Local Anesthetic Neurotoxicity: Clinical Injury and Strategies That May Minimize Risk

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Continued reports of major and minor neurologic sequelae after central neuraxial blockade have generated concern regarding the potential toxicity of currently available local anesthetic agents. These reports, along with the evolving experimental literature, have led to modifications in clinical practice. The following summarizes some of this recent clinical experience and the experimental findings that form the basis of these modifications. It focuses on major toxicity or neurologic injury with only brief mention of transient neurologic symptoms (TNS) because this topic is the subject of a separate review. Prudent practitioners may disagree, and the clinical recommendations that are presented represent modifications in anesthetic practice adopted by this author; they are offered with the intent to encourage critical review and debate rather than slavish adherence.

Cauda Equina Syndrome and Continuous Spinal Anesthesia

In 1991, we reported 4 cases of cauda equina syndrome after continuous spinal anesthesia (CSA).[1] In all 4, there was evidence of a restricted sacral block that required repetitive doses of local anesthetic to achieve an adequate level of anesthesia. Three of these cases were associated with the administration of 5% lidocaine delivered through a 28-gauge catheter specifically marketed for CSA; in the fourth case, 0.5% tetracaine was administered through a standard epidural catheter. We hypothesized that the combination of maldistribution and the high dose of anesthetic led to neurotoxic anesthetic concentrations in a restricted area of the subarachnoid space. Within a year, 8 additional cases were reported to the Food and Drug Administration (FDA), all consistent with this etiology.[2]

Studies performed with models of the subarachnoid space supported this etiology of injury. Administration of hyperbaric local anesthetic through a sacrally directed catheter was shown to produce a restricted distribution,[3-5] and high concentrations could be achieved with doses consistent with reports of clinical deficits.[3,4] Data from other in vitro and in vivo investigations have provided additional support for anesthetic toxicity.[6-15] Most critically, administration of anesthetic in a restricted sacral pattern could induce functional loss that closely paralleled clinical injury and caused histologic damage consistent with impairment.[6,10,13]

The reports of clinical injury induced the FDA to rescind 510K approval for small-bore catheters (<24 gauge) marketed for continuous spinal anesthesia. However, this decision did not eliminate risk. Practitioners have remained at liberty to use epidural equipment for this purpose, and it is still common practice to convert to a continuous spinal technique if dural puncture accidentally occurs during attempted epidural placement. Furthermore, the ability to titrate anesthetic may minimize hemodynamic alterations, making CSA a particularly valuable neuraxial technique for the elderly or fragile patient. Consequently, despite withdrawal of dedicated devices for CSA, the technique remains clinically relevant. It is therefore critical that the practitioner appreciates the factors that may contribute to neurotoxicity, and how they impact clinical management of an intrathecal catheter (Table 1). Additionally, when considering insertion depth of an intrathecal catheter, it is critical to appreciate the distance between the insertion site and the likely termination of the spinal cord.

Anesthetic Neurotoxicity: A Broader Clinical Problem

Repeat Injection After Failed Spinal

The experience with continuous spinal anesthesia uncovered basic issues of toxicity that have proven to have broad relevance to the safe conduct

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Accepted for publication July 31, 2002.

Presented at the ASRA Conference on Local Anesthetic Toxicity, Miami Beach, Fl, November 17-18, 2001. Supported by the National Institutes of Health (grant GM51887).

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1098-7339/02/2706-0006$35.00/0
doi:10.1053/rapm.2002.37410

Table 1. CSA: Recommendations for Anesthetic Administration

1. Insert catheter 2-4 cm, which should be adequate to confirm and maintain placement.
2. Use the lowest effective anesthetic concentration.
3. Place a limit on the amount of anesthetic to be used.
4. Administer a test dose and assess the extent of block.
5. If maldistribution is suspected, use maneuvers to increase the spread of local anesthetic (e.g., change the patient's position, alter the lumbosacral curvature, switch to a solution with a different baricity).
6. If well-distributed sensory anesthesia is not achieved before the dose limit is reached, abandon the technique.

Data from Rigler ML, Drasner K. Distribution of catheter-injected local anesthetic in a model of the subarachnoid space. *Anesthesiology* 1991;75:684-692.[3]

of central neuraxial blockade. As with CSA, inadequate sensory block with single-injection spinal anesthesia is often the result of maldistribution. Under such circumstances, there is again the potential for repeat injections to distribute in the same pattern, resulting in neurotoxic concentrations of local anesthetic within a restricted area of the subarachnoid space. Review of the closed claims database[16] and subsequent case reports[17,18] have confirmed these concerns.

Based on these considerations, we previously proposed suggestions for management of a failed spinal, which included assessment of the likelihood of technical error and adjustment of dosage for the second injection (Table 2).[16] However, adherence to these recommendations imparts significant delay because one must allow sufficient time for achievement of near-maximal block before assessment of sensory anesthesia. A more efficient alternative strategy is to simply limit the combined anesthetic dosage to the maximum amount a clinician would consider reasonable to administer as a single intrathecal injection.

Inadvertent Subarachnoid Injection of an Epidural Dose

There is a third circumstance under which excessively high doses of anesthetic are delivered into the subarachnoid space—accidental injection of a dose intended for epidural administration. In the 1980s, reports of deficits associated with apparent subarachnoid administration of chloroprocaine with bisulfite generated concern that injury might occur if epidural doses of this anesthetic solution are administered intrathecally.[19,20] Beginning in 1992, similar cases have been reported with lidocaine,[21,22] expanding this concern to include an anesthetic once considered the gold standard of safety. These cases serve to reinforce the critical importance of the test dose and fractional administration of anesthetic during performance of epidural anesthesia. Additionally, should high doses of an anesthetic be administered through a misplaced catheter, repetitive withdrawal of small volumes (4-5 mL) of cerebrospinal fluid (CSF) and replacement with saline should be considered, regardless of the anesthetic agent. Although objective outcome data supporting this maneuver are lacking, clinical experience with CSA has taught us that CSF withdrawal will hasten recovery from anesthetic block. It is therefore reasonable to conclude that this maneuver might lessen exposure of the nerve roots and minimize or reduce neurotoxic insult. Moreover, this technique appears to have been used successfully to treat a patient who received an overdose of intrathecal morphine.[23]

Single-Injection Lidocaine Spinal Anesthesia

The aforementioned volley of clinical reports provides compelling evidence that injury can result if high doses of anesthetic are administered intrathecally. Perhaps more surprising, 2 subsequent reports published in September of 1997 have raised suspicion that neurologic deficits might occur with administration of lidocaine at doses recommended for single-injection spinal anesthesia.[24,25] One is a case report of cauda equina syndrome after intrathecal injection of 100 mg of lidocaine with epinephrine.[25] The second is a prospective study of regional anesthesia from France. In a database that included roughly 10,000 lidocaine spinals, there were 8 cases of persistent deficits after single-injection spinal anesthesia that could not be explained on any other basis.[24] All of these injuries occurred with relatively high doses (▫ 75mg); 2 of these cases were permanent, both of which followed injection of the maximum recommended clinical dose (100

Table 2. Recommendations for Anesthetic Administration After a "Failed Spinal"

1. Aspiration of CSF should be attempted before and after injection of anesthetic.
2. Sacral dermatomes should always be included in an evaluation of the presence of a spinal block.
3. If CSF is aspirated after anesthetic injection, it should be assumed that the local anesthetic has been delivered into the subarachnoid space; total anesthetic dosage should be limited to the maximum dose a clinician would consider reasonable to administer in a single injection.
4. If an injection is repeated, the technique should be modified to avoid reinforcing the same restricted distribution (e.g., alter patient position or switch to a local anesthetic of different baricity).
5. If CSF cannot be aspirated after injection, repeat injection of a full dose of local anesthetic should not be considered unless careful sensory examination (conducted after sufficient time for development of sensory anesthesia) reveals no evidence of block.

Data from Drasner K, Rigler M. Repeat injection after a "failed spinal"—at times, a potentially unsafe practice. *Anesthesiology* 1991;75:713-714.[16]

Table 3. Lidocaine Spinal Anesthesia: Proposed Parameters

1. Dosage should be limited to 60 mg.
2. Concentration should not exceed 2.5%.
3. Epinephrine should not be used to enhance anesthesia or prolong the duration of block.

Data from Drasner K. Lidocaine spinal anesthesia: A vanishing therapeutic index. *Anesthesiology* 1997;87:469-472.[26]

mg). The lack of an alternative etiology and the occurrence of injury at the high end of the dose range make toxicity the most likely explanation.[26] Accordingly, modifications in technique have been suggested by this author that might reduce risk of injury (Table 3). Some of the relevant clinical and experimental data supporting these modifications are as follows:

Concentration. Review of the cases of cauda equina syndrome with CSA led us to suggest that 5% lidocaine be abandoned in favor of lower concentrations.[1,27] Four years later, Astra Pharmaceuticals modified the package insert and sent out a "Dear Doctor" letter to advise clinicians to dilute 5% lidocaine with an equal volume of CSF or preservative-free saline.[28] However, our suggestion to use a more dilute solution was based on data showing concentration-dependent injury derived from in vitro studies,[29] peripheral nerve models,[30] or experiments that failed to control for anesthetic dose.[31] Surprisingly, more recent in vivo data in rats suggest that the toxicity from a fixed dose of intrathecal lidocaine may be only modestly affected by dilution of lidocaine from 5% down to 1.25%.[32] Nonetheless, there is little justification for spinal administration of lidocaine at concentrations exceeding the manufacturer's recommendation of 2.5% for spinal anesthesia; there is no clinical advantage to higher concentrations, whereas there may be some additional, albeit small, risk.

Dose. Spinal anesthesia involves administering fluid into fluid, and, thus, barring extreme maldistribution, dose becomes the primary factor affecting the concentration of anesthetic bathing the nerves within the subarachnoid space. This factor likely accounts for the discrepancy between in vitro[8,11,29] and in vivo[32] data concerning the effect of anesthetic concentration on neurotoxicity. It also suggests that dose should be a dominant factor affecting neurotoxic risk.

There are several reasons to consider a reduction in the maximal dose of lidocaine used for spinal anesthesia. First, the available data suggest a potency ratio of lidocaine to bupivacaine in the range of 1:4,[10] yet the maximum doses recommended for spinal anesthesia are 100 mg and 20 mg, respectively. This discrepancy assumes even greater significance when one considers that lidocaine is inherently more neurotoxic than bupivacaine.[6,7] Second, virtually all of the reported cases of suspected neurotoxicity have been associated with administration of 75 mg or higher.[24,25] Finally, 100 mg exceeds the dose of lidocaine needed for reliable spinal anesthesia. Although the data are inadequate to know the impact of modest reduction in dose on neurotoxic risk, it is my personal practice not to exceed 60 mg.

Glucose. Most of the recent cases of clinical injury involved the intrathecal administration of a solution containing a high concentration of glucose and a tonicity exceeding the normal physiologic range. Although this association could merely reflect common usage of glucose in anesthetic solutions, glucose has well-documented effects that might enhance toxicity. Despite this theoretical concern, in vitro, 7.5% glucose does not affect the compound action potential or potentiate anesthetic-induced conduction failure.[7] More critically, dose-dependent loss of sensory function produced by intrathecal lidocaine in vivo is unaffected by the presence of 7.5% glucose,[9] whereas administration of 10% glucose does not induce impairment or morphologic damage.[13] These findings suggest that it is reasonable to continue to use glucose to increase baricity.

Vasoconstrictors. These agents are commonly added to spinal anesthetic solutions to increase the intensity and prolong the duration of anesthesia. However, vasoconstrictors might contribute to toxicity by promoting ischemia, decreasing anesthetic uptake, or by directly affecting neural elements. Recent data obtained in our laboratory indicate that epinephrine potentiates sensory impairment induced by intrathecal lidocaine.[33] These data, combined with the narrow therapeutic index for spinal lidocaine and the report of a clinical deficit following 100 mg lidocaine with epinephrine, argue against using a vasoconstrictor with lidocaine for spinal anesthesia. Moreover, the principal reason for using epinephrine is to provide a longer duration of anesthesia, which can be achieved with plain bupivacaine. In addition to having a better therapeutic index than lidocaine (even without epinephrine's potentiation of toxicity), bupivacaine is rarely associated with transient neurologic symptoms.[34-36] Consequently, it is difficult to justify continuing the practice of adding epinephrine to lidocaine for spinal anesthesia.

It should be appreciated that, the present discussion notwithstanding, permanent deficits with spinal and epidural lidocaine have been relatively rare. Nonetheless, recent experience and experimental data point to changes in practice that might elimi-

nate, or at least reduce, the occurrence of neurotoxic injury.

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