Clinical Update

Naval Postgraduate Dental School
National Naval Dental Center
Bethesda, Maryland

Vol. 24, No. 10 October 2002

Local anesthetics (Part II): assessment of adverse reactions and drug interactions

(This *Clinical Update* is part two of a three-part series)

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Local anesthetics are very safe (1,2). Estimates report that in excess of 6 million dental cartridges are administered weekly in the United States, totaling more than 300 million per year (3). Although considered routine, the use of local anesthetics carries the potential for untoward events. The purpose of this clinical update is to review the adverse reactions that may develop with the use of local anesthetics and to discuss potential interactions with other medications.

Adverse reactions

Systemic (toxic) reactions

Local anesthetic toxicity occurs when blood levels of the drug accumulate in a very short period of time and is achieved in the following ways: (4)

- Unusually large dosage of local anesthetic
- Intravascular injection or unusually rapid absorption of the drug
- Slow biotransformation
- Slow elimination

The dose necessary to induce toxicity is variable and is influenced by a number of factors to include the patient's age, weight, liver and kidney conditions as well as the type and amount of anesthetic used (3).

Both the central nervous system (CNS) and cardiovascular system (CVS) are susceptible to toxic levels of local anesthetics. Of the two systems, the CNS is more readily affected by anesthetics (3). Signs of mild CNS toxicity include sedation, slurred speech, shivering, twitching and mild tremors of the face and limbs, and numbness of the tongue and perioral regions. The patient may report a warm, flushed feeling, pleasant dreamlike state, lightheadedness, drowsiness, disorientation, and visual and auditory disturbances. Moderate CNS toxicity is signaled by the onset of tonic-clonic convulsions. Signs and symptoms of severe CNS toxicity include lethargy, coma, dyspnea, apnea, hypotension, shock, cardiac arrest, and respiratory arrest (3).

The negative effects on the cardiovascular system are not manifested until significantly high blood levels of anesthetic are reached. Local anesthetics produce a dose-dependent depression of the myocardium. In low concentrations, local anesthetics can be useful in correcting cardiac dysrhythmias. Toxic levels of local anesthetics can cause profound myocardial depression (3). In addition, the primary effect of local anesthetics on peripheral blood vessels is vasodilation. At overdose levels, this may lead to circulatory collapse (3).

Prevention is the key to management of local anesthetic toxicity and includes careful review of the medical history, attention to dose and route of administration, use of vasoconstrictor, and slow injection technique with aspiration.

Localized reactions

Injury to tissue can be caused by the chemical components of the anesthetic solution as well as mechanical factors such as needle trauma, fast injection rates, and cartridge contamination. Localized reactions may cause damage to connective tissue, neuronal tissue, or blood vessels. Manifestations include pain and burning on injection, persistent anesthesia, paresthesia, hematoma, trismus, infection, edema, facial nerve paralysis, and formation of soft tissue lesions (5).

These complications can be prevented by minimizing the number of needle penetrations, aspirating prior to injection, injecting slowly, and avoiding over-insertion of the needle. Trismus can be managed by application of hot, moist towels to the site and use of analgesics. Gradual opening and closing of the mouth provides a form of physiotherapy (5). If a hematoma forms, pressure should be applied to the site followed by intermittent application of ice to the site during the first several hours. Heat application should be avoided until after six hours (5). Analgesics may be administered for pain, and the patient should be warned of subsequent discoloration.

Facial nerve paralysis that results from injection into the parotid capsule is usually temporary and lasts through the expected duration of anesthesia (5). If signs and symptoms persist, consultation with ophthalmology is indicated.

Of the commercially available local anesthetic solutions in the United States, articaine and prilocaine are more likely to be associated with paresthesia due to their higher concentrations (4%) (5).

Allergic reactions

True hypersensitivity to injectable local anesthetics is extremely rare (6). It is estimated that less than one percent of adverse reactions caused by local anesthetics are true allergies (7). The low molecular weights of some local anesthetics render them too small to be antigenic. Nonetheless, various components of local anesthetic solutions – the vehicle used to suspend the drug, preservatives such as methylparaben and sodium metabisulfite, and the anesthetic drug itself – can cause allergic reactions (7).

Amide anesthetics (lidocaine, mepivicaine, bupivicaine, articaine, prilocaine, etidocaine) are generally nonallergenic. After decades of use, only a few cases of allergy to amide local anesthetic have been reported (4). Ester anesthetics (procaine) have a higher likelihood than amides to cause an allergic reaction. Esters are hydrolyzed into para-amino benzoic acid (PABA), a highly allergenic molecule (7).

Historical reports of allergy to amide anesthetics were likely caused by methylparaben, a preservative that is structurally related to PABA (7). Methylparaben has been removed from injectable cartridges, but is still used in multidose local anesthetic vials (3). Allergic reactions to sodium metabisulfite, another preservative used to prolong the shelf-life of anesthetics with vasoconstrictors, are also well-documented in the literature (6).

Patients with a history of anesthetic allergy present a unique challenge to clinicians. Obtaining a detailed history of past signs and symptoms of untoward events is beneficial in differentiating toxic and idiosyncratic responses from true allergic reactions, and can help prevent misdiagnoses (2). True allergic reactions result from basophils and mast cells releasing chemical mediators that produce clinical manifestations of allergy (redness, swelling, hives, itching, difficulty breathing, and a drastic fall in blood pressure) (7). These signs and symptoms usually do not occur in toxic and idiosyncratic responses.

Evaluation of a patient for local anesthetic allergy may require referrals to an allergist, dermatologist and immunologist (6). Identification of the offending agent involves skin testing, incremental challenge techniques, and biopsy. However, definitive identification of the allergen may remain elusive. For pa-

tients with unconfirmed lidocaine allergy, the use of bisulfite-free formulations, such as amide anesthetics without vasoconstrictors, lowers the likelihood of an allergic reaction (6). Diphenhydramine 1% with 1:100,000 epinephrine has been used as an alternative anesthetic, but has had varying degrees of success in terms of efficacy (2).

Drug interactions

Beta-blockers and other anti-hypertensive medications

Physiologic effects associated with stimulation of beta-adrenergic receptors include increased heart rate and contraction force (mediated by B_1 receptors) and dilation of peripheral blood vessels (mediated by B_2 receptors). Nonselective beta-blockers (propranolol, timolol, nadolol) prevent the stimulation of both types of receptors and in so doing, decrease cardiac output but also counter peripheral vasodilation. In contrast, cardioselective beta-blockers (atenolol, metoprolol) exert minimal effects on peripheral blood vessels (3).

Vasoconstrictors such as epinephrine constrict arterial vessels in many organs through alpha-adrenergic stimulation. In patients taking nonselective beta-blockers, this unopposed alpha-adrenergic stimulation can result in a marked increase in blood pressure followed by reflex bradycardia (9). This risk, however, is considered minimal if dosages are limited to amounts contained in one to two cartridges (0.04 milligrams of epinephrine) of local anesthetic (8).

The use of peripherally-acting adrenergic blockers (guanethidine, reserpine) and alpha-adrenergic blockers (prazosin, terazosin) may amplify cardiovascular responses to vasoconstrictors. These drugs reduce blood pressure by inhibiting the release and depleting the levels of catecholamines in nerve endings. When used long-term in the management of hypertension, the adrenergic receptors may be up-regulated by the body in an attempt to restore normal function. The increase in receptor number and sensitivity results in heightened responsiveness to vasoconstrictors (10). Centrally-acting alpha-agonists (clonidine, methyldopa) exert an anti-hypertensive effect by interacting with alpha receptors within the brainstem. These drugs have a potential for causing severe rebound hypertension. The risk for interactions involving these alpha-adrenergic drugs, however, is considered minimal, if vasoconstrictors are limited to amounts contained in one to two cartridges of anesthetic (8). The patient's blood pressure should be monitored during the appointment.

Tricyclic antidepressants (TCAs)

Tricyclic antidepressants (amitriptyline, doxepin, nortriptyline) elevate mood by preventing the reuptake of endogenous serotonin and norepinephrine in neuronal synapses. Addition of exogenous epinephrine in patients taking TCAs may result in abnormally high concentrations of catecholamines, thereby potentiating a hypertensive effect. Reports, however, have indicated that one to two cartridges of epinephrine-containing anesthetics can be used safely (8). The patient should be constantly observed for increased sympathomimetic reactions.

Levonordefrin, a synthetic vasoconstrictor, has adrenergic effects that result mainly in the constriction of blood vessels. It therefore carries a higher risk than epinephrine of causing hypertension (8). In patients taking TCAs, the use of levonordefrin-containing anesthetics (mepivicaine 3% with 1:20,000 levonordefrin) should be avoided (3,8).

Monoamine oxidase (MAO) inhibitors

Monoamine oxidase inhibitors are used for the management of depression (phenelzine, tranylcypromine, isocarboxazid), Parkinson's disease (selegiline), anxiety states and obsessive-compulsive disorders. MAO inhibitors prevent the breakdown of amine-containing substances, including catecholamines. Exogenous catecholamines, however, are metabolized mostly by catechol-O-methyltransferase and MAO has little impact on their degradation and cardiovascular actions (2). Local anesthetics containing epinephrine, therefore, may be used without special reservations in patients taking MAO inhibitors (2).

Phenothiazines and Lithium

Phenothiazines (chlorpromazine, risperidone, thioridazine) are prescribed for the management of psychotic disorders. The most common cardiovascular side effect of phenothiazines is postural hypotension (3). These drugs counteract the vasoconstricting action of epinephrine, allowing the inherent vasodilating effects of local anesthetics to work unopposed. This may result in fluctuations in blood pressure.

This response is unlikely to occur if local anesthetics are kept to the smallest effective dose and intravascular injection is avoided (3). Vasoconstrictor-containing anesthetics pose no contraindications in patients taking phenothiazines; however, consultation with the patient's physician is recommended before dental treatment (8). The patient should be closely monitored for possible hypotensive episodes during the appointment.

Patients taking lithium for bipolar disorder and depression pose no contraindications to the use of local anesthetics, with or without vasoconstrictors (8).

Antianxiety drugs (Benzodiazepines)

Diazepam, alprazolam, and lorazepam are central nervous system depressants which, when used with local anesthetics, may have increased depressive effects. Amounts of local anesthetics should be kept to the minimum dosages necessary for adequate pain control in order to minimize the additive depressive effects (8).

Cocaine

Cocaine is a sympathomimetic drug that predisposes abusers to arrhythmias, hypertension, and myocardial ischemia. Peak blood levels occur within 30 minutes, and the effects may linger for 4 to 6 hours (9). Due to the potential medical risks, any elective dental treatment should be postponed for at least 24 hours since the last cocaine use in order to allow elimination of the drug (9,10).

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