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The Addition of 7.5% Glucose Does Not Alter the Neurotoxicity of 5% Lidocaine Administered Intrathecally in the Rat

Shinichi Sakura, M.D., Vincent W. S. Chan, M.D.,† Ricardo Ciriales,‡ Kenneth Drasner, M.D.§*

Background: **Recent reports of major and minor neurologic sequelae after spinal anesthesia have generated concern regarding the safety of some currently used intrathecal agents. The role of glucose, if any, in neurotoxic injury associated with spinal anesthesia is not known. The current experiments sought to determine whether the presence of 7.5% glucose alters the neurotoxicity of intrathecally administered 5% lidocaine.**

Methods: **Two experiments were performed. First, 48 rats were implanted with an intrathecal catheter and randomly divided into eight equal groups. Each animal received a single intrathecal infusion of 5% lidocaine (groups P1–P4) or 5% lidocaine with 7.5% glucose (G1–G4) for 0.5, 1, 2, or 4 h at a rate of 1 μl/min. Sensory function was assessed using the tail-flick test; a deficit was defined as a complete lack of response to the heat stimulus at the proximal, mid or distal portion of the tail persisting 4 days after the infusion. In the second experiment, 60 rats were randomly divided into two groups to receive a 1-h intrathecal infusion of 5% lidocaine or 5% lidocaine with 7.5% glucose. Animals were evaluated for increase in the latency of the tail-flick reflex 4 days after infusion.**

Results: **In the first experiment, the two lidocaine solutions produced similar dose-dependent loss of sensory function. In the second experiment, the two solutions induced similar alterations in tail-flick latency.**

Conclusions: **The presence of 7.5% glucose does not affect the potential of intrathecally administered 5% lidocaine to induce sensory impairment. These findings provide further support for the hypothesis that recent injuries after spinal anesthesia resulted from a direct neurotoxic effect of the local anesthetic. (Key words: Anesthetics, local: lidocaine. Anesthetic techniques, spinal: continuous. Complications, neurologic: cauda equina; transient radicular irritation.)**

RECENT reports of neurologic injury after continuous spinal anesthesia[1,2,‖] have generated concern about the relative toxicity of currently used anesthetic agents. This concern has been reinforced by data suggesting similar injuries have occurred with repeat injection after a "failed spinal" [3] and reports of transient radicular irritation after single subarachnoid injection.[4] Although increasing evidence indicates that these complications resulted from a direct effect of local anesthetic, all involved the administration of a solution containing a relatively high concentration (5–7.5%) of glucose. This association may reflect merely common use of glucose in anesthetic solutions. However, glucose does have well documented effects that might potentiate neurotoxicity.

Hyperglycemia has deleterious effects on neural function. In both experimental and clinical diabetes mellitus, the degree and duration of hyperglycemia correlate with the progressive damage to nerve fibers.[5] Of greater relevance, hyperglycemia and glucose administration have been demonstrated to increase neurologic impairment,[6] cytologic damage,[7] and biochemical disturbance[8] after experimentally induced ischemia. Although little is known about the mechanism of local anesthetic-induced nerve injury, ischemia is believed to be an important etiologic factor.[9]

Adding glucose to a solution increases its tonicity. This, in turn, might induce damage or potentiate local anesthetic-induced injury. It has been suggested that the lack of a nerve sheath might make the cauda equina particularly vulnerable to osmotic damage.[10] *In vitro* experiments using cat rootlets demonstrate persistent block of some C fibers after brief exposure of rootlets

* Research Fellow, Department of Anesthesia.

† Assistant Professor of Anesthesia.

‡ Staff Research Associate, Department of Anesthesia.

§ Associate Professor of Anesthesia.

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Address reprint requests to Dr. Drasner: Department of Anesthesia, San Francisco General Hospital, Room 3C-38, 1001 Potrero, San Francisco, California 94110.

‖ Food and Drug Administration: FDA Safety Alert: Cauda Equina Syndrome Associated with the Use of Small-bore Catheters in Continuous Spinal Anesthesia. Washington, D.C., Food and Drug Administration, May 29, 1992.

to sucrose solutions having osmolalities as low as 500 mOsm.[11] The tonicity of 5% lidocaine in 7.5% glucose is 837 mOsm.[12]

Glucose could contribute to injury indirectly by causing a more limited distribution of anesthetic. Data obtained from *in vitro* models of the subarachnoid space show that potentially neurotoxic concentrations may occur when doses of lidocaine, normally used for spinal anesthesia, have restricted spread.[13,14]

Despite the common use of glucose in anesthetic solutions for spinal anesthesia, little is known about the effect, if any, on local anesthetic neurotoxicity. Although *in vitro* data suggest that glucose does not affect the reversibility of conduction block of a desheathed amphibian nerve,[15] *in vivo* mammalian data are lacking. Accordingly, the present study examines the effect of 7.5% glucose on the neurotoxicity of intrathecally administered 5% lidocaine in an *in vivo* rat model.

Materials and Methods

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

Surgical Preparation

Rats were anesthetized by intraperitoneal injection of methohexital (40–60 mg/kg), and intrathecal catheters composed of polyethylene (PE-10) tubing were introduced into the subarachnoid space using a previously described modification[16] of the method of Yaksh and Rudy[17]: 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 5 days before studies began. Rats exhibiting any evidence of sensory or motor dysfunction were excluded from study.

Measurements

To assess sensory function, the tail-flick test was performed at the proximal, mid, and distal portions of the tail. The animal's tail was placed over a slit through which a beam of light from a projection lamp was focused, which produced a reproducible heat stimulus. The endpoint we measured was the time (latency) for the rat to move its tail. To prevent tissue damage, the heat stimulus was terminated if no response occurred by 8 s (cutoff). Anesthesia/sensory deficit in the perineum, hind limbs or trunk was defined as a lack of both vocal response and withdrawal in response to skin-clamping in these regions.

Experiment I

Forty-eight rats were randomly divided into eight equal groups to receive a single intrathecal infusion of the test solution. Rats in groups G1–G4 received 5% lidocaine hydrochloride in 7.5% glucose for 0.5, 1, 2, or 4 h; those in groups P1–P4 received glucose-free 5% lidocaine hydrochloride for the same durations. The solutions were prepared immediately before injection by dissolving crystalline lidocaine hydrochloride (Sigma, St. Louis, MO) and glucose (Sigma, St. Louis, MO) in distilled water (Abbott, North Chicago, IL).

All infusions were administered at a rate of 1 μl/min 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.

Rats were placed in a horizontal acrylic restraint, and baseline tail-flick latency was assessed. During infusion of test solution, tail-flick latency was assessed every 10 min until the animal failed to respond on two consecutive occasions. To evaluate extent of anesthesia, a skin clamp was applied to the tip of the tail and moved progressively cephalad until a response was elicited; this assessment was performed every 10 min for 1 h, then every 30 min thereafter for infusions lasting 2 or 4 h. Animals were tested 4 days after infusion, with sensory dysfunction defined as a negative response to the heat stimulus at some portion of the tail. Animals were killed by injection of an overdose of pentobarbital, and the location of the distal end of the intrathecal catheter was verified by postmortem examination.

Experiment II

Sixty rats were randomly divided into two equal groups to receive a single intrathecal infusion of 5% lidocaine with or without 7.5% glucose for 1 h at a rate of 1 μl/min. Animals were evaluated for increase in the latency of the tail-flick response 4 days after the infusion.

Statistical Analyses

For both experiments, tail-flick latencies at the proximal, mid, and distal portions of the tail were averaged to give a mean tail-flick latency. Mean baseline tail-flick latencies for the groups were compared using one-way

analysis of variance or an unpaired *t*-test, as appropriate. The extent of anesthesia during infusions was scored on a scale of 1–4, where 1 = tail, 2 = perineum, 3 = hind limb, and 4 = trunk, and compared using the Kruskal-Wallis test and the Mann-Whitney U test, as appropriate. $P < 0.05$ was considered significant.

Experiment I. ED_{50} values and confidence intervals were determined, and the potency ratio was calculated and tested for significance using the method of Litchfield and Wilcoxon.[18]

Experiment II. Average tail-flick latencies were converted to percent maximal possible effect, calculated as [(tail-flick latency − baseline)/(cutoff − baseline)] × 100 and compared using an unpaired *t* test.

Results

Experiment I

Three animals were excluded from the study: one each in groups G1 and G4 had developed bladder distention and were killed 2 and 3 days, respectively, after the infusion. The third animal (group G2) developed anesthesia extending to the forelimbs during infusion; postmortem dissection revealed that the tip of the implanted catheter was positioned cephalad to the conus medullaris.

There was no significant difference in baseline tail-flick latencies for the eight groups. During infusion, sensory block of the tail was evident in 82%, 93%, and 100% of the animals at 10, 20, and 30 min, respectively. The level of sensory block approximated steady-state at 30 min and ranged from the hind limb to the trunk. There was no significant difference in the level of anesthesia for any of the infusions.

The two test solutions induced similar dose-dependent loss of sensation (fig. 1). The ED_{50} (95% confidence limits) for the glucose-containing and plain solutions was 2.25 (0.66–7.47) mg and 3.03 (1.35–6.81) mg, respectively, which did not differ significantly.

Sensory deficits were associated with variable degrees of motor weakness in the tail. Postmortem examination revealed that all catheters were correctly positioned (except as noted above).

Experiment II

Data were not obtained from three animals given glucose because of unrelated injury sustained during the interval between glucose administration and testing.

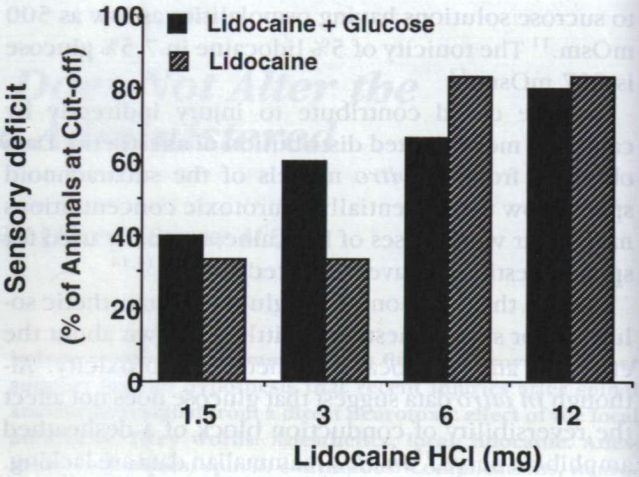

Fig. 1. Experiment I. The effect of intrathecal administration of 5% lidocaine and 5% lidocaine with 7.5% glucose on sensory impairment. Sensory deficit was assessed using the tail-flick test, with deficit defined as a negative response to the heat stimulus by 8 s (cutoff) 4 days after infusion. The two test solutions produced similar dose-dependent loss of sensory function.

There was no significant difference between the two groups in baseline tail-flick latency. Sensory block ranged from the perineum to the trunk; the extent of anesthesia did not differ between the two groups. The two test solutions produced a similar increase in tail-flick latency (fig. 2). The percentage of animals that failed to respond to the heat stimulus was calculated and displayed graphically with the data from experiment I (fig. 3).

Postmortem examination of the spinal cord revealed that the catheter was correctly positioned in all animals.

Discussion

Two experiments were performed. In the first, dose-response determinations were performed for loss of sensation with 5% lidocaine and 5% lidocaine with 7.5% glucose. The two solutions induced similar dose-dependent impairment. However, examination of the individual data points raised concern that a difference in effect might be present at low doses. Consequently, a second study was performed in which the two lidocaine solutions were each administered for 1 h to 30 animals. This number was determined by power analysis based on the variability observed in the first experiment and the ability to detect a 20% difference in tail-flick latency with β set at 0.2 and α set at 0.05. The

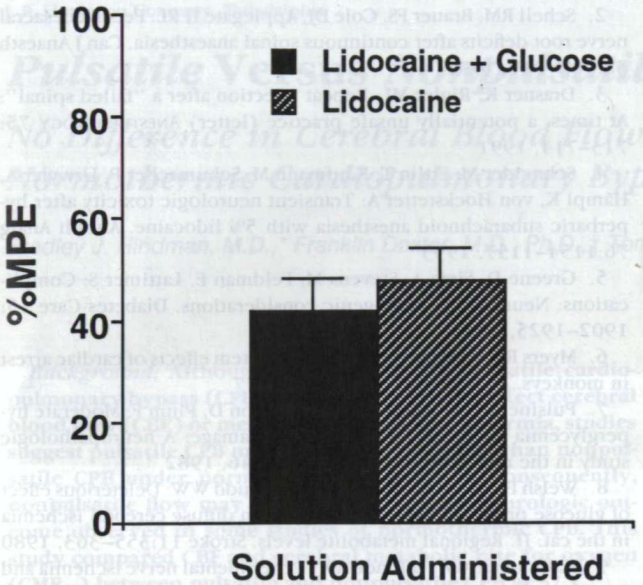

Fig. 2. Experiment II. Sensory function 4 days after a 1-h intrathecal infusion (1 μl/min) of 5% lidocaine or 5% lidocaine with 7.5% glucose. Tail-flick latency values were calculated as the average of latencies for the proximal, mid, and distal portions of the tail and are expressed as percent maximum possible effect (%MPE), where %MPE = [(tail-flick latency − baseline)/(cutoff − baseline)] × 100. Data are expressed as mean ± SEM. There was no significant difference in sensory dysfunction between the two groups.

two solutions produced similar alterations in sensory function. Taken together, these data demonstrate that the addition of 7.5% glucose does not alter the sensory impairment caused by 5% lidocaine.

The data also demonstrate that intrathecal administration of local anesthetic to produce a restricted distribution results in dose-dependent sensory impairment. We previously demonstrated that sensory impairment could result from the administration of a relatively high dose of local anesthetic to a restricted area of the subarachnoid space.[16] However, the use of repetitive infusions in that study precluded establishing a dose-dependent relationship.

We studied only one local anesthetic and only one concentration of glucose. However, the results likely have relevance to all local anesthetic solutions currently used for spinal anesthesia. First, the concentration of glucose used in the current study is only slightly less than the highest concentration found in a commercial formulation, 8.25%, used in combination with 0.75% bupivacaine; moreover, we have previously found that, when equal volumes are administered intrathecally, the neurotoxicity owing to 5% lidocaine with 7.5% glucose exceeds that of 0.75% bupivacaine with 8.25% glucose.[16] Second, 5% lidocaine with 7.5% glucose has the highest tonicity of any commercially available anesthetic solution. However, because the extent of anesthesia was equivalent with or without glucose (likely because of anesthetic delivery by continuous infusion), we did not assess any indirect effect that might derive from the potential for glucose to promote a more restricted anesthetic distribution.

The effect of glucose alone was not studied. However, glucose is not routinely administered intrathecally, except in combination with local anesthetic. Moreover, in previous experiments,[16] a higher concentration of glucose (0.75% bupivacaine with 8.25% glucose) was administered for 4 h without producing a significant increase in tail-flick latency. In other preliminary experiments, repetitive 1-h infusions of 7.5% glucose (in combination with 0.25% to 1.6% lidocaine) failed to induce sensory impairment. However, neither of these studies included neuropathologic examination and, therefore, did not exclude the possibility that "subclinical" damage occurred, *i.e.*, the threshold for neuropathologic changes may be lower than that for sensory impairment. Neuropathologic examination was not performed, because we have found that catheterization *per se* induces histologic changes that impair meaningful interpretation of anesthetic-induced changes. These effects are most severe in the region distal to the

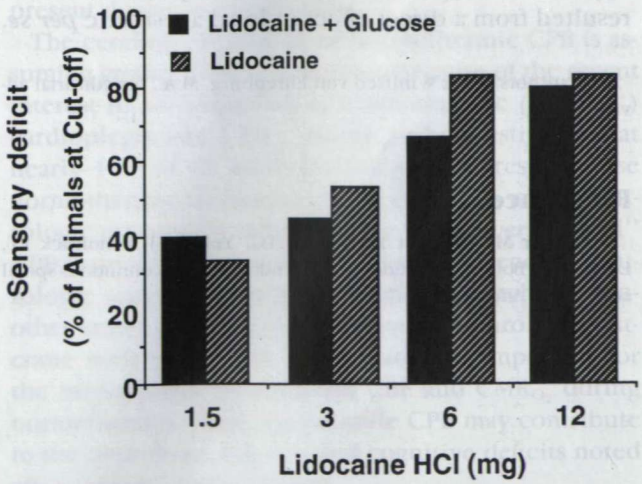

Fig. 3. The percentage of animals failing to respond to the heat stimulus 4 days after the respective infusion. The percentage values for the 1.5-, 6.0-, and 12.0-mg infusions of lidocaine are based on data from experiment I. The values for the 3.0-mg infusion are based on the combined data from experiments I (n = 11) and II (n = 57).

conus, the area of greatest interest. Consequently, although the current model provides a direct parallel for the functional loss that occurs clinically, worthwhile histologic evaluation will likely require an alternative model.

Bladder distention developed in two rats given 5% lidocaine with glucose; these rats were killed before testing. A low incidence of urinary retention despite severe sensory impairment is somewhat surprising but has been a consistent feature of this animal model. Only these two animals have developed this complication in the studies performed to date. However, it is likely that mild degrees of dysfunction are undetected because of lack of a sensitive measure of bladder function.

Although the relative incidence of bladder distention does not imply a difference between the effect of the two solutions, it highlights an important limitation of the present study, *i.e.,* injury or impairment was assessed only in terms of a response to a noxious thermal stimulus. Consequently, it is possible, albeit unlikely, that glucose might selectively potentiate an adverse effect on other sensory modalities, motor or autonomic function, or morphology.

In summary, we have demonstrated that the addition of 7.5% glucose does not alter the potential for sensory impairment after intrathecal injection of a 5% lidocaine solution. These data suggest that the presence of glucose does not alter the neurotoxic potential of an anesthetic solution and provide further support for the hypothesis that recent injuries after spinal anesthesia resulted from a direct effect of local anesthetic *per se*.

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