strophic complications may occur. This represents a challenge to methods and content of training and continuing education. Spinal anesthesia has a remarkable safety record in high-risk surgical populations, but the concern over the continued use of 5% lidocaine for spinal anesthesia deepens. Those of us on this side of the Atlantic thank the French for this contribution and join them in their conclusion, "Vive l'anesthesie locoregionale!"

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Lidocaine Spinal Anesthesia

A Vanishing Therapeutic Index?

In 1991, reports of cauda equina syndrome after continuous spinal anesthesia generated concern about the potential neurotoxicity of anesthetics currently used for spinal anesthesia.[1] Almost all of these cases occurred with use of 5% lidocaine, an anesthetic considered by many to be the gold standard for safety. That neurotoxic damage could occur with clinically relevant concentrations was reinforced by reports of deficits with repeat injection after a failed spinal block[2] and with inadvertent intrathecal injection of an intended epidural dose of 2% lidocaine.[3] Subsequent reports demonstrated that, in addition to permanent deficits associated with high doses, transient neurologic symptoms, *i.e.*, pain/dysesthesia in the buttocks or lower extremity, frequently follow standard intrathecal doses of lidocaine.[4,5]

In this issue of ANESTHESIOLOGY, two manuscripts now present cases in which neurologic deficits were associated with administration of local anesthetic at a dose recommended for single injection spinal anesthesia.[6,7] Gerancher details a single case of cauda equina syndrome after uncomplicated spinal anesthesia with 100 mg of lidocaine with epinephrine.[6] Auroy *et al.*, the subject of a separate editorial, found 24 neurologic deficits among approximately 40,000 spinal anesthetics,[7] 12 of which were associated with trauma evidenced by either paresthesia or pain with injection. Of the remaining 12, 9 occurred with lidocaine (including all three that were permanent). For these nontraumatic deficits, the authors failed to identify an etiology of injury, leaving the anesthetic as a potential cause. But what evidence is there that injuries resulted from the anesthetic? Certainly, lack of an alternative etiology, *per se,* is a weak argument for toxicity.

First injury as a result of the toxicity of an anesthetic should be dose-dependent. That is, injuries should cluster at the high end of the clinical dose range, with the most severe at the highest doses. One of the permanent deficits described by Auroy *et al.* occurred with 350 mg of lidocaine administered through a continuous spinal catheter. Although the manuscript reports only a range (75-100 mg) for injury with single injections of lidocaine, a query to the authors elicited data supporting dose-dependence - seven of the eight deficits followed injections of 100 mg; two deficits were permanent, and five lasted from 2 days to 16 weeks. Only one patient received a lower dose (75 mg) and symptoms lasted only 3 days.

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Additionally that 9 of 12 nontraumatic deficits occurred with lidocaine does not appear to be a result of relative use. As the authors note, sales of bupivacaine in France during the study period exceeded lidocaine by a factor of nearly three. Actual usage by the study's 736 anesthesiologists is not known, but 11 of the 12 trauma-related deficits occurred with bupivacaine, further supporting its greater use. Although association with a particular anesthetic solution does not rule out all other etiologies, it does narrow the field to those that could be correlated with the anesthetic.

Finally, the association of more severe nontraumatic deficits with lidocaine is consistent with experimental data, suggesting that with relative clinical doses, toxicity of lidocaine exceeds that of bupivacaine.[8-10] However, transient deficits associated with bupivacaine are surprising: 2 of the 3 occurred with 12 and 15 mg, which are relatively low doses. The actual frequency of lidocaine-associated deficits is also surprising: if use of lidocaine were proportionate to overall French use, then 9 cases occurred among approximately 10,000 spinal block, which is not consistent with the frequency of deficits reported in the literature. However, we should not assume this incidence is incorrect because we lack previous reports—of the original eight cases of cauda equina syndrome after continuous spinal anesthesia, five came to light only after clinicians were informed of other cases.

In 1995, Astra revised their prescribing information to recommend dilution of this anesthetic solution with an equal volume of cerebrospinal fluid (CSF) or saline. Yet, lidocaine appears to have been administered as a 5% solution with 7.5% dextrose. However, assuming anesthetic neurotoxicity to be the mechanism of injury, this recommendation may not have prevented these deficits.

First, although the details of sensory anesthesia are not provided in the Auroy study,[7] the case described by Gerancher appeared to have a fairly well-distributed block,[6] suggesting adequate dilution within the subarachnoid space. Thus, dilution of the injectate is unlikely to have had a major impact on clinical outcome. Second, modest reduction in concentration clearly does not eliminate risk; as noted previously, permanent deficits have followed intrathecal injection of 2% lidocaine intended for epidural administration.[3] Third, the extent to which the risk of toxicity from an intrathecal dose of lidocaine is reduced by use of a lower, clinically effective, concentration remains to be established—data demonstrating increased toxicity with increased concentration are derived primarily from *in vitro* studies,[11,12] peripheral nerve models,[12,13] or experiments that fail to control for anesthetic dose.[8] Finally, although concentrations associated with *in vitro* "toxicity" should be interpreted with caution, irreversible changes have been observed in neural tissue exposed to low concentrations of lidocaine. For example, in an isolated rabbit vagus nerve, irreversible conduction block, swelling of axons, mitochondria, and Schwann cells, and complete loss of rapid axonal transport were documented after exposure to 0.6% lidocaine.[11] More recently, a similar threshold for irreversible block was observed in isolated axonal segments of desheathed frog sciatic nerve.[12]

Nonetheless, a lower injectate concentration might pose less risk should maldistribution occur and anesthetic not be diluted with CSF. Accordingly, we previously recommended that, to the extent that concentration may be reduced without loss of efficacy, dilution is indicated.[1] Although further studies of efficacy are required, 1.5% lidocaine provides sensory anesthesia clinically equivalent to higher concentrations—the manufacturer's 1995 recommendation to dilute 5% lidocaine 1:1 was therefore not quite adequate.

Recent clinical experience and experimental data provide insight into other modifications of technique that might minimize neurotoxic risk; these are best addressed by considering three questions:

1. Should we continue to administer up to 100 mg of lidocaine for spinal anesthesia?

Most studies indicate a potency ration of lidocaine to bupivacaine of approximately 4:1.[8,14] Yet the maximum recommended doses of 100 mg and 20 mg, respectively, or administration of whole ampules of these agents (100 mg and 15 mg), result in ratios of 5:1 or 6.7:1. Thus, although adequate evaluation of toxicity for equipotent doses has not been performed, available data comparing these two agents at a 6.7:1 ratio (5% lidocaine to 0.75% bupivacaine) have clinical relevance and suggest that the lidocaine has greater toxicity, producing more significant conduction failure in an isolated segment of axon[9] and more profound sensory dysfunction when administered intrathetically in the rat.[10]

The issue of relative toxicity aside, 100 mg exceeds the dose of lidocaine required for reliable spinal anesthesia. This, combined with the possibility that the cases of Gerancher[6] and Auroy *et al.*[7] reflect neurotoxicity, leaves little justification for continued use of a 100-mg ceiling. The data are inadequate to make firm recom-

mendations regarding maximum safe dose; it is my personal practice not to exceed 60 mg.

2. Should we continue to add epinephrine to enhance the intensity and prolong the duration of lidocaine spinal anesthesia?

Recent data indicate that adding epinephrine potentiates persistent sensory impairment induced by intrathecal lidocaine.[15] This epinephrine-enhanced toxicity may help explain injury in the absence of maldistribution in the case reported by Gerancher.[6]

Moreover, the principal argument for continued use of spinal lidocaine is the lack of alternative anesthetics with well-documented safety and efficacy. There is, however, an acceptable alternative to lidocaine with epinephrine–bupivacaine. In addition to major deficits, transient neurologic symptoms frequently occur after administration of lidocaine;[5] although their importance is unknown, they are undesirable and rarely occur with bupivacaine administration.[5] Even strong proponents of lidocaine have suggested that it might be prudent to substitute bupivacaine rather than add epinephrine.[16] It is difficult to imagine a cogent argument for the continued use of epinephrine with lidocaine.

3. Should we continue to administer lidocaine in a hyperbaric, hyperosmolar solution containing glucose?

Despite theoretical concern, recent experimental evidence does not support glucose or tonicity as significant etiologic factors in injury associated with spinal anesthesia. *In vitro*, 7.5% glucose does not affect the compound action potential, nor potentiate anesthetic-induced conduction-failure.[9] *In vivo,* dose-dependent loss of sensory function produced by intrathecal administration of 5% lidocaine is unaffected by the presence of 7.5% glucose.[17]

Glucose could also contribute to injury indirectly by promoting maldistribution, *i.e.,* if hyperbaric solution is placed caudal to the peak of the lumbosacral curve, distribution will be restricted, and high subarachnoid concentration may be achieved.[18] However, restricted distribution is, at times, desirable. Conversely, hyperbaric solution placed cephalad to the lumbosacral peak tends to promote spread by gravitating to the thoracic curvature. These desirable effects dictate continued clinical use of hyperbaric solutions. However, the specific gravity of solutions such as 5% lidocaine with 7.5% glucose (1.033) far exceeds that required for gravitational control and might enhance toxicity in cases of maldistribution.

Whether lidocaine should continue to be used for spinal anesthesia has been, and no doubt will continue to be, the source of much debate. And there is little doubt that this current volley of cases will intensify this discussion. Although not conclusive, the weight of evidence points to toxicity as the etiology of injury in the present cases, and the suggested modifications in technique may decrease risk. Additionally, bupivacaine may impose less risk of clinical injury, which, combined with a dramatically lower incidence of transient neurologic symptoms, argues strongly for its use in lieu of lidocaine whenever possible. The choice of an alternative, short-acting agent is more difficult. Substitution of other agents such as procaine, prilocaine, or mepivacaine may be appealing, but data on which to base this selection do not exist. Although it is possible that transient neurologic symptoms represent the lower end of a spectrum of toxicity, their relationship to neurologic injury remains speculative–at the present time, their use as a surrogate marker for major toxicity would be inappropriate. The results of the study of Auroy *et al.* underscore the need for large-scale prospective surveillance studies for low frequency neurologic events.

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Epidural Analgesia and the Incidence of Cesarean Section

Time for Another Close Look

The relationship between epidural analgesia and the incidence of cesarean section remains controversial. Three years ago, Dewan and Cohen[1] reviewed this subject for ANESTHESIOLOGY. Their editorial accompanied reports of two prospective, randomized studies that showed that early administration of epidural analgesia (*i.e.*, cervical dilation of 3-5 cm) did not increase the incidence of cesarean section in nulliparous women, when compared with early administration of nalbuphine followed by late administration of epidural analgesia.[2,3] In contrast, Thorp *et al.*[4] earlier observed that epidural analgesia resulted in an increased incidence of cesarean section in nulliparous women. They concluded that this effect may be limited by delaying administration of epidural analgesia until cervical dilation of at least 5 cm.

Subsequently, two prospective, randomized trials were performed at the University of Texas Southwestern Medical Center at Dallas. Ramin *et al.*[5] randomized 1,330 women of mixed parity to receive either epidural bupivacaine-fentanyl or intravenous meperidine analgesia during labor. Among the 664 women randomized to an offer of epidural analgesia, 232 (35%) did not receive the allocated treatment. Approximately one half of the patients refused epidural analgesia, and the rest delivered before epidural analgesia could be administered. Among the 666 women randomized to an offer of intravenous meperidine, 229 (34%) were not treated as planned. Approximately one half of those women requested and received epidural analgesia because the meperidine provided inadequate pain relief. When the authors evaluated outcome according to intention to treat, they noted that 60 (9%) of the 664 women in the epidural group, compared with 35 (5%) of the 666 women in the meperidine group, had operative delivery for dystocia ($P < 0.01$). However, the authors defined operative delivery as either low forceps or cesarean delivery. Within the intention to treat analysis, the authors did not report the number of cesarean deliveries in the two groups. Thus it

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