4 Local Anesthetic Toxicity

David L. Brown

Effective regional block is not possible without the use of local anesthetics. Even though local anesthetics have been used for more than 115 years, details about balancing risks of their toxic effects with the benefits of their therapeutic effects remain poorly focused for many clinicians. In this chapter, the most frequent toxic effect of local anesthetics – local anesthetic systemic toxicity – will be covered, as will the less-frequent clinical situations of allergy to local anesthetics and myelotoxicity.

History of Local Anesthetic Systemic Toxicity

Local anesthetic toxicity was recognized even before cocaine was introduced as a surgical anesthetic in humans. In 1868, the first report of cocaine-induced seizures in animals was cited by Moreno y Maiz.[1] At the same time, Maiz also reported cutaneous anesthesia and asked whether cocaine might be used as a local anesthetic.[2] Almost 20 years passed before Koller introduced regional anesthesia to the world by applying cocaine to the eye.[3] Shortly after the introduction of cocaine as a topical anesthetic, physicians across the world began injecting cocaine near peripheral nerves, as well as into the spinal and epidural spaces.[1] Within 10 years of the introduction of regional anesthesia, reviews of "cocaine poisoning" appeared in the literature. Mattison[4] cited more than 125 cases of toxic reactions to cocaine, including seven deaths, with the initial report.

Despite this cocaine toxicity, the use of cocaine for peripheral nerve block was a real advantage during the later half of the 19th century, when general anesthetic techniques were still in their infancy. Nevertheless, although knowledge about the pharmacodynamics of cocaine accumulated, individuals paid a price in terms of toxicity and time. Rapid absorption limited the safe quantity of cocaine to 30 mg and the useful duration of anesthesia to 10–15 minutes.[3] Reclus suggested that during infiltration anesthesia with cocaine, a weak solution be used to avoid toxic reactions and fatalities. It seems that Reclus clearly understood that the basic cause of accidental deaths during cocaine anesthesia was from the use of unnecessarily high concentrations and, thus, high total doses.[5] It was this toxicity of cocaine, coupled with its tremendous advantages for surgery, which led to a search for less-toxic substitutes. In 1904, such a substitute – procaine (Novocain) – was introduced by Einhorn.[6]

The introduction of a safer local anesthetic did not stop interest in local anesthetic toxicity. In 1919, Eggleston and Hatcher[7] published a comprehensive summary of the prevention and treatment of local anesthetic reactions. At this early time, they were able to identify most issues of importance in the prevention and treatment of local

B. T. Finucane (ed.), *Complications of Regional Anesthesia*

anesthetic systemic toxicity. They found that animals were a suitable experimental model, that different local anesthetics were additive in their toxicity, that the combination of artificial respiration and stimulation of the heart by intravenous epinephrine allowed twice the average fatal dose of local anesthetics to be administered to cats, and that the addition of epinephrine to subcutaneous injection of local anesthetics significantly reduced local anesthetic systemic toxicity. In 1925, Tatum, Atkinson, and Collins matured the concepts of Eggleston and Hatcher by identifying that artificial respiration alone was insufficient to increase the minimal fatal dose of cocaine in the rabbit, whereas the prophylactic administration of barbiturates to the dog produced a condition in which the tolerance to a toxic dose increased fourfold.[8] Likewise, they identified that seizures related to local anesthetic systemic toxicity are completely, practically, and instantaneously controlled by barbiturate injection and that the likelihood of recovery from such a reaction to cocaine in the dog is roughly inversely proportional to the duration the seizures were permitted to continue.

In addition to the insights about local anesthetic systemic toxicity provided by these early researchers, Vandam[9] identified two other major contributions to the understanding and treatment of local anesthetic reactions. He believed that Tanaka and Yamasaki's[10] report on the selective blocking of cortical inhibitory synapses by lidocaine (a surrogate for other local anesthetics) with the excitatory synapses being more resistant to the drug was a major contribution. He outlined a second major contribution by Englesson, who in 1974 reported the observance of seizure activity in the amygdala on cortical electroencephalography (EEG) after the intravenous infusion of several different local anesthetics in the cat. These two contributions helped mature physicians' understanding of the anatomic and neurophysiologic locus of local anesthetic-induced seizures and led to more complete knowledge of the basic science of a local anesthetic reaction.

Basic Science

As the researchers detailed, local anesthetic systemic toxic responses are related to blood levels of the local anesthetic and, more specifically, to the levels found in the central nervous system (CNS). There is an initial generalized excitatory phase of a local anesthetic systemic toxic reaction related to increasing levels of local anesthetic in the blood of the CNS, which again is a result of a blocking of inhibitory pathways in the amygdala. This inhibition allows facilitatory (excitatory) neurons to function unopposed.[11] As levels of local anesthetic in the blood and brain increase further, both inhibitory and facilatory pathways are inhibited, eventually resulting in CNS depression. Can this brief and simplified view of neurophysiologic anatomy and reaction to local anesthetic systemic toxicity be expanded to deepen our understanding?

The amygdala is indeed central to understanding a local anesthetic-induced seizure and is part of the limbic system. It is located anterior to and partly superior to the tips of the inferior horn of the lateral ventricle[12] (Figure 4-1). The amygdala itself can be divided into basilateral and corticomedial nuclear groups, of which the former is highly developed in humans. Afferent pathways to the amygdala include dual olfactory sensory pathways, and efferent paths projecting to the hypothalamus, the thalamus, and the reticular formation.[13] The function of the amygdala is complex. In humans, ablation of lesions in the amygdala results in a decrease in aggressive behavior[14,15] and electrical stimulation of the amygdala in animals reveals changes in both visceral and autonomic function. With electrical stimulation, animals often turn their head and eyes to the contralateral side and demonstrate chewing, licking, and swallowing movements, as well as reactions of attention, rage, and fear.[16] Amygdala stimulation in humans results in confusional states and amnesia.[17]

Although most information suggests that the amygdala is the main and initial neurophysiologic focus for local anesthetic-induced seizures, some investigators have

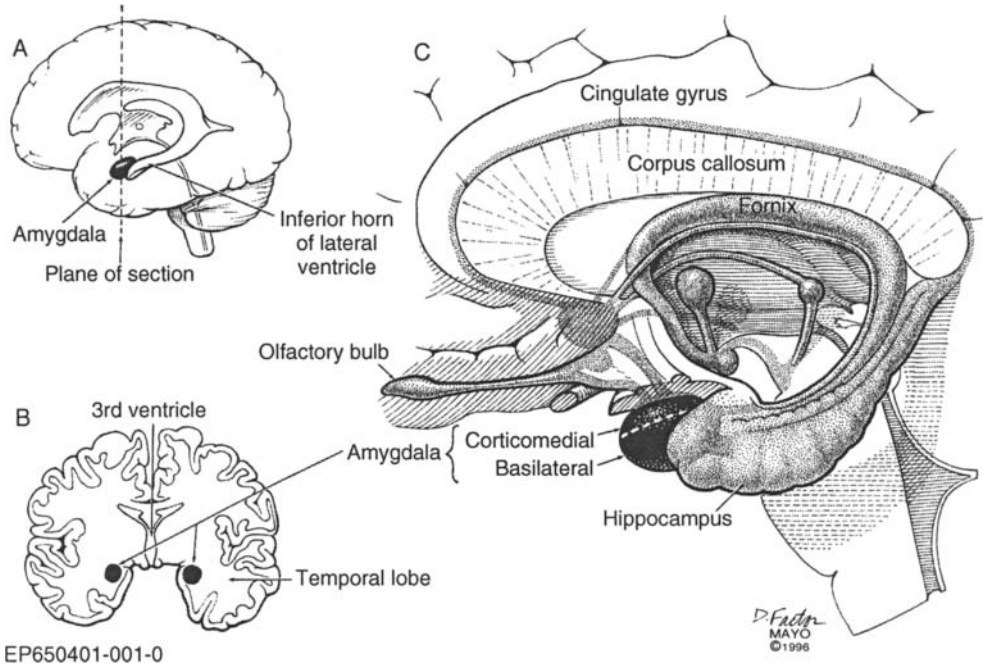

FIGURE 4-1. Anatomy of the amygdala and neuronal pathways connecting it to other CNS structures. The neuronal pathways to and from the amygdala are stippled in the illustration. **(A)** Parasagittal image of amygdala, lateral ventricle, and brain. **(B)** Cross-sectional image through the amygdala in the temporal lobe. **(C)** Expanded parasagittal image of structures immediately adjacent to the amygdala, including the corticomedial and basilateral areas of the amygdala. (Brown DL. Complications of Regional Anesthesia. New York: Churchill Livingstone; 1999:94–104. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

demonstrated that the hippocampus is a secondary focus.[13] Despite this secondary focus, the amygdala seems necessary for local anesthetic-induced seizures to develop, because they fail to occur during typical cocaine-induced local anesthetic systemic toxic reactions in rats when the amygdala has been ablated.[18] With the amygdala as the initial limbic structure activated through local anesthetic systemic toxic reactions, the seizure activity both electrically and behaviorally mimics temporal lobe epilepsy, with subsequent progression to generalized seizures.[19–21] It seems that cerebral blood flow more than compensates for the increased oxygen demands in the cortex during lidocaine-induced seizures.[22] Furthermore, animal behavior data show that if local anesthetic-induced seizures are brief, no permanent neurologic or behavioral sequelae are produced.[23] With these brief basic science observations as a background, what can we learn from clinical episodes of systemic toxicity to local anesthetics?

Clinical Science

During clinical care, the systemic toxic responses to local anesthetic drugs are the result of either an unintentional intravascular injection of the drug or administration of excessive amounts of the local anesthetic to a given patient. Clinically, it seems that most local anesthetic-induced seizures are a result of unintentional injection into the vascular system rather than uptake from excessive doses administered during regional block.[24] Part of the reason that most local anesthetic-induced seizures result from unintentional vascular injection rather than absorptive uptake is that the lung uptake of local anesthetic seems to exceed 90% of the drug. The lung seems to have a very

important function as a buffer to unintentional vascular injection.[25] Nevertheless, this buffering action in the lung is saturable. Again, for emphasis, both central nervous excitation and cardiovascular manifestations of systemic toxic responses are attributable to blood levels of local anesthetic.

Before the classic local anesthetic-induced seizure develops, patients may experience various symptoms and signs leading up to the seizure (Figure 4-2). Some of the early symptoms include light-headedness and dizziness, both frequently associated with difficulty in focusing the eyes and the development of tinnitus. As blood levels increase, shivering, muscle twitching, and tremors are displayed. Often the tremors involve facial musculature and distal parts of the extremities, similar to the effects of amygdala stimulation in animals.[13] As blood and brain levels of anesthetic further increase, then the generalized tonic clonic convulsions occur.[26] Many clinicians suggest that numbness of the tongue, or circumoral numbness, may be one of the first symptoms of a systemic toxic reaction, and Scott[27] suggested that this is not a CNS effect but rather a result of drug leaving the vascular space and affecting the sensory nerve endings in the extravascular space.

In addition to these typical signs and symptoms developing during local anesthetic systemic toxic reactions, many clinical variables affect their development. For example, CNS depressant drugs often modify the clinical presentation of a systemic toxic reaction. In general, CNS depressant drugs minimize the signs and symptoms of CNS excitation, thus contributing to an appearance that CNS and cardiovascular toxicity occur nearer the same plasma concentration of local anesthetic.[28,29] Some have even suggested that sedative drugs used before a regional block mask the "early warning" that CNS excitation provides.[30] Nevertheless, most clinicians continue to appropriately provide anxiolysis and analgesia before administration of regional blocks.

Furthermore, the local anesthetic systemic toxic reactions are influenced by a patient's acid-base status. Generally, the convulsive threshold of local anesthetics is inversely proportional to the patient's $Paco_2$.[26] If there is an increase in $Paco_2$ or a decrease in pH, the convulsive threshold is decreased or the incidence of a systemic toxic reaction is increased. Presumably, effects of hypercapnia on cerebral blood flow explain this effect. Increasing $Paco_2$ increases cerebral blood flow, which may lead to increased uptake of local anesthetic by the brain. Additionally, plasma protein binding is decreased in the presence of acidosis or hypercapnia (or both), which results in an increased free drug level.[31]

Despite the basic science evidence, attempts to correlate EEG changes with the subjective and objective signs of CNS activity after administration of local anesthetic have been difficult. There does not seem to be a good correlation between changes in EEG activity and the subjective symptoms of CNS excitation in clinical situations.[32]

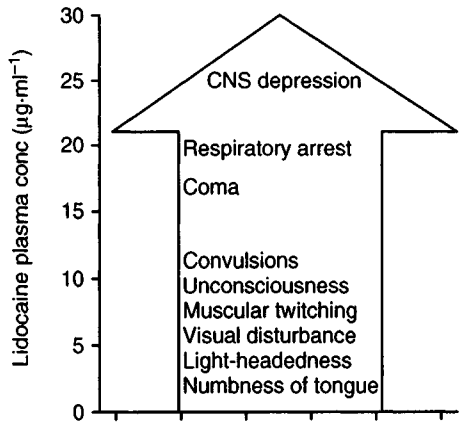

FIGURE 4-2. Local anesthetic systemic toxic symptoms are represented on a scale corresponding to the typical plasma lidocaine concentration producing respective symptoms.

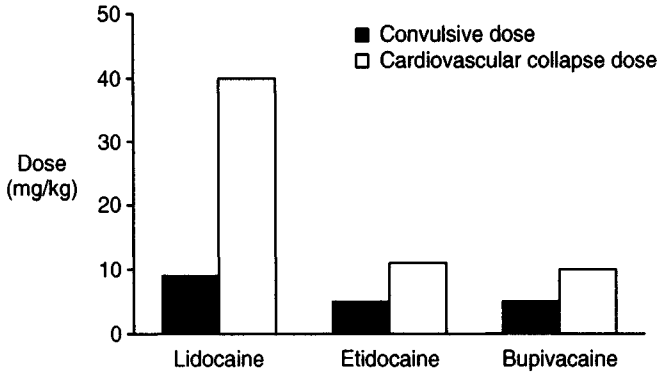

FIGURE 4-3. Relationship among doses of lidocaine, etidocaine, and bupivacaine that cause toxic responses in the CNS and doses that produce cardiovascular collapse. (Covino.[26] Reproduced with permission from the publisher.)

As outlined, the cardiovascular system is typically more resistant to the effects of local anesthetic drugs than the CNS; that is, the CNS toxic responses occur at lower blood levels than the cardiovascular system toxic responses. This general dictum is modified by the individual drug used. Each local anesthetic has an individual "circulatory collapse/CNS excitation ratio." For example, potent, long-acting local anesthetics such as bupivacaine and etidocaine have a lower circulatory collapse/CNS excitation ratio than other, less-potent aminoamides[33] (Figure 4-3).

Local anesthetic toxicity in the cardiovascular system results from drug effects on both vascular smooth muscle and cardiac muscle. The local anesthetics have dual effects on the heart, affecting both electrical and mechanical activities. Early during a systemic toxic reaction, sympathetic discharge may predominate and hypertension and tachycardia may be associated with an excitatory phase of CNS toxic response. As blood levels of local anesthetic increase, this initial phase may be followed by myocardial depression, moderate hypertension, and decreased cardiac output. Finally, as the severity of toxicity progresses, there is peripheral vasodilatation, profound hypotension, myocardial conduction abnormalities, sinus bradycardia, ventricular arrhythmias, and ultimately cardiovascular collapse. In general, basic science studies suggest that doses of local anesthetic agents that cause significant cardiovascular effects are approximately three times higher than the doses that will have distinct effects on the CNS.[32]

When the clinical science of the cardiac effects of local anesthetic systemic toxic reactions are examined, it is clear that the cardiac effects of local anesthetics are related to inhibition of sodium channels in the cardiac membranes, similar to the sought-after effect of local anesthetics on sodium channels in nerve membranes. There are also local anesthetic effects on potassium and calcium channels,[34] although understanding the effects of the drugs on the sodium channels allows the mechanism of systemic toxicity and its treatments to be easily conceptualized.

This sodium channel inhibition in the myocardium results in a decreased maximal rate of depolarization (V_{max}) of Purkinje fibers and ventricular muscle as well as decreased action potential duration and effective refractory period.[35–37] At high blood levels, local anesthetics prolong conduction time, and at even higher levels, these drugs depress spontaneous pacemaker activity.[25] In addition to these electrophysiologic effects, local anesthetics exhibit a negative inotropic action on the myocardium. As outlined, the more potent local anesthetics typically have a greater arrhythmogenic potential and cardiovascular depressive potential than do drugs such as lidocaine and mepivacaine. Albright[38] highlighted these cardiovascular systemic toxic effects with the potent local anesthetics in his 1979 editorial. Since that time, there has been extensive basic science and clinical investigation of the cardiovascular effects of potent, long-acting local anesthetics.

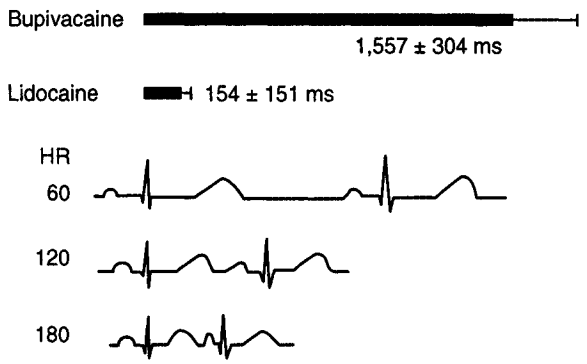

FIGURE 4-4. Comparison of time course of recovery after sodium channel block with lidocaine and bupivacaine. The dark "time bars" (lidocaine and bupivacaine) indicate the amount of time necessary for recovery of sodium channel availability in guinea pig papillary muscle. The simulated electrocardiographic traces [heart rate (HR): 60, 120, and 180bpm] indicate that after bupivacaine block there is not an opportunity for sodium channel recovery even at slow heart rates, whereas with lidocaine the sodium channel has an opportunity to recover even at heart rates of 180bpm. (Modified after data from Arlock P. Actions of three local anaesthetics: lidocaine, bupivacaine and ropivacaine on guinea pig papillary muscle sodium channels (V_{max}). Pharmacol Toxicol 1988;63:96–104. Reproduced with permission from Blackwell Publishing.)

A logical question is why the potent agents, with bupivacaine as the primary example, should cause more profound clinical effects. It was Clarkson and Hondeghem[37] who performed electrophysiologic studies on guinea pig ventricular muscle with bupivacaine and lidocaine and showed that block development and recovery are different with two drugs. In their study, lidocaine rapidly blocked inactivated and open sodium channels during the action potential, whereas bupivacaine block developed more slowly at low concentrations but rapidly at higher concentrations; additionally, recovery from the bupivacaine block was significantly slower than that from lidocaine. These authors developed a concept that lidocaine blocks sodium channels in a "fast-in fast-out fashion" and bupivacaine should be considered to block sodium channels in either a "slow-in slow-out manner" at low concentrations or in a "fast-in slow-out manner" at higher concentrations. Figure 4-4 demonstrates that at typical heart rates after lidocaine sodium channel blockade, the lidocaine has time to leave the sodium channel before the next QRS complex, whereas with bupivacaine the "slow-out" sodium channel effect prevents sodium channel release of the bupivacaine before the next QRS cycle.

The peripheral vascular effects of local anesthetics have been demonstrated to have a biphasic action on the smooth muscle of the peripheral blood vessels.[39] Typically, at low concentrations local anesthetics may cause increased tone in vascular beds, whereas at higher concentrations they produce a decrease in vascular tone. At extremely high blood levels, there is profound peripheral dilatation because of a direct relaxing effect on vascular smooth muscle in almost all beds. It should be remembered that cardiovascular collapse is also a result of the profound negative inotropic action of the local anesthetics at these extremely high blood levels.

Recommended Doses of Local Anesthetic

In an effort to minimize local anesthetic systemic toxic reactions, many anesthesiologists look to recommended maximal doses as an absolute ceiling for local anesthetic administration. As Scott[40] suggested, acceptance of a maximal recommended dose of any particular drug may be a welcome "piece of information" for anesthesiologists; nevertheless, those recommendations are illogical and without scientific foundation. Presumably, the purpose of stating a maximal recommended dose for local anesthetics

is to prevent the administration of an excessive amount, which then might result in systemic toxicity. For example, recommendations for "maximal doses" can be found in several anesthesia texts.[41,42] These maximal recommended doses have been developed for the clinical situation in which "too much drug" is injected. In reality, and as outlined, the cause of most episodes of local anesthetic systemic toxicity is unintentional intravascular injection of local anesthetic.[24] In that clinical situation, maximal recommended doses are irrelevant (Chapter 8). Another clinical factor that makes maximal recommended doses problematic is that the site of injection alters the rate of absorption, and thus the eventual local anesthetic blood levels.[43,44] Figure 4-5 demonstrates that the uptake is most rapid after interpleural or intercostal block and least rapid after spinal injection.

One other factor that affects peak blood levels is the addition of vasoconstrictors (usually epinephrine) to the local anesthetic solution. Epinephrine in a 1:100,000 to 1:200,000 concentration causes an approximately 50% decrease in peak plasma concentration of lidocaine after subcutaneous infiltration, but only a 20%–30% decrease after intercostal, epidural, or brachial plexus block.[45–48] Additionally, epinephrine decreases the peak blood level of bupivacaine significantly less than that of lidocaine, thus further confounding real understanding of establishing maximal doses of local anesthetics.[49–51] Pälve and colleagues[52] further highlighted the difficulties with maximal recommended doses during a study of adult patients undergoing brachial plexus block with 1.5% lidocaine plus epinephrine. After a dose of 900mg of lidocaine plus epinephrine, the 17 patients (all more than 50kg in weight) had a peak mean lidocaine value of 2.9μg/mL, and the highest individual plasma concentration of lidocaine was 5.6μg/mL. This highest individual level resulted from a patient receiving approximately 18mg/kg. The investigators suggested that maximal doses of local anesthetics need to be individualized but leave "individualization" of dose undefined.

Another clinical example of the difficulties in establishing maximal doses is that shown by Samdal and colleagues,[53] who administered dilute (0.1%) lidocaine with epinephrine (1:1,000,000) in patients undergoing suction-assisted lipectomy of the abdomen, flanks, and lower extremities. In the 12 patients, the total dose of 1260–2880mg of lidocaine (corresponding to 10.5–34.4mg/kg) was administered with an

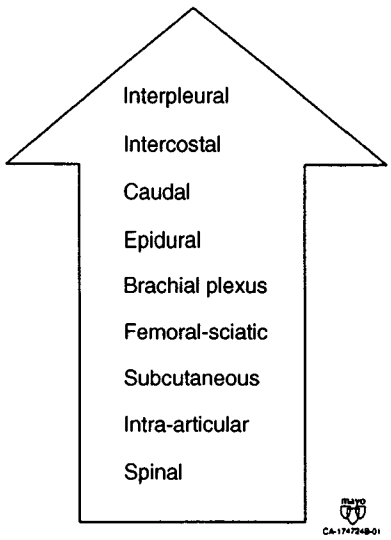

FIGURE 4-5. Ranking of the peak blood levels of local anesthetics after a wide variety of regional blocks. (Modified after Carpenter RL, Mackey DC. Local anesthetics. In: Barash PG, Cullen BF, Stoelting RK, eds. Clinical Anesthesia. Philadelphia: JB Lippincott; 1989:371–403; de Jong RH. Local Anesthetics. St. Louis: Mosby; 1994:152; and Covino BG, Vassallo HG. Local Anesthetic: Mechanism of Action and Clinical Use. New York: Grune and Stratton; 1976:97.)

injection speed of 60–78 mL per minute. In these patients, the peak concentration of lidocaine varied from 0.9 to 3.6 μg/mL and occurred between 6 and 12 hours postoperatively. These investigators also suggested that the maximal recommended dose needs to be individualized, but they went on to suggest that in addition to individualizing maximal recommended dose, the period of postprocedure observation should also be individualized. In their clinical setting, they suggested at least 18 hours of observation be applied to patients undergoing the large-volume subcutaneous injections of lidocaine.

Treatment of Local Anesthetic Systemic Toxicity

Similar to most clinical recommendations, Feldman[1] suggested that the best treatment for local anesthetic toxicity is prevention. Because most local anesthetic systemic toxic reactions result from unintentional intravascular injection, efforts should be made to minimize that potential. This can be accomplished by both aspiration via the needle after the needle has been positioned for the regional block, and inclusion of "intravascular markers" such as epinephrine in the local anesthetic solution. When epinephrine-containing solution is injected, the heart rate increases; if dosing of the regional block is incremental, the total dose administered may be minimized before recognition of unintentional intravascular injection. This is the rationale behind the epidural test dose advocated by Moore and Batra.[54]

Brown and colleagues[24] showed that of 26 patients experiencing local anesthetic-induced systemic toxicity during regional block, all developed seizures without cardiovascular collapse. These data are supported by similar findings in a French survey of major complications with regional anesthesia, when none of the 24 patients experiencing local anesthetic systemic toxicity developed cardiovascular toxicity.[55] Fourteen of these French patients received bupivacaine, whereas 16 of Brown's patients did. These data highlight that most anesthesiologists focus on managing the CNS toxic responses (seizure) during the treatment of a systemic toxic reaction. Many anesthesiologists reflexively reach for sedatives or hypnotics at the onset of seizure activity, and it is known that barbiturates as well as benzodiazepines will effectively treat many of the local anesthetic-induced seizures.[56–60] Doses of these sedatives and hypnotics are important because their associated myocardial depression seems to be additive to that of the local anesthetic-induced myocardial depression (personal communication with Dan Moore, 1989). Moore and Bridenbaugh[61] suggested more than 30 years ago that the key to successful treatment of local anesthetic-induced CNS toxicity is provision of oxygen and the use of succinylcholine if it is needed to allow adequate oxygenation. Critics of this approach suggest that the succinylcholine simply masks local anesthetic-induced seizures, whereas Moore and colleagues emphasized that one of the reasons for using succinylcholine is to minimize the rapid development of acidosis that occurs from the motor seizures accompanying the local anesthetic-induced CNS excitation.[62,63] It is not mandatory to intubate a patient's trachea if an adequate airway can be maintained during the local anesthetic-induced seizure. Rather similar to maximal recommended doses of local anesthetics, this decision needs to be individualized.

If cardiovascular depression is present during a local anesthetic systemic toxic reaction, the first step is to concentrate on correcting the physiologic derangements that may potentiate the cardiac toxicity of local anesthetics (particularly bupivacaine), including hypoxemia, acidosis, and hyperkalemia.[64] There is little information regarding the best treatment of cardiovascular toxicity in humans, although investigators have highlighted some interesting new concepts. One of the new concepts is partitioning the lipid-soluble long-acting local anesthetics into a lipid-soluble medium. Weinberg and colleagues[65] have introduced the concept that bolus injection of intralipid may be a clinically effective method in patients unresponsive to basic resuscitative

maneuvers. A more novel approach is to incorporate the lipid-soluble medium on the interior of a nanoparticle, and use injection of the nanoparticles to "sponge up" the long-acting local anesthetics on the interior of the nanoparticles, thus effectively reducing the systemic blood levels.[66] Others have explored insulin and glucose infusions in animal models, and this may hold promise.[67]

There are data from animals to suggest that large doses of epinephrine may be necessary to support heart rate and blood pressure, and there is more recent evidence that vasopressin (40 units(u) intravenous, once) may be used in place of, or in addition to, epinephrine.[68] Furthermore, atropine may be useful to treat bradycardia, direct current cardioversion often is successful, ventricular arrhythmias are probably better treated with amiodarone than with lidocaine, and cardiopulmonary bypass may be a useful adjunct to resuscitation.[3,68–73] Amiodarone, an inotropic agent, increases intracellular cyclic AMP and calcium via the inhibition of phosphodiesterase fraction 3. Again, the most effective treatment for cardiovascular toxic reactions associated with local anesthetic toxicity is prevention.

Other Local Anesthetic Toxicity

Allergic Reactions

Allergic reactions to local anesthetics are rare.[74] Nevertheless, clinical reactions associated with local anesthetics seem to be common, and often they are difficult for non-anesthesiologists to differentiate from true allergic reactions.[75–77] This clinical confusion seems to explain why many patients are labeled "allergic" to local anesthetics even when signs and symptoms are more consistent with an adverse reaction.

The amino-ester local anesthetics such as procaine, chloroprocaine, and tetracaine are all derivatives of paraaminobenzoic acid (PABA). PABA is known to be an allergen and is, in fact, a byproduct of the hydrolysis of the amino-ester local anesthetics. Allergic reactions to amino-ester compounds are much more common than those to amino-amide compounds. Confounding this further, some commercial preparations of amino-amide agents use methylparaben as a preservative. Methylparaben is also chemically related to PABA and has been identified as a true allergen.[75] When an amino-amide is linked to an allergic reaction, the allergy is likely attributable to the preservative rather than to the amino-amide local anesthetic. If PABA-like compounds are linked to allergic reactions, why are they added to local anesthetics?

One of the primary reasons for the use of the paraben-esters is the excellent bacteriostatic and fungistatic properties associated with the compounds. These compounds are widely used in multidose local anesthetic preparations, other drugs, cosmetics, and foods. Thus, a large percentage of the population has been exposed to the parabens, whether or not they have ever received local anesthetic compounds.[78]

It has been suggested that provocative skin testing is safe and effective in differentiating patients with adverse and true allergic reactions to local anesthetics.[76,79] The proponents of testing suggest that if the local anesthetic skin test and progressive challenge is negative, it is safe to use a local anesthetic. It should be emphasized that this concept of skin testing with local anesthetics is not universally shared, and some question the reliability of the skin testing.[76,80]

Myotoxicity

Local anesthetic injection into muscle may cause focal necrosis, and usually this focal necrosis is followed by rapid regeneration within a few weeks.[81] When the longer-acting drug bupivacaine is injected into muscle, muscle repair is slower. It should be emphasized that the myotoxicity is limited to muscle and does not involve nerves[82] (Chapter 6). Bupivacaine seems to create myotoxicity by suppressing muscle protein synthesis through the inhibition of amino acylation of RNA.[83] The recognition

experimentally that bupivacaine can be linked to myotoxicity needs to be correlated with the widespread use of bupivacaine in mixtures for muscle trigger-point injections.[84] One may speculate that some of the effects of trigger-point injection are produced through a beneficial myotoxicity mechanism. It should be remembered that in typical clinical situations, bupivacaine, lidocaine, procaine, and tetracaine seem to produce only isolated, localized myotoxicity, which does not spread to neural structures.[85]

References

1. Feldman HS. Toxicity of local anesthetic agents. In: Rice SA, Fish KJ, eds. Anesthetic Toxicity. New York: Raven Press; 1994:107–133.
2. Holmstedt B, Fredga A. Sundry episodes in the history of coca and cocaine. J Ethnopharmacol 1981;3:113–147.
3. Fink BR. History of neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. Neural Blockade in Clinical Anesthesia and Management of Pain. Philadelphia: JB Lippincott; 1988: 3–15.
4. Mattison JB. Cocaine poisoning. Med Surg Rep 1891;60:645–650.
5. Reclus P. Analgésie locale par la cocaïne. Rev Chir 1889;9:913.
6. Braun H. Ueber einige neuerörtliche Anesthetica (Stovain, Alypin, Novocain). Dtsch Klin Wochenschr 1905;31:1667.
7. Eggleston C, Hatcher RA. A further contribution to the pharmacology of the local anesthetics. J Pharmacol Exp Ther 1919;13:433.
8. Tatum AL, Atkinson AJ, Collins KH. Acute cocaine poisoning, its prophylaxis and treatment in laboratory animals. J Pharmacol Exp Ther 1925;26:325–335.
9. Englesson S. The influence of acid-base changes on central nervous system toxicity of local anaesthetic agents. Acta Anaesthesiol Scand 1974;18:79–87.
10. Tanaka K, Yamasaki M. Blocking of cortical inhibitory synapses by intravenous lidocaine. Nature 1966;209:207–208.
11. Wagman IH, DeJong RH, Prince DA. Effects of lidocaine on the central nervous system. Anesthesiology 1967;28:155–172.
12. Truex RC, Carpenter MB. The basal ganglia and rhinencephalon, olfactory and limbic system pathways. In: Human Neuroanatomy. 6th ed. Baltimore: Williams & Wilkins; 1971: 498–542.
13. Garfield JM, Gugino L. Central effects of local anesthetic agents. In: Strichartz G, ed. Local Anesthetics. Vol 81. New York: Springer-Verlag; 1987:253–284.
14. Green JD, Duisberg REH, McGrath WB. Focal epilepsy of psychomotor type. A preliminary report of observations on effects of surgical therapy. J Neurosurg 1951;8:157–172.
15. Pool JL. Neurophysiological symposium: visceral brain in man. J Neurosurg 1954;11: 45–63.
16. MacLean PD, Delgado JMR. Electrical and chemical stimulation of fronto-temporal portion of limbic system in the waking animal. Electroencephalogr Clin Neurophysiol 1952;5:91–100.
17. Feindel W, Penfield W. Localization of discharge in temporal lobe automatism. AMA Arch Neurol Psychiatry 1954;72:605–630.
18. Eidelberg E, Lesse H, Gaulta FP. An experimental model of temporal lobe epilepsy. Studies of the convulsant properties of cocaine. In: Glaser GH, ed. EEG and Behavior. New York: Basic Books; 1963:Chapter 10.
19. DeJong RH. Central nervous system effects. In: DeJong RH, ed. Local Anesthetics. 2nd ed. Springfield, IL: Charles C. Thomas; 1977:84–114.
20. Stein PA, Michenfelder JD. Neurotoxicity of anesthetics. Anesthesiology 1979;50:437–453.
21. Moore DC. Administer oxygen first in the treatment of local anesthetic-induced convulsions. Anesthesiology 1980;53:346–347.
22. Maekawa T, Oshibuchi T, Takao, Takeshita H, Imamura A. Cerebral energy state and glycolytic metabolism during lidocaine infusion in the rat. Anesthesiology 1981;54:278–283.

23. DeJong RH, Heavner JE. Diazepam prevents local anesthetic seizures. Anesthesiology 1971;34:523–531.
24. 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.
25. Löfström JB. Physiologic disposition of local anesthetics. Reg Anesth 1982:33–38.
26. Covino BG. Pharmacology of local anesthetic agents. In: Rogers MC, Tinker JH, Covino BG, et al., eds. Principles and Practice of Anesthesiology. St. Louis: Mosby Year Book; 1993:1235–1257.
27. Scott DB. Toxic effects of local anaesthetic agents on the central nervous system. Br J Anaesth 1986;58:732–735.
28. Gerard JL, Edouard A, Berdeaux A, Duranteau J, Ahmad R. Interaction of intravenous diazepam and dupivacaine in conscious dogs. Reg Anesth 1989;14:298–303.
29. Bernards CM, Carpenter RL, Rupp SM, et al. Effect of midazolam and diazepam premedication on central nervous system and cardiovascular toxicity of bupivacaine in pigs. Anesthesiology 1989;70:318–323.
30. Ausinsch B, Malagodi MH, Munson ES. Diazepam in the prophylaxis of lignocaine seizures. Br J Anaesth 1976;48:309.
31. Englesson S. The influence of acid-base changes on central nervous system toxicity of local anaesthetic agents. I. An experimental study in cats. Acta Anaesthesiol Scand 1974;18: 79–87.
32. Covino BG. Toxicity and systemic effects of local anesthetic agents. In: Brown DL, ed. Local Anesthesia. Vol 81. New York: Springer-Verlag; 1987:187–212.
33. Concepcion M. Acute complications and side effects of regional anesthesia. In: Regional Anesthesia and Analgesia. Philadelphia: WB Saunders; 1996:Chapter 23.
34. Heavner JE. Cardiac toxicity of local anesthetics in the intact isolated heart model: a review. Reg Anesth Pain Med 2002;27:545–555.
35. Lynch C III. Depression of myocardial contractility in vitro by bupivacaine, etidocaine, and lidocaine. Anesth Analg 1986;65:551–559.
36. Moller RA, Covino BG. Cardiac electrophysiologic effects of lidocaine and bupivacaine. Anesth Analg 1988;67:107–114.
37. 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.
38. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine [editorial]. Anesthesiology 1979;51:285–287.
39. Blair MR. Cardiovascular pharmacology of local anaesthetics. Br J Anaesth 1975;47: 247–252.
40. Scott DB. "Maximal recommended doses" of local anaesthetic drugs. Br J Anaesth 1989; 63(4):373–374.
41. Strichartz GR, Berde CB. Local anesthetics. In: Miller RD, ed. Anesthesia. 4th ed. New York: Churchill Livingstone; 1994:489–521.
42. DiFazio CA, Woods AM. Drugs commonly used for nerve blocking: pharmacology of local anesthetics. In: Prithi R, ed. Practical Management of Pain. 2nd ed. St. Louis: Mosby Year Book; 1992:685–700.
43. Braid DP, Scott DB. The systemic absorption of local analgesic drugs. Br J Anaesth 1965; 37:394–404.
44. Rosenberg PH, Veering BT, Urmey WF. Maximum recommended doses of local anesthetics: a multifactorial concept. Reg Anesth Pain Med 2004;29:564–575.
45. Braid DP, Scott DB. The effect of adrenaline on the systemic absorption of local anaesthetic drugs. Acta Anaesthesiol Scand 1996;(suppl 23):334–346.
46. Raj RP, Rosenblatt R, Miller J, Katx RL, Corden E. Dynamics of local anesthetic compounds in regional anesthesia. Anesth Analg 1977;56:110–117.
47. Mather LE, Tucker GT, Murphy TM, Stanton-Hicks M, Bonica JJ. Effect of adding adrenaline to etidocaine and lignocaine in extradural anaesthesia. II. Pharmacokinetics. Br J Anaesth 1976;48:989–994.
48. Wildsmith JAW, Tucker GT, Cooper S, Scott DB, Covino BG. Plasma concentrations of local anaesthetics after interscalene brachial plexus block. Br J Anaesth 1977;49:461–466.

49. Wilkinson GR, Lund PC. Bupivacaine levels in plasma and cerebrospinal fluid following peridural administration. Anesthesiology 1970;33:482–486.
50. Appleyard TN, Witt A, Atkinson RE, Nicholas ADG. Bupivacaine carbonate and bupivacaine hydrochloride: a comparison of blood concentrations during epidural blockade for vaginal surgery. Br J Anaesth 1974;46:503–533.
51. Abdel-Salam AR, Vonwiller JB, Scott DB. Evaluation of etidocaine in extradural block. Br J Anaesth 1975;47:1081–1086.
52. Pälve H, Kirvelä O, Olin H, Syvälahti E, Kanto J. Maximum recommended doses of lignocaine are not toxic. Br J Anaesth 1995;74:704–705.
53. Samdal F, Amland PF, Bugge JF. Plasma lidocaine levels during suction-assisted lipectomy using large doses of dilute lidocaine with epinephrine. Plast Reconstr Surg 1994;93(6): 1217–1223.
54. Moore DC, Batra MS. The components of an effective test dose prior to epidural block. Anesthesiology 1981;55(6):693–696.
55. Auroy Y, Benhamou D, Bargue L, et al. Major complications in regional anesthesia in France: the SOS regional anesthesia hotline service. Anesthesiology 2002;97:1274–1280.
56. Liu P, Feldman HS, Covino BM, Giasi R, Covino BG. Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs. Anesth Analg 1982; 61:317–322.
57. Feldman HS, Arthur GR, Covino BG. Comparative systemic toxicity of convulsant and supraconvulsant doses of intravenous ropivacaine, bupivacaine, and lidocaine in the conscious dog. Anesth Analg 1989;69:794–801.
58. Feldman HS, Arthur GR, Pitkanen M, Hurley R, Doucette AM, Covino BG. Treatment of acute systemic toxicity after the rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Anesth Analg 1991;73:373–384.
59. Covino BG. Toxicity and systemic effects of local anesthetic agents. In: Strichartz G, ed. Local Anesthesia. New York: Springer-Verlag; 1987:187–209.
60. Davis NL, deJong RH. Successful resuscitation following massive bupivacaine overdose. Anesth Analg 1982;61:62–64.
61. Moore DC, Bridenbaugh LD. Oxygen: the antidote for systemic toxic reactions from local anesthetic drugs. JAMA 1960;174:842–847.
62. Moore DC, Crawford RD, Scurlock JE. Severe hypoxia and acidosis following local anesthetic-induced convulsions. Anesthesiology 1980;53(3):259–260.
63. Moore DC, Thompson GE, Crawford RD. Long-acting local anesthetic drugs and convulsions with hypoxia and acidosis. Anesthesiology 1982;56(3):230–232.
64. Reis S, Nath S. Cardiotoxicity of local anaesthetic agents. Br J Anaesth 1986;58: 736–746.
65. Weinberg G, Ripper R, Feinstein DL, Hoffman W. Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. Reg Anesth Pain Med 2003;28:198–202.
66. Varshney M, Morey TE, Shah DO, et al. Pluronic microemulsions as nanoreservoirs for extraction of bupivacaine from normal saline. J Am Chem Soc 2004;126:5108–5112.
67. Kim JT, Jung CW, Lee KH. The effect of insulin on the resuscitation of bupivacaine-induced severe cardiovascular toxicity in dogs. Anesth Analg 2004;99:728–733.
68. Weinberg GL. Current concepts in resuscitation of patients with local anesthetic toxicity. Reg Anesth Pain Med 2002;27:568–575.
69. Bennett A. The physiological action of coca. Br Med J 1874;1:510.
70. Freud S. Über Coca. Zentralbl Ges Ther 1884;2:289–314.
71. Bull CS. The hydrochlorate of cocaine as a local anaesthetic in ophthalmic surgery. NY Med J 1884;40:643–644.
72. Hall RJ. Hydrochlorate of cocaine. NY Med J 1884;40:609–611.
73. Corning JL. Spinal anaesthesia and local medication of the cord. NY Med J 1885;42: 483–485.
74. Adriani J. Reactions to local anesthetics. JAMA 1966;196:119.
75. Aldrete JA, Johnson DA. Evaluation of intracutaneous testing for investigation of allergy to local anesthetic agents. Anesth Analg 1970;49:173.
76. Incaudo G, Schatz M, Patterson R, et al. Administration of local anesthetics to patients with a history of prior adverse reaction. J Allergy Clin Immunol 1978;61:339.
77. Brown DT, Beamish D, Wildsmith JAW. Allergic reaction to an amide local anaesthetic. Br J Anaesth 1981;53:435.

78. Nagel JE, Fuscaldo JT, Fireman P. Paraben allergy. JAMA 1977;237:1594.
79. DeShazo RD, Nelson HS. An approach to the patient with a history of local anaesthetic hypersensitivity: experience with 90 patients. J Allergy Clin Immunol 1979;63:387.
80. Fisher MM. Intradermal testing in the diagnosis of acute anaphylaxis during anaesthesia – results of five years' experience. Anaesth Intensive Care 1979;7:58.
81. Benoit PW, Belt WD. Some effects of local anesthetic agents on skeletal muscle. Exp Neurol 1972;34:264–278.
82. Hall-Craggs ECB. Rapid degeneration and regeneration of a whole skeletal muscle following treatment with bupivacaine (Marcaine). Exp Neurol 1974;43:349–358.
83. Johnson ME, Jones GH. Effects of Marcaine, a myotoxic drug, on macromolecular synthesis in muscle. Biochem Pharmacol 1978;27:1753–1757.
84. Zink W, Graf BM. Local anesthetic myotoxicity. Reg Anesth Pain Med 2004;29: 333–340.
85. Foster AH, Carlson BM. Myotoxicity of local anesthetics and regeneration of the damaged muscle fibers. Anesth Analg 1980;59:727–736.