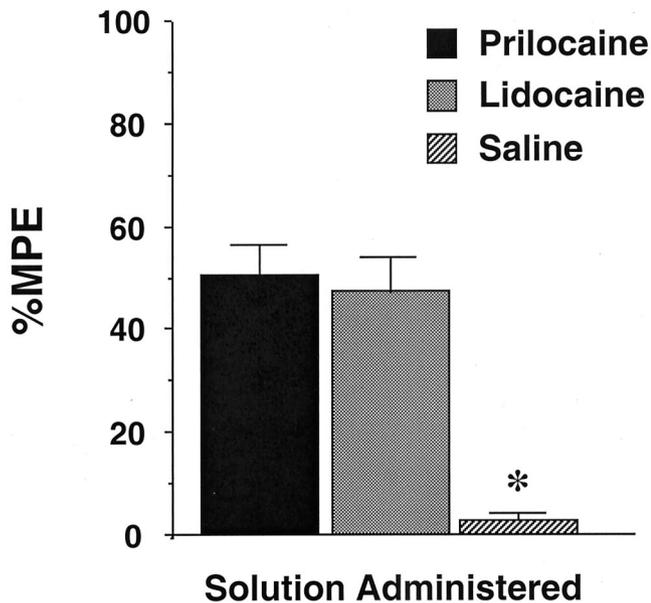


Fig. 1. Sensory function 4 days after intrathecal administration of 2.5% prilocaine (n = 30), 2.5% lidocaine (n = 28), or saline (n = 30). Tail-flick latency values were calculated as the average of latencies for the proximal, mid, and distal portions of the tail and are expressed as percent maximum possible effect (%MPE), where %MPE = [(tail-flick latency - baseline)/(cutoff - baseline)] × 100. Data represent mean ± SEM. *P < 0.05 versus the other groups.

Results

Two animals in the lidocaine group were excluded from study. In one case, bleeding occurred within the catheter. In the second case, the animal failed to develop anesthesia during infusion, and at necropsy the catheter was noted to have advanced out of a nerve root.

Neurologic Function

There was no significant difference in baseline tail flick for the three groups (mean latencies ± SEM were 2.21 ± 0.02, 2.21 ± 0.03, and 2.19 ± 0.03 for prilocaine, lidocaine, and saline, respectively). When assessed 4 days postinfusion, tail-flick latencies (percent maximal possible effect) in prilocaine- and lidocaine-treated animals were similar, and both differed significantly from latencies in saline-treated animals (fig. 1).

Histopathologic Findings

Sections obtained from prilocaine-, lidocaine-, and saline-treated animals demonstrated moderate to severe injury in 42, 33, and 1%, respectively. The nerve injury scores for prilocaine exceeded those for lidocaine, but this difference did not reach statistical significance (fig. 2).

Discussion

The present data indicate that prilocaine and lidocaine induce comparable functional impairment and morphologic damage when administered intrathecally in the rat. Considering their equivalent potency,¹¹ these data sug-

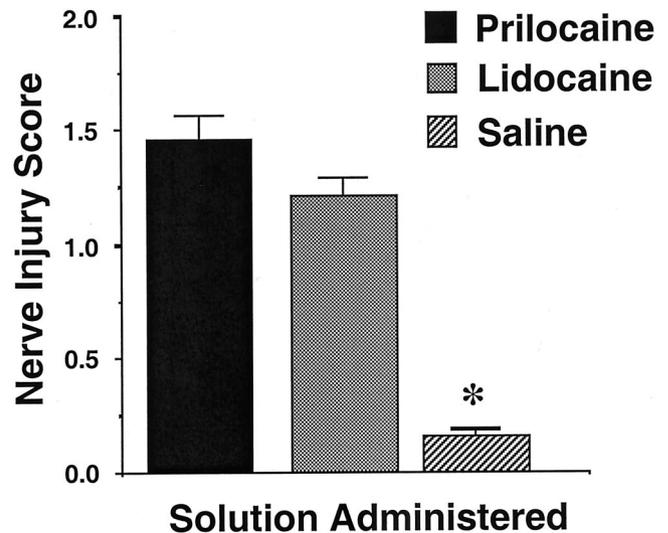


Fig. 2. Nerve injury scores for sections obtained 7 days after intrathecal administration of 2.5% prilocaine (n = 30), 2.5% lidocaine (n = 28), or saline (n = 30). Nerve injury scores for each animal were based on all fascicles present in a cross-section 12 mm caudal to the conus medullaris. Each fascicle was assigned an injury score of 0–3, where 0 = normal, 1 = mild, 2 = moderate, and 3 = severe. The injury score for the animal was then calculated as the average score of all fascicles in the section. Data represent mean ± SEM. *P < 0.05 versus the other groups.

gest that prilocaine and lidocaine have comparable therapeutic indices with respect to neurologic injury. Although caution must be exercised when extrapolating from laboratory data to clinical practice, substitution of prilocaine for lidocaine is thus unlikely to be an effective strategy to reduce the risk of permanent neurologic deficits.

In contrast to the routine clinical practice of single-injection spinal anesthesia, an infusion pump was used in the present experiments to deliver anesthetics through indwelling catheters. This method of administration was chosen for several reasons. First, administration by infusion rather than by bolus injection produces far more consistent anesthetic distribution, reducing the variability in anesthetic exposure. Second, use of an infusion limits rostral spread, minimizing or eliminating possible confounding hemodynamic or respiratory effects of spinal anesthesia. Third, and most critical, the preferential sacral block (or “maldistribution”) results in relatively high anesthetic concentrations within the subarachnoid space, essentially unmasking the inherent toxicity of these anesthetic agents (as occurred in clinical cases of cauda equina syndrome). By intentionally modeling the clinical circumstances under which neurologic injury is likely to occur, we are able to compare the potential neurotoxicity of anesthetics that have relatively low, but very important, toxicity in humans. In contrast, were we to model routine spinal anesthesia, the incidence of injury would be extremely low (as in clinical practice) and would require thousands of animals to detect differences in neurotoxicity among these agents.

Nerve injury scores were slightly higher with prilocaine, but this difference failed to reach statistical significance. It is possible that this failure to identify a significant difference represents a type II error. However, the number of animals studied was determined by power analysis based on the variability observed in prior experiments and the ability to detect a 20% difference with β set at 0.2 and α set at 0.05. Thus, if there is a true difference between these agents, the effect size should be relatively small. More importantly, this difference would only serve to reinforce the principle conclusion of this study—substitution of prilocaine for lidocaine is not likely to decrease the risk of clinical injury.

The present findings may provide insight into the etiology and significance of TNS. There is currently substantial concern that clinical deficits such as cauda equina syndrome and episodes of pain and/or dysesthesia following intrathecal lidocaine administration represent different points on a single spectrum of toxicity. However, in contrast to the present findings, spinal administration of prilocaine appears to have a relatively low incidence of TNS.^{11,17,18} In a review of over 5,000 episodes of spinal anesthesia induced with prilocaine, Konig and Ruzicic¹⁷ did not uncover any patients with TNS. However, data collection was retrospective, and, as the authors note, failure to detect cases of TNS could reflect inadequate patient assessment. In addition, the incidence of TNS with prilocaine was not compared to that of lidocaine, which is problematic, as the reported incidence is highly variable. In an effort to overcome these limitations and to confirm these findings, Hampl *et al.*¹¹ performed a prospective, randomized, double-blind study of women undergoing short gynecologic procedures in the lithotomy position, a population at high risk for TNS. Ninety patients were randomly allocated to receive 2.5 ml hyperbaric prilocaine, 2%; lidocaine, 2%; or bupivacaine, 0.5%. Times to ambulate and to void with prilocaine were similar to those with lidocaine, but the incidence of TNS differed significantly, occurring in 9 of the 30 patients receiving lidocaine but in only one patient receiving prilocaine. In a more recent double-blind study by de Weert *et al.*,¹⁸ 7 of 35 patients receiving 4 ml isobaric lidocaine, 2%, had TNS, whereas no patient receiving a similar dose and concentration of prilocaine had such complaints. Although far more data are required to draw firm conclusions regarding the incidence of TNS with prilocaine, the discrepancy between these clinical reports and the present experimental data increases the uncertainty regarding a common mechanism. In addition, in previous experiments we have demonstrated marked potentiation of lidocaine neurotoxicity by epinephrine,¹⁴ but considerable clinical data^{8,9} indicate that this adjuvant does not alter the incidence of TNS following lidocaine spinal anesthesia. Although such comparisons between laboratory and clinical data have important limitations, it should be

appreciated that there is currently no animal model of TNS, and experimental studies of clinical neurotoxicity are obviously unethical.

In summary, the present experiments demonstrate that intrathecal prilocaine and lidocaine produce similar functional impairment and morphologic damage. Substitution of prilocaine for lidocaine is therefore unlikely to reduce the risk of persistent or permanent neurologic injury. In addition, the present findings of equivalent neurologic injury with prilocaine and lidocaine are inconsistent with the available clinical data that suggest a lower incidence of TNS with prilocaine. This discrepancy may indicate that neurologic injury (*e.g.*, cauda equina syndrome) and TNS are not mediated by the same mechanism.

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