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Adverse drug reactions to local anesthesia

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A dentist's ability to safely administer regional anesthesia is essential for dental practice. Local anesthetic solutions used in the United States for dental anesthesia are formulated with several components. The contents of a standard local anesthetic cartridge may include an amide or ester local anesthetic drug, an adrenergic vasoconstrictor, and an antioxidant. In susceptible patients, any of these components may induce systemic, dose-dependent adverse reactions. Although extremely rare, allergic reactions may also occur. Signs and symptoms of the various adverse reactions associated with local anesthetics are quite distinctive, permitting rapid diagnosis and treatment (see box below). Serious reactions are extremely infrequent and, when treated properly, are unlikely to result in significant morbidity or mortality.

Local anesthesia toxicity

When the local anesthetic contained in a dental cartridge diffuses away from the site of injection, it is absorbed into the systemic circulation where it is metabolized and excreted. The doses of a local anesthetic used in dentistry are usually minimal, and systemic effects are therefore uncommon. However, if an inadvertent vascular injection occurs or when repeated injections are administered, blood levels of a local anesthetic may become elevated.

Signs and symptoms

Initially, excitatory reactions to local anesthetic overdose are seen such as tremors, muscle twitching, shivering, and clonic-tonic convulsions [1–3].

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Diagnosis of local anesthesia reactions

Local anesthesia toxicity

Initial symptoms include tremors, muscle twitching, and convulsions. Following the initial phase, respiratory depression, lethargy, and loss of consciousness are possible. Cardiovascular depression may induce hypotension at extremely high blood concentrations. Hypoxia secondary to respiratory depression can rapidly produce the most serious outcomes including cardiovascular collapse, brain damage, and death.

Vasoconstrictor reactions

Initial signs of the sympathetic nervous system stimulation include palpitations, increased heart rate, and elevated blood pressure. Anxiety, nervousness, and fear are often associated with the palpitations. With severe overdose, arrhythmia, stroke, and myocardial infarction are possible.

Methemoglobinemia

Because methemoglobinemia is caused by metabolites of prilocaine, symptoms frequently do not occur for 1–3 hours following treatment. Methemoglobinemia also has been reported following benzocaine and other local anesthetics. Cyanosis without signs of respiratory distress may be apparent when methemoglobin levels reaches 10–20%. Vomiting and headache have been described. At higher blood concentrations of methemoglobin, dyspnea, seizures, stupor, coma, and death are possible.

Allergic reactions to local anesthetics

Mild manifestations of allergy to systemic drugs include urticaria, erythema, and intense itching. More severe reactions may include angioedema and respiratory distress. Although extremely unlikely, one should be prepared for the life-threatening anaphylactic responses including dyspnea, hypotension, and loss of consciousness.

Sulfite antioxidant reactions

Asthma-like signs of taychypnea, wheezing, bronchospasm, dyspnea, tachycardia, dizziness, and weakness have been reported, usually after exposure to foods (salads, shellfish, wines) containing sulfite antioxidants. Severe flushing, generalized urticaria, angioedema, tingling, pruritis, rhinitis, conjunctivis, dysphagia, nausea, and diarrhea have also been reported.

These initial excitatory reactions are thought to be disinhibition phenomena resulting from selective blockade of small inhibitory neurons within the limbic system of the central nervous system (CNS). Whether this initial excitatory reaction is seen or not, a generalized CNS depression with symptoms of sedation, drowsiness, lethargy, and life-threatening respiratory depression follow as blood levels continue to rise [4,5]. With extremely high toxic doses, myocardial excitability and conductivity may also be depressed, particularly with the highly lipid-soluble long-acting local anesthetics etidocaine and bupivacaine. Cardiac toxicity to local anesthetic overdose is most often manifested as ectopic cardiac rhythms and bradycardia. With extreme local anesthetic overdose, cardiac contractility is depressed and peripheral vasodilation occurs, leading to significant hypotension.

Prevention

Compliance with local anesthetic dosing guidelines is the first and most important strategy for preventing this adverse event. Dosing calculations and systemic reactions to local anesthetics are dependent on body weight. True dose-dependent toxicity reactions to local anesthetics are most frequently reported in pediatric patients. Children may be at greater risk of toxicity reactions because their lower body weight does not represent a proportionate decrease in orofacial anatomy. Because the mandible and maxilla of a 50-lb child are not one third the size of an adult (150 lbs), there is an apparent need to use relatively larger volumes when inducing local anesthesia in pediatric dental patients. The consequence of this disparity is that local anesthetic toxicity reactions occur more frequently in children. Additionally, systemic drug interactions involving local anesthetics and other CNS depressant drugs are more likely to occur in children [2,6].

The local anesthetic formulation of 3% mepivacaine plain appears to be associated with a disproportionate number of local anesthetic toxicity reports [6–9]. This may be caused by the absence of a vasoconstrictor, thereby allowing more rapid systemic absorption of the anesthetic. Additionally, the higher concentration used in its anesthetic formulation (3%) may result in the administration of larger relative doses. Pharmacokinetic studies by Goebel et al have demonstrated that peak anesthetic blood levels of 3% mepivacaine occur more rapidly and exceed that of an equal volume of 2% lidocaine with 1:100,000 epinephrine by approximately threefold following maxillary infiltration injections [10,11].

The 3% mepivacaine formulation is often chosen for children because it is considered by some to have a shorter duration of soft tissue anesthesia, therefore limiting severe lip biting and oral trauma seen in children following dental local anesthesia. The results of a recent double-blind randomized trial has found, however, that onset time, peak effects, and duration of soft tissue anesthesia following mandibular block injections with 2% lidocaine 1:100,000 epinephrine, 3% mepivacaine plain, or 4% prilocaine plain were

very similar [12]. The selection of anesthetic formulations that do not contain a vasoconstrictor, such as 3% mepivacaine, may not be a significant therapeutic advantage when anesthetizing children.

The maximum volume of 3% mepivacaine plain for anesthetic injection (7 cartridges for a 150-lb adult) is the most restrictive of any local anesthetic used in dentistry. In comparison, the maximum volume for 2% lidocaine with epinephrine (14 cartridges for a 70 kg adult) permits the greatest volume for safe anesthesia injection. With children, selection of 2% lidocaine with 1:100,000 epinephrine is the least likely to cause toxicity reactions if multiple injections are required [13].

The calculation of maximum recommended doses (MRDs) for children receiving local anesthetics is complicated by the conflicting published dosage recommendations found in the literature and the various units involved in the determination (mg, %, cc, ml, kg, lb, cartridges). The MRDs for dental local anesthetics recently published in the American Dental Association (ADA) Guide to Dental Therapeutics is possibly the most current authoritative source [14]. These values are summarized in Table 1. It should be noted that these recommendations for lidocaine with epinephrine permit the largest volume of anesthetic, and for mepivacaine permit the smallest volume of anesthetic. Additionally, because of our desire to prevent oral trauma following dental anesthesia, the long-acting local anesthetics are generally not indicated for young children [15].

A simplified alternative for calculating maximum safe doses of local anesthesia has been to establish a conservative recommendation that can be applied to all anesthetic formulations used in dentistry. This recommendation, "The Rule of 25," states that a dentist may safely use 1 cartridge of any marketed local anesthetic for every 25 lbs of patient weight: ie, 3 cartridges for a 75-lb patient, 6 cartridges in a 150-lb patient [13].

Practical management

Tonic-clonic convulsions are the most common manifestation of a true overdose situation. Fortunately, local anesthetic-induced convulsions are usually transient. Following a convulsive episode, loss of consciousness and severe, prolonged respiratory depression is likely. Immediate treatment of this emergency should address both the convulsions and the potential respiratory depression. One must monitor vital signs (particularly respiratory adequacy), protect the patient from injury, place the patient in supine position, and maintain the airway. If the patient is unconscious, positive pressure oxygen is essential. Although rarely required, intravenous diazepam 5–10 mg is the definitive treatment if convulsions persist.

Vasoconstrictor reactions

With the possible exception of mepivacaine (Carbocaine®, Polocaine®) and prilocaine (Citanest®), most local anesthetics induce some degree of

Table 1
Dosage guidelines for local anesthetics[a]

Anesthetic agent	Max rec dose		Conc	mg/ cartridge	Max # cartridges	
	dose	mg/lb			150-lb adult	50-lb child
Lidocaine						
2% with epinephrine	500 mg	3.3 mg/lb	20 mg/ml	36 mg	14	5
2% plain	300 mg	2.0 mg/lb	20 mg/ml	36 mg	8	3
Mepivacaine						
3% plain	400 mg	2.6 mg/lb	30 mg/ml	54 mg	7	2
2% with levonordefrin	400 mg	2.6 mg/lb	20 mg/ml	36 mg	11	4
Prilocaine						
4% plain or epi	600 mg	4.0 mg/lb	40 mg/ml	72 mg	8	3
Articaine[b]						
4% with epinephrine	500 mg	3.3 mg/lb	40 mg/ml	68 mg[c]	7	2
Bupivacaine						
0.5% with epinephrine	90 mg	0.6 mg/lb	5 mg/ml	9 mg	10	–[d]
Etidocaine						
1.5% with epinephrine	400 mg	2.6 mg/lb	15 mg/ml	27 mg	15	–[d]

[a] *Data from* Yagiela J, Malamed SF. Injectable and topical local anesthetics. In: Ciancio SG, editor. ADA guide to dental therapeutics. Chicago: ADA Publishing Co; 1998, and manufacturer's product information; with permission.

[b] Cartridges are packaged with 1.8 ml except articaine which is available as 1.7 ml.

[c] Some manufacturers uses a lower dosage recommendation for articaine (2.3 mg/lb) with children 4–12 years of age.

[d] The long-acting local anesthetics bupivacaine and etidocaine are not recommended for children younger than 12 years of age.

vasodilation at the site of injection [16]. To limit systemic uptake and to prolong the duration of the anesthesia, vasoconstrictors are often added to local anesthetic formulations. A concentration as low as 1:200,000 epinephrine (0.005 mg/mL) improves the onset, profundity, and duration of regional anesthesia.

The vasoconstricting agents most commonly used in dental local anesthetic formulations, epinephrine and levonordefrin, have catecholamine structures and act by stimulating postsynaptic receptors of the sympathetic nervous system. Vasoconstriction at the site of injection is the therapeutic goal for adding adrenergic vasoconstrictors to local anesthetic solutions. Systemic epinephrine and levonordefrin have both alpha and beta adrenergic-stimulating properties, thereby increasing cardiac heart rate and contraction, as well as inducing vasoconstriction in skin and vasodilation in muscle tissue.

Signs and symptoms

Following injection of one or two cartridges of a dental local anesthetic containing epinephrine, normal circulating levels of epinephrine may increase two or threefold [17]. This additional exogenous epinephrine is generally well tolerated in healthy adults. Reactions associated with the vasoconstrictor in

a local anesthetic solution are usually seen as mild stimulation of the cardiovascular system; the resulting rises in heart rate and blood pressure are usually transient. Of greater concern, particularly with a massive adrenergic vasoconstrictor overdose, are cardiac dysrhythmias including premature ventricular contractions and ventricular fibrillation. When considering a patient's tolerance to cardiovascular stimulation, there is little to indicate that epinephrine 1:100,000 or levonordefrin 1:20,000 differ substantially.

Prevention

Slow injections and careful aspiration will prevent rapid systemic absorption of epinephrine and levonordefrin. A patient's health history that indicates significant cardiovascular impairment may indicate limiting the use of vasoconstrictors. Although rarely contraindicated, a common recommendation, when there is a medical history that suggests a need for caution, is to limit the dose of epinephrine to 0.018–0.036 mg, the amount of epinephrine contained in one to two cartridges of 2% lidocaine with 100,000 epinephrine [18].

Additionally, practitioners must be alert to drug-patient interactions when using local anesthetics containing the vasoconstrictors epinephrine and levonordefrin. Vasoconstrictors should be used with caution with patients currently taking nonselective beta-adrenoreceptor blockers, tricyclic antidepressants, cocaine, and alpha-adrenergic blockers [19]. Patients taking nonselective beta-adrenergic antagonists such as propranolol may experience exaggerated systemic vasoconstrictive responses to epinephrine or levonordefrin [20]. The tricyclic antidepressants may also enhance the systemic adrenergic response. Cocaine and the halogenated general anesthetics, most notably halothane, may increase the sensitivity of the heart to life-threatening arrhythmias following the use of adrenergic vasoconstrictors. These interactions are clinically relevant and potentially life-threatening [19]. Other drugs that may adversely interact with adrenergic vasoconstrictors, such as alpha adrenergic blockers (ie, chlorpromazine), adrenergic neuronal blockers (ie, guanadrel), local anesthetics, thyroid hormones, and monoamine oxidase inhibitors are poorly documented and are probably of little clinical significance when dose guidelines are followed. These reactions are addressed more comprehensively in Yageila's article, ''Vasoconstrictors: indications and contraindications.''

Practical management

If a reaction does result from local anesthetic administration, treatment recommendations include monitoring vital signs, explaining to the patient the cause of the symptoms, and assuring the patient that the response will last only a few minutes. If a significant rise in blood pressure is noted, definitive drug treatment in a dental office is sublingual nitroglycerin and immediate transport to the local hospital emergency room.

Methemoglobinemia

Methemoglobinemia is a unique dose-dependent reaction reported to occur following the administration of nitrates, aniline dyes, and some amide-containing medications. When administered in excessive doses, the dental anesthetics prilocaine and benzocaine (and rarely lidocaine and articaine) may also induce methemoglobinemia. These local anesthetics, as well as nitrogylcerin and various nitrite preparations and the antimicrobials dapsone and the sulfonamide antibiotics (such as sulfamethoxazole and sulfasoxazole), can cause the oxidation of the iron atom within hemoglobin, producing methemoglobin.

Signs and symptoms

With toxicity, clinical signs of cyanosis are initially observed as blood levels of methemoglobin reach 10–20%. Dyspnea and tachycardia are observed as methemoglobin levels reach 35–40%. Reports of methemoglobinemia following administration of prilocaine and benzocaine are most often associated with large doses. Because this reaction is associated with prilocaine's metabolite toluidine, symptoms often develop after the patient has left the dental office. This serious reaction has been repeatedly documented following dental anesthesia using prilocaine, although fatalities have not been reported [21,22]. Methemoglobinemia following the topical administration of EMLA, a Eutectic Mixture of Prilocaine and Lidocaine, has occurred in infants [23].

Prevention

Risk factors for this reaction include extremes of age, anemia, respiratory disease, hereditary methemoglobinemia, deficiencies in glucose-6-phosphate dehydrogenase and methemoglobin reductase, and possibly combinations of oxidant drugs [1,24]. It is recommended that the total dose of prilocaine and other local anesthetics be calculated carefully and that weight-based MRDs not be exceeded.

Practical management

Treatment strategies are usually symptomatic. This drug reaction reverses itself within a few hours in healthy patients, as the drug and/or its metabolites are eliminated. In general, if the patient is not in distress, treatment recommendations include: monitoring cardiovascular and respiratory function, administering 100% oxygen via facemask, and transportation to the local emergency room. If cyanosis, hypoxia, and respiratory distress are clinically significant, intravenous methylene blue (1–2 mg/kg), which rapidly reverts the methemoglobin to hemoglobin, is the definitive treatment.

Allergic reactions to local anesthetics

Although extremely rare, allergic reactions to local anesthetics may occur. True allergy has been reported most often for ester local anesthetics such as procaine and tetracaine. Fortunately, the most common agents used in dentistry are the amide anesthetics that possess very limited ability to induce hypersensitivity reactions [25].

Additionally, the removal of methylparaben, a preservative additive, from dental local anesthetic formulations in the 1980s, has also diminished reports of allergic reactions in dentistry [26]. Since then, serious allergic reactions following local anesthesia administration in dentistry are almost never reported. Although a practitioner should be prepared to treat local anesthetic hypersensitivity reactions, most suspected reactions are psychogenic. Experience reported by allergy clinics have suggested that most patients referred for local anesthetic allergenicity testing have been misdiagnosed [27,28]. Comprehending a patient's anxiety and fear of dental injections may provide useful information for recognizing psychogenic reactions.

Signs and symptoms

Although patients often report allergy to local anesthetics, confirmed responses of true allergy are extremely rare. Reactions considered to indicate true allergy include cutaneous responses such as rash and urticaria, as well as systemic anaphylactoid responses such as dyspnea and hypotension.

Prevention

Taking a complete drug history and avoiding medications listed under allergies can prevent most of these reactions. Because alternatives to local anesthetics, such as diphenydramine injection, deep sedation, and general anesthesia, are not ideal, a referral for allergy testing to confirm the diagnosis is recommended. Results of allergy testing will most often rule out true allergy or will identify a specific local anesthetic agent that can be used for dental anesthesia.

Practical management

Allergic reactions to injected medications range from mild to severe. Mild skin responses are managed with an antihistamine such as diphenhydramine 25–50 mg administered either orally or intramuscularly. Frequently, a patient having an allergic reaction for the first time will be extremely anxious. A rapid rate of onset of an allergic drug reaction should alert practitioners to a possible anaphylactoid response. If dyspnea, nausea, vomiting, hypotension, or other acute signs of anaphylaxis occur, immediate treatment is required. Recommended treatment includes basic life support, intramuscular or subcutaneous

epinephrine 0.3–0.5 mg, summoning medical assistance, and transportation to the local hospital emergency room. Additional therapy including antihistamines and corticosteroids may be required subsequent to the acute therapy.

Sulfite antioxidant reactions

Concern has recently developed for possible dose-dependent reactions to the antioxidant sulfites used in the local anesthetic formulations containing epinephrine or levonordefrin [29]. Sulfites are included in local anesthetic solutions to prevent nonenzymatic oxidation of the catecholamine vasoconstrictors, thereby prolonging the shelf life of these formulations. Local anesthetic solutions that do not include vasoconstrictors, such as 3% mepivacaine and 4% prilocaine, do not include antioxidants in their formulations. Sulfite antioxidants (sulfur dioxide, sulfites, bisulfites, and metabisulfites) have been found to sensitize some asthmatic patients when they are exposed to rather large amounts of these preservatives. Large doses, such as those previously used in restaurant salad bars and homemade wines, had been linked to six deaths in 1984 [30]. Five percent of the 9 million asthmatic patients in the United States may be sulfite-sensitive [31].

Signs and symptoms

Reactions of urticaria, angioedema, bronchospasm, and anaphylactic shock have been reported [22]. The most common reactions are wheezing and bronchospasm. Other symptoms of sulfite sensitivity include tachypnea, dizziness, nausea, and weakness [32].

Prevention

Adverse reaction to sulfites occurs most frequently in patients with a history of atopic allergy or asthma. History of asthma, particularly if sulfite sensitivity is noted, may be important in selecting an anesthetic agent. Although some concern and caution is justified when using local anesthetics containing vasoconstrictors and sulfites, a documented reaction in dental practice has not been published, probably because the amount of this antioxidant sulfite in a dental formulation is too small to stimulate a significant life-threatening reaction.

Practical management

Reactions usually occur within 30 minutes of oral ingestion. Severe respiratory distress should be treated with a beta-agonist inhaler if possible. Anaphylactoid reactions should be treated immediately with intramuscular or subcutaneous epinephrine (0.3–0.5 mg).

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