Toxicity and Allergy to Local Anesthesia

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The first widely used local anesthetic was cocaine. In the mid-1860s, Bennett, a physician, studied the effects and uses of cocaine for surgical procedures. He reported that with increased dosage of cocaine, seizures and respiratory arrest typically followed glossal numbness.\(^1\) Despite the reports of toxicity, cocaine provided good anesthesia for a variety of surgical procedures. Hall reported the first use of cocaine by a dental surgeon; Nash operated painlessly on his own upper incisors after an injection of cocaine into the infraorbital nerve. Thus was cocaine introduced as a local anesthetic in dentistry.\(^2,3\)

Cocaine had certain drawbacks. Its propensity to cause addiction and acute systemic toxicity made it less desirable than was originally thought. Hall himself became addicted to cocaine. Because of this tremendous addiction factor and systemic toxicity, a search for a synthetic substitute was undertaken. In 1905, procaine, an ester local anesthetic, was developed. In subsequent years, other ester-type local anesthetics were used in dentistry and anesthesia. In 1948, Lofgren reported the successful use of lidocaine as a local anesthetic.\(^4\) Lidocaine represented a new type of local anesthetic, which differed chemically from the earlier ester-type drugs in several ways. Subsequently introduced anesthetics -- such as mepivacaine, prilocaine, bupivacaine, etidocaine and articaine -- are classified as amide local anesthetics.

As is the case in the development of any new class of medications, the early use of cocaine inspired the development of a safer class of local anesthetics. Though local anesthetics are invariably toxic at higher doses when administered accidentally intravenously, they are devoid of the addiction problems associated with cocaine.

Typical toxic responses occur in the central nervous and cardiovascular systems, with the most frequent clinical toxic reactions involving the central nervous system. Early toxic effects include alterations in consciousness and seizures, followed by respiratory arrest, myocardial depression and eventually death. In 1970, Lofstrom reported numerous fatal cases involving overdose of local anesthetics. Few cases however, involved small doses...
administered during dental treatment. In 1979, Albright demonstrated a correlation between cardiovascular system toxicity and the longer-acting, highly lipid-soluble local anesthetics (bupivacaine, etidocaine). Of 49 fatal cases, 43 percent involved bupivacaine. Subsequently, the Food and Drug Administration recommended against the use of 0.75 percent bupivacaine. The FDA further recommended the slower and more accurate delivery of bupivacaine. Since then, the fatality rate due to cardiovascular collapse secondary to bupivacaine administration has significantly decreased.

**Local Anesthesia Toxicity**

Local anesthetic toxicity is the result of increased blood levels of a local anesthetic in a very short duration. This can occur with accidental intravenous injection during a regional nerve block, excessive doses, and/or incorrect anatomical locations. The rate of administration, pre-existing medical conditions, acid-base imbalances, age, weight, and other physical and medical factors can also influence toxicity of local anesthetics. Lipid solubility, pKa, rate and route of metabolism change the level of toxicity.

The high blood concentration of anesthetic necessary to cause toxic overdose comes about in four ways:

- Too large a dose of local anesthetic drug;
- Unusually rapid absorption of the drug or intravascular injection;
- Unusually slow biotransformation; and
- Slow elimination.

The dose necessary to induce toxicity varies among patients and is influenced by numerous factors:

- The patient's general health;
- Rapidity of injection;
- Route of administration;
- Amount of local anesthetic administered; and
- Patient's age.

**Chemical Structure**

The chemical structure of the local anesthetics may also affect the drug toxicity. The right and left stereoisomers of bupivacaine differ in cardiotoxicity, d-bupivacaine being more cardiotoxic than l-bupivacaine. The ester local anesthetic is hydrolyzed rapidly by cholinesterases in the blood. Therefore, the toxicity associated with these local anesthetics is typically of shorter duration. The metabolism of the amides in the liver lacks the immediacy of the esters. Since local anesthetics do not have active metabolites, there is little risk of complications from hydrolyzed or biotransformed local anesthetics.

**Lipid Solubility**

The amount of local anesthetic required to produce toxicity tends to parallel the lipid solubility and the potency
of the particular drug (Table 1). Because of the lipid bilayer in the cell membranes of nerves and tissues, the more lipid-soluble anesthetics diffuse intracellularly more easily and are more potent. Central nervous and cardiovascular system toxicity are directly correlated to the potency of the local anesthetic -- more potent local anesthetics produce greater toxicity at lower doses than do less potent agents. Furthermore, studies show that the negative inotropic and convulsant effects of procaine are less than those of bupivacaine, procaine being the less potent of the two anesthetics.\textsuperscript{14,15} Therefore, local anesthetics with low lipid solubility (prilocaine, lidocaine, mepivacaine) are less toxic than anesthetics with high lipid solubility (bupivacaine, etidocaine).\textsuperscript{13}

Table 1.

The Amount of Local Anesthetic Required to Produce toxicity as Compared to Lipid Solubility and Potency.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Potency</th>
<th>Lipid Solubility\textsuperscript{7}</th>
<th>Absolute Toxicity\textsuperscript{16}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procaine</td>
<td>1</td>
<td>1.7</td>
<td>1</td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>1.5</td>
<td>N/A</td>
<td>0.5</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>10</td>
<td>76</td>
<td>10</td>
</tr>
<tr>
<td>Amides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2</td>
<td>43</td>
<td>2</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>2</td>
<td>25</td>
<td>1+</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>2</td>
<td>21</td>
<td>1.5</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>4</td>
<td>800</td>
<td>4</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>4</td>
<td>346</td>
<td>4</td>
</tr>
</tbody>
</table>

The correlation between toxicity and the pKa of a local anesthetic is minimal. However, since the pKa of an anesthetic is directly related to the onset of anesthesia, the onset of toxicity is more rapid in rapid-acting drugs. The closer the pKa of an anesthetic to the pH of the injected tissues, the more rapid the onset of action. Because of the greater number of uncharged anesthetic molecules, more anesthetic is able to diffuse into the nerve sheath and surrounding tissues.

Protein Binding

Protein binding is not a significant a factor in local anesthetic toxicity. Increased protein binding of a local anesthetic allows for tighter and longer binding of anesthetic molecules to drug receptor sites in the nerve, providing for a longer duration of action and potentially increasing the risk of toxicity when additional doses are administered.

Other predisposing factors influencing local anesthetic toxicity are patient-related. They include the patient's age, weight, gender, genetics, and pre-existing disease or medications.

Age

Age is a factor in younger and older patients. The lack of development or dysfunction of the liver and kidneys in these populations increases the level of local anesthetic in the bloodstream.\textsuperscript{14} However, studies have demonstrated the opposite with immaturity of the other organs. Budgwell and colleagues suggested that immaturity of the central nervous and cardiovascular systems in the younger population might play a role in the resistance to local anesthetic toxicity.\textsuperscript{15} McIlvaine and colleagues suggested that children have a higher threshold for bupivacaine toxicity than adults.\textsuperscript{16}

Weight

The guideline for maximum dose of a local anesthetic is usually based upon the patient's body weight. Lean body weight is important in determining blood volume of the patient. The greater the body weight, the larger the volume of distribution of the local anesthetic. With a greater volume of distribution, a larger dose of local anesthetic could be administered prior to inducing toxicity. The greater the lean body weight, the more tolerant a
Pregnancy

Local anesthetic toxicity has been studied extensively in pregnant animals, but not much is known for pregnant women. Any information regarding pregnancy and local anesthetic toxicity is extrapolated from animal studies. From studies with pregnant animals, pregnancy does not seem to alter the level of systemic toxicity with lidocaine and mepivacaine. However, bupivacaine is more toxic in pregnant women than lidocaine, prilocaine, and mepivacaine.14

Physical changes occurring in pregnancy may also affect the amount of local anesthetic necessary to cause toxicity. When a woman is pregnant, several changes may occur: a decrease in renal function, increase in volume of blood, and increase in weight. In a person with less than normal renal function, local anesthetic metabolites may accumulate in the bloodstream. However, with the increase in body weight and blood volume, the patient would be able to tolerate a larger volume of local anesthetic.14

Pseudocholinesterase Deficiency

Serum cholinesterase is an enzyme produced by the liver. It hydrolyzes ester anesthetics (procaine, chloroprocaine, tetracaine) and the depolarizing muscle relaxant succinylcholine. A hereditary pseudocholinesterase deficiency retards the hydrolysis of ester local anesthetics. The result is a prolonged half-life of the ester anesthetics. Low serum cholinesterase levels are capable of doubling or tripling the half-life of a local anesthetic. Lack of pseudocholinesterase or atypical pseudocholinesterase could have devastating consequences when large doses of ester local anesthetics are administered. Other causes of low pseudocholinesterase levels include pregnancy, liver disease, and certain drugs (i.e. Echothiophate, Phenelzine, and Trimethaphan).14

Pre-existing Disease

Pre-existing hepatic dysfunction decreases the rate at which amide local anesthetics are metabolized, leading to the elevation of blood levels of local anesthetics circulating to target organs (heart, brain). Renal insufficiency leads to elevated electrolyte levels and an increase in the blood concentration of local anesthetics. This results in hyperkalemia and acidosis, both of which may increase the risk of morbidity and mortality associated with bupivacaine administration.19 Cardiac insufficiency reduces blood flow, causing stasis and elevated levels of local anesthetic in end organs, increasing anesthetic risk.

Medications

Besides the drugs that alter pseudocholinesterase levels, drugs that alter functioning of the central nervous and cardiovascular systems may also lower the toxicity threshold of local anesthetics. This is especially so for drugs that decrease liver or cardiac function or stimulate the central nervous system.

Local anesthetics, such as lidocaine and procainamide, are administered in advanced cardiac life support as antiarrhythmics. Patients who are receiving antiarrhythmics and cardiovascular depressants have inhibited myocardial impulse propagation. Therefore, concomitant use of high doses of local anesthetics along with their cardiac medications may have additive effects on the heart.20 These medications may include digoxin, beta-blockers, and calcium channel blockers. Another concern is patients who are on H1-blockers since these drugs compete for the same enzyme system that metabolizes amide anesthetics. This would result in a delayed metabolism of the local

http://www.cda.org/cda_member/pubs/journal/jour998/allergy.html
Central nervous system depressants may indirectly be detrimental when used to prevent local anesthetic induced seizures. Diazepam and phenobarbital are occasionally used to prevent seizures in the epileptic population. However, clinical practice has abandoned the prophylactic use of these drugs in the prevention of local anesthetic-induced seizures.

As positive as these intentions are, premedication with benzodiazepines may, in fact, lower the incidence of local anesthetic-induced seizures, but it does not alter the threshold for cardiovascular system toxicity. In fact, suppression of the initial central nervous system warning signs of overdosage may lead to an increased risk of severe cardiovascular collapse.

The onset of toxicity is the direct result of the rate and site of drug administration. Direct intravenous injection of local anesthetics would induce the most rapid and intense level of central nervous and cardiovascular system toxicity. Highly vascular injection sites, i.e., sublingual regions, have a higher correlation to an increased incidence of local anesthetic toxicity than do less vascular areas. Therefore, multiple injections into highly vascularized areas should proceed with extreme caution.

de Jong and colleagues showed that mixtures of local anesthetics are no more toxic than the parent anesthetic. To be safe, alternative injection sites and local anesthetics should be considered. Scott studied the threshold dose for central nervous system toxicity of etidocaine in healthy volunteers. When etidocaine was administered slowly via an intravenous infusion at 10 mg/min and 20 mg/min, the faster rate caused threshold central nervous system symptoms at two-thirds the dose of the slower rate. Malamed recommends injection of 36 mg of lidocaine consistently over 60 seconds. Intravenous injections of the same dose in less than 15 seconds significantly increase the risk of overdose reactions. It is recommended, therefore, that aspiration and slow injection techniques be utilized for all injections.

**Toxic Effects on the Central Nervous System**

<table>
<thead>
<tr>
<th>Table 2. Signs and Symptoms of Central Nervous System Stimulation</th>
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<tbody>
<tr>
<td><strong>Mild Signs</strong></td>
</tr>
<tr>
<td>Talkativeness</td>
</tr>
<tr>
<td>Slurred speech</td>
</tr>
<tr>
<td>Apprehension</td>
</tr>
<tr>
<td>Localized muscle twitching</td>
</tr>
<tr>
<td>Lightheadedness and dizziness</td>
</tr>
<tr>
<td>Tinnitus</td>
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<tr>
<td>Difficulty focusing the eyes</td>
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</table>

The central nervous system is the initial target organ for local anesthesia toxicity. The effects of local anesthetics on the central nervous system are biphasic (stimulation/depression). Although most clinical signs of central nervous system actions related to local anesthetic toxicity are stimulatory, the actual physiologic cause is depressive. The stimulatory effect is the indirect result of a depression of cerebral inhibitory centers. This results in unopposed facilitatory neurons causing random stimulatory firing of the neurons in the brain. This generalized stimulation of the brain causes generalized tonic-clonic seizures. In subtoxic blood levels, 0.05 to 4 mcg/ml of serum blood, lidocaine may produce anticonvulsant and sedative effects. At 4 to 7 mcg/ml, mild central nervous system stimulatory signs are seen (Table 2) with lidocaine. The mild signs represent depression of higher cerebral and cortical centers. Cognitive and reasoning centers are depressed. Perioral numbness, which occurs, is not entirely a direct effect of paresthesia; rather this represents the effect of local anesthetic blood levels in the highly vascularized tissue of the oral cavity. As lidocaine blood levels approach 7 mcg/ml, the basal centers and then the medullary centers of the brain are depressed. Lidocaine and procaine may produce
progressive symptoms (Table 2) without the initial mild signs. If blood levels of lidocaine reach 7.5 to 10 mcg/ml, generalized tonic-clonic seizures occur.19 The seizure is typically of short duration and self-limiting. However, respiratory arrest is common because of the lack of muscle control, which accompanies the seizure. Progression to hypoxia, cyanosis, and cardiac arrest may be rapid because of the detrimental combination of increased oxygen consumption of the tonic muscles and respiratory arrest. Postictal cortical depression may vary from stupor to coma. Respiratory and/or cardiac depression may deteriorate to respiratory and/or cardiac arrest during the postictal medullary depression.

Toxic Effects on the Cardiovascular System

The cardiovascular system is more resistant to elevated local anesthetic blood levels. Similar to the anticonvulsant effects on the central nervous system, subtoxic doses of local anesthetics have demonstrated cardiodepressive actions comparable to quinidine.27 Local anesthetics produce a direct depression of the myocardium, slow conduction of impulses through the AV node, and prolong the refractory period. Lidocaine and procainamide have been used as antiarrhythmics for three decades.28,29 The minimum initial antiarrhythmic dose of lidocaine recommended by the American Heart Association is 1 to 1.5 mg/kg, which produces a blood level of 1.5 to 5 mcg/ml in the blood of an average 150 pound adult. At blood levels above 5 mcg/ml, moderate to severe myocardial depression is noted. Bradycardia, negative inotropic actions, and peripheral vasodilation occur progressively until a blood level of 10 mcg/ml. At levels above 10 mcg/ml, severe vasodilatation and bradyarrhythmia leads to ventricular fibrillation and asystole.30 Asystole secondary to local anesthetics is virtually irreversible.8 Numerous cases of local anesthetic-induced cardiovascular collapse have been reported in humans, with a majority of these findings occurring with the potent, highly lipid-soluble, highly protein-bound local anesthetics.31,32,33 Bupivacaine, etidocaine, and tetracaine produced more depressant effects at lower concentrations than did lidocaine, mepivacaine, or prilocaine.27,34,35 Furthermore, bupivacaine is more arrhythmogenic than lidocaine. Bupivacaine blocks the SA node; prolongs the P-R interval and induces more re-entrant type of arrhythmias. All this is due to the fact that bupivacaine is more strongly bound to the receptor site within the sodium channel than is lidocaine, especially in cardiac muscle.36 Liu and colleagues studied the relative cardiovascular toxicity of numerous local anesthetics on dogs and found lethality to be in direct correlation with the relative potencies of the anesthetics. He demonstrated that bupivacaine produced the greatest degree of hypotension and cardiovascular collapse with the lowest lethal dose, followed by tetracaine and etidocaine.13,37 Lidocaine was least likely to induce negative inotropic and chronotropic effects.12,34

Unlike inotropic effects, the exact mechanism of the negative chronotropic action is unknown. It is speculated, however, that the decrease in myocardial contractility may be due to sodium channel blockade or to increased calcium release. De La Coussaye and colleagues reported that the greater negative inotropic effect of bupivacaine is related to the amount of the drug entering into the myocardium.38 The lower lipid solubility of lidocaine prevents a higher intracellular concentration of lidocaine and thereby lessens its negative inotropic potential.

Management of Toxicity

Prevention is the key to local anesthesia toxicity. To prevent intravascular injections, use an aspirating syringe.
with a slow injection technique. Malamed recommends using needles not smaller than 25 gauge, aspirating in at least two planes before injection, and slowly injecting the anesthetic. Needles smaller than 25 gauge are difficult to aspirate through, especially when located in fibrous tissues. Reorientation of the bevel of the needle ensures that the needle is not resting against the vascular wall, thus providing a better determination of non-intravascular injections. Many reported local anesthetic toxicity cases are associated with a rapid injection of local anesthetics. Injecting 1.8 ml of solution over 60 seconds should prevent a rapid rise intravascularly and minimize toxicity.14

Other techniques to prevent toxicity are paying careful attention to dose and route of administration, using test doses, and using vasoconstrictors. All three techniques should prevent toxicity when injecting into highly vascular areas.7

Vasoconstrictors, such as epinephrine, serve two purposes. As blood vessels are constricted, local anesthetics are absorbed intravascularly more slowly. Second, as a sympathomimetic drug, epinephrine may serve as a marker for intravascular injection. Intravascular epinephrine will typically elicit an acute tachycardic response. Furthermore, during initial cardiovascular system toxicity, the positive chronotropic and inotropic effects of epinephrine will counteract the myocardial depression of the local anesthetic.

Initial signs of toxicity may be difficult to differentiate from anxiety. The patient may appear more verbose and apprehensive. The best treatment is to reassure the patient because, at this stage, the situation is mild and not life-threatening. Planned dental treatment can usually be completed at the same appointment.

If an episode of tonic-clonic seizures arises within two to five minutes after the injection, suspect rapid absorption of the anesthetic from the interstitial tissues. This is more common with injections into the base of the tongue. However, if seizures are seen within 10 to 30 seconds, the local anesthetic was inadvertently administered intravascularly.

Treatment for both instances involves termination of dentistry and immediate airway management. Protect the patient from injuries by moving any loose items away from him or her. Suction should be readily available to remove vomitus, especially during the postictal phase. Patency of the airway should be of primary concern after tonic-clonic seizures. Mechanical ventilation and head tilt/chin lift of the patient may be necessary when seizures stop. Supplemental oxygen and oral airways are also advisable.7

During a severe postictal phase of depression, the patient may be unconscious, unresponsive, and incapable of maintaining a patent airway. The ABCs of resuscitation should be followed. Respiratory arrest is common; therefore, controlled ventilation is required. Cardiac responses may vary from moderate hypotension to asystole. A supine or Trendelenburg position is recommended, producing the least peripheral pooling and increasing vascular circulation. Pulse rate and blood pressure should be closely monitored to prevent complete collapse.

Each patient's response is distinct, thus sensible clinical judgment is recommended to determine the feasibility of continuing with dental treatment. Be attentive to the patient's deteriorating condition. Due to the pre-existing local anesthetic dose present in the cardiovascular system, subsequent local anesthetic injections should proceed with caution.

Central Nervous System Management

Due to the rapid onset and duration of central nervous system toxicity, administration of intravenous anticonvulsant drugs is not expeditious enough to terminate this self-limiting condition, although as a prophylactic measure, barbiturates and benzodiazepines have been administered to prevent seizures.31,37 Typically the
administration of 50 to 100 mg of pentobarbital or 5 to 10 mg of diazepam at the earliest sign of toxicity will prevent the development of seizures. These central nervous system depressants decrease the incidence of seizures but do not alter the dose of bupivacaine necessary to cause cardiovascular system collapse.\textsuperscript{21} In fact, these central nervous system depressants may obscure the primary central nervous system warning signs, which develop prior to cardiovascular system collapse.

Barbiturates and benzodiazepines do not interrupt the neuronal activity during seizures, they merely prevent the tonic-clonic movements exhibited during an episode. However, respiratory function may be obtunded by these drugs; therefore, controlled ventilation may be necessary to prevent the development of hypoxia and hypercarbia.\textsuperscript{8} This is of extreme importance during the postictal depression, where these drugs could intensify the magnitude of central nervous system and respiratory depression. The primary reason for administration of these central nervous system depressants is to control overt seizure activity and facilitate ventilation if a seizure occurs.\textsuperscript{7}

**Cardiovascular System Management**

The importance of airway and respiration management supercedes any cardiovascular system support. As in basic life-support, airway is the primary step prior to assessing circulatory function. Thus, before considering the use of any drug therapy for the cardiovascular system, supplemental oxygen and a patent airway must be established. Moore reported successful control of local anesthetic-induced seizures in 84 of 93 patients with oxygen via bag and mask.\textsuperscript{39}

Cardiovascular response to local anesthesia toxicity is extremely complicated. Clinical manifestations vary from simple hypotension to electromechanical dissociation, ventricular fibrillation, or asystole.

One of the easiest treatments does not involve the use of pharmacology. Repositioning the patient in a supine position with their feet elevated slightly and administering intravenous fluid could overcome the hypotension caused by venous pooling. If further treatment is necessary, vasopressors could be considered. Phenylephrine or ephedrine should be considered prior to epinephrine. Epinephrine has been shown to induce arrhythmias and seizures at lower doses of bupivacaine.\textsuperscript{40} Because of its immediate and direct cardiac effects, epinephrine sensitizes the heart to arrhythmias, whereas phenylephrine or ephedrine, to a lesser degree, has relatively little or no direct effect on the myocardium or AV node.\textsuperscript{40}

Bradycardia is also commonly seen with local anesthesia toxicity. A heart rate lower than 40 beats per minute in an average patient indicates the need for pharmacologic intervention. Again, rather than use epinephrine, alternatives such as glycopyrrolate or atropine should first be considered. These anticholinergics increase heart rate indirectly via vagal blockade. Both of these medications should be administered intravenously. Atropine 0.5 mg or glycopyrrolate 0.2 mg should prove effective against bradycardia.\textsuperscript{8}

Treatment of arrhythmias induced by local anesthetic overdose is difficult, since local anesthetics are also antiarhythmic. Bretylium tosylate, calcium chloride, and magnesium sulfate have been effective for resuscitation.\textsuperscript{41,42} Ultimately, however, cardioversion may be necessary. With the increasing availability of automatic external defibrillators, the mandate may be to have them in all dental offices.

**Allergy to Local Anesthesia**

True immunoglobulin-E mediated allergic reactions to local anesthetics are rare. Many patients and clinicians mistake any idiosyncratic response after local anesthetic injection for an allergic reaction. Giovanitti and Bennett estimated that no more than 1 percent of the adverse reactions to local anesthesia is true allergy.\textsuperscript{43} However,
once reactive to an antigen, the patient is allergic to this drug for the rest of his or her life.

The immunoglobin-E allergic reaction is acquired through exposure to an antigen. With re-exposure, the antigen-antibody response is heightened until a point where mast cells respond with the release of chemical mediators that produce the clinical manifestations of allergy. These mediators include histamines, leukotrienes, chemotactic substances, lysozomal enzymes, prostaglandins, kinins, and platelet-activating factor.44,45 These mediators cause capillaries to leak and permit extravasation of plasma into the surrounding area. True drug allergies manifest as asthma, rhinitis, angioneurotic edema, urticaria, and rash. Urticaria is caused by release of histamine, which induces peripheral capillary leakage along with erythema, pruritis, and edema. Immunoglobin-E anaphylaxis may be severe enough to cause respiratory distress and cardiovascular collapse. Anaphylaxis is the result of a generalized increase in capillary permeability leading to a drop in blood pressure. Furthermore, released leukotrienes cause bronchiolar smooth muscle to spasm, eliciting an asthmatic-type response.

No matter how doubtful their claim, treat all patients as "allergic to local anesthetics" until the patient is allergy-tested.

**Allergy Signs and Symptoms**

Mild signs of an allergic reaction include urticaria and rash. Urticaria is associated with pruritis (itching) and wheals (elevated skin patch). These mild dermatological signs are usually visible within six minutes. As the allergic reaction progresses, the cardiovascular, respiratory and gastrointestinal systems become involved. Hypotension is the initial cardiovascular response. Increased histamine release during allergy causes increased plasma extravasation to the interstitial tissues leading to a decrease in blood pressure and to generalized angioneurotic edema. Angioedema typically involves the face, hands, feet, and genitalia. During severe cases, the lips, tongue, larynx, and pharynx are also involved. Angioedema of the upper tracheobronchial tree (laryngeal edema) induces stridor by limiting air exchange to and from the lungs. Spasm of bronchial smooth muscle in the lower tracheobronchial tree causes bronchospasm. Bronchospasm and asthmatic-type reactions are the result of leukotrienes. Leukotrienes, similar to histamines, are chemical mediators of allergy that cause increased swelling and spasm of the tracheobronchial tree. Other symptoms of bronchospasm may include dyspnea, wheezing, flushing, cyanosis, tachycardia, and increased use of accessory muscles of respiration.

**Predisposing Factors to Allergy**

Many patients claim allergies to Novocain. Ester-type local anesthetics, i.e., procaine, chloroprocaine, and tetracaine, are derived from para-amino benzoic acid, a known allergen. Furthermore, when ester local anesthetics are hydrolyzed by plasma cholinesterase, its metabolites include para-amino benzoic acid. Amide local anesthetics are almost entirely devoid of this problem. After years of countless carpules of amide local anesthetics being administered, only a few cases have been reported with an amide local anesthetic challenge.46

Older commercial preparations of local anesthetics included preservatives, such as methylparaben. Methylparaben is chemically related to para-amino benzoic acid and is also identified as an allergen.47 Methylparaben is a bacteriostatic agent found in many drugs, cosmetics, and foods. Currently, methylparaben has been removed from dental local anesthetic cartridges but is still found in multiple dose vials. Another preservative used is sodium bisulfite or metabisulfite. Bisulfites are antioxidants used to prevent the early breakdown of epinephrine in dental cartridges. No allergic reactions to dental cartridges without epinephrine have been reported. Bisulfites are also found in food, preventing the food from "browning" (oxidizing) when exposed to air. Most patients who are intolerant to bisulfites are also dependent upon inhaled steroids to prevent acute episodes of bronchospasm.

**Treatment of Allergic Reaction**

http://www.cda.org/cda_member/pubs/journal/jour998/allergy.html
Delayed mild cases of an allergic reaction are usually treated by 50 mg of intravenous, intramuscular or oral diphenhydramine (Benadryl). Follow-up doses of 50 mg oral diphenhydramine every four hours is recommended for three days.

If the initial signs of anaphylaxis proceed to conjunctivitis, rhinitis, urticaria, pruritis, and erythema within 60 minutes, 50 mg or IM diphenhydramine (25 mg for a child) and/or 0.3 mg of intramuscular epinephrine (0.15 mg for a child) is recommended.8 Corticosteroids, such as dexamethasone or methylprednisone, are effective in decreasing edema and capillary permeability. Intravenous 8 mg of dexamethasone (4 mg for a child) should be considered if the condition appears to be eminent. When speed is not a factor, Medrol Dosepak is an oral corticosteroid of choice. Subsequently, Benadryl should be prescribed orally for three to four days as precaution.

Bronchospasm or allergic asthma is treatable if diagnosed early. The patient will typically complain of difficulty in breathing and expresses a desire to sit upright. Wheezing may be heard with air exchange. For an asthmatic response, aerosolized albuterol or MediHaler-Epi is considered the first line of treatment.14 Intramuscular antihistimines, like diphenhydramine 50 mg, may also be beneficial. If aerosol or antihistamine treatments are not effective or the patient is unconscious, 0.3 mg intramuscularly of epinephrine will activate the beta-2-agonist receptor sites causing bronchodilation. If these treatments are ineffective or the episode recurs, activate emergency medical services. Medical consultation and follow-up with a physician is recommended.

Although no known cases of anaphylaxis to an amide local anesthetic have occurred within 30 minutes, prevention and immediate intervention is important, especially with laryngeal edema. Laryngeal edema is one of the most ominous events following an initial allergic reaction. Immediate attention should be paid to evaluation of the patency of the airway. Complete obstruction of the larynx results in no sound and air passage. If a high-pitched crowing sound is heard the airway is partially obstructed. Either obstruction requires the same treatment.8 Emergency medical services should be immediately activated. Administer 0.3mg of intramuscular epinephrine and maintain a patent airway with bag, mask, and supplemental oxygen. Intravenous steroids and histamine-blockers are also recommended. If the patient does not improve, consider opening an air passage below the obstruction. Typically this involves cricothyrotomy.8,14

Fortunately, anaphylaxis to an amide local anesthetic in a dental office is nearly non-existent. However, generalized anaphylaxis is one of the most urgent emergencies in the dental office. Most of the signs and symptoms have a rapid onset and significant morbidity. In most cases, the patient will become cyanotic and lose consciousness within minutes. All of the above symptoms with laryngeal edema, bronchospasm, and cardiovascular collapse may occur simultaneously. Unless treatment is immediate, the mortality rate is extremely high. Following airway maintenance, intravenous 0.3 mg epinephrine is the first line of treatment; followed by 8 mg dexamethasone. Assisted ventilation with supplemental oxygen is recommended. Management of the cardiovascular component of the reaction requires 15 mg of intravenous ephedrine to combat the severe hypotension, which is often present.8 Chest compressions may be necessary if the patient is pulseless. Activation of emergency medical services is important, however basic life support is the most important step in successful management of anaphylaxis. Prompt and definitive treatment may be the difference of life and death.

Allergy Testing

Due to the rarity of local anesthetic allergy, the simplest in vivo allergy testing technique is recommended. The probability of an anaphylactic response is minimal, especially with the intracutaneous testing technique. However, with any allergy testing, a specialist should complete the testing with an intravenous line started and emergency equipment and drugs at the ready.
Summary

Due to the morbidity and mortality involved with toxicity studies, most clinical studies involve animals. Few case presentations of toxicity and allergy in humans have been reported. The dosages necessary to produce toxicity and allergy vary between species; however, there is a direct correlation between animals and humans with respect to central nervous and cardiovascular system toxicity.

Local anesthetics are central nervous system depressants. At critical low blood levels, their depressant effects can be therapeutic in the prevention of certain types of seizures. At higher blood levels, the suppression of inhibitory pathways results in facilitatory pathways functioning unopposed, resulting in seizures. At very high blood levels, the facilitatory pathways also are blocked, resulting in complete suppression of the central nervous system. This condition is associated with coma and depression of respiratory and circulatory centers ultimately leading to death.

The cardiovascular system tends to be more resistant to the toxic effects. Local anesthetics have a suppressant effect on the heart, reducing myocardial contractile force and prolonging or blocking intracardiac conduction. They are also vasodilators. High doses of local anesthetics cause a reduction in heart rate and blood pressure, cardiac conduction defects, and arrhythmias, including ventricular tachycardia and fibrillation. There is, for the most part, a separation between the dose and blood concentration required to cause central nervous and cardiovascular system toxicity.

In general, the cardiotoxic and neurotoxic effects of local anesthetics do not differ greatly, but their relative potential for toxicity does. At certain dosages, bupivacaine produces effects different from those of other local anesthetics. There is considerable evidence to support the contention that bupivacaine exerts a strong direct effect on the myocardium and the brain.

The treatment of systemic toxicity due to local anesthetics should be instituted rapidly and aggressively. Appropriate equipment and pharmacological agents should be kept close at hand. Maintenance of an open airway and administration of oxygen is important. Support of the circulation and control of arrhythmias are essential for maintaining adequate perfusion of the vital organs as well as assisting in the removal of local anesthetic from the tissue and its detoxification. Persistence in the resuscitation process is essential, as some patients may prove difficult to resuscitate.

Allergic reactions to local anesthetics agents are extremely rare. Ester local anesthetics produce para-amino benzoic acid as a metabolite, and it is a known allergen. Methylparaben is also a known allergen, and it is used occasionally as a preservative in commercial preparations of some amide local anesthetics. Reactions are generally dermatologic when they occur and rarely are systemic or anaphylactoid. Recommendations for screening suspect patients can be found in the literature and generally involve skin tests.47,48

The intent of this article is to review the pharmacology of the local anesthetics and the mechanisms to toxicity and allergy. A good knowledge of the pharmacokinetics and pharmacodynamics of local anesthetics is important; both the patient and the practitioner should have a proper understanding of the consequences of local anesthesia administration. Early intervention can be started when all persons involved know the initial signs and symptoms of toxicity and allergy. Precaution is the best prevention, whether it is overdose toxicity or allergy; and knowledge is the first key to prevention.

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