Local anesthetic toxicity: 
Review and case studies

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The ester and amide local anesthetic compounds are useful and versatile agents. They are not, however, without inherent dangers. Some of the more outstanding problems associated with local anesthetic toxicity are illustrated in this article by representative case histories. Both recognition and management are discussed.

Knowledge of the current clinical application of anesthetic agents is incumbent on the skillful and versatile anesthetist. Historically, studies of the distribution, fate, and metabolism of direct, intravenous agents have provided the clinician with an understanding of the normal sequence of events observed in the now widespread use of local anesthetic compounds.

When properly administered, local anesthetics cause few, if any, unwanted side effects. Selection of a particular agent is usually based on consideration of the agent’s efficacy for the indicated procedure compared with its incidence of adverse reactions. The agent’s anesthetic index, defined as the drug’s ratio of potency to toxicity, is a reflection of the two. However, all local anesthetic agents are potentially toxic and any patient receiving them is, in theory, subject to an untoward reaction.

The commonly employed local anesthetics vary greatly in potency and duration of action, but all share a common characteristic: the ability and tendency to produce unwanted reactions in a dose-dependent manner. Recently, three such incidents have occurred at this author’s institution. All were produced and manifested somewhat differently, but all were apparently causally related to a relative local anesthetic overdose. The following case studies serve to illustrate potential complications and their management.

Case 1
A 24-year-old primigravida presented with “failure to progress” in labor secondary to cephalopelvic disproportion. The patient had had a successful continuous lumbar epidural catheter in place throughout labor. An additional 10 ml of 0.5% bupivacaine solution was injected in the operative suite to extend the level for cesarean section. During the injection, the patient quickly lost consciousness and experienced a grand mal seizure. Diazepam 10 mg was administered intravenously, and oxygen was delivered by mask. A general anesthetic ensued and the patient was quickly delivered of a healthy infant with Apgar scores of 6 and 8. The operative course was uneventful. An in-depth postoperative neurologic evaluation of the mother noted “hyperreflexia” and determined that the mother had developed an “idiopathic convulsive disorder . . . secondary to a ‘-caine’ reaction.”

Case 2
A 16-year-old, 57-kg male was admitted for June/1983

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elective, second-stage removal of previously applied orthopedic hardware from his right elbow. The preoperative evaluation was unremarkable and negative for any history of seizure. After intravenous sedation with 50 µg fentanyl, initial anesthesia was achieved using local infiltration with 8 ml of 0.5% bupivacaine solution.

However, the patient complained of moderate discomfort, prompting injection of an additional 2 ml of 1% lidocaine into the olecranon. The patient then experienced a questionable loss of consciousness (evidenced by his lack of response to verbal stimuli), followed by a generalized seizure lasting about 10 seconds. Continued postictal agitation was noted for a short period of time, and the patient recovered spontaneously. No further treatment was initiated and the surgery proceeded without incident. The postoperative course was normal.

**Case 3**

A 43-year-old, 75-kg female was admitted for an elective total abdominal hysterectomy for carcinoma in situ. After receiving an explanation of the options, the patient requested an epidural anesthetic for the procedure. There were no contraindications. In the sitting position, a 17-gauge Tuohy needle was easily placed into the epidural space at the L-2,3 level using loss-of-resistance technique. After the standard test dose, 20 ml of 0.75% bupivacaine solution was slowly injected. Thereafter, an epidural catheter was advanced 4 cm cephalad without resistance.

Aspiration for blood and cerebrospinal fluid (CSF) was negative. Approximately five minutes after the initial injection, another 5 ml of the same solution was administered through the catheter. Almost immediately, the patient reported "ringing in my ears," and complained of feeling "light-headed." She was quickly assisted into the supine position; thiopental sodium 100 mg was injected intravenously, and oxygen was delivered by mask. Vital signs remained stable and the patient remained lucid throughout the incident.

No further sequelae were noted and sedation was continued with diazepam (total 5 mg). Once a satisfactory level of analgesia was established, the surgery commenced without further incident, and the postoperative course was normal.

**Discussion**

The observable systemic effects of local anesthetic agents are directly related to the resulting serum levels of the drug. The blood concentration achieved represents a balance between the uptake from the site of injection and the drug's clearance from the blood. Drug uptake is directly related to the speed of absorption from the site of application. Although maximal blood levels are observed after direct intravenous injection, rapid absorption from highly vascular tissues may produce levels that approach those seen with comparable intravenous doses. The entire clinical picture must be considered in ascertaining whether a toxic state is present. Established maximal safe dosages offer only guidelines for the overall administration of local anesthetics, even in the uncompromised patient. Acid-base status, serum chemistries, systemic and organ blood flows, hepatic and serum clearance, possible drug interactions and, where applicable, pre-existing pathological processes must be considered.

**Toxic effects**

In general, the toxic effects of local anesthetics are manifest in three areas: (1) peripheral vasodilatation or vasoconstriction, (2) cardiovascular depression, (3) and the central nervous system (CNS) effect of stimulation and, later, depression. (See Table I.)

**Peripheral and cardiovascular system.** In general, local anesthetics cause vasodilatation and depress cardiac output. At moderate concentrations (1-5 µg/ml, or about the concentration required to combat arrhythmias), lidocaine will produce peripheral vasodilatation. A transient fall in blood pressure may occur. Higher blood levels

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eventually cause myocardial depression with reduced conduction velocity and amplitude of action potential.4

All local anesthetic agents have a directly negative impact on the myocardium, leading to a decrease in cardiac output. When decreased cardiac output is compounded by generalized vasodilatation secondary to arteriolar and venous smooth muscle relaxation, the result is a progressive hypotension. Therapy is aimed at restoring and supporting mean systolic blood pressure and tissue perfusion.

Central nervous system. As serum levels of the anesthetic agents gradually rise, the CNS is stimulated. Unless a massive intravenous bolus is given, the prodromal signs and symptoms of CNS excitement appear even in the moderately sedated patient. Some signs may be masked, though not prevented, by premedication. The patient may experience nausea, dizziness, tinnitus, and difficulty focusing, or may simply describe his condition as one of “feeling strange.” Early signs may also include circumoral and glossal numbness.

Initially, mild sedation and disorientation with superimposed confusion, restlessness, and agitation may be anticipated; this may eventually lead to decreased level of consciousness. It is prudent to watch for any unexpected change in mentation and to quickly determine the cause. Signs of anesthetic toxicity may easily be misinterpreted as signs of fear, anxiety, or neurotic behavior. Many of the signs may appear insidiously, escaping the untrained or casual observer. Usually, however, early indications are evident before severe complications occur.

Lidocaine serum levels between 8-12 µg/ml indicate that a toxic threshold has been reached.8 Slurred speech, shivering, muscle twitching, and tremors appear to be the more outstanding and immediate precursors of a generalized convulsive state. The signs and symptoms of CNS excitement are related to the inhibition of cerebral cortical neurons. This initial selective blockade allows facilitory fibers to function unopposed, leading to excitation and convulsions. Further increases in dosage depress both facilitory and inhibitory pathways, precipitating a general state of CNS depression.4

Management and prevention
Prompt recognition and treatment are the elements of success in the arrest of iatrogenic seizures. CNS excitement increases the oxygen requirements of the brain, thus supportive respiratory therapy is also indicated.

Two convenient approaches can be used to reduce CNS irritability when it appears. Since an increased pCO2 and subsequent tissue hypercapnia decrease both toxic and convulsive thresholds, restoring a normal CO2 tension roughly doubles the amount of local anesthetic required to produce a seizure.8,9 Having the patient hyperventilate also protects the cerebrum by further lowering the arterial pCO2 and elevating seizure threshold.6

Another, more practical, method of elevating the seizure threshold is to pharmacologically alter the brain’s susceptibility to an otherwise convulsant serum level of the drug. Recent literature advocates the use of intravenous diazepam in doses of 0.1 mg/kg lean body weight in both preventing and aborting local anesthetic-induced seizures.7 Because this is not always appropriate (in the antepartum obstetrical patient, for example), other methods, including the use of skeletal muscle relaxants and short-acting barbiturates, have also been recommended. These methods have their drawbacks, but they are readily available in the clinical setting and their value in skilled hands should not be overlooked.

An advantage of neuromuscular blocking agents is that paralysis resulting from their use halts the muscular manifestations of a seizure, while subsequent hyperventilation provides oxygenation and lowers CO2 tension. However, note that paralysis does not cure the underlying cerebral irritability; it merely treats one symptom by masking the external muscular activity.6

It has been demonstrated that lowering the cerebral metabolic rate by decreasing cortical blood flow and cerebral oxygen consumption causes thiopental sodium to have a protective effect on the brain and may, in effect, be useful in aborting seizure activity.8,10,11 However, thiopental sodium is apparently effective only in raising the dose threshold required to induce seizure activity.

Diazepam and, to a lesser extent, lorazepam, have a calming effect on the cerebrum, greatly increasing the seizure threshold without significantly depressing respiration. Although the onset of action is much faster and the duration of action much shorter, respiratory depression and recovery time from the obtunded state is longer with thiopental than with equivalent anti-convulsive doses of diazepam.7

Prevention of unwanted sequelae during the use of local anesthetics is easily achieved by incorporation of meticulous technique, proper dosage, appropriate premedicants, and common sense. It is ideal to aim for the smallest dosage of the
least toxic drug for any given procedure, using a concentration and quantity sufficient to produce an adequate block. The same drugs mentioned earlier (barbiturates and benzodiazepenes) may be used as premedicants and in prophylaxis against such problems. Above all, constant vigilance and observation of the patient's status is vital.

Summary

One of the very real complications possible in the use of local anesthetic agents is a relative overdose of the drug, resulting in an inordinate and potentially dangerous serum level. Even when using strict and careful technique, problems can occur.

The reactions cited in the aforementioned cases were most likely the result of the accidental intravenous injection of a local anesthetic agent. Two cases were treated with anticonvulsants; one was not. In retrospect, it is possible that the seizure activity seen in Case 2 may have been prevented by an intravenous injection of benzodiazepene.

A variety of currently available local anesthetic compounds has been deemed safe for common usage in the field of anesthesia. The majority of problems associated with their use stem from faulty technique, ignorance, mismanagement, or simple oversight, and are not necessarily due to any intrinsic property of the drug. Nevertheless, local anesthetics are potentially toxic and their use should be approached with knowledge of and a healthy respect for their associated complications.

It should also be remembered that virtually all local anesthetic toxic reactions are preventable and treatable. Their occurrence need not necessarily result in a poor outcome.

REFERENCES


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