Local Anesthetic Toxicity: Optimal Management to Avoid Neurotoxic Injury and Treat Cardiac Arrest

Kenneth Drasner, M.D. San Francisco, California

Continued reports of major and minor neurologic sequelae following central neuraxial blockade have renewed concern regarding the potential toxicity of currently available local anesthetic agents. These reports, along with the experimental literature, have led to modifications in clinical practice. This lecture will summarize some of this clinical experience and the experimental findings that form the basis of these modifications, with particular emphasis on the rational selection of a local anesthetic for short-duration outpatient spinal anesthesia. In addition, the lecture will review the issue of local anesthetic systemic toxicity, focusing on the recent development of lipid rescue for bupivacaine cardiotoxicity, and the extension of lipid resuscitation beyond cardiotoxicity, and beyond treatment of the local anesthetics.

ANESTHETIC NEUROTOXICITY

Cauda equina syndrome and continuous spinal anesthesia (CSA).

In 1991, reports of cases of cauda equina syndrome following continuous spinal anesthesia (CSA) created concern regarding the potential neurotoxicity of local anesthetics (1). Most involved lidocaine administered through microcatheters, though some occurred with other anesthetics and/or macro (epidural) catheters. In all of these cases, there was evidence of a restricted sacral block that required repetitive doses of local anesthetic to achieve an adequate level of anesthesia, and it was hypothesized that the combination of maldistribution and the high dose of anesthetic led to neurotoxic concentrations in the subarachnoid space. Studies performed with models of the subarachnoid space (2), and other in vitro (3-6) and in vivo (7,8) investigations provided support for this mechanism of injury. 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.

In response to these reported injuries, spinal microcatheters were removed from the U.S. market. However, they remain available in some countries, while CSA is still practiced in the U.S. using epidural equipment, and this technique is commonly used when dural puncture accidentally occurs during epidural placement. It is therefore essential that the practitioner appreciate the factors that may contribute to neurotoxicity, and how they impact clinical management of an intrathecal catheter. Most critically, the clinician should limit the combined anesthetic dosage used to achieve surgical anesthesia to the maximum amount reasonable to administer as a single intrathecal injection.

Continuous Spinal Anesthesia: Guidelines for Anesthetic Administration

- Insert the catheter just far enough to confirm and maintain placement.
- Use the lowest effective local anesthetic concentration.
- Place a limit on the dose of local anesthetic to be used.
- Administer a test dose and assess the extent of any sensory and motor block.
- If maldistribution is suspected, use maneuvers to increase the spread of local anesthetic (change the patient’s position, alter the lumbosacral curvature, switch to a solution with a different baricity).
- If well-distributed sensory anesthesia is not achieved before the dose limit is reached, abandon the technique.

Risk associated with repetitive injection after failed spinal.

As with CSA, inadequate sensory block with single-injection spinal anesthesia is often the result of maldistribution. Under such circumstances, there is also the potential for repeat injections to distribute in the same pattern resulting in neurotoxic concentrations of anesthetic within a restricted area of the subarachnoid space. Review of the closed claims database (9) and subsequent case reports (10) have confirmed these concerns.
Based on these considerations, there have been suggestions for management of a failed spinal that include assessment of the likelihood of technical error and adjustment of dosage for the second injection (9). However, adherence to these recommendations imparts significant delay, as one must allow sufficient time for achievement of near-maximal block prior to assessment of sensory anesthesia. A more efficient and safer alternative strategy is to assume that the injected anesthetic has been administered intrathecally. Accordingly, similar to the strategy used for CSA, the practitioner should simply limit the combined anesthetic dosage to the maximum amount reasonable to administer as a single intrathecal injection.

Injury associated with inadvertent subarachnoid injection of an “epidural” dose.

There is a third circumstance under which excessive doses of anesthetic might be 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. Beginning in 1992, similar cases have been reported with lidocaine (11), 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 CSF and replacement with saline should be considered, regardless of the anesthetic.

Injury following single-injection lidocaine spinal anesthesia.

The aforementioned volley of clinical reports provides compelling evidence that injury can result if high doses of any anesthetic are administered intrathecally. More surprising, two subsequent reports raised suspicion that neurologic deficits might occur with administration of lidocaine at doses recommended for single-injection spinal anesthesia (12,13). One was a case report of cauda equina syndrome following intrathecal injection of 100 mg of lidocaine with epinephrine (13). The second was a prospective study of regional anesthesia from France (12). In a database that included roughly 10,000 lidocaine spinals, there were eight cases of persistent deficits following single-injection spinal anesthesia that could not be explained on any other basis. All of these injuries occurred with relatively high doses (≥75mg); two of these cases were permanent, both of which followed injection of the maximum recommended clinical dose (100 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 (14), and argue that the potential benefit of using a dose higher than 75 mg of intrathecal lidocaine would seem inadequate to override the added risk.

Transient neurologic symptoms (TNS) following single-injection lidocaine spinal anesthesia.

In 1993, Schneider and colleagues reported four cases in which transient pain/dysesthesia followed routine administration of conservative doses of intrathecal lidocaine (15). These symptoms were initially called “transient radicular irritation”, but this term was later abandoned in favor of “transient neurologic symptoms” or “TNS”; owing to the lack of certainty regarding their etiology. In this initial report, all four patients were in lithotomy position, which led the authors to postulate that this position put stretch on the nerve roots of the cauda equina, reducing blood flow, and potentiating toxicity (15). A follow-up study documented a 37% incidence of TNS with spinal lidocaine, but a near-zero incidence with bupivacaine (16). Abundant data from numerous studies have subsequently confirmed these findings, and have established the co-factors that contribute to the occurrence of symptoms. In addition to lithotomy, positioning for knee arthroscopy and outpatient status markedly enhance risk (17,18). While self-limited, the pain can be quite severe, often exceeding that induced by the surgical procedure. Importantly, TNS is not associated with sensory loss, motor weakness, or bowel or bladder dysfunction. The etiology and significance of these symptoms remains to be established, but discrepancies between factors affecting TNS and experimental animal toxicity cast doubt that TNS and persistent neurologic deficits represent opposite extremes on a single spectrum of toxicity. While these recent issues have led to restricted use for spinal anesthesia, lidocaine remains a popular agent for all other applications, including epidural anesthesia.
Chloroprocaine spinal anesthesia: back to the future?

The problems associated with lidocaine spinal anesthesia, particularly the high incidence of TNS have led many clinicians to abandon the use of this anesthetic for spinal anesthesia. While there are reports describing the use of low-dose bupivacaine combined with fentanyl (19), many practitioners report a high failure rate with this technique, and complete recovery may still be delayed. Of other available options, neither procaine (20) nor mepivacaine (21) appear to offer sufficient advantage with respect to TNS. There are some data to suggest that prilocaine may be an acceptable alternative, but there is currently no formulation of this anesthetic in the United States that would be appropriate to administer in the subarachnoid space.

Despite a rather blemished past, considerable attention has been focused on the possibility of using chloroprocaine to fill this anesthetic void. Introduced into clinical practice over 50 years ago, chloroprocaine never evolved as a spinal anesthetic agent, perhaps related to the development and marketing of the amide, lidocaine. In any case, reports of neurologic deficits associated with possible intrathecal injection of epidural chloroprocaine in the early 80s raised concern regarding the potential neurotoxicity of this anesthetic, which, until recently, would have subdued any enthusiasm for deliberate intrathecal administration.

The dissatisfaction with spinal lidocaine encouraged Kopacz and colleagues to re-investigate the use of spinal chloroprocaine. Their rigorous systematic volunteer studies documented effective spinal anesthesia with little, if any, risk of TNS (22-26). Duration of effect was shorter with chloroprocaine than with an equal dose of lidocaine (23), and institutional discharge criteria were achieved more rapidly than with lidocaine (23), procaine (22), or low-dose bupivacaine (26). As expected, anesthesia could be prolonged or enhanced by co-administration of fentanyl (25) or epinephrine (24). However, an unexpected and worrisome finding was the occurrence of “flu-like” symptoms in volunteers receiving chloroprocaine containing epinephrine (24), the etiology of which remains obscure. Several small clinical reports have confirmed the suitability of chloroprocaine for outpatient spinal anesthesia, both in terms of its short duration and low risk of TNS (27,28), though the published data regarding chloroprocaine as a spinal anesthetic is limited, and certainly insufficient to establish safety. However, the evolving “off-label” clinical experience with this drug is fairly substantial, and use of chloroprocaine at this point would not seem imprudent. While the issue of bisulfite toxicity has not been settled, the recent experience in volunteer studies and this “off-label” clinical use have been restricted to preservative-free chloroprocaine. Accordingly, should chloroprocaine be used for spinal anesthesia, the solution used should be bisulfite-free. Additionally, the available data and clinical experience would suggest that the dose limited to 60 mg, and the use of epinephrine be avoided.

ANESTHETIC CARDIOTOXITY AND LIPID RESCUE

Historical context

The most feared complication associated with administration of local anesthetics is the profound effect that these agents can have on cardiac conduction and function. In the past, it was conventional wisdom that the cardiovascular system is more resistant than the central nervous system to toxic effects of modern local anesthetics. It was also well accepted that prompt treatment of CNS toxicity, particularly maintenance of ventilation and oxygenation, could avert catastrophe. This conventional wisdom was called into question by a sentinel case reported by Prentiss, in which administration of etidocaine for caudal anesthesia in a healthy 31-yr-old male was associated with near simultaneous convulsions and cardiac arrest. Shortly thereafter, a seminal editorial by Albright incorporated Prentiss’ case, along with five others, to support the concept that these long acting lipid-soluble anesthetic agents (etidocaine and bupivacaine) could induce profound cardiac toxicity preceding or concurrently with CNS toxicity, and independent of hypoxia (29). Although this suggestion met with considerable resistance, cases of bupivacaine-induced cardiac collapse continued to occur. By early 1983, the FDA had received reports from the pharmaceutical industry of twelve cases of cardiac arrest, ten fatal, associated with the use of bupivacaine in obstetrics, most associated with the use of the 0.75% solution. In response, the package labeling was modified, and a “Dear Doctor” letter was sent stating that the 0.75% solution of bupivacaine was no longer to be used for
obstetrical anesthesia, nor any concentration to be used for intravenous regional anesthesia or paracervical block. This communication also stressed the importance of an adequate test dose, and injection of anesthetic in incremental doses. In addition to putting into play these changes in clinical practice, the occurrence of these cases stimulated an enormous literature, which has provided evidence for the distinctive cardiotoxicity of these agents. The most likely mechanism seems to relate to the nature of bupivacaine’s interaction with cardiac sodium channels (30). Simply put, recovery from bupivacaine blockade during diastole is relatively prolonged, making it far more potent with respect to depressing the maximum upstroke velocity of the cardiac action potential (Vmax) in ventricular cardiac muscle. As a result, bupivacaine has been labeled a “fast-in, slow-out” local anesthetic, which likely creates conditions favorable for unidirectional block and reentry. Other mechanisms may contribute to bupivacaine’s cardiotoxicity, including disruption of atrioventricular nodal conduction, depression of myocardial contractility, and indirect effects mediated by the central nervous system (31). This cardiotoxicity has obviously been the driving force for development of the single enantiomer anesthetics, ropivacaine and levo-bupivacaine. Unfortunately, despite these pharmaceutical advancements and the aforementioned modifications in clinical practice, cardiotoxicity has remained a concern, and with the exception of cardiopulmonary bypass, treatment options have been largely ineffective.

**Lipid Rescue**

Recently, a series of clinical events, insightful observations, systematic experimentation, and astute clinical decisions have identified a practical and apparently effective therapy for bupivacaine cardiotoxicity. Additionally, this therapy appears to have applications that go well beyond the initial problem of bupivacaine cardiotoxicity, finding application in the treatment of other manifestations of local anesthetic systemic toxicity, as well as resuscitation from cardiotoxicity secondary to a wide variety of toxicological challenges.

After learning of a case of apparent cardiotoxicity from only 22 mg of bupivacaine in a patient with carnitine deficiency (32), Weinberg postulated that this metabolic derangement led to enhanced toxicity due to the accumulation of fatty acids within the mitochondria. He then hypothesized that administration of lipid would potentiate cardiotoxicity. However, experiments he conducted to test this hypothesis demonstrated protection rather than enhancement of bupivacaine’s cardiotoxicity by lipid. Encouraged by this serendipitous finding, he instituted a series of deliberate systematic investigations in rats (33) and dogs (34), which clearly demonstrated the potential efficacy of intravenous lipid for treating the highly-resistant cardiotoxicity of bupivacaine.

Clinical confirmation came eight years after Weinberg’s initial studies. Faced with a patient who developed cardiotoxicity refractory to standard ACLS after receiving 20 mL 0.5% bupivacaine and 20 mL 1.5% mepivacaine for an interscalene block, Rosenblatt administered a 100 mL bolus of 20% Intralipid® (35). The patient subsequently responded to defibrillation, ultimately making a complete recovery. A subsequent report by Litz provided additional confirmation, while extending the potential utility of this treatment to cardiotoxicity induced by ropivacaine (36). Several reports soon followed, including a report by Spence suggesting that lipid may have utility in treating local anesthetic CNS toxicity (37), as well as others suggesting efficacy in treating toxicity induced by other classes of compounds. With respect to the latter, laboratory investigations have demonstrated utility for resuscitation from cardiotoxicity secondary to various compounds including verapamil (38) and clomipramine (39), and there are anecdotal clinical reports of successful resuscitations from bupropion-induced cardiovascular collapse (40) and multiform ventricular tachycardia provoked by haloperidol (41).

The mechanism by which lipid is effective is incompletely understood, but it’s predominant effect is almost certainly related to its ability to extract bupivacaine (or other lipophilic drugs) from aqueous plasma or tissue targets, thus reducing their effective concentration (“lipid sink”). Alternatively, or additively, bupivacaine has been shown to inhibit fatty acid transport at the inner mitochondrial membrane, and lipid might act by overcoming this inhibition, and thus serve to restore energy to the myocardium.

Although the mechanism is uncertain, and numerous questions remain, the evidence is more than sufficient to warrant administration of lipid in cases of systemic anesthetic toxicity. The timing of lipid is somewhat controversial, though the trend over time has been toward earlier use. While it is has been argued that infusing lipid at the earliest signs of systemic toxicity could result in unnecessary treatment of some patients, it seems imprudent to wait until severe cardiovascular dysfunction is evident. With respect to treatment of severe cardiac toxicity, there is evidence to suggest that vasopressin is best avoided (42), as is the use of high dose epinephrine (43) which, if
employed, might be preferably administered in the 10-100 mcg bolus range. Based on the foregoing, it should be evident that solutions of 20% lipid should be stocked and readily accessible in any area where local anesthetics are administered, as well as locations where overdoses from any lipophilic drug might be treated. Importantly, propofol should not be administered for this purpose, as the relatively enormous volume of this solution required for lipid therapy (~200 ml) would deliver potentially lethal quantities of propofol. However, small doses of propofol might be appropriate for seizure control, particularly in the case where there would be a delay in administering a benzodiazepine.

Many critical questions have yet to be addressed in this rapidly developing area, and timely information on this topic, as well as downloadable treatment protocols, can be found at lipidrescue.org, a website established and maintained by Guy Weinberg. Additionally, a recent issue of Regional Anesthesia and Pain Medicine (March-April 2010) contains a collection of articles developed by an ASRA Practice Advisory Panel. (44-49). The summary recommendations from this group (48) are available for download without subscription at journals.lww.com/rapm. The recommendations from this manuscript for treatment of systemic toxicity and the level of evidence for each intervention are presented in the following table (48).
Recommendations for Treatment of Local Anesthetic Systemic Toxicity (LAST)

- If signs and symptoms of LAST occur, prompt and effective airway management is crucial to preventing hypoxia and acidosis, which are known to aggravate LAST (I; B).
- If seizures occur, they should be rapidly halted with benzodiazepines. If benzodiazepines are not readily available, small doses of propofol or thiopental are acceptable. Future data may support the early use of lipid emulsion to treat seizures (I; B).
- Although propofol can stop seizures, large doses further depress cardiac function; propofol should be avoided when there are signs of cardiovascular compromise. (III; B). If seizures persist despite benzodiazepines, small doses of succinylcholine or similar neuromuscular blocker should be considered to minimize acidosis and hypoxia (I; C).
- If cardiac arrest occurs, we recommend standard Advanced Cardiac Life Support, with the following modifications:
  - If epinephrine is used, small doses (10 to 100 mcg boluses in the adult) are preferred (IIa; C)
  - Vasopressin is not recommended (III; B)
  - Avoid calcium channel blockers and beta-adrenergic receptor blockers (III; C)
  - If ventricular arrhythmias develop, amiodarone is preferred (IIa; B); treatment with local anesthetics (lidocaine or procainamide) is not recommended (III; C)
- Lipid emulsion therapy (IIa; B):
  - Consider administering at the first signs of LAST, after airway management
  - Dosing:
    - 1.5 mL/kg 20% lipid emulsion bolus
    - 0.25 mL/kg/min infusion, continued for at least 10 minutes after circulatory stability is attained.
    - If circulatory stability is not attained, consider re-bolus and increasing infusion to 0.5 mL/kg/min
    - Approximately 10 ml/kg lipid emulsion over 30 minutes is recommended as the upper limit for initial dosing.
- Propofol is not a substitute for lipid emulsion (III; C)
- Failure to respond to lipid emulsion and vasopressor therapy should prompt institution of cardiopulmonary bypass (CPB) (IIa; C). Because there can be considerable lag in beginning CPB, it is reasonable to notify the closest facility capable of providing it when cardiovascular compromise is first identified during an episode of LAST.
References

Disclosure

This speaker has indicated that he or she has no significant financial relationship with the manufacturer of a commercial product or provider of a commercial service that may be discussed in this presentation.