

APPROACH TO THE PATIENT WITH SUSPECTED LOCAL ANESTHETIC SENSITIVITY

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Local anesthetics prevent the generation and conduction of nerve impulses. This result is accomplished by decreasing or blocking the increase in the permeability of excitable membranes to sodium that normally is produced by a slight depolarization of the membrane.³² This action of local anesthetics is caused by their direct interaction with one or more sites in the voltage-gated sodium channels. The degree of block produced by a given concentration of local anesthetic depends on how frequently the nerve is stimulated and on its resting membrane potential. These frequency- and voltage-dependent effects occur because the local anesthetic molecule in its charged, active form gains access to its binding site(s) in the sodium channel only when it is in an open state.¹²

The binding characteristics vary among local anesthetics depending on their dissociation constant (pKa), lipid solubility, pH at the injection site, protein binding, and molecular size. Local anesthetics that have a low pKa or higher lipid solubility have a faster onset of action.⁴⁷ Duration of anesthesia, on the other hand, is directly proportional to plasma protein binding. The addition of vasoconstrictors (epinephrine) to local anesthetics limits systemic absorption, promotes local hemostasis, and prolongs duration of action. Although variation exists, the differential rate and type of nerve block follows a predictable pattern. Generally, small unmyelinated C fibers and autonomic fibers (mediating pain sensations), and small myelinated A δ fibers (mediating pain and temperature sensations) are blocked before larger myelinated A γ , A β , and A α fibers (carrying postural, touch, pressure, and motor information).^{12, 32, 61}

Systemic absorption of local anesthetics depresses the conduction and other electrical functions of the myocardium and cardiac contractility, and can induce

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peripheral vasodilation in a dose-dependent fashion, which can lead to decreased cardiac output, severe hypotension, or cardiac arrest. Drug effects on the central nervous system include stimulation, depression, or both.³⁸

FAMILIES OF LOCAL ANESTHETICS

Local anesthetics have three structural segments: a lipophilic or aromatic group, an intermediate chain linkage that determines to which category they belong (e.g., benzoate esters or amides), and a hydrophilic or amine group (Fig. 1).^{5, 23}

Cocaine was discovered by Carl Koller in 1884, who used a 2% solution to desensitize the cornea. Unfortunately, various toxic effects were encountered with widespread use.^{5, 24} Therefore, procaine, a benzoic acid ester derivative of cocaine, was developed in 1904. Other local anesthetics, such as tetracaine and chloroprocaine, followed. In 1948, the first agent without the ester configuration, the amide lidocaine, was developed by Löfgren. In the following decades newer amides and other groups were introduced (Table 1), culminating in the development of ropivacaine.

Before the availability of ropivacaine, bupivacaine served as the drug of choice for regional anesthesia. In 1979, however, Albright² published an alarming editorial reporting six cases of sudden ventricular arrhythmias and seizures that occurred with the accidental intravascular administration of either bupivacaine or etidocaine. Following Albright's publication, sporadic reports of maternal death appeared from the accidental intravenous administration of 0.75% bupivacaine during epidural anesthesia for cesarean section.⁴⁴ Even with the implementation of strict bupivacaine administration guidelines that exist today, episodic toxicity is still reported. This cardiotoxicity appears to be related to the "R" enantiomer of bupivacaine. Unlike mepivacaine and bupivacaine, which are marketed as a racemic mixture of equal proportions of the "R" and "S" enantiomers, ropivacaine is prepared and marketed to a chemical purity of 99.5% as the "S" enantiomer.⁴⁴ Although ropivacaine's exact place in therapy remains to be determined, compared with bupivacaine, it produces similar sensory block, less motor block, and much less toxicity when used in equivalent doses.

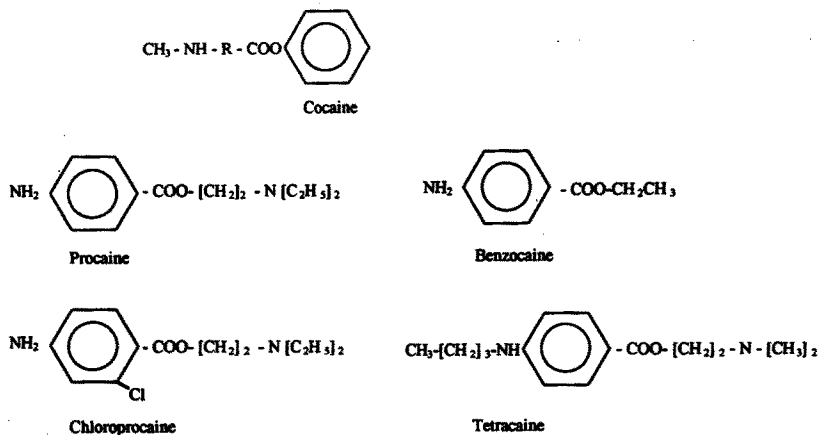
The amides are metabolized primarily in the liver by microsomal enzymes and excreted in the urine as metabolites, with only a small fraction as unchanged drug. Ropivacaine is extensively metabolized in the liver by the cytochrome P-450 family, and as with other amides, special caution is required in debilitated patients and in patients with impaired cardiovascular function. Other idiosyncratic reactions affecting amide agents are methemoglobinemia with the use of prilocaine in doses greater than 400 mg and trismus in patients receiving etidocaine for dental anesthesia.³⁸

Local anesthetics of the ester family are derivatives of para-aminobenzoic acid (PABA) and are partly or completely hydrolyzed by plasma pseudocholinesterase, and to a much lesser extent, by hepatic pseudocholinesterase. An exception is cocaine, of which 10% to 12% is excreted unchanged in the urine. Patients with genetically abnormal pseudocholinesterase or decreased pseudocholinesterase activity are at increased risk for systemic toxicity if an ester agent is used.⁴⁷

ADVERSE REACTIONS ASSOCIATED WITH LOCAL ANESTHETICS

As discussed previously, a variety of adverse reactions have been reported (Table 2).^{17, 19, 22, 23, 26, 31, 32, 67, 68} Reactions could possibly occur on the basis of

BENZOATES ESTERS



AMIDES

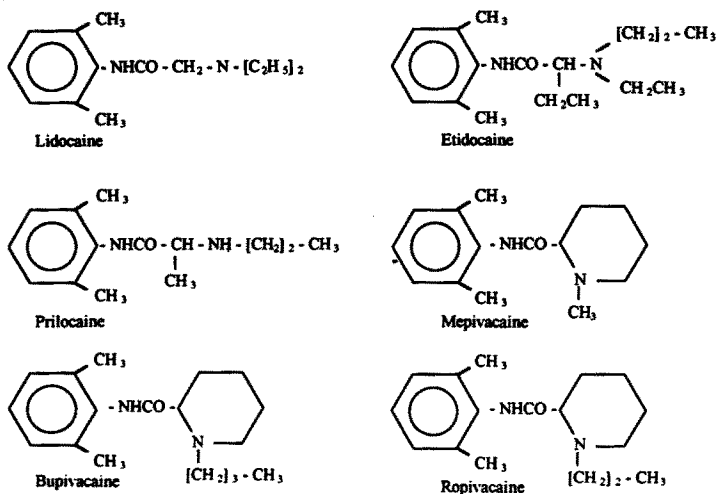


Figure 1. Chemical structure of local anesthetics.

untoward reactions to local anesthetics themselves or to the paraben or sulfite preservatives in them.^{39, 46, 64, 65, 70} Unfortunately, history alone rarely allows a precise diagnosis of the mechanism or cause of the reaction.

Most untoward reactions to local anesthetics appear to be vasovagal (psychomotor), anxiety, or toxic reactions. In dental and surgical procedures requiring local anesthesia, vasovagal reactions associated with the procedures may produce bradycardia and hypotension that are exacerbated by the upright position. Inadvertent intravascular administration of epinephrine may result in car-

Table 1. LOCAL ANESTHETIC AGENTS**Injectable Anesthetics****Benzoate Esters**

Chloroprocaine

Procaine

Tetracaine

Amides

Bupivacaine

Etidocaine

Lidocaine

Mepivacaine

Prilocaine

Ropivacaine

Ophthalmic Agents

Proparacaine

Tetracaine

Nesacaine (Astra), 1%, 2% in 30 mL vials with 1 mg methylparaben and EDTA per mL
 Nesacaine-MPF, 2%, 3% without methylparaben
 Generic (Abbott), 1%, 2% in 30 mL vials
 Novocain (Sanofi Winthrop), 1%, 2%, 10% in 2 mL, 6 mL, and 30 mL vials; contains < 1 mg acetone sodium bisulfite and < 2.5 mg chlorobutanol per mL
 Pontocaine (Sanofi Winthrop), 1% in 2 mL amps, 0.2% with 6% dextrose in 2 mL amps, and 0.3% with 6% dextrose in 5 mL amps; also in 20 mg Niphanoid amps

Marcaine (Sanofi Winthrop), Sensorcaine (Astra), generic, 0.25%, 0.5%, 0.75% with/without epinephrine in 3, 5, 10, 30, and 50 mL amps
 Most contain 1 mg methylparaben per mL, marcaine with epi. preparations contain 0.5 mg sodium metabisulfite per mL
 Duranest and Durnest MPF (Astra), 1%, 1.5% with/without epi. in 20 and 30 mL amps; also in 1.8 mL dental cartridge

Xylocaine (Astra), Lidocaine (various), Dilocaine (Hauck), Lidoject-1 (Mayrand), Nervocaine 1% (Keene), Duo-Tract Kit (Astra), Octocaine (Novocol), 0.5%, 1%, 1.5%, 2%, 4%, 5%, 10%, 20% with/without epi., with/without parabens in 1.8, 2, 5, 10, 20, 30, 50 mL amps
 Carbocaine (Sanofi Winthrop), Mepivacaine (various), Polocaine (Astra), Isocaine (Novocol), 1%, 1.5%, 2%, 3%, and 2% with levonordefrin (1.8 mL dental cartridge), 20 mL, 30 mL, 50 mL amps
 Citanest (Astra), 4% with/without epi., in 1.8 mL dental cartridge
 Naropin (Astra), 2, 5, 7.5, and 10 mg/mL concentrations in 5, 10, 20, 30, 100, and 200 mL bottles

Proparacaine (various), Alcaine (Alcon), Ophthacaine (Apothecon), Ophthethic (Allergan), 0.5% in 1, 2, 15 mL drop containers
 Tetracaine (various), Pontocaine (Sanofi Winthrop), 0.5% in 1, 2, 15 mL bottle; Pontocaine contains 0.4% chlorobutanol

Topical Agents

Benzoate Esters

Butamben picrate

Benzocaine

Butesin (Abbott), 1% ointment containing lanolin, parabens, mineral oil in 28.4 g Benzocaine (various), Boil-Ease (Del), Dermoplast (Whitehall-Robbins), Lanacaine (Combe), Solarcaine (Schering-Plough), Bicozene (Sandoz), Foille Plus (Blistex), Chigger-Tox (Scherer), Maximum Strength Anbesol (Whitehall), Hurricane (Beutlich), Americaine Anesthetic Lubricant (Ciba), Orjel (Del), Orabase (Colgate-Palmolive), from 5%–20% in varying sizes as ointments, sprays, lotions, gels, liquids, and creams
Cocaine (various), 4%–10% in solution and powder; in 10 mL multidose bottles and unit dose 4 mL; powder in 5 and 25 g
Pontocaine (Sanofi Winthrop), 0.5% ointment and 1% cream in 28.35 g; cream contains glycerin and parabens and sodium metabisulfite

Cocaine

Tetracaine

Amides

Dibucaine

Lidocaine

Dibucaine (various), Nupercainal (Ciba), in 0.5% cream and 1% ointment in 30, 42.5, and 60 g; both contain bisulfite
Lidocaine (various), Xyllocaine (Astra), Anestacon (PolyMedica), in 2%, 4%, 5%, and 10% as ointment, spray, liquid, solution, and jelly; some contain parabens; flavored solutions contain saccharin; various sizes

Miscellaneous

Dyclonine

Pramoxine

Dyclone (Astra), in 0.5%–1% solution containing chlorobutanol in 30 mL
Tronothane (Abbott), PrameGel (GenDerm), Prax (Femdale), and Itch-X (Ascher), 1% cream, gel, lotion, and spray; some contain benzyl alcohol, parabens, aloe vera gel, and/or glycerin; many sizes

Lidocaine/Prilocaine

EMLA (Astra), in 5 g with Tegaderm dressings and 30 g

EDTA = Ethylenediamin tetraacetic acid.

Data from Kastrup E: Drug Facts and Comparisons. St. Louis, Facts and Comparisons, 1997.

Table 2. REPORTED ADVERSE REACTIONS TO LOCAL ANESTHETICS

Systemic	Local
Vasomotor/vasovagal	Delayed hypersensitivity
Sympathetic stimulation/anxiety reactions	Urticaria
Anaphylactoid/anaphylactic reactions	Maculopapular eruption
Neurotoxic (seizures, acute disorientation, tremors, restlessness, depression, and coma)	
Cardiotoxic (myocardial depression, hypotension, cardiac arrest)	
Idiosyncratic/metabolic	

diac or neurologic symptoms. Neurologic responses to high levels of local anesthetics are usually associated with neurologic stimulation at low toxic doses (manifested by talkativeness, agitation, or seizures) and neurologic depression at high toxic doses. Tremulousness, palpitations, tachycardia, diaphoresis, light-headedness, or near syncope may occur.

Hypersensitivity reactions reported to local anesthetics or preservatives in them include immediate type I hypersensitivity (specific IgE to the drug or preservatives); type II and III hypersensitivity (immune complex mechanism); and delayed, type IV hypersensitivity (cell-mediated).²³ IgE-independent anaphylactoid reactions have also been postulated on the basis of nonspecific mast cell degranulation. The most frequently described allergic reaction to local anesthetics, however, is contact dermatitis mediated by sensitized lymphocytes. These reactions account for 80% of reactions reported to local anesthetic.^{1,7}

IMMUNOLOGIC MECHANISMS AND LOCAL ANESTHETIC SENSITIVITY

Local anesthetics are compounds of low molecular weight (MW). Complete antigens generally have MW of more than 10,000 d. For local anesthetics such as lidocaine (MW 234 d) to become complete antigens, they would have to function as haptens and bind to protein carriers.^{1,69} Because contact dermatitis occurs with ester local anesthetics, this phenomenon obviously occurs in some cases.

On the other hand, Yanagi et al⁶⁹ demonstrated that lidocaine directly inhibits the IgE-dependent and IgE-independent histamine release from human peripheral leukocytes and cultured human basophils in a dose-dependent manner. In those studies, lidocaine inhibited increases in intracellular Ca^{2+} by inhibiting Ca^{2+} influx, the central mechanism of histamine release in IgE-dependent reactions. IgE-independent histamine release such as occurs in anaphylactoid reactions is less dependent on extracellular Ca^{2+} . Intradermal lidocaine has been known to inhibit IgE-mediated skin test reactions, although its irritant effects may cause local wheal and flare reactions (false positive skin tests) at high concentrations given intradermally. Inhalation of lidocaine inhibits bronchospasm induced by substance P in asthmatic patients.^{43, 51} Yanagi et al⁶⁹ also suggest that because of the effects of local anesthetics on mast cells, clinical allergic reactions caused by direct effects of lidocaine on mast cells and basophils would be impossible. Perhaps this suggestion explains why anaphylactic and anaphylactoid reactions to local anesthetics are usually not reproducible.

Immediate Hypersensitivity Reactions Purported to Occur to Local Anesthetics

Patients with histories of anaphylaxis and anaphylactoid reaction to local anesthetics have been evaluated on the basis of clinical history, skin testing, and provocative dose challenge testing.^{3, 7, 19, 27, 35, 54, 55, 62} We have contended, on the basis of negative local anesthetic challenge studies in a large number of patients with reactions simulating anaphylaxis, that anaphylaxis to these agents occurs rarely, if ever.^{13, 19} Most of the literature supporting the existence of immediate hypersensitivity reactions to local anesthetics consists of case reports, some of which are more convincing than others. For instance, one paper reported a patient with allergic-like reactions to prilocaine and lidocaine who had positive intradermal tests to dilute (1:1000) concentrations of both agents in a preservative-free preparation but tolerated bupivacaine after a negative skin test.²⁵ Holti and Hood³⁴ described a patient with an anaphylactic-type reaction and positive skin test to lidocaine whose serum was capable of passively transferring cutaneous reactivity to lidocaine in a volunteer (Prausnitz-Küstner reaction). Another paper reports 14 patients with histories of local anesthetic allergy, positive skin tests, and positive Prausnitz-Küstner phenomenon⁴; however, relevant clinical information regarding the type of anesthetic agent, presence or absence of preservatives, and type of reaction was not described.

Assem and Punnia-Moorthy⁷ report 30 patients with suspected allergy to local anesthetics. Five had positive intradermal skin tests to three or more local anesthetics. The authors contend that the *in vitro* leukocyte histamine release test (LHRT) to the drugs "confirmed" the diagnosis of allergy in 11 patients. They also suggest increased sensitivity of this diagnostic method compared with the skin tests.⁷ As mentioned previously, intradermal injection of concentrated solutions of local anesthetics causes a wheal and flare response in normal individuals. Therefore, the role for local anesthetic skin testing in the diagnosis of local anesthetic reactions is limited to use in the direct challenge procedure. Several large series and reviews since 1971 have demonstrated 10% to 36% false-positive skin tests, particularly when using undiluted or 1:10 dilutions of 1% local anesthetics for intradermal tests.^{4, 6, 19, 35, 48, 55, 62, 68} Patients with positive tests failed to react to 1:100 dilutions or to challenge tests. Moreover, it is unlikely that *in vitro* studies such as those described previously are useful because of the pharmacologic activities of these drugs, as previously described.

Patch test data have suggested that amide agents do not cross-react with each other in the context of contact dermatitis to local anesthetics; however, several recent reports have claimed cross-reactivity of amides in some situations.^{9, 15, 33, 59} In one report, a young woman with a history of urticaria and bronchospasm after lidocaine required multiple dental extractions.⁵⁹ She was reported to have positive skin tests to lidocaine, mepivacaine, prilocaine, and procaine by intradermal testing. In another report, urticaria was reproduced to lidocaine and mepivacaine after double-blind challenge.¹⁵ No specific IgE antibodies could be detected by RAST or by prick tests. The patient had positive intradermal immediate hypersensitivity skin tests with three preservative-free amide preparations, suggesting cross-reactivity to the authors. No reaction with procaine was noted. The caveats about intradermal skin testing with local anesthetics were not addressed. Bourezane et al described a patient who developed dyspnea, hypotension, edema, and malaise after the use of lidocaine on different occasions (administered by different routes), and mepivacaine, and demonstrated positive intradermal tests to three different amides at dilutions of 1:1000 for lidocaine and 1:10,000 for mepivacaine and articaine.⁹ The LHRT was

positive for mepivacaine, and interestingly, both prick tests and patch tests for the same were negative. In another report, an anaphylactoid reaction to bupivacaine was described after subcutaneous challenge in a patient with negative prick tests. The same patient tolerated lidocaine and mepivacaine.⁴⁵ The meaning of these observations is unclear.

More convincing is the work of Gall et al²⁷ who performed a comprehensive study of patients with purported systemic reactions to local anesthetics including immunologic testing and challenge. The authors found that only 1 of a total of 177 patients had evidence to support drug allergy. This was a delayed-type reaction to amide agents, demonstrated by subcutaneous challenge (mepivacaine) and patch tests (lidocaine more reactive than mepivacaine) after 48 and 72 hours. None of the patients had reactions to dilute concentrations of local anesthetics; however, 3 of 120 patients had a positive prick test to sodium metabisulfite, a preservative in some local anesthetic solutions, and 2 of 164 individuals reacted to parahydroxybenzoic acid ester. Subcutaneous challenges failed to produce symptoms in the patients with positive skin tests to preservatives. Two other patients who had reactions on subcutaneous challenge with lidocaine or articaine (i.e., local wheal and erythema and an urticarial reaction shortly after exposure to the drug) failed to have detectable IgE antibodies in radioimmunoassay studies and subsequently tolerated other amide agents. The investigators suggested that the reactions were anaphylactoid in those patients, probably caused by a direct histamine release mechanism similar to that observed in radiocontrast media sensitivity.

Local Anesthetic Reactions Purported to be Caused by Immune Complex Mechanisms

A patient with rheumatoid arthritis developed a systemic reaction with dyspnea, cyanosis, and hypotension after subcutaneous and intra-articular injection of lidocaine.⁶⁶ The reaction was associated with decreased total serum complement, evidence of complement activation, an elevated histamine level, and negative passive transfer test. Another patient with anti-nuclear antibodies had an urticarial reaction associated with a decreased level of C4 after intradermal injection of bupivacaine.¹¹ In another unusual case, a patient developed severe thrombocytopenia 3 days after the administration of lidocaine. This reaction was believed to have resulted from a drug-dependent reaction with IgM antibody to lidocaine and complement, wherein antigen-antibody complexes adhered to platelets as innocent bystanders and caused the platelet lysis.⁶³ Although the clinical presentations of the first two patients were anaphylactoid and postulated to reflect complement activation and presence of anaphylatoxins, some authors suggest that circulating immune complexes also play a role in such reactions.⁵⁶

Cellular or Delayed Hypersensitivity Reactions

Contact dermatitis predominantly occurs to ester class agents because of the metabolite PABA.⁵³ PABA, present in sunscreens and other cosmetic products, is a highly antigenic substance and may cross-react with other PABA-related substances such as para-phenylenediamine and sulfonamides.³³ Esters are generally cross-reactive as demonstrated by patch tests in individuals with contact sensitivity. Amide agents do not appear to cross-react with esters. Parabens, found in

both ester and amide local anesthetic preparations, are esters of parahydroxybenzoic acid, closely related to sodium benzoate, and are also metabolized to PABA. Benzocaine is used in more than 600 different products alone.³⁰ Because of its widespread use and potential as a contact sensitizer, the International and North American Contact Research Group recommended that benzocaine be included in the standard patch test series. Theoretically, patients reactive to PABA may show cross-reactivity among both groups of local anesthetics if methylparaben is present. The concentration of parabens and sulfites in multidose vials of ester and amide local anesthetics is sufficient to cause reactions in sensitive individuals.

Delayed hypersensitivity reactions to amides have been described.^{14, 16, 40} A patient who presented with contact dermatitis had delayed cutaneous reactivity to both lidocaine and bupivacaine, whereas a patient with a fixed drug eruption to lidocaine reacted consistently in the perineal region when the drug was applied elsewhere.^{28, 33}

Parabens and Sulfite Preservatives in Local Anesthetic Reactions

Several studies have supported the notion that preservatives in local anesthetic solutions may cause IgE-mediated, anaphylactoid, and delayed hypersensitivity reactions.^{10, 21, 30, 37, 41, 42, 46, 70} Multidose vials of local anesthetics available in the United States contain 1 mg/mL of methylparaben as preservative, and epinephrine-containing preparations also contain 0.5 mg/mL of sodium metabisulfite. Procaine, used in spinal anesthesia, contains acetone sodium bisulfite, another potential cause of sensitization.

Parabens, in the form of methylparaben or propylparaben, were the most widely used preservatives in local anesthetics until the early 1980s. These chemicals are structurally related to the benzoic acid ester local anesthetics and their metabolite PABA, and are bacteriostatic and fungistatic agents. They are simple molecules that bind to proteins and become immunogenic in the form of a hapten. Compounds with a free amino group in the *para*-position of the benzene ring, like PABA, benzocaine, procaine, and *p*-phenylenediamine, are frequent sensitizers. Parabens have a hydroxyl group rather than an amino group in the *para*-position; however, *p*-amino and *p*-hydroxyl compounds can show cross-reactivity. Parabens are present in over-the-counter oral and topical medications, a large number of prescribed drugs (e.g., antibiotics, corticosteroids, diuretics, radiocontrast preparations, vitamins, insulin, heparin, chemotherapeutic agents, and others), cosmetics, and foods.⁴⁶ Thus, the opportunities for exposure to parabens are high. The North American Contact Dermatitis Group found a 3% incidence of delayed hypersensitivity to paraben esters in 1973, and most reports of reactions relate to delayed hypersensitivity in the form of eczema.

More uncommon are cases of IgE-mediated hypersensitivity reactions to parabens, which appear to occur independently of contact sensitivity.^{4, 54, 60} Kahn et al³⁶ report positive immediate intradermal tests with negative patch (delayed) tests in eight patients who were sensitive to methylparabens and ester local anesthetics. One patient had contact sensitivity to parabens and *p*-phenylenediamine and reacted with a positive patch test to parabens and benzocaine but failed to react to immediate intradermal tests.³⁶ Nagel et al⁴⁶ describe a child who developed immediate generalized pruritus and worsened bronchospasm after intravenous administration of a hydrocortisone preparation that contained parabens for treatment of status asthmaticus. In that patient, IgE-mediated-

sensitivity to parabens was demonstrated directly by intradermal tests to different paraben preparations and indirectly by passive transfer (Prausnitz-Küstner) skin tests to methylparaben and propylparaben but not to ethylparaben. Patch tests were negative.

The role of preservatives in local anesthetic reactions was studied by Kajimoto et al³⁷ in a prospective randomized study of 200 intravenous administrations of prilocaine with methylparaben (Citanest) and prilocaine without the preservative. Of 100 patients who received Citanest for regional anesthesia, 17 developed nonpruritic local erythema and mild swelling in the anesthetized area a few minutes after releasing the tourniquet cuff. This reaction disappeared within 60 minutes. Four of 100 patients in the methylparaben-free prilocaine group had similar reactions. Intradermal tests using 0.05 mL of 0.5% Citanest, 0.1% methylparaben, and normal saline failed to show any reaction. Kajimoto et al³⁷ hypothesize that the reactions were caused by the methylparaben-induced release of a vasoactive substance or direct venous endothelial toxicity.

Newer regulations require more precise labeling of drugs, foods, and cosmetic contents that contain parabens and sodium benzoate. Also, preservative-free local anesthetics are available for single use and diagnostic testing.

Sulfiting agents are widely used as antioxidants in pharmaceutical preparations to stabilize solutions containing sympathomimetic amines. Local anesthetics with vasoconstrictors have sulfite concentrations that may range up to 2.0 mg/mL.⁵⁷ Bisulfite and metabisulfite components are used to prevent oxidative discoloration or browning of restaurant, catered, or processed food and in wine, beer, and fruit drinks. These uses inadvertently expose potentially sensitive persons. Hypersensitivity reactions of anaphylaxis, asthma, urticaria or angioedema, seizure, gastrointestinal symptoms, and death have been reported to sulfites.^{52, 58, 70} Severe asthmatic patients, who are often sensitive to high atmospheric levels of SO₂, may develop bronchospasm and hypotension after ingestion of sulfite and retrograde inhalation of sulfur dioxide.

IgE-mediated reactions to sulfites have been proposed. Boxer et al¹⁰ demonstrated IgE to sulfites by passive transfer to a rhesus monkey in the serum of one of four patients previously reported to have positive skin tests and oral challenges to metabisulfites. To the contrary, Schwartz and Sher⁵⁷ describe a patient with systemic cutaneous and vasomotor reaction after receiving dental injections of novocaine with epinephrine. A single-blind oral bisulfite challenge was positive, but negative skin tests to bisulfite and local anesthetics suggest that the reaction was anaphylactoid, not anaphylactic. In a larger series of sulfite-sensitive individuals, four patients had positive intradermal skin tests, one had a positive prick test, and one of four who responded to an oral challenge had a negative skin test. Two of those patients with positive skin tests had positive passive transfer tests, leading the authors to suggest that at least some of the reactions were mediated by IgE antibodies.⁷⁰

APPROACH TO THE PATIENT WITH REACTIONS TO LOCAL ANESTHETICS

The approach to the patient with a previous untoward reaction to a local anesthetic and a requirement for local anesthetics to facilitate a surgical procedure focuses on attempts to identify the local anesthetic least likely to cause a subsequent reaction regardless of mechanism.⁴⁹ That is, no attempt is made to confirm that an untoward reaction occurred to the original agent. This approach presumes that cross-reactivity exists among ester class local anesthetics but not

among amide class agents.^{7,20} Although it is agreed that this is the case in almost all instances, some evidence to the contrary exists as reviewed previously. Until this issue is totally resolved, a prudent approach to management seems appropriate. Because paraben or sulfite preservatives may be common to some multidose formulations of ester and amide preparations, preservative-free, unit-dose vials of the local anesthetics are recommended for use in provocative dose challenges. If contact dermatitis to a local anesthetic agent occurred, that and structurally similar local anesthetics should be avoided. If the drug is unknown, patch testing techniques and reagents are available for evaluation of such patients, which is beyond the scope of this article.

In reactions with characteristics of immediate hypersensitivity, such as urticaria, angioedema, wheezing, laryngospasm, or itching, an attempt is made by history to identify the agent causing the purported reaction. If the agent is an ester, an amide can be used without further evaluation. If the agent is an amide, another amide or an ester can be administered in the context of the concerns mentioned previously (Fig. 2). If the drug causing the reaction is not known, a provocative dose challenge with an amide local anesthetic has been demon-

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Figure 2. Suggested management and evaluation of patients with history of local anesthetic reactions. *Positive control is 1.8 mg/mL of histamine base. Negative control is phosphate-buffered saline.†If history suggests delayed onset of symptoms or contact allergy, wait 24 hours and evaluate patient before therapeutic administration. (From deShazo RD, Nelson HS: An approach to the patient with a history of local anesthetic hypersensitivity: Experience with 90 patients. *Allergy Clin Immunol* 63:387–394, 1979; with permission.)

strated to be the most expeditious and safe approach in the large series of studies mentioned previously. Prick testing with full-strength drug and intradermal testing with 1:100-strength drug followed by a subcutaneous challenge is recommended. Wheal and flare dermal reactions to such testing are rare. If such reactions occur, the provocative dose challenge should proceed with great caution, if at all. On successful completion of the challenge procedure, the local anesthetic may be used for therapeutic purposes.

Because a number of local anesthetic reactions may be psychomotor in origin, it may be prudent in some patients to perform the entire challenge procedure, with the requisite 20-minute intervals between each dose, with a saline diluent ("provocaine" solution) prior to the actual procedure. If the patient develops a reaction, the psychomotor origin is established. The explanation of such reactions is welcome and reassuring to patients, especially if the procedure is explained beforehand. Obviously, positive and negative controls with saline and histamine should be performed with prick and intradermal testing.

Finally, injectable antihistamine solutions, such as diphenhydramine hydrochloride, are quite effective for suturing skin wounds and may preclude the necessity for a challenge procedure in some cases.⁵⁰ On the other hand, dyclonine hydrochloride, a ketone structurally different from ester and amide agents, can be a very effective topical agent in airway anesthesia.⁸

CONCLUSION

Local anesthetic agents are used in almost every field of medicine, including dentistry, surgery, interventional radiology, dermatology, and obstetrics. In the United States, dentists administer them at an estimated rate of over half a million injections per day.⁵⁹ Various adverse reactions have been attributed to local anesthetics over the years, yet the percentage of true immunologic hypersensitivity reactions remains less than 1%.^{29, 56, 68} Most reactions occurring during dental procedures are caused by vasovagal or anxiety episodes, with other common events caused by toxicity, inadvertent systemic administration of the drug, or intolerance. An understanding of the pharmacology of local anesthetics is an important first step to management of these reactions.

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