

Persistent Sacral Sensory Deficit Induced by Intrathecal Local Anesthetic Infusion in the Rat

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Background: Several cases of cauda equina syndrome after continuous spinal anesthesia have been recently reported. One possible etiology is toxic exposure of the sacral roots resulting from intrathecal maldistribution of a relatively large dose of local anesthetic. The current experiments sought to determine whether a local anesthetic solution, injected intrathecally to produce a restricted distribution of anesthesia, could result in a sacral deficit. In addition, we sought to test the hypothesis that, when equal volumes are administered intrathecally, significant differences exist in the potential of three commonly used anesthetic solutions to induce sensory impairment.

Methods: Thirty-two rats were implanted with intrathecal catheters to permit repetitive infusion of local anesthetic. Animals were randomly assigned to four groups of eight to receive either 5% lidocaine with 7.5% dextrose; 0.75% bupivacaine with 8.25% dextrose; 0.5% tetracaine with 5% dextrose; or normal saline. Each rat received, in sequence, a 1-h (60 μ l), a 2-h (120 μ l), and a 4-h (240 μ l) infusion; the infusions were separated by a 4-day rest period. Sensory function was assessed using the tail-flick test, which was performed immediately before each infusion and 6 days after the last infusion by an investigator blinded to the solution infused.

Results: There was no significant difference in baseline tail-flick latencies for the four groups. Tail-flick latency for the lidocaine group was significantly prolonged when compared with the bupivacaine, tetracaine, and saline groups. This difference was apparent after the first infusion and persisted throughout the study.

Conclusions: In the rat, restricted anesthetic distribution can be achieved, and sensory impairment may result. These findings further support an etiology of local anesthetic neurotoxicity for recent clinical injuries after continuous spinal anesthesia. The functional model described appears to be suitable for *in vivo* study of local anesthetic neurotoxicity. (Key words: Anesthetic techniques, spinal: continuous. Anesthetics, local: bupivacaine; lidocaine; tetracaine. Complications, neurologic: cauda equina syndrome.)

CAUDA equina syndrome results from injury to the sacral nerve roots and is thus characterized by varying degrees of bladder and bowel dysfunction, perineal sensory loss, and lower extremity motor weakness. We recently reported four cases of this syndrome occurring secondary to a continuous spinal technique.¹ We postulated that maldistribution combined with a relatively high dose of local anesthetic resulted in toxic exposure of neural tissue. In models of the subarachnoid space, administration of anesthetic through a sacrally directed catheter can result in a restricted distribution,²⁻⁴ and relatively high concentrations may occur with dosages that have been administered clinically.^{3,4}

The report to the Food and Drug Administration of eight additional cases^{||} increased concern about the safety of continuous spinal anesthesia and the neurotoxic potential of local anesthetics. Of the twelve documented cases of cauda equina syndrome, eleven were associated with the use of 5% lidocaine with 7.5% dextrose. Although this could reflect relative usage or sampling bias, it might reflect differential toxicity of currently used local anesthetics. Moreover, recent reports of transient radicular irritation after use of 5% lidocaine solution for single-injection spinal anesthesia suggest that this anesthetic may also induce less severe, but more common, neurologic abnormalities.⁵

The current experiments were conducted to determine whether local anesthetic injected intrathecally to produce a restricted distribution could result in sacral sensory impairment. In addition, we sought to test the hypothesis that, when equal volumes are administered

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|| Cauda equina syndrome associated with the use of small-bore catheters in continuous spinal anesthesia. FDA Safety Alert May 29, 1992.

Table 1. Total Volume and Dose of Local Anesthetic and Dextrose Administered during Each Infusion*

Infusion	Volume (μl)	5% Lidocaine with 7.5% Dextrose		0.75% Bupivacaine with 8.25% Dextrose		0.5% Tetracaine with 5% Dextrose	
		Lidocaine	Dextrose	Bupivacaine	Dextrose	Tetracaine	Dextrose
1 (1 hr)	60	3.0	4.5	0.45	4.95	0.3	3.0
2 (2 hr)	120	6.0	9.0	0.90	9.90	0.6	6.0
3 (4 hr)	240	12.0	18.0	1.80	19.8	1.2	12.0

All values are in milligrams.

* Control animal received equivalent volume of saline during each infusion.

intrathecally, significant differences exist in the potential of three commonly used anesthetic solutions to induce sensory dysfunction.

Materials and Methods

These studies were approved by the Committee on Animal Research of the University of California at San Francisco. All experiments were conducted on male Sprague-Dawley rats (200–300 g).

Rats were anesthetized with methohexital (40–60 mg/kg intraperitoneally), and intrathecal catheters, composed of polyethylene tubing (PE-10), were introduced into the subarachnoid space using a modification of the method of Yaksh and Rudy⁶; catheters were passed through a slit in the atlantooccipital membrane and advanced 11 cm to lie with the tip caudal to the conus medullaris. Animals were allowed to recover for at least 7 days before experimental trials.

The tail-flick test was used to assess sensory function. The tail was placed over a slit through which a beam of light from a projection lamp was focused, with latency to movement as the measured end-point. To prevent tissue damage, the heat stimulus was discontinued if there was no response by 8 s (cut-off). Anesthesia/sensory deficit in the perineum, hind limbs, or trunk was defined by the absence of both vocal response and withdrawal to skin clamp.

Animals were randomly assigned to four groups of eight to receive either 5% lidocaine with 7.5% dextrose (Astra Pharmaceutical Products, Westboro, MA); 0.75% bupivacaine with 8.25% dextrose (Astra Pharmaceutical Products); 0.5% tetracaine with 5% dextrose; or preservative-free normal saline (Abbott Laboratories, North Chicago, IL). The tetracaine solution was prepared by combining equal volumes of 1% tetracaine (Winthrop Pharmaceuticals, New York, NY) and 10% glucose (Abbott Laboratories).

Intrathecal injections were administered at a rate of 1 μl/min using a mechanical infusion pump (model 975, Harvard Apparatus, South Natick, MA). A segment of calibrated polyethylene tubing was inserted between the syringe and the intrathecal catheter, and the injection was monitored by observing the movement of a small air bubble within the tubing. Each rat received, in sequence, a 1-h, a 2-h, and a 4-h infusion (table 1); they were permitted to recover for 4 days between each infusion.

Rats were placed in an acrylic restraint (Harvard Bioscience, South Natick MA), and baseline tail-flick latency was assessed using a set of three determinations performed at the proximal, middle, and distal portions of the tail. The investigator administering anesthetic and assessing sensory function was blinded to the solution administered to each animal. After initiation of each infusion, tail-flick latency was assessed every 10 min until the animal failed to respond on two consecutive occasions. To evaluate extent of anesthesia, a clamp was applied to the skin, progressively cephalad, until a response was elicited; this assessment was performed every 10 min for 1 h, and every 30 min thereafter for the remainder of the infusion. Animals were evaluated for persistent sensory dysfunction 4 days after the first and second infusions (immediately before the

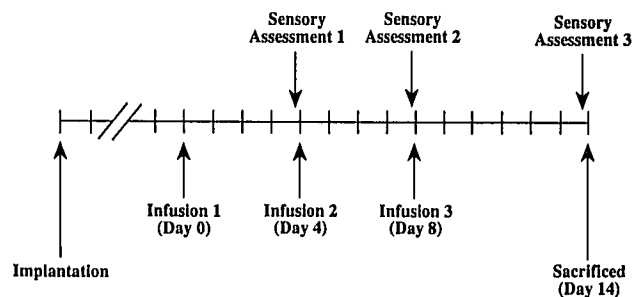


Fig. 1. Timeline of the experimental protocol.

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next infusion) and 6 days after the last infusion (fig. 1). Animals were then killed by injection of an overdose of pentobarbital. The location of the distal end of the intrathecal catheter was verified by postmortem examination.

Tail-flick latencies at the proximal, middle, and distal portions of the tail were averaged to give a mean tail-flick latency for each time point. Mean baseline tail-flick latencies for the four groups were compared using one-way analysis of variance. To assess the effect of intrathecal infusions on sensory function, the data were converted to percent maximum possible effect, calculated as $([\text{latency} - \text{baseline}] / [\text{cut-off} - \text{baseline}]) \times 100$. Alterations in tail-flick latency after each of the three infusions were evaluated using repeated measures analysis of variance and Scheffé's *F* tests. *P* less than 0.05 was considered significant.

Results

There was no significant difference in baseline tail-flick latencies for the four groups. One animal receiving tetracaine failed to develop a demonstrable block during the first infusion, but anesthesia extending to the perineum was apparent during the second and third infusions. All other animals receiving local anesthetic developed sensory anesthesia during all three infusions. Anesthesia appeared to achieve steady state after approximately 30 min. Anesthesia was restricted to the hind limb except, on three occasions, where it extended to midtrunk; all three animals had received lidocaine. Two of the bupivacaine-treated animals developed seizures during the third infusion and died shortly thereafter; complete data are thus presented for 30 animals.

Infusion of lidocaine solution was associated with a persistent increase in tail-flick latency when compared with the bupivacaine, tetracaine, and saline solutions (fig. 2). This difference was significant after the first infusion and persisted throughout the study. When tested after the first infusion, five of the animals receiving lidocaine had no response to the heat stimulus at all three portions of the tail; one additional animal in this group failed to respond at one portion of the tail. Sensory impairment extended to the perineum in two animals in this group, but only after the second infusion. Sensory deficits were associated with variable degrees of motor weakness in the tail manifested by decreased spontaneous movement, failure to lift the tail while ambulating, and loss of normal tone of the

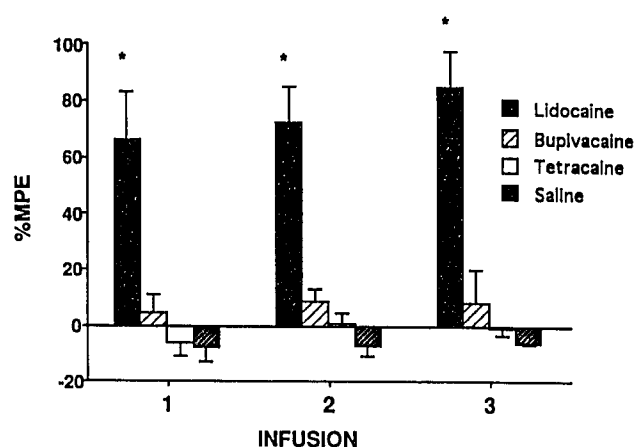


Fig. 2. Sensory function after first, second, and third infusions of local anesthetic solutions or saline. Tail-flick latency values were calculated as the average of latencies for the proximal, middle, and distal portions of the tail and were expressed as percent maximum possible effect (%MPE), where $\%MPE = ([\text{latency} - \text{baseline}] / [\text{cut-off} - \text{baseline}]) \times 100$. Data represent means \pm SEM. After each infusion, %MPE for lidocaine was significantly greater than that for bupivacaine, tetracaine, or saline.

tail resulting in a more rapid drop to the ground when lifted and released. A portion of the tail of one animal receiving bupivacaine demonstrated no response to the heat stimulus 6 days after the third infusion.

At dissection, all but two catheters were found to be correctly positioned. In these two instances, the catheter was within the subarachnoid space, but the tip was cephalad to the conus medullaris. One of these animals had received lidocaine and was the only animal in this group that failed to develop a deficit after three infusions. The other animal had received saline.

Discussion

The current experiments demonstrate that, in the rat, local anesthetic administered intrathecally to produce a restricted distribution of anesthesia can result in a persistent sensory deficit. Further, the experiments demonstrate that deficits may occur with concentrations of lidocaine currently used for spinal anesthesia. These findings further support the hypothesis that recent clinical injuries after continuous spinal anesthesia were the direct consequence of local anesthetic administered at a relatively high dose and in a relatively restricted distribution.¹

The results also indicate that, when equal volumes are administered intrathecally, significant differences

exist in the potential of these three anesthetic solutions to induce sensory impairment. Because injury may be, at least in part, concentration-dependent,⁷⁻¹⁰ we selected three clinically common solutions containing anesthetic at the highest concentration generally administered intrathecally. However, we did not evaluate anesthetic potency, nor did we administer anesthetics in solutions containing equivalent dextrose; thus, further studies are underway to determine the "therapeutic index" for these solutions and the neurotoxic potential of the anesthetic agents *per se*.

Each animal received three intrathecal infusions; with each exposure, a longer infusion and, consequently, a larger dose were administered. However, the relationship between sensory impairment and infusion of anesthetic solution cannot be explained on the basis of repetitive exposure because significant functional abnormalities were present in the lidocaine group after the initial infusion—indeed, when tested 4 days after this single infusion, five of the eight animals in this group showed no response to the heat stimulus at all three sections of the tail.

Exposure to repetitive escalating doses could lead to an overestimate or perhaps even an underestimate of toxicity after the second and third infusions (*i.e.*, the effect of repeated exposure, if any, is not known). Nonetheless, that impairment was minimal with either of the other two anesthetic solutions even after the second and third infusions (*i.e.*, greater volumes and longer duration of exposure) provides further evidence for a significant difference in neurotoxic potential between the lidocaine and the bupivacaine and tetracaine solutions.

It is highly unlikely that residual lidocaine could contribute to deficits present 4 days after administration; further, the two longer-acting local anesthetics did not produce significant abnormalities.

Sensory deficits were associated with variable degrees of motor impairment in the tails. However, lack of response to the heat stimulus cannot be explained on the basis of a motor deficit alone because animals retained the ability to withdraw their tails from the heat source. Moreover, none of the rats that failed to withdraw from the stimulus vocalized.

Catheters were introduced into the subarachnoid space using the method of Yaksh and Rudy.⁶ However, to facilitate a restricted distribution, catheters were advanced 11 cm from the atlantooccipital membrane, 2.5 cm further than described by these investigators. This placed the tip of the catheter among the nerve roots

of the cauda equina, rather than at the rostral portion of the lumbar enlargement. (Preliminary experiments had shown that advancement beyond 11 cm incurred an unacceptable incidence of dural penetration.) In the current experiment, all but two dissections revealed a correctly positioned catheter.

We chose to administer anesthetic by continuous infusion because anesthesia limited to the tail and hind limbs could be readily and reliably achieved. (Preliminary experiments had shown that bolus injections produced highly variable and often extensive levels of anesthesia.) A limited distribution was necessary for modeling the clinical exposure of the sacral roots; it also minimized the potential for alterations in blood pressure, respiration or sensorium that might be induced by more extensive blockade. (Preliminary data we have obtained from intra-arterial monitoring suggest that blood pressure remains stable under the current experimental conditions.)

Neurotoxicity from intrathecal infusion of local anesthetic in the rat has been reported previously,¹¹ but important features distinguish the current model. In the previous model, catheters were inserted *via* a laminectomy and positioned in the lumbar region with the tip directed cephalad. A higher rate of infusion was used (100 μ l/h), which, combined with the catheter's position, resulted in significant cephalad spread. Significant spread, in turn, likely accounted for the hind limb paralysis observed. In contrast, in the current experiment, persistent sensory and motor impairment were limited to the tail in all but two animals. This would suggest that primarily the coccygeal and the most caudal sacral roots were affected.¹² Thus, the protocol used in the current study resulted in deficits more closely resembling recent clinical injuries. Moreover, injury in the current study occurred at a lower anesthetic dose than previously reported.¹¹ This greater sensitivity to injury in our model is likely due to the more restricted distribution of local anesthetic, but also could represent differential sensitivity, particularly of the smaller sensory fibers.¹³

Although the doses of anesthetic associated with injury in the current experiments are lower than those previously reported,¹¹ they exceed, on a per kg basis, commonly administered clinical doses. However, the lowest dose of lidocaine used in the current study (approximately 12 mg/kg) produced a near-maximal effect (fig. 2), and preliminary data demonstrate significant changes in sensory function at doses 2.5-fold lower.¹⁴ In addition, available data indicate that, relative to hu-

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mans, the dose–response curve for intrathecal lidocaine in the rat is shifted to the right: in a similar animal model, we found the average doses of intrathecal lidocaine for sacral sensory anesthesia and for hind limb paralysis to be 1.2 and 3.1 mg/kg, respectively.¹⁵ In humans, however, sensory and motor block occur with markedly lower doses. For example, in one study, detectable sensory block was achieved in 100% of patients with 25 mg (0.3 mg/kg) of lidocaine, and 50 mg (0.6 mg/kg) produced lower extremity paralysis in 70%.¹⁶ Consequently, when expressed as a “therapeutic index,” the doses associated with toxicity in the current model and those associated with clinical injury after continuous spinal anesthesia appear to be similar.

We did not observe bowel or bladder dysfunction, both prominent features in the clinical reports of cauda equina syndrome.^{1,17} That these did not occur may, again, be due to a more limited anesthetic distribution in our model or, perhaps, functional differences between species in susceptibility or expression of injury. However, there may have been minor changes in bowel and bladder function that were undetected.

Previous experimental data have, for the most part, suggested that local anesthetic concentrations that produce functional impairment after subarachnoid injection exceed those commonly used clinically.^{7,8,18} For example, in rabbits, persistent deficits were induced with intrathecal injection of 8%, but not 4%, lidocaine.⁸ However, there are data to suggest that intrathecal injection of clinically relevant concentrations of anesthetic may, under certain circumstances, induce neurotoxic damage. In sheep, a single large dose of anesthetic (2% lidocaine, 3% 2-chloroprocaine, or 0.75% bupivacaine) has produced neurologic deficits,¹⁹ and in rats with indwelling catheters, hind limb paralysis was observed after prolonged subarachnoid infusion of various local anesthetics, including 1.5% lidocaine.¹¹

Two factors may account for the apparently contradictory findings. First, toxicity is both dose- and concentration-dependent, and studies in which functional impairment did not occur after intrathecal local anesthetic did not administer clinically relevant concentrations at high doses. Second, as maldistribution becomes more significant, exposure of some neural elements increases as the same dose of local anesthetic is delivered

to a more restricted area. Thus, injury in the current study and in previous experiments using subarachnoid infusion¹¹ might result, in part, from the more restricted distribution associated with a continuous infusion. Indeed, based on clinical experience, one would not expect neural injury in the absence of a relatively large dose, excessive concentration, or extreme maldistribution—significant functional deficits secondary to local anesthetic toxicity have rarely, if ever, occurred in the absence of one of these factors.

The bupivacaine solution had the highest concentration of glucose yet did not induce significant impairment, suggesting that glucose, per se, is not an important factor. However, based on the current results, one cannot exclude the possibility that glucose contributed to toxicity by increasing the tonicity of the lidocaine solution (because lidocaine was present in a higher concentration than bupivacaine or tetracaine, the tonicity of this solution was greater than that of the other two anesthetics). However, there are data to suggest that this degree of hypertonicity is unlikely to induce injury.²⁰ Further, preliminary data from *in vitro* studies also suggest that the presence of glucose does not contribute to the neurotoxic potential of this lidocaine formulation.¹⁰ Nonetheless, determination of the effect of glucose and tonicity will require additional studies specifically controlling for these factors.

In summary, we have demonstrated that, in the rat, restricted distribution of anesthesia can be achieved, and sensory impairment may result. These findings provide further support for local anesthetic neurotoxicity as the etiology for recent injuries after continuous spinal anesthesia. The results also suggest that, when equal volumes are administered intrathecally, significant differences exist in the neurotoxic potential of these three anesthetic solutions. The experimental preparation appears to be a useful functional model for *in vivo* study of the mechanism(s) of, and the factors that affect, local anesthetic neurotoxicity.

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