Systemic Toxicity and Cardiotoxicity From Local Anesthetics: Incidence and Preventive Measures

Michael F. Mulroy, M.D.

Central nervous system toxicity from unintentionally high blood levels has been a significant concern and risk with local anesthetics since their discovery. Cardiotoxicity associated with toxic blood levels of long-acting local anesthetics[1] has heightened concern about systemic blood levels in the last 20 years. This review will discuss the apparent incidence of systemic toxicity, the situations in which it occurs, some of the other risks of regional anesthesia, and appropriate safety steps to reduce the frequency of both systemic reactions and cardiotoxicity.

Systemic Toxicity

Systemic toxic reactions to local anesthetics are manifested by a progressive spectrum of neurological symptoms as blood levels rise. Initial symptoms suggest some form of central nervous system excitation and are often described as a ringing in the ears, a metallic taste in the mouth, or a circumoral tingling. With increasing blood levels of local anesthetics, there is progression to motor twitching in the periphery followed by grand mal seizures. These higher blood levels are associated with coma and eventually respiratory arrest. At extremely high levels, cardiac arrhythmia or hypotension and cardiovascular collapse occur. Unintentionally toxic blood levels are possible after intra-arterial, intravenous, or peripheral tissue injections of local anesthetics.

Intra-arterial injections are usually associated with regional anesthetic techniques in the neck (interscalene block, cervical plexus block, stellate ganglion block) and are usually characterized by a rapid onset of symptoms as the local anesthetic directly enters the cerebral circulation. Small quantities are sufficient to produce symptoms because the blood concentration in the arterial supply to the brain is higher than with any other source of toxicity. Fortunately, this type of seizure is short lived because the quantity injected is relatively small and the blood flow to the brain rapidly removes the drug.

More commonly, blood levels are elevated after unintentional intravenous injection during the performance of epidural or caudal anesthesia. The engorgement of veins in the epidural space, especially in the pregnant state, makes vessel entry easy, whereas the frequently subatmospheric pressure of the epidural space may retard a positive flow of blood to warn the anesthesiologist. Bolus injections of local anesthetic used for these blocks, despite clearance by the pulmonary and hepatic tissues, are sufficient to produce blood levels high enough to cause central nervous system toxicity. Seizures in this situation can be more prolonged than after arterial injection.

A third source of toxicity is the absorption of local anesthetic from peripheral injection, such as peripheral nerve block or plastic surgery procedures. In this situation, the onset of symptoms may be delayed 20 to 30 minutes, and the concentration of local anesthetic in the circulation may remain elevated for an even longer period of time than after intravenous injection. The blood levels produced depend on the site of injection, the total mass of drug, and the presence or absence of vasoconstrictors.

Prevention of arterial injection is best accomplished with frequent aspiration and injection of small increments when performing regional techniques in the neck. Safety steps to guard against unintentional intravenous injection, particularly during epidural and caudal anesthesia, have been the subject of much research and discussion,[2] especially since the recognition of the potential cardiotoxicity of long-acting aminoamide local anesthetics after 1980.[1] These safety steps include aspiration (gentle negative pressure on the needle or catheter), incremental injection, dose limitation, and the use of markers of intravascular injection. With peripheral injection, these steps are also of some use, but the principal precaution has been the limitation

From the Department of Anesthesiology, Virginia Mason Medical Center, Seattle, Washington.

Presented at the ASRA Conference on Local Anesthetic Toxicity, Miami, FL, November 2001.

Reprints not available.

1098-7339/02/2706-0003$35.00/0
doi:10.1053/rapm.2002.37127

Table 1. Frequency of Systemic Toxic Reactions

Author	Epidural	STR	Rate	PNB	STR	Rate
Pre-1982 rate						
Blundell, 1955[29]	790	87	110			
Bonica, 1957[3]	3,637	116	320			
Moore, 1978[30]	6,729	13	20			
Kenepp, 1981[31]	4,003	40	100			
Post-1982 rate	15,159	550	100*			
Tanaka, 1993[4]	17,439	20	11			
Brown, 1995[5]	16,870	2	1.2	7,532	15	20
Auroy, 1997[6]	30,413	4	1.3	21,278	16	7.5
	64,722	26	4*			
Giaufre, 1996[8] (pediatric patients)	2,824	3	10	9,396	0	0
Borgeat, 2001[9]				521	1	20

Abbreviations: STR, systemic toxic reactions; PNB, peripheral nerve block.
NOTE. Rate = frequency per 10,000.
*Difference significant at $P < .001$, χ^2 analysis.

of dosage to the "maximum recommended doses" of local anesthetics (as described in standard texts and in the *Physicians' Desk Reference* [PDR]) and the reduction of blood levels by the addition of epinephrine to the local anesthetic. Although these recommended maximum doses have served as useful guidelines, the scientific basis for their determination is tenuous, and actual blood levels vary considerably with the site of injection. Toxic reactions have occurred with doses below the recommended maximum, and higher quantities have been used without apparent ill effect. Nevertheless, these guidelines appear to be useful, although they do not appear to be as effective as the steps suggested to prevent toxicity from epidural injection (see later).

The frequency of systemic toxicity appears to have changed dramatically since 1981. Before this time, the cumulative frequency of systemic toxicity in published series of large numbers of patients receiving epidural injections is 100 per 10,000 (Table 1). Bonica et al.[3] reported an incidence of over 3% in obstetrical patients who developed systemic toxicity. After 1981, when awareness of the potential for serious cardiotoxicity emerged, there was greater attention to safety steps with local anesthetics, particularly with epidural injection. Recent reports of large-scale experiences with regional anesthetic techniques in adults have shown a clinically and statistically significant reduction in the frequency of systemic toxic reactions, especially associated with epidural anesthesia.[2] Tanaka et al.[4] reported a frequency of 11 per 10,000 epidural anesthetics in a university practice in which safety steps were used but not the use of epinephrine test doses. Brown et al.[5] reviewed the Mayo Clinic experience, where epinephrine test doses are commonly used, and reported an incidence of 1.2 per 10,000 epidural anesthetics, similar to the frequency of systemic toxic reactions after epidural anesthesia reported by Auroy in the French experience.[6] In these large series using multiple safety steps, the risk of systemic toxic reaction after epidural anesthesia appears to have declined significantly, perhaps by a factor of 25.

This decline in the frequency of systemic toxicity is confirmed by other morbidity reports. A review of the maternal morbidity and mortality statistics in the United States from the Center for Communicable Diseases by Hawkins et al.[7] reported "a significant decline in maternal mortality related to regional anesthesia techniques following 1984." A similar pattern appears in the data available from the American Society of Anesthesiologists Closed Claims study project.[8] That database contains 42 cases involving intravascular local anesthetic injection, representing 0.7% of recorded closed claims filed against anesthesiologists. Within that small subset, there has been a trend toward a decreasing representation of this syndrome over the last 3 decades, paralleled by a decrease in frequency of serious outcomes (death and permanent brain damage) associated with intravascular injection (Fig 1). Interestingly, over the same 3 decades, it appears that test doses have been used more frequently because there has been a steady decline in the percentage of claims for local anesthetic toxicity that did not use some form of a test dose.

The decline in systemic toxicity is most dramatic in lumbar epidural anesthesia. The potential for systemic toxic reactions after other regional techniques appears to be relatively higher, although there are not comparative data to allow an evaluation of any change in the time period after 1980. In Brown's report,[5] the Mayo Clinic experienced a higher frequency of systemic toxic reactions after caudal epidural anesthesia (69/10,000) than after

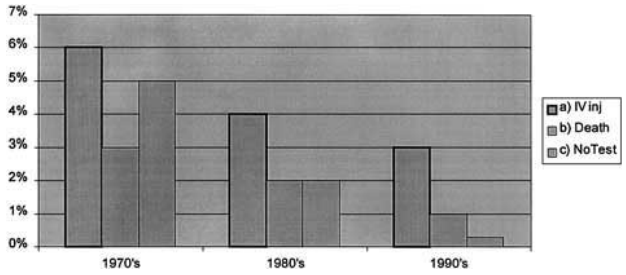

Fig 1. Closed Claims Data Experience. Percentage of regional anesthesia cases in the ASA Closed Claims database that involved claims that arose from an intravascular injection of local anesthetic, resulted in death, or did not involve the use of a test dose sorted by decade. IV inj, intravenous injection.

lumbar epidural injections, although this does not appear to be confirmed in a pediatric practice in which caudal anesthesia is used more frequently (1.3/10,000, Giaufre et al.[8]). This lower frequency in children could be related to greater familiarity of the practitioners or the lower drug mass frequently used for analgesia in this population. Peripheral nerve blocks, especially brachial plexus anesthesia, also appear to be associated with a relatively higher risk for systemic toxic reactions. Brown et al.[5] reported a frequency of 20 per 10,000 in the Mayo Clinic experience. Auroy's rate was 7.5 systemic toxic reactions per 10,000 peripheral nerve blocks in France (6). Borgeat et al.[9] found a similar frequency of 20 per 10,000 in his smaller report on brachial plexus blocks.

Cardiotoxicity

Much of the change in frequency of systemic toxic reaction was associated with the focus on cardiotoxicity of local anesthetics after 1980. This was based on case reports by Albright[1] suggesting that the longer acting aminoamides, bupivacaine and etidocaine, had the potential for cardiac arrhythmias and arrest at blood levels associated with the production of systemic toxic reactions. Extensive animal research has confirmed that bupivacaine blocks sodium conduction in the cardiac conduction fibers at concentrations slightly above those associated with the development of seizures in other animal studies.[10] There have been multiple case reports of cardiac arrest and electrical standstill after bupivacaine systemic toxicity.[11-15] Many have been associated with difficult resuscitation, particularly in the obstetrical population. Large doses of epinephrine are required to reverse this cardiotoxicity. Because of the difficulty of resuscitation, the Food and Drug Administration has recommended reduced dosing in the obstetrical practice in the form of proscribing the 0.75% concentration for use in this setting. Although other mechanisms may have some impact, it appears that cardiotoxicity is produced primarily by a "fast in, slow out" blockade of the sodium channel. Laboratory data suggest this toxicity is associated with the dextro (R−) enantiomer of bupivacaine. The L-enantiomer is associated with significantly less toxicity in animal models and the L-enantiomer of ropivacaine appears to be even less toxic.[16-18] Although there is some concern that ropivacaine may be less potent than bupivacaine (and thus require higher milligram dosages),[19] there still appears to be a greater safety margin than with racemic bupivacaine. Several clinical trials have suggested that the L-enantiomer alternatives (levobupivacaine and ropivacaine) both produce effective analgesia in appropriate concentrations and might serve as safer alternatives to bupivacaine if systemic toxicity or cardiotoxicity are significant risks.

The frequency of bupivacaine cardiotoxicity is difficult to evaluate. The true incidence cannot be determined from large claims studies.[20,21] Cardiotoxicity does not appear to be an inevitable consequence of bupivacaine systemic toxicity. In the Mayo Clinic series,[5] 16 of the 17 patients who had systemic toxic reactions had received bupivacaine and none had cardiac arrhythmias. Similarly, in Auroy's report of the French series 14 of the 24 patients experiencing seizures had been given bupivacaine and none developed cardiac symptoms.[6] Thus, it is difficult to project the potential risk for cardiotoxicity after the use of bupivacaine. The method of Hanley and Lippman-Hand can be used to estimate the risk of an event that has not occurred in prospective series.[23] Their probability analysis predicts that the upper limit of a 1-sided 95% confidence interval for a low-frequency risk that has not been observed is equivalent to 3/n, where n is the number of observations without an adverse event. In this case, n = 30, suggesting that the maximum risk of cardiotoxicity after a systemic toxic reaction involving bupivacaine would be 10%, although the numbers to justify this conclusion are small. Although there have been a handful of case reports of systemic toxic reactions after levobupivacaine and ropivacaine, there are no reports of cardiotoxicity. There are too few reports of systemic toxicity to allow the calculation of a presumed risk frequency with these drugs.

Safety Steps to Avoid Intravascular Injection

Many factors may have been associated with the apparent decline in systemic toxic reactions, includ-

Table 2. Criteria for Positive Epinephrine Test Dose

Patient under age 60, awake, not on beta blockers	HR increase > 20 bpm
	SBP increase > 15 mm Hg
Beta blockade	SBP > 15 mm Hg
Age over 60 years	HR increase > 9 bpm
	SBP increase > 15 mm Hg
General anesthesia	HR increase > 8 bpm
	SBP increase > 13 mm Hg

NOTE. All changes in first 120 seconds after injection.
Abbreviations: HR, heart rate SBP, systolic blood pressure.

ing a generalized increased emphasis on safety as reflected by the creation of the Closed Claims database, better anesthesia teaching as required by changes in the Residency Review Committee requirements, or better monitoring. Nevertheless, 1981 marked the beginning of the publication and discussion of specific enhanced safety measures for the performance of epidural anesthesia. Safety steps that appear to have been associated with the decreased frequency of systemic toxic reactions include aspiration, incremental injection, dose control, and the use of test doses. Of all of these, the issue of the test dose has been most extensively studied. Among the drugs used, epinephrine has been most frequently advocated and most extensively studied. Injection of 15 μg epinephrine into the venous system in normal, healthy adults will produce a tachycardia within 20 seconds of the injection, which is readily detectable by mechanical or electrical pulse monitors. Test dose reliability is diminished in the presence of beta blockade, advanced age, or in the presence of general or combined epidural-general anesthesia. Its efficacy and reliability have been debated in the obstetrical population, and adaptation to the pediatric population also remains controversial. Several modifications of the criteria for assessing positive response in the presence of the interfering factors mentioned above have been published[2] (Table 2). Despite these drawbacks and modifications, the epinephrine test dose still remains the simplest and most reliable test under most circumstances. In situations in which it is not practical, the use of moderate doses of local anesthetics themselves have been shown to be effective as alternatives. This requires the use of 100 mg lidocaine or chloroprocaine or 25 mg bupivacaine to produce subtoxic clinical symptoms in the unpremedicated patient. Midazolam premedication will interfere with the detection of the symptoms.[2]

It appears that no single test or procedure is completely reliable for detecting or preventing intravascular injection. A combination of all of these steps, however, does seem to be associated with the decreased frequency of systemic toxic reactions, and the use of all of these safety steps appears to be justified and should be encouraged.

Other Risks

Although systemic toxicity remains the historical focus of concern with local anesthetics, data suggest other risks associated with regional anesthetic techniques may be similar in frequency and significance (Table 3). In the French experience, for example, neurologic injury and cardiac arrest were both more frequent than systemic toxic reaction.[6] In the United States Closed Claims experience, spinal cord injuries were the leading cause of nerve injury claims in the last decade.[24] The risk of cardiac arrest with spinal anesthesia appears to be 3 times higher than the risk of having a systemic toxic reaction with all regional techniques combined. Pollard[25] concluded that the apparent risk of cardiac arrest during spinal anesthesia is approximately 7 for every 10,000 anesthetics. Although most of these cardiac arrests are resuscitated, the American Society of Anesthesiologists closed claims data suggest that there are a number of them with more serious adverse outcomes.[26] Death from this complication occurred in 1.5/10,000 spinals in the French experience (Table 3), and it remains the leading cause of regional anesthesia-related deaths in the ASA Closed Claims experience.[21]

In considering mortality risk, death after elective liposuction has been a recent concern. After 5 unexpected deaths in the New York area,[27] a review of plastic surgery experiences suggested that cardiac arrest and systemic local anesthetic reactions were a

Table 3. Regional Anesthetic Nonvascular Complications (rate per 10,000)

Author	Subjects	Nerve Injury	Cardiac Arrest	Death
Dahlgren, 1995[32]	8,501 spinal	3.5	NA	NA
	9,232 epidural	7.5	NA	NA
Auroy, 1997[6]	40,640 spinal	5.9	6.4	1.5
	30,413 epidural	2	1	0
	21,278 PNB	1.9	1.4	0.5
Borgeat, 2001[9]	521 brachial plexus blocks	20	none	0
Grazer, 2000[28]	495,246 lipoplasties	NA	NA	1.9

Abbreviation: NA, data not available.

significant risk during tumescent liposuction. A survey of cosmetic surgeons revealed an overall mortality rate estimated at 1.9 per 10,000 cases, from all causes.[28] The authors note that this is similar to the overall annual rate of motor vehicle accident mortality in the United States in 1996 (1.6/10,000). These probabilities are similar to the apparent frequency of systemic toxic reactions with epidural anesthesia. If the above calculations of the probability of bupivacaine cardiotoxicity after a systemic toxic reaction are valid, then one might speculate that risk of death from driving a car or having liposuction is ten times greater than that of bupivacaine cardiotoxicity after a systemic toxic reaction during an epidural anesthetic using appropriate safety steps.

Overall, available data suggest that although systemic toxic reactions to local anesthetics and cardiotoxicity remain significant risks, these problems appear to have evolved to a level where they are comparable to other significant risks of regional techniques, all of which deserve our continued attention and vigilance.

Summary and Recommendations

In light of the data reviewed, several observations appear warranted:

1. Systemic toxicity from local anesthetics appears to have declined in frequency in the last 20 years but still remains a potential risk.
2. The safety steps introduced around 1980 (specifically, aspiration, incremental injection, dose limitation, and test doses) appear to be effective contributions to producing this change, and should be continued in anesthetic practice.
3. There appear to be other significant risks associated with regional anesthesia, especially nerve injury and cardiac arrest, which merit further study and development of aggressive strategies to reduce their frequency and severity.
4. Cardiotoxicity from bupivacaine, along with the frequency of systemic toxic reactions, appears to have declined since 1980 but still remains a risk for patients. Continued vigilance is certainly required, particularly when performing procedures (caudal anesthesia, peripheral nerve block), which appear to have a higher potential for systemic toxicity. In these situations, the use of alternative long-acting aminoamide levoenantiomers may be justified to further reduce the risk to our patients.

References

1. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979;51:285-287.
2. 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.
3. Bonica J, Backup P, Anderson C. Peridural block: Analysis of 3,637 cases and a review. *Anesthesiology* 1957;18:723-784.
4. 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.
5. 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.
6. 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.
7. Hawkins JL, Koonin LM, Palmer SK, Gibbs CP. Anesthesia-related deaths during obstetric delivery in the United States, 1979-1990. *Anesthesiology* 1997;86: 277-284.
8. Giaufre E, Dalens B, Gombert A. Epidemiology and morbidity of regional anesthesia in children: A one-year prospective survey of the French-Language Society of Pediatric Anesthesiologists. *Anesth Analg* 1996;83:904-912.
9. Borgeat A, Ekatodramis G, Kalberer F, Benz C. Acute and nonacute complications associated with interscalene block and shoulder surgery: A prospective study. *Anesthesiology* 2001;95:875-880.
10. Clarkson CW, Hondeghem LM. Mechanism for bupivacaine depression of cardiac conduction: Fast block of sodium channels during the action potential with slow recovery from block during diastole. *Anesthesiology* 1985;62:396-405.
11. Conklin KA, Ziadlou-Rad F. Bupivacaine cardiotoxicity in a pregnant patient with mitral valve prolapse. *Anesthesiology* 1983;58:596.
12. Gould DB, Aldrete JA. Bupivacaine cardiotoxicity in a patient with renal failure. *Acta Anaesthesiol Scand* 1983;27:18-21.
13. Fortuna A, Fortuna Ade O. Bupivacaine-induced cardiac arrest. *Anesth Analg* 1990;71:561-562.
14. Long WB, Rosenblum S, Grady IP. Successful resuscitation of bupivacaine-induced cardiac arrest using cardiopulmonary bypass. *Anesth Analg* 1989;69:403-406.
15. McCloskey JJ, Haun SE, Deshpande JK. Bupivacaine toxicity secondary to continuous caudal epidural infusion in children. *Anesth Analg* 1992;75:287-290.
16. Graf BM, Martin E, Bosnjak ZJ, Stowe DF. Stereospecific effect of bupivacaine isomers on atrioventricular

conduction in the isolated perfused guinea pig heart. *Anesthesiology* 1997;86:410-419.
17. Groban L, Deal DD, Vernon JC, James RL, Butterworth J. Cardiac resuscitation after incremental overdosage with lidocaine, bupivacaine, levobupivacaine, and ropivacaine in anesthetized dogs. *Anesth Analg* 2001;92:37-43.
18. Weiskopf RB, Nau C, Strichartz GR. Drug chirality in anesthesia. *Anesthesiology* 2002;97:497-502.
19. Polley LS, Columb MO, Naughton NN, Wagner DS, van de Ven CJ. Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor: Implications for therapeutic indexes. *Anesthesiology* 1999;90:944-950.
20. Aromaa U, Lahdensuu M, Cozanitis DA. Severe complications associated with epidural and spinal anaesthesias in Finland 1987-1993. A study based on patient insurance claims. *Acta Anaesthesiol Scand* 1997; 41:445-452.
21. Cheney FW. High-severity injuries associated with regional anesthesia in the 1990s. *ASA Newsletter* 2001;65:6-8.
22. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. *JAMA* 1983;249:1743-1745.
23. Ho AM, Dion PW, Karmakar MK, Lee A. Estimating with confidence the risk of rare adverse events, including those with observed rates of zero. *Reg Anesth Pain Med* 2002;27:207-210.
24. Cheney FW, Domino KB, Caplan RA, Posner KL. Nerve injury associated with anesthesia: A closed claims analysis. *Anesthesiology* 1999;90:1062-1069.
25. Pollard JB. Cardiac arrest during spinal anesthesia: common mechanisms and strategies for prevention. *Anesth Analg* 2001;92:252-256.
26. Caplan RA, Ward RJ, Posner K, Cheney FW. Unexpected cardiac arrest during spinal anesthesia: A closed claims analysis of predisposing factors. *Anesthesiology* 1988;68:5-11.
27. Rao RB, Ely SF, Hoffman RS. Deaths related to liposuction. *N Engl J Med* 1999;340:1471-1475.
28. Grazer FM, de Jong RH. Fatal outcomes from liposuction: Census survey of cosmetic surgeons. *Plast Reconstr Surg* 2000;105:436-446; discussion 447-438.
29. Blundell A, Bodell B, Andorko J. Clinical evaluation of drugs used in obtaining lumbar epidural anesthesia. *Anesthesiology* 1955;16:386-393.
30. Moore DC, Bridenbaugh LD, Thompson GE, Balfour RI, Horton WG. Bupivacaine: A review of 11,080 cases. *Anesth Analg* 1978;57:42-53.
31. Kenepp NB, Gutsche BB. Inadvertent intravascular injections during lumbar epidural anesthesia. *Anesthesiology* 1981;54:172-173.
32. Dahlgren N, Tornebrandt K. Neurological complications after anaesthesia. A follow-up of 18,000 spinal and epidural anaesthetics performed over three years. *Acta Anaesthesiol Scand* 1995;39:872-880.