Prevention of Local Anesthetic Systemic Toxicity

Michael F. Mulroy, MD and Michael R. Hejtmanek, MD

Abstract: Although new drugs and techniques may improve outcomes when unintended high blood levels of local anesthetics occur, the primary focus of daily practice should remain the prevention of such events. Although adoption of no single "safety step" will reliably prevent systemic toxicity, the combination of several procedures seems to have reduced the frequency of systemic toxicity since 1981. These include the use of minimum effective doses, careful aspiration, and incremental injection, coupled with the use of intravascular markers when large doses are used. Epinephrine remains the most widely used and studied marker, but its reliability is impaired in the face of β-blockade, anesthesia, advanced age, and active labor. As an alternative, the use of subtoxic doses of local anesthetics themselves can produce subjective symptoms in unpremedicated patients. Fentanyl has also been confirmed to produce sedation in pregnant women when used as an alternative. The use of ultrasound observation of needle placement and injection may be useful, but has also been reported as not completely reliable. Constant vigilance and suspicion are still needed along with a combination of as many of these safety steps as practical.

(*Reg Anesth Pain Med* 2010;35: 177–180)

Avoiding local anesthetic systemic toxicity (LAST) is a goal of the regional anesthesiologist. Toxicity occurs when threshold blood levels are exceeded, which can occur with unintentional direct arterial or venous injection or slow systemic absorption of a large volume of extravascular local anesthetic. Toxicity is manifest as central nervous system symptoms with increasing levels, progressing to cardiac signs with higher levels. Although newer drugs and treatments have potentially decreased the risk of systemic toxicity, prevention of toxic blood levels remains the first priority in regional anesthesia.

Peripheral nerve blockade, with the use of large volumes of local anesthetic, represents a potential for systemic blood levels, both from unintentional intravascular injection and from slower absorption of drug. The frequency of LAST with peripheral nerve block has been reported to vary from 7.5 (Auroy et al[1]) to 20 (Brown et al[2]) per 10,000 blocks in earlier reports, to a level of 2.5 per 10,000 most recently.[3] Epidural anesthesia, given the volume of local anesthetic administered and the vascularity of the epidural space, is particularly susceptible to unintended intravascular injections.[1] Published series documented the frequency of systemic toxicity with epidural anesthesia to be 100 per 10,000 patients before 1981 (Kenepp and Gutsche[4]) and 1.2 to 11 per 10,000 subsequently[2,5] (apparently lower than the risk associated with peripheral nerve blockade[1,2]). This change reflects the adoption of certain "safety steps" after 1981 (introduction of intravenous test doses,[6] emphasis on incremental injection[7]), in response to the case reports of serious cardiotoxicity associated with unintentional intravascular injection of the then-new potent aminoamide local anesthetics. This review seeks to document those recommendations that might be responsible for the perceived decline in frequency of LAST and their current status.

Search Methods

This subject has been reviewed several times. We have reviewed, synthesized, and updated the principal publications from 1997 (Mulroy et al[7]), 2006 (Guay[8]) and 2007 (Bell and Leslie[9]), as well as a previous American Society of Regional Anesthesia and Pain Medicine consensus statement in 2002.[10] Pertinent references in these reviews were consulted. For completion, a further Entrez PubMed search was undertaken using the search words *test dose*, *local anesthetics* and *toxicity*, and then following the *related articles* links in each of these topics. Emphasis was placed on English-language publications and reviews and focused on randomized controlled trials, although relevant case reports were reviewed.

For the purpose of this review, studies that have been analyzed and documented in previous reviews are generally not quoted directly (unless considered "classic" references), and the reader is referred to the previous reviews for detailed bibliographies. Reports and studies published since the latest reviews are cited for completeness.

Dose Limitation

One of the first recommendations (from the US Food and Drug Administration) was to limit the total dose of local anesthetic administered, which was accomplished by restricting the use of 0.75% bupivacaine in obstetric anesthesia. The principle of using the lowest possible total dose of local anesthetic (the product of concentration and volume) is a reasonable precaution. "Maximum recommended doses" for peripheral nerve blocks have been recommended by the manufacturers, but their scientific basis has been questioned.[11] Although they may serve as general guidelines, systemic blood levels vary considerably, depending on the area of injection and the specific drug. Of particular concern is the observation that blood levels cannot be predicted on the milligram-per-kilogram basis, and thus, body weight should not be used as a dosage guideline except in the pediatric population. Local anesthetic systemic toxicity has occurred with lower doses,[12] and vigilance is essential. It seems likely that interpatient variability in sensitivity to the toxic effects of local anesthetic could account for some instances of LAST at very low doses.

Incremental Injection

The concept of limiting individual injections to subtoxic quantities (generally 3–5 mL) and waiting an appropriate interval between increments has not been tested in a scientific manner

From the Department of Anesthesiology, Virginia Mason Medical Center, Seattle, WA.
Accepted for publication March 19, 2009.
Address correspondence to: Michael F. Mulroy, MD, Faculty Anesthesiologists, Virginia Mason Medical Center, 1100 9th Ave, Seattle, WA (e-mail: Michael.Mulroy@vmmc.org).
This work was presented in a preliminary form at the open forum at the American Society of Regional Anesthesia and Pain Medicine Annual Meeting; May 2008; Cancun, Mexico.
James P. Rathmell, MD, served as acting editor-in-chief for this article.

ISSN: 1098-7339
DOI: 10.1097/AAP.0b013e3181d26068

but has been recommended since 1981 by many authors. The exact increment has not been established but is most appropriately seen as a compromise between an interval long enough to be certain that symptoms indicating intravascular injection are detected (eg, ~1 circulation time, ~30–45 secs) and one not so long as to be impractical or increase the likelihood of needle movement that could reduce success of the block or, paradoxically, increase the chance of an intravascular injection.

Use of Local Anesthetics With Lower Toxicity

L-Enantiomers of the more potent aminoamides seem to be less toxic than the racemic mixtures,[13,14] and the use of ropivacaine or levobupivacaine might convey an additional margin of safety compared with racemic bupivacaine when large quantities of local anesthetic are used. Both of these are more potent than lidocaine, and toxicity remains a potential with these drugs.[15,16] Their use does not eliminate the need for the other safety steps discussed here.

Aspiration of Needle or Catheter

Intermittent aspiration of a needle or a catheter has also been recommended in publications and texts, but aspiration alone may fail to identify 0.6% to 2.3% of intravascularly placed catheters.[17] The one exception to this seems to be the use of aspiration with multiorifice catheters in obstetrics, where intravascular markers are less reliable. In this setting, Norris et al[18] reported that aspiration was sufficient to identify 47 of 48 intravascular catheters in 532 patients, whereas epinephrine injection produced an 87% false-positive test (7 of 11 positive tests were associated with catheters that were not intravascularly placed).

Markers of Intravascular Injection

Multiple recommendations have been made regarding potential pharmacologic and mechanical indicators of intravascular injection. The goal of such an intravascular "test dose" is to avoid the consequences associated with the subarachnoid or intravascular deposition of a large volume of local anesthetic by reliably identifying a misplaced catheter or needle. An ideal test dose is safe, simple, reliable (few false-positive tests necessitating removal of a properly placed catheter and no false-negative results after which bolus injection of anesthetic could be disastrous), quick in onset, and widely applicable clinically. Generally, the recommended agents have been described in single publications or from a single institution. Guay[8] has proposed that confirmation of broader applicability and reproducibility for test dosing should be based on at least 2 randomized controlled trials at 2 separate centers. This standard supports the conclusion that a heart rate (HR) increase of 10 beats/min or greater and/or an increase in systolic blood pressure (SBP) of 15 mm Hg or greater with an injection of 10 to 15 μg of epinephrine has both an 80% sensitivity and positive predictive value in nonpregnant adults. Similar criteria establish a positive test in children with an SBP increase 15 mm Hg or greater with an epinephrine dose of 0.5 μg/kg. For pregnant patients, only the injection of 100 μg fentanyl to produce drowsiness or sedation meets these criteria.

Epinephrine

Epinephrine was the first indicator proposed. In 1981, Moore and Batra[6] reported that epinephrine (15 μg) used in combination with 45 mg lidocaine would produce an increase in HR and SBP when injected intravascularly. The small dose of local anesthetic was used historically to produce spinal anesthesia within 2 mins if there was an unintentional subarachnoid injection. Epinephrine was historically used to enhance spinal anesthesia, with a proven clinical safety record for subarachnoid injection, although its potential cardiac effect with intravascular injection was not recognized. Although the epinephrine test dose has been widely adopted after the initial report of its potential usefulness, its efficacy has yet to be confirmed prospectively in a large series. Nevertheless, the HR and blood pressure changes with this marker are the only ones to meet the criteria referenced by Guay.[8]

T-wave monitoring of the epinephrine test response has also been reported.[19] A 25% increase in amplitude is as reliable as the standard HR change but may require off-line analysis of the electrocardiographic tracing, and this approach does not seem to have reached common practice.

Limitations of the Epinephrine Test Dose

Several studies have confirmed that certain patients (those being treated with β-blockers,[20] the elderly,[21] and those sedated[22] or under general[23] or epidural[24] anesthesia) may have an attenuated HR response to the standard epinephrine test dose, and alternatives need to be considered. Parturients present the clinician with unique concerns of test dose sensitivity and applicability given the possibility of simultaneous uterine contractions, patients at risk with an epinephrine injection (preeclampsia), a lowered threshold of HR increase, and the proposed epinephrine-induced decreases in uteroplacental perfusion,[25] although this latter presumption has been questioned.[26] It is not surprising that the largest numbers of alternative tests have been suggested in this group, including air, fentanyl, and isoproterenol. In this situation, careful aspiration of a multiorifice catheter,[18] as mentioned above, may be helpful, but the reliance on small doses, incremental injections, and very-low-dose infusions may provide the greatest safety.

The safety of the epinephrine test dose has also been questioned on the basis of a presumed potential contribution of epinephrine to peripheral nerve toxicity. This presumption has not been documented in humans, and the demonstrated advantages of the epinephrine test outweigh any theoretical risks in this regard.

Local Anesthetic

Subtoxic does of local anesthetics themselves, in the absence of premedication (particularly with benzodiazepines), produce subjective symptoms indicating unintentional intravascular injection. Doses of 100 mg lidocaine or chloroprocaine or 25 mg bupivacaine have been shown to produce subjective symptoms in unpremedicated adults.[7] L-Bupivacaine and ropivacaine do not produce reliable subjective symptoms in adults in a 25-mg dose.[27] The utility of these tests that require subjective reporting may be compromised by the presence of heavy sedation.[28] Ropivacaine at a dose of 60 mg (12 mL of a 0.5% solution) reliably produces symptoms even in premedicated volunteers.[29] Although useful for peripheral injections, all of these proposed local anesthetic test doses include volumes sufficient to produce extensive spinal anesthesia: if used in epidural techniques, a preliminary smaller test dose to exclude subarachnoid injection is required.

Air

Leighton and Gross[30] showed that the injection of 2 mL of air produces an audible response on a precordial Doppler monitor if the needle or catheter is intravenously placed. Although their small series showed statistically reliable changes, their results have not been reproduced elsewhere. This test may not be practical in areas outside the delivery suite, where Doppler monitoring may not be readily available. The safety of

TABLE 1. Recommendations for Preventing LAST

- There is no single measure that can prevent LAST in clinical practice.
- Use the lowest effective dose of local anesthetic (dose = product of volume × concentration) (I, C).
- Use incremental injection of local anesthetics—administer 3- to 5-mL aliquots, pausing 15–30 secs between each injection. When using a fixed needle approach, eg, landmark, paresthesia-seeking, or electrical stimulation, time between injections should encompass 1 circulation time (~30–45 secs); however, this ideal may be balanced against the risk of needle movement between injections. Circulation time may be increased with lower-extremity blocks. Use of larger dosing increments would dictate the need for longer intervals to reduce the cumulative dose from stacked injections before an event of LAST. Incremental injection may be less important with ultrasound guidance, given that frequent needle movement is often used with the technique (I, C).
- Aspirate the needle or catheter before each injection, recognizing that there is ~2% false-negative rate for this diagnostic intervention (I, C).
- When injecting potentially toxic doses of local anesthetic, use of an intravascular marker is recommended. Although epinephrine is an imperfect maker and its use is open to physician judgment, its benefits likely outweigh its risks in the majority of patients (IIa, B):
  - Intravascular injection of epinephrine 10–15 μg/mL in adults produces a ≥10-beat HR increase or a ≥15–mm Hg SBP increase in the absence of β-blockade, active labor, advanced age, or general/neuraxial anesthesia.
  - Intravascular injection of epinephrine 0.5 μg/kg in children produces a ≥15–mm Hg increase in SBP.
  - Appropriate subtoxic doses of local anesthetic can produce subjective symptoms of mild systemic toxicity (auditory changes, excitation, metallic taste, etc) in unpremedicated patients.
  - Fentanyl 100 μg produces sedation if injected intravascularly in laboring patients.
- Ultrasound guidance may reduce the frequency of intravascular injection, but actual reduction of LAST remains unproven in humans. Individual reports describe LAST despite the use of ultrasound-guided regional anesthesia. The overall effectiveness of ultrasound guidance in reducing the frequency of LAST remains to be determined (IIa, C).

The class of recommendation and level of evidence for each intervention are given in parenthesis.

this technique in the presence of a patent foramen ovale has not been established.

Other Markers

Isoproterenol has been studied as a potential marker in obstetrics patients, but its safety (in regard to potential neurotoxicity) for subarachnoid injection has not been documented. Both succinylcholine and fentanyl have been studied, the latter meeting Guay's[8] criteria for acceptance, but both of these markers have limitations in the event of systemic absorption or intravascular injection.

Detection by Imaging Methods

The recent introduction of ultrasound guidance for peripheral nerve blockade has raised the potential of reducing the possibility of unintentional intravascular injection by constant visualization of the needle tip. One case report supports this hypothesis because the intravascular injection was detected by the ultrasound, but the needle had already entered the artery while being visualized, raising concern that this may not be a reliable safety measure.[31] Other case reports have confirmed the occurrence of intravascular injection despite ultrasound use.[32,33] Taken together, these reports confirm that even when the needle is visualized using the in-line technique, the tip is not always accurately identified. Another imaging proposal has been the suggested use of radiopaque contrast dye when placing catheters,[34] but this would not seem to be practical in common use.

DISCUSSION

Although there is agreement that prevention is a critical step in avoiding the consequences of local anesthetic toxicity, as yet there is no single method to ensure prevention of unwanted high blood levels. With peripheral nerve block, avoidance of high doses of local anesthetic (to reduce the chance of slow absorption of toxic amounts) coupled with aspiration, incremental injection, and the use of intravascular markers (to detect intravascular injection) seems to reduce the potential for toxicity. The role of ultrasound in avoiding unintentional intravascular needle placement is unclear. For epidural injections, the use of the same steps is critical, and the use of some marker for intravascular injection has become common practice. Although epinephrine remains the most common marker, there are limitations on its use that require awareness of alternatives and caution in interpretation of results. There is no single safety step that ensures avoidance of toxicity, so employment of multiple safety steps and constant vigilance are essential, as well as preparedness to treat the rare occurrence of a toxic reaction.

Recommendations regarding prevention of LAST are summarized in Table 1.

REFERENCES

1. Auroy Y, Narchi P, Messiah A, Litt L, Rouvier B, Samii K. Serious complications related to regional anesthesia: results of a prospective survey in France. *Anesthesiology.* 1997;87:479–486.
2. Brown DL, Ransom DM, Hall JA, Leicht CH, Schroeder DR, Offord KP. Regional anesthesia and local anesthetic-induced systemic toxicity: seizure frequency and accompanying cardiovascular changes. *Anesth Analg.* 1995;81:321–328.
3. Auroy Y, Benhamou D, Bargues L, et al. Major complications of regional anesthesia in France: the SOS Regional Anesthesia Hotline Service. *Anesthesiology.* 2002;97:1274–1280.
4. Kenepp NB, Gutsche BB. Inadvertent intravascular injections during lumbar epidural anesthesia. *Anesthesiology.* 1981;54:172–173.
5. Tanaka K, Watanabe R, Harada T, Dan K. Extensive application of epidural anesthesia and analgesia in a university hospital: incidence of complications related to technique. *Reg Anesth.* 1993;18:34–38.
6. Moore DC, Batra MS. The components of an effective test dose prior to epidural block. *Anesthesiology.* 1981;55:693–696.
7. Mulroy MF, Norris MC, Liu SS. Safety steps for epidural injection of local anesthetics: review of the literature and recommendations. *Anesth Analg.* 1997;85:1346–1356.
8. Guay J. The epidural test dose: a review. *Anesth Analg.* 2006;102:921–929.
9. Bell DN, Leslie K. Detection of intravascular epidural catheter placement: a review. *Anaesth Intensive Care.* 2007;35:335–341.
10. Mulroy MF. Systemic toxicity and cardiotoxicity from local anesthetics: incidence and preventive measures. *Reg Anesth Pain Med.* 2002;27:556–561.
11. Rosenberg PH, Veering BT, Urmey WF. Maximum recommended

doses of local anesthetics: a multifactorial concept. *Reg Anesth Pain Med*. 2004;29:564–575.

12. Ala-Kokko TI, Löppönen A, Alahuhta S. Two instances of central nervous system toxicity in the same patient following repeated ropivacaine-induced brachial plexus block. *Acta Anaesthesiol Scand*. 2000;44:623–626.
13. Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth Analg*. 1989;69:563–569.
14. Mather LE, Chang DH. Cardiotoxicity with modern local anaesthetics: is there a safer choice? *Drugs*. 2001;61:333–342.
15. Plowman AN, Bolsin S, Mather LE. Central nervous system toxicity attributable to epidural ropivacaine hydrochloride. *Anaesth Intensive Care*. 1998;26:204–206.
16. Khoo LP, Corbett AR. Successful resuscitation of an ASA 3 patient following ropivacaine-induced cardiac arrest. *Anaesth Intensive Care*. 2006;34:804–807.
17. Pan PH, Bogard TD, Owen MD. Incidence and characteristics of failures in obstetric neuraxial analgesia and anesthesia: a retrospective analysis of 19,259 deliveries. *Int J Obstet Anesth*. 2004;13:227–233.
18. Norris MC, Ferrenbach D, Dalman H, et al. Does epinephrine improve the diagnostic accuracy of aspiration during labor epidural analgesia? *Anesth Analg*. 1999;88:1073–1076.
19. Takahashi S, Tanaka M, Toyooka H. The efficacy of hemodynamic and T-wave criteria for detecting intravascular injection of epinephrine test dose in propofol-anesthetized adults. *Anesth Analg*. 2002;94: 717–722.
20. Guinard JP, Mulroy MF, Carpenter RL, Knopes KD. Test doses: optimal epinephrine content with and without acute beta-adrenergic blockade. *Anesthesiology*. 1990;73:386–392.
21. Guinard JP, Mulroy MF, Carpenter RL. Aging reduces the reliability of epidural epinephrine test doses. *Reg Anesth*. 1995;20:193–198.
22. Tanaka M, Sato M, Kimura T, Nishikawa T. The efficacy of simulated intravascular test dose in sedated patients. *Anesth Analg*. 2001;93:1612–1617.
23. Liu SS, Carpenter RL. Hemodynamic responses to intravascular injection of epinephrine-containing epidural test doses in adults during general anesthesia. *Anesthesiology*. 1996;84:81–87.
24. Liu SS. Hemodynamic responses to an epinephrine test dose in adults during epidural or combined epidural-general anesthesia. *Anesth Analg*. 1996;83:97–101.
25. Mulroy M, Glosten B. The epinephrine test dose in obstetrics: note the limitations. *Anesth Analg*. 1998;86:923–925.
26. James FM 3rd, Greiss FC Jr, Kemp RA. An evaluation of vasopressor therapy for maternal hypotension during spinal anesthesia. *Anesthesiology*. 1970;33:25–34.
27. Owen MD, Gautier P, Hood DD. Can ropivacaine and levobupivacaine be used as test doses during regional anesthesia? *Anesthesiology*. 2004;100:922–925.
28. Bernards CM, Hadzic A, Suresh S, Neal JM. Regional anesthesia in anesthetized or heavily sedated patients. *Reg Anesth Pain Med*. 2008;33:449–460.
29. McCartney CJ, Murphy DB, Iagounova A, Chan VW. Intravenous ropivacaine bolus is a reliable marker of intravascular injection in premedicated healthy volunteers. *Can J Anaesth*. 2003;50: 795–800.
30. Leighton BL, Gross JB. Air: an effective indicator of intravenously located epidural catheters. *Anesthesiology*. 1989;71:848–851.
31. VadeBoncouer TR, Weinberg GL, Oswald S, Angelov F. Early detection of intravascular injection during ultrasound-guided supraclavicular brachial plexus block. *Reg Anesth Pain Med*. 2008;33:278–279.
32. Loubert C, Williams SR, Hélie F, Arcand G. Complication during ultrasound-guided regional block: accidental intravascular injection of local anesthetic. *Anesthesiology*. 2008;108:759–760.
33. Zetlaoui PJ, Labbe JP, Benhamou D. Ultrasound guidance for axillary plexus block does not prevent intravascular injection. *Anesthesiology*. 2008;108:761.
34. Skinner AV, Chalkiadis GA. Clinically unrecognized intravascular placement of epidural catheter in a child—an argument for the use of radio-opaque contrast? *Paediatr Anaesth*. 2007;17:387–392.