

Local Anesthetic Toxicity—Does Product Labeling Reflect Actual Risk?

Terese T. Horlocker, M.D., and Denise J. Wedel, M.D.

The potential for systemic toxicity and neurotoxicity is considered during drug evaluation and approval and is included in the “Adverse Reactions” and “Warnings” sections in the labeling of local anesthetic solutions. An adverse reaction is defined as an undesirable effect that may occur as part of the pharmacologic action of the drug, whereas warnings identify any potentially fatal adverse reaction. Postmarketing reports of systemic or neurotoxicity may result in modifications in the labeling, the local anesthetic formulation, or both. This review discusses historical and current controversies surrounding the labeling of local anesthetics. The usefulness of local anesthetic labeling in guiding regional anesthetic management will also be examined. Although many of the issues and events were reported internationally, this article pertains mainly to the United States and labeling mandated by the Food and Drug Administration (FDA).

The description of local anesthetic systemic toxicity paralleled the emerging field of regional anesthesia. In the first edition of *Regional Anesthesia, Its Technic and Clinical Application*, Labat¹ writes, “Novocain is six to ten times less toxic than cocaine, but still its toxicity must be remembered. Such symptoms as pallor of the face, cyanosis, nausea and cold sweats prompt the immediate injection of a cardiac stimulant. . . . If not watched for and carefully avoided or treated, they may prove fatal.” The actual frequency of systemic toxic reactions is not reported, but described as “rare.” Conversely, Labat included limited discussion on neurologic complications. Although this may have been because of lack of recognition, local anesthetic neurotoxicity may not have been a significant problem at the time because the predominant local anesthetic of the era

was procaine, an agent with little neurotoxic potential.² With the introduction of new local anesthetic solutions, anesthesiologists have sought to balance potency, duration of action, speed of onset, and toxicity³ (Table 1).

Local Anesthetic Systemic Toxicity and Neurotoxicity

Local anesthetic toxicity is usually divided into systemic and neurologic toxic reactions. The systemic toxicity of local anesthetic agents primarily results from accidental intravascular injection and is characterized by central nervous system excitation and seizure activity. Negative inotropic and chronotropic effects, combined with peripheral vasodilatation may lead to circulatory collapse. In addition to cardiovascular depression, long-acting amides, such as bupivacaine, etidocaine, and ropivacaine, may precipitate refractory ventricular arrhythmias and ventricular fibrillation. Local anesthetic neurotoxicity may result in dysesthesia, paresthesia, and prolonged sensory/motor deficits.

The Bupivacaine “Black-Boxed Warning”

In 1979, Albright⁴ described in an editorial 6 cases of sudden cardiovascular collapse following intravascular injection of clinical doses of bupivacaine or etidocaine. Only 2 cases had been previously published. The regional anesthetics included 1 caudal (1% etidocaine, 25 mL), 2 interscalene (0.5% bupivacaine, 40 mL), 1 epidural (0.75% bupivacaine, 12 mL), 1 axillary (0.5% bupivacaine, 40 mL), and 1 Bier block (0.5% bupivacaine, 25 mL, 2% 2-chloroprocaine [2-CP], 15 mL). Resuscitation was difficult and outcome poor.

These cases were significant in that cardiovascular collapse sometimes occurred *without* prior evidence of central nervous system toxicity. Subsequent similar cases were reported, and the FDA convened a meeting of the Anesthetic and Life Support Drugs Advisory Committee on October 4, 1983, to address growing concerns. Albright presented information on 53 cardiac reactions after blocks with bupivacaine; 35 involved obstetrical patients, the remaining 18 patients were undergoing nonobstetrical surgery. An epidural anesthetic was performed in 39 cases; other regional techniques

From the Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota.

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Reprint requests: Terese T. Horlocker, M.D., Department of Anesthesiology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905. E-mail: horlocker.terese@mayo.edu

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Table 1. Synthesis and Clinical Introduction of Local Anesthetics

Local Anesthetic	Year of Synthesis	Year of Clinical Introduction
Cocaine	1860	1884
Procaine	1904	1905
Dibucaine	1925	1930
Tetracaine	1928	1932
Lidocaine	1943	1947
2-CP	1950	1952
Mepivacaine	1956	1957
Prilocaine	1959	1960
Bupivacaine	1957	1963
Etidocaine	1971	1972
Ropivacaine	1957	1997
Levobupivacaine	1972	1999

implicated included retrobulbar, intercostal, axillary, interscalene, and Bier blocks. The patients had received 0.75% bupivacaine in 27 cases and 0.5% bupivacaine in 8 cases. There were 31 deaths (24 involving a parturient and/or her fetus), 3 patients with partial recovery, and 19 patients with full recovery (FDA Anesthetic and Life Support Drug Advisory Committee meeting, October 4-5, 1983). These cases did not appear in the literature (other than those included in the 1979 editorial). The significance of these cases was intensely debated by those present. Local anesthetic toxicity had not previously been a cause for concern. In 1983, the most strongly worded section, which was identical for all local anesthetics, was one sentence in capital letters: "Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED." The panel considered markedly differing actions, including removal of bupivacaine from the market. In the end, bupivacaine remained available, but the labeling was significantly revised to include the following warning:

"THE 0.75% CONCENTRATION OF MARCAINE IS NOT RECOMMENDED FOR OBSTETRICAL ANESTHESIA. THERE HAVE BEEN REPORTS OF CARDIAC ARREST WITH DIFFICULT RESUSCITATION OR DEATH DURING USE OF MARCAINE FOR EPIDURAL ANESTHESIA IN OBSTETRICAL PATIENTS. IN MOST CASES, THIS HAS FOLLOWED USE OF THE 0.75% CONCENTRATION. RESUSCITATION HAS BEEN DIFFICULT OR IMPOSSIBLE DESPITE APPARENTLY ADEQUATE PREPARATION AND APPROPRIATE MANAGEMENT. CARDIAC ARREST HAS OCCURRED AFTER CONVULSIONS RESULTING FROM SYSTEMIC TOXICITY, PRESUMABLY FOLLOWING UNINTENTIONAL INTRAVASCULAR INJECTION. THE 0.75% CONCENTRATION SHOULD BE RESERVED FOR SURGICAL PROCEDURES WHERE A

HIGH DEGREE OF MUSCLE RELAXATION AND PROLONGED EFFECT ARE NECESSARY."

This wording has remained virtually unchanged over time.

Ropivacaine Labeling

Ropivacaine was approved for general use in 1997. Questions regarding the cardiotoxic potential lead to a proposed "black-boxed" warning similar to that of bupivacaine. However, the Code of Federal Regulations states, "Special problems, particularly those that may lead to death or serious injury may be required by the FDA to be placed in a prominently displayed black box. The box warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data" (Code of Federal Regulations. Last updated: July 16, 2001). Based on the presented animal studies and clinical trials, ropivacaine was released without a black-boxed warning. However, the 0.75% ropivacaine solution was not approved for obstetrical use, and a maximum 0.5% ropivacaine dose of 150 mg was recommended in the obstetrical population.

Levobupivacaine Labeling

Although there was no question as to the efficacy of the L-enantiomer of bupivacaine, considerable controversy surrounded the potential for toxicity. If the racemic mixture was labeled with a black box, did one (or both) of the stereoisomers warrant similar warnings? Levobupivacaine was also approved in 1999 without a black box. Again, the 0.75% solution was not approved for obstetrics.

It is interesting to note that although ropivacaine and levobupivacaine were released without a boxed label warning, both labels state that the potential for successful resuscitation (relative to bupivacaine) is unknown. Although the "Warnings" statements for ropivacaine and levobupivacaine include recommendations for slow and incremental injection, both labels refer to the cases of cardiac arrest during epidural anesthesia in obstetrics, implying that this is the population at risk for serious complications. Recent studies suggest that intravascular injection and systemic toxicity are more likely to occur following peripheral techniques.^{5,6}

Direct Neural and Tissue Toxicity

Local anesthetic toxicity focused on systemic reactions, rather than neurologic complications, during the early years of regional anesthesia. General anesthesia was considered so dangerous that the risk of serious nerve damage after spinal anesthesia was minimized. Although cauda equina syndrome and radiculomyelitis were reported, the etiology of neurologic complications remained unclear. The Woolley and Roe case for the first time examined

the potential sources of neurotoxicity associated with spinal anesthesia.

Cecil Roe and Albert Woolley were 2 healthy middle-aged men who became paraplegic after undergoing spinal anesthesia for minor surgery on October 13, 1947. The spinal anesthetics were administered by the same anesthetist, using the same drug (hypobaric dibucaine). The following day both patients developed an acute myelopathy. The flaccid paralysis progressed to spastic paraparesis from which neither man recovered. A third patient, who received hypobaric dibucaine that same morning and died 5 days later of unrelated causes, also showed signs of neurologic sequelae. In 1953, the court determined that phenol used to sterilize the ampules of local anesthetics had percolated through invisible cracks and contaminated the solution. A re-examination of the evidence suggests that the neurologic injury was presence of an acidic descaling liquid in the sterilizing pan. The spinal syringes and needles were boiled in the acid and subsequently contaminated the local anesthetic solution.⁷ Contemporary series focus on the direct neurotoxicity of intrathecal agents and adjuncts, rather than contaminants. The introduction of new applications or reformulation of local anesthetics with established safety records may result in unexpected consequences.

2-CP Toxicity

Numerous changes in pH and formulation have occurred since 2-CP was introduced into clinical practice in 1952. The majority of these modifications has been response to reports of serious neurologic and tissue toxicity. However, there has been no significant change in the labeling. Solutions of 2-CP were initially prepared by dissolving crystals in 0.9% sodium chloride (peripheral nerve blocks) or 10% dextrose (spinal anesthesia). In 1956, the manufacturer supplied premixed 1.0%, 2.0%, and 3.0% solutions of 2-CP. Methylparaben 1 mg/mL (preservative) and sodium bisulfite 2 mg/mL (antioxidant) were added to prolong shelf life. The pH was also lowered to 2.7 to 4.0 to further stabilize the solution. During this time interval, thrombophlebitis was reported with the use of 2-CP for intravenous regional anesthesia. However, the etiology of the tissue toxicity was never determined.⁸

Methylparaben was removed from the 2% and 3% solutions in 1964, which were then marketed as Nesacaine-CE and were indicated for caudal and epidural anesthesia. Sodium bisulfite and pH remained unchanged from prior formulation. In the late 1970s, several cases of persistent sensory and motor deficits, including cauda equina syndrome, were reported after accidental intrathecal injection of 10 to 20 mL of 3% 2-CP.⁹ In vitro^{10,11} and in

vivo¹² investigations determined that the combination of low pH and sodium bisulfite present in the 2-CP solutions was the etiology of the neurologic toxicity. As a result, the sodium bisulfite concentration was decreased to 0.7 mg/mL in 1984 and eventually removed completely in 1987 and the chelating agent, calcium disodium ethylenediamine tetraacetic acid (EDTA) was added. The new formulation was marketed as Nesacaine-MPF (methylparaben-free), even though methylparaben had not been included in the 2% and 3% 2-CP solutions since 1964. Soon afterward, cases of severe back pain following epidural anesthesia with Nesacaine-MPF were reported. Clinical evaluations suggested the combination of 2-CP and EDTA may produce abnormal skeletal muscle contraction.¹³

The 2-CP solution was once again reformulated in 1996. This time all additives were removed from 2% and 3% Nesacaine-MPF solutions. The new product was packaged in a dark bottle to retard decomposition by light. However, although Nesacaine-MPF solutions do not contain additives, 1% and 2% Nesacaine solutions contain methylparaben and EDTA. Presently, generic 2-CP includes 1.8 mg/mL sodium metabisulfite.¹⁴ Throughout the varied reports of tissue and neurotoxicity associated with 2-CP, there were no major changes in the "Adverse Reactions" or "Warnings" sections. Although the labeling states that Nesacaine and Nesacaine-MPF are not for spinal anesthesia, the epidural and caudal indications remain. In addition, the potential for tissue toxicity/thrombophlebitis is not described.

Lidocaine, Cauda Equina Syndrome, and Transient Neurologic Symptoms

The potential for neurologic complications including persistent anesthesia, paresthesia, weakness, and loss of sphincter control is reported in the "Adverse Reactions" section of all local anesthetics approved for intrathecal use. The safety and stability of lidocaine led to its increased clinical use as a spinal anesthetic. Although initially marketed as 5% lidocaine in saline, the solution was reformulated to 5% lidocaine in 7.5% dextrose. However, in 1991, 4 cases of cauda equina syndrome after continuous spinal anesthesia through a microbore catheter were reported; 3 cases involved 175 to 300 mg of hyperbaric lidocaine administered in divided doses.¹⁵ There were a total of 14 similar cases of cauda equina syndrome associated with microcatheter continuous spinal anesthesia over the next year, for an estimated incidence of 1:1,000.¹⁶ As a result, microcatheters were withdrawn from the United States market in May 1992. Ironically, subsequent studies supported local anesthetic neurotoxicity as the etiology for clinical injuries after

continuous spinal anesthesia.¹⁷ Shortly after resolution of the microcatheter-cauda equina syndrome controversy, Schneider et al.¹⁸ reported 4 cases of transient neurologic symptoms (TNS) (severe radicular back and leg pain without sensory or motor deficits) occurring after resolution of hyperbaric lidocaine spinal anesthesia. While the etiology and clinical significance of TNS are unclear,¹⁹ neurotoxicity remains a possibility.

Several editorials have called for a reappraisal of the safety of spinal lidocaine. However, no major changes in the formulation or indications have resulted.^{20,21} In April 1995, the FDA revised the "Precautions" and "Adverse Reactions" sections. In general, the added text reported the apparent increased risk of neurologic deficits with small-bore needles and microcatheters and recommended mixing 5% lidocaine in an equal volume of saline or cerebrospinal fluid to reduce the risk of nerve injury caused by pooling of concentrated local anesthetic. A recent safety-related change in the labeling occurred in March 1999 in response to reports of TNS. Text was once again added to the "Adverse Reactions" section stating, "Transient pain developing in the buttocks and radiating to the thighs and calves may be seen after spinal administration of lidocaine 5% with dextrose. . . ." These revisions, which were added to the labeling 4 to 6 years after the original reports, are included on only the 5% hyperbaric solutions of lidocaine. However, isobaric solutions do not contain these labeling revisions because the isobaric formulations are not approved for spinal use, and labeling may only reflect the approved indications. As a result, the clinician may assume the differences in labeling to imply a difference in neurotoxicity. This assumption is erroneous because neither concentration nor baricity of lidocaine significantly affects the risk of cauda equina syndrome or TNS.^{19,21}

The Present: Has Labeling Affected the Frequency of Systemic and Neurotoxicity Reactions?

Controversy remains regarding the relative safety (or danger) of the long-acting amides. How much of the initial morbidity and mortality associated with bupivacaine was related to the drug, and how much to the practice of regional anesthesia? At the time, the use of a test dose, incremental injection with intermittent aspiration, and measured loading through indwelling catheter, rather than the needle, were not "standard" practice. Likewise, hemodynamic monitoring was inconsistent, particularly in the obstetrical suite.

Several large reviews have suggested that the safety has improved.^{5,6} Brown et al.⁵ retrospectively determined the frequency of local anesthetic sys-

temic toxicity. A total of 25,697 patients underwent brachial plexus, caudal, or epidural block between 1985 and 1992; 26 patients experienced seizures (Table 2). There was a significant difference in the rate of seizure frequency between anesthetic techniques, with caudal > brachial plexus and brachial plexus > epidural. Within brachial plexus techniques, supraclavicular and interscalene had a higher frequency than axillary. All 15 patients developing seizures associated with brachial plexus block received bupivacaine; 7 of 15 received a bupivacaine/2-CP mixture. None of 26 patients required hemodynamic support more extreme than intravenous ephedrine or atropine combined with supplemental oxygen and controlled ventilation. There were no adverse cardiovascular, pulmonary, or central nervous system sequelae associated with any of the seizures.

A recent investigation reflecting modern trends prospectively evaluated the incidence and characteristics of serious complications related to regional anesthesia.⁶ A total of 103,730 regional anesthetics were performed over a 5-month period (Table 3). Reports of 98 serious complications were noted. In 89 cases, complications were related to the regional anesthetic. There were 32 cardiac arrests; 26 occurring during spinal anesthesia. Of the 34 neurologic complications, 21 were associated with pain on needle placement or injection, suggesting direct nerve trauma. There were 12 patients with neurologic complications after uneventful spinal anesthesia; their deficits were attributed to local anesthetic neurotoxicity. Nine of 12 patients, including 5 with cauda equina syndrome, received hyperbaric 5% lidocaine. The incidence of cardiac arrest and neurologic complications was significantly higher after spinal anesthesia than other types of regional procedures. Seizures attributed to elevated plasma concentrations of local anesthetic occurred in 23 patients. All seizures were preceded by minor auditory symptoms and complaints of a metallic taste. Al-

Table 2. Overall Seizure Rates After 25,697 Regional Techniques

Anesthetic	Total No. of Procedures	Total No. of Seizures	Seizure Rate/1,000 Procedures
Caudal*	1,295	9	6.9
Brachial plexus	7,532	15	2.0
Axillary	6,620	8	1.2
Interscalene	659	5	7.6
Supraclavicular	253	2	7.9
Epidural†	16,870	2	0.1

*Includes patients >18 years of age.

†Excluding epidural blocks placed solely for postoperative analgesia.

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Table 3. Number and Incidence of Severe Complications Related to Regional Anesthesia

Regional Technique	Cardiac Arrest	Death	Seizure	Neurologic Injury
Spinal (N = 40,640)	26 (0.64)	6 (0.15)	0 (0)	24 (0.59)
Epidural (N = 30,413)	3 (0.1)*	0 (0)	4 (0.13)	6 (0.2)*
Peripheral blocks (N = 21,278)	3 (0.14)†	1 (0.05)	16 (0.75)‡	4 (0.19)‡
IVRA (N = 11,229)	0 (0)	0 (0)	3 (0.27)	0 (0)§
Total (N = 103,730)	32 (0.31)	7 (0.09)	23 (0.22)	34 (0.33)

NOTE. Data presented are number and (the incidence/1,000 procedures).

Abbreviation: IVRA, intravenous regional anesthesia.

*Epidural versus spinal ($P < .05$).

†Peripheral nerve blocks versus spinal ($P < .05$).

‡Peripheral nerve blocks versus epidural ($P < .05$).

§Intravenous regional versus epidural and spinal ($P < .05$).

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though bupivacaine 0.5% was injected in 14 of 23 patients having seizure after peripheral or epidural block, it was never associated with cardiac arrest. During intravenous regional techniques, 3 seizures occurred after tourniquet deflation. In all 3 patients, the tourniquet deflation occurred more than 40 minutes after injection of 30 to 45 mL of lidocaine 0.5%.

This study showed that the incidence of serious complications related to local anesthetic systemic or neurotoxicity is very low. However, because serious complications were noted to occur even in the presence of experienced anesthesiologists, continued vigilance in patients undergoing regional anesthesia is warranted.²² In addition, since information is reported only on the patients with serious complications, it is difficult to determine relative systemic (and neuro) toxicities of the local anesthetics used.²¹ It is of interest that cardiac arrest continues to occur during spinal anesthesia, despite increased monitoring.^{6,23} Indeed, cardiac arrest during neuraxial block may be the most serious manifestation of "local anesthetic toxicity." Ongoing analyses are required to identify trends and risk factors.

Toxicity Associated With "Off-Label" Applications

The series by Brown et al.⁵ and Auroy et al.⁶ report a low incidence of both systemic toxicity after intravascular injection as well as direct neurotoxicity. The relative safety associated with current standards of practice shows that labeling (and awareness) may have had a positive effect. Recently, the report of numerous deaths after "tumescent" liposuction has once again brought the issue of local anesthetic toxicity to the forefront.

Liposuction is the most common cosmetic operation in the United States. Tumescent liposuction has recently gained popularity and is characterized by subcutaneous infusion of a local anesthetic-containing solution followed by aspiration of fat

through microcannulas. The solution consists of 1 L lactated Ringer's or normal saline containing 500 to 1,000 mg lidocaine, 0.25 to 1.0 mg epinephrine, and 12.5 mmol of sodium bicarbonate.²⁴ Although the traditional maximum recommended dose of lidocaine is 7 mg/kg, the safe maximum dosage of tumescent lidocaine is purportedly between 45 to 50 mg/kg. Previous studies have documented that plasma lidocaine levels have continued to rise for 16 to 23 hours, although sampling intervals were wide.²⁴ Although initially considered a "safe" procedure, often performed in an office under conscious sedation, recent accounts of fatalities have led to a reexamination of the safety of tumescent liposuction.²⁵⁻²⁷ A recent survey of aesthetic plastic surgeons estimated the mortality rate was 1 in 5,224 procedures.²⁶ Pulmonary embolism was the cause of death in 23% of cases. Because toxicology data was often missing, the role of local anesthetic cardiotoxicity could not be determined. In addition to lidocaine toxicity or lidocaine-related drug interactions, other factors contributing to morbidity and mortality after tumescent liposuction include fluid overload leading to pulmonary edema, high-dose epinephrine effects on the cardiovascular system, residual sedative and anesthetic drug actions, the application of a close-fitting abdominal compression garment that could decrease venous return, and early discharge home.^{25,28} A multidisciplinary approach will be needed to improve the perioperative outcome associated with this surgical procedure.

In summary, the labeling of the local anesthetics has reflected animal studies, clinical trials, and also the opinions of experts. New applications, which are often "off-label," may result in serious complications and adverse reactions that were not initially reported, as shown by the spinal lidocaine neurotoxicity. Likewise, improvements in management or monitoring may improve the safety of a technique. For example, with current standards of prac-

