

Accidents Resulting from Local Anesthetics

True or False Allergy?

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HISTORY OF LOCAL ANESTHETICS

The history of local anesthetics is a fascinating one and involves the Spanish conquistadors, the Inca Indians, Sigmund Freud, and William Halsted. Suffice it to say, cocaine and a number of other esters of *para*-aminobenzoic acid were in use medically by the early 1900s. The first synthetic agent was benzocaine, the ethyl ester of *para*-aminobenzoic acid. Since it is poorly soluble, it is useful only when applied topically. Changes in the structure of its side chain led to the first injectable agent, procaine. Procaine became the standard local anesthetic for 40 years. In 1943, lidocaine was introduced by Lofgren and Lundquist, and the amide family of local anesthetics came into being.

A PRACTICAL CLASSIFICATION OF LOCAL ANESTHETICS

As shown in Table 1, local anesthetics are conveniently classified as benzoic acid esters, so-called Group 1 local anesthetics, or others, frequently referred to as Group 2. The rationale for this classi-

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Table 1
Classes of Available Local Anesthetics and Examples of Each

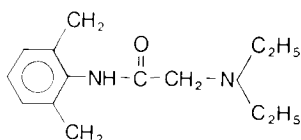
Benzoic acid ester group (group I)	Others (group II)
1. Esters of <i>para</i> -aminobenzoic acid: procaine (Novocaine), chlorprocaine (Nesacaine), butethamine (Monocaine)	1. Amides: dibucaine (Nupercaine), lidocaine (Xylocaine), mepivacaine (Carbocaine), prilocaine (Citanest), etidocaine (Duranest), Bupivacaine (Marcaine)
2. Esters of benzoic acid: cocaine, meprylcaine (Oracaine), tetracaine (Pontocaine)	2. Ethers: pramoxine (Tronothane) ^a
3. Esters of <i>meta</i> -aminobenzoic acid: metabutethamine (Unacaine), isobucaine	3. Ketones: dyclonine (Dyclone) ^a (Kincaine)
	4. Phenetidin derivative: phenacaine (Holocaine) ^a
	5. Antihistamines: chlorpheniramine, tripelenamine, and so on

^aAvailable for topical use only.

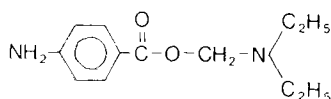
fication will be discussed in more detail later. There are three different groups of benzoic acid esters: esters of *para*-aminobenzoic acid, of which procaine is a representative; esters of benzoic acid, of which tetracaine and cocaine are representative; and esters of *meta*-aminobenzoic acid, of which isobucaine is a derivative. Group 2 local anesthetics include the amide group, of which lidocaine, mepivocaine, prilocaine, and etiocaine are constituents. Ether, ketone, and phenetidin derivatives make up topically useful anesthetic compounds, whereas antihistamines also have local anesthetic characteristics (1,2).

METABOLISM OF LOCAL ANESTHETICS

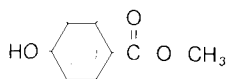
Absorption of local anesthetics is dependent on regional blood flow. Absorption through highly vascular tissues, including mucosa, can result in local anesthetic blood levels similar to those obtained with iv administration. Metabolic breakdown is not carried out in the local tissue, however. Group 1 anesthetics are metabolized almost completely by the pseudocholinesterases of the plasma. The only exception is cocaine, which is excreted in the urine,



Lidocaine (amide bond)



Procaine (ester linkage)



Methylparaben

Fig. 1 Structures of Lidocaine, Procaine, and Methylparaben showing differences and similarities.

intact. Metabolism of the Group 2 drugs occurs in the liver where degradation occurs through a variety of processes (3). Thus, metabolites of the ester-type drugs are produced rapidly after injection and, conceivably, could be reactive. This may explain previous suggestions that ester-type local anesthetics are more likely to cause allergy than are amide-type local anesthetics (4).

COMPONENTS OF LOCAL ANESTHETIC SOLUTIONS

Local anesthetics generally consist of three parts: A hydrophilic amino group, an intermediate or connecting group, and a lipophilic aromatic residue. The link between the intermediate group and the aromatic residue is either an amide bond, as in lidocaine, or an ester linkage, as in procaine (Fig. 1). The structure of the benzoic acid group formed by the ester linkage on the ring is chemically similar to that of methylparaben, a compound previously used as a preservative in many multidose preparations of local anesthetics. This agent has been replaced by bisulfite as a preservative in most local

anesthetic solutions, but continues to be used in a number of topical medications. Methylparaben is a contact sensitizer. More importantly, there are at least two convincing reports to suggest that it has caused anaphylaxis when given intravenously (5). The relationship of methylparaben to purported hypersensitivity reactions to local anesthetics is unclear. There is a possibility that some previously reported reactions to local anesthetics could have resulted from sensitivity to paraben in local anesthetic solutions or cross-sensitivity to the *para*-aminobenzoic acid structure common to ester-local anesthetics and methylparaben (6–10). Available data suggest, however, that patients with contact hypersensitivity to local anesthetics do not demonstrate immediate hypersensitivity reactions to them when exposure occurs by other routes (11).

Local anesthetics frequently contain, in addition to the anesthetic, a vasoconstrictor and sodium bisulfite. Bisulfite preservatives have been incriminated in the production of hypotension and bronchospasm in a group of steroid-dependent asthmatics who normally had increased bronchospasm associated with high atmospheric SO₂ levels (12). At least two patients with reactions to local anesthetics that were postulated to occur on the basis of bisulfite sensitivity have been reported. One of these occurred in a steroid-dependent asthmatic with a negative oral metabisulfite challenge, but an apparently positive challenge to injected metabisulfite (13). The role of sulfite sensitivity in purported local anesthetic reactions is unclear.

REACTIONS TO LOCAL ANESTHETICS

In addition to the desired nerve block, a number of adverse reactions to these agents can also occur. As shown in Table 2, these may be classified into one of four types: toxic, drug-unrelated, idiosyncratic, and allergic. All local anesthetics have the capacity to stimulate the central nervous system (CNS) at low toxic doses and to suppress the CNS at higher toxic doses (14). This is seen clinically as anxiety, tremulousness, excitement, or convulsions, followed at higher toxic doses by vasomotor collapse with hypotension, apnea, and stupor. Quinidine-like effects of these agents are well known and useful in decreasing cardiac irritability at therapeutic levels. Myocardial function is depressed at toxic levels (15).

Table 2
Adverse Reactions to Local Anesthetics

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1. Toxic responses in normal individuals
 - A. Central nervous system effects: Stimulation and depression
 - B. Cardiovascular effects: Myocardial and peripheral vascular
 2. Drug-unrelated reactions
 - A. Psychomotor responses
 - B. Sympathetic stimulation
 - C. Operative trauma
 3. Idiosyncratic Responses: Methemoglobinemia (prilocaine)
 4. Allergic Reactions: Urticaria, angioedema, anaphylaxis, contact dermatitis, delayed hypersensitivity (?)
-

Attention was focused on *toxic reactions* to local anesthetics in a report reviewing five deaths in young women receiving paracervical anesthesia for therapeutic abortion (16). Four of the five reactions appeared to be clinically typical toxic reactions, whereas the fifth appeared to be an idiosyncratic reaction, that is, a toxic reaction at a low dose. In two of the three instances where blood levels were obtained, lidocaine was present at toxic levels (5–12 mg/mL). The article emphasized the point that individuals using these agents must be aware of maximum acceptable doses of the agents that they are using.

Drug-Unrelated Reactions

Drug-unrelated reactions seem to be the most common form of untoward reaction to local anesthetics, and include hyperventilation syndrome and vasovagal reactions, especially common in dental situations. Faints have been said to occur in 2–3% of patients undergoing dental procedures, and, in fact, death has been reported in patients kept upright in dental chairs during such episodes. Sympathetic stimulation caused either by endogenous or administered epinephrine is probably a negligible factor in these reactions, unless severe atherosclerotic cardiovascular disease is present. The recommended limits of epinephrine administration are usually not reached before maximum acceptable doses of the local anesthetics containing them are administered. In fact, most individuals under stress release more epinephrine than that present in 10 2-mL dental anesthetic carpules. Obviously, the use of epineph-

rine is contraindicated in circumstances where endocrinopathy or vasoactive drugs are present (17).

Hypersensitivity Reactions

Hypersensitivity reactions to local anesthetics appear to be extremely rare, comprising less than 1% of all reactions. The largest experience is that of the British National Health Service, where from 1964 to 1971 only 12 reactions thought to be hypersensitivity reactions to local anesthetics occurred. This included three urticarial reactions, two angioedema reactions, and one episode thought to be anaphylactic in type. Six nonspecific dermal reactions also occurred (17).

THE LITERATURE ON LOCAL ANESTHETIC REACTIONS

There are a number of problems with the literature on local anesthetic reactions that complicate understanding the reactions reported. The great majority of reports are single-case reports, most containing incomplete data, with observations made by individuals with little previous experience with clinical hypersensitivity. Many of these case reports include unorthodox testing methods used to support the observations made. These include the use of test methods for the study of delayed hypersensitivity reactions, such as patch and in vitro lymphocyte proliferation assays, in the study of reactions with the timing of immediate hypersensitivity reactions (18), the use of skin testing with large enough volumes of local anesthetic solutions known to cause false-positive wheal and flare responses on an irritant basis, and intranasal (19) and intraocular (20) testing techniques, which are difficult to interpret with these agents. Assem and Punnia-Moorthy (21) attempted to combine leukocyte histamine release, skin test, lymphocyte transformation, and history of local anesthetic reactions suggestive of an IgE-mediated sensitivity. However, they used the history as a gold standard. Historically, a history of local anesthetic reactions and positive skin tests to concentrated solutions of local anesthetics have been consistently associated with negative challenges (22-24). Further confusion has been caused by the paraben and bisulfite questions previously mentioned. Case reports and even large prospective studies have made

no comment regarding whether or not paraben was present in solutions purported to cause clinical reactions. This is important because anecdotal cases have been reported of patients hypersensitive to parabens, but not to the local anesthetics containing them (8,9). Furthermore, the timing of reactions ascribed to local anesthetic hypersensitivity has been strange. Generalized urticaria usually associated with immediate hypersensitivity has been reported to occur immediately, and at 2, 7–10, or 10–15 h after local anesthetic injection. Local swelling, which could result from trauma or hypersensitivity, has also been noted over extensive ranges of time and attributed to “allergy.”

PROBLEMS WITH ASCRIBING LOCAL ANESTHETIC REACTIONS TO IgE-MEDIATED HYPERSENSITIVITY

Urticaria, angioedema, pruritus, and hypotension are clinical manifestations of systemic mast-cell degranulation. If such reactions occur on the basis of IgE-mediated processes, they are called “anaphylactic reactions.” If they occur independent of IgE, they are termed “anaphylactoid reactions.” If type I hypersensitivity to local anesthetics occurs, the production of anesthetic-specific IgE must also occur. Local anesthetics have mol mass of 200–300 daltons. Antibody responses to molecules of this small size depend on the ability of the molecule to form stable conjugates with carrier molecules (25). This conjugating process appears to be quite rare, and has not been demonstrated with local anesthetics or their metabolites (26). However, even after the generation of an IgE antibody response to a drug/hapten, there is another requirement if a type I hypersensitivity reaction is to occur. Mast cells and basophils are activated by polyvalent antigens, not monovalent antigens. Monovalent antigens may serve as blocking agents to type I reactions (27). The production of anaphylaxis or a positive skin test to a local anesthetic through an IgE mechanism requires formation of drug carrier conjugates, which function as polyvalent antigens. The model for such interactions is penicillin allergy. Thus, skin testing with conjugated penicilloyl polylysine is more informative than testing with native penicillin to detect penicillin-specific IgE.

The paradigm for anaphylactoid reactions occurs with radioiodinated contrast dye infusion. Sensitive patients appear to have classical anaphylaxis, although convincing evidence of IgE-mediated hypersensitivity to these agents has not been forthcoming. It is clear, however, that these agents have the ability to release mediators from mast cells independent of IgE such that anaphylactoid reactions occur. Since some local anesthetics, especially those of the ester class, cause wheal and flare reactions when injected into the skin at high concentrations, it is possible that these agents (probably in high doses) could cause anaphylactoid reactions. The possibility has not been investigated clinically for reasons discussed below.

INCREMENTAL DOSE CHALLENGE: A PRAGMATIC APPROACH TO THE PATIENT WITH PURPORTED LOCAL ANESTHETIC ALLERGY

Because of the complexity of this problem, as discussed above, a simple approach to management of these patients was developed (24). As mentioned, it was clear from the literature that local anesthetics, administered intradermally in large volumes, caused wheal and flare reactions of a nonimmunologic type. In a study reported in 1970 in which individuals were tested with 0.1-mL vol of intradermally injected local anesthetics while under general anesthesia, ester derivatives routinely produced such reactions (28).

RESULTS OF SKIN TESTING IN NORMAL INDIVIDUALS

As shown in Table 3, initially 50 normal volunteers with no history of adverse reactions to local anesthetics were skin-tested using standard 0.02-mL intradermal injections of 1% lidocaine or procaine with and without paraben. These solutions were used at either full-strength or 1:100 dilutions. False-positive reactions did not occur in this group of individuals at 1:100 dilutions, although they were again noted intradermally at full strength concentrations with ester derivatives. This information was useful in the application of a progressive skin testing and challenge protocol, and our

Table 3
Number of Positive Intradermal Skin Tests in 50 Volunteers
with No History of Adverse Reactions to Local Anesthetics

Local anesthetic	Concentration	
	1-100	Full strength
1. 1% lidocaine without paraben	0	0
2. 1% lidocaine with paraben	0	0
3. 1% procaine without paraben	0	2
4. 1% procaine with paraben	0	2

application of it in a large group of individuals referred for the evaluation of possible local anesthetic hypersensitivity.

RESULTS OF SKIN TESTING IN PATIENTS WITH HISTORIES OF LOCAL ANESTHETIC REACTIONS

The skin test challenge protocol used in patient studies is shown in Table 4. In these studies, skin testing was first performed using 1:100 dilutions and full-strength drug for standard prick testing followed by intradermal skin testing with 0.02-mL vol of 1:100 dilutions and full-strength drug. Subsequently, subcutaneous challenges with 0.1 mL and 0.5 mL of full-strength drug were performed. Individuals with histories of delayed onset of symptomatology were observed over time. Skin testing was performed with drug, both with and without paraben, and challenges were performed with paraben-containing drugs.

This skin test and challenge protocol was applied to 90 consecutive patients referred for consultation for possible local anesthetic hypersensitivity. A careful and detailed history was taken in an attempt to determine whether or not a given reaction had the characteristics of an anaphylactic reaction and what drug caused it. As shown in Table 5, historical data were considered adequate to allow a clinical classification of the type of reaction in only 38 of 90 patients evaluated in our study. Of these, 14 experienced reactions compatible with anaphylaxis. This group included nine patients with generalized urticaria, four with hypotension and shock, and one with laryngeal edema and shock. An additional 24 patients had reactions

Table 4
Method of Skin Testing and Progressive Challenge
with Local Anesthetics in the Study Described in the Text

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1. Prick test with 1% drug diluted 1:100
 2. Prick test with 1% drug full strength
 3. Intradermal skin test with 0.02 mL 1% drug diluted 1:100
 4. Intradermal skin test with 0.02 mL 1% drug full strength. If history suggests delayed onset of symptoms, wait 24 h before proceeding
 5. Subcutaneous injection of 0.1 mL of 1% drug
 6. Subcutaneous injection of 0.5 mL 1% drug. If history suggests delayed onset of symptoms, wait 24 h before therapeutic administration of drug
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Table 5
History of Reactions in 90 Patients Referred
for Evaluation of Local Anesthetic Hypersensitivity:
Classification on Basis of Probability of Immediate Hypersensitivity

-
1. High probability group (14)
 - A. Generalized urticaria (9)
 - B. Laryngeal edema requiring intubation (1)
 - C. Hypotension with shock (4)
 2. Low probability group (24)
 - A. Facial or oral edema occurring hours after administration (9)
 - B. Syncope (2)
 - C. Urticaria beginning later than 6 h after administration (3)
 - D. Other (10): Includes one each with combative behavior, palpitations, tingling, psychosis, convulsions, tightness in throat, fever, severe malaise with myalgia, and two with papular rashes.
 3. Indeterminate group (52)
-

* Parentheses indicate number of patients.

that historically did not appear to be anaphylactic in type. Many had reactions that began hours following drug administration. This group included nine patients with late facial or oral edema, three with late urticaria, two patients with papular rashes, and one each with a variety of other complaints. Two individuals in this group gave histories compatible with vasovagal syncope. The type of reaction could not be characterized in 52 patients. Many of these occurred in the remote past, and the patient recalled only having been cautioned against future use of local anesthetics. Information about which agent was involved was rarely available in this group.

Table 6
Results of Skin Testing and Progressive Challenge
in 14 Patients Giving a History Compatible With Immediate
Hypersensitivity Reactions to Local Anesthetic Drugs

Agent causing Reaction by History	Number of negative skin tests and challenges	
	to lidocaine	to mepivacaine
Lidocaine (7)	5	2
Procaine (5)	5	ND ^a
Prilocaine (1)	1	ND
Unknown (1)	1	ND

^aND = not done

*As above, parentheses indicate number of patients.

RESULTS OF SKIN TESTS AND CHALLENGES IN SUBJECTS WITH HISTORIES COMPATIBLE WITH ANAPHYLAXIS

Results of skin testing and challenge in the 14 patients who gave a history compatible with immediate hypersensitivity are shown in Table 6. Incriminated agents included lidocaine in seven, procaine in five, and prilocaine in one. No patient had a positive skin test or challenge. Five of seven patients reporting sensitivity to lidocaine were skin tested and challenged with that drug without difficulty. In two other patients, the physician caring for the patient chose to challenge with mepivocaine and did so without difficulty. The other seven patients tolerated challenge with a local anesthetic other than the one incriminated by history. Lidocaine was used in each case.

CUMULATIVE RESULTS OF THE STUDY

Table 7 shows the cumulative results of skin testing and challenges. Some individuals were skin-tested and challenged to more than one agent. Eighty patients had negative skin test and challenge to lidocaine. Two individuals had positive intradermal skin tests to full-strength lidocaine and were challenged to that drug without reaction. Four patients had negative skin tests and challenges to procaine. Five individuals had positive skin tests to full-strength intradermally administered procaine. Of these five, one had a negative challenge. Similarly, one patient with a positive

Table 7
Results of Skin Testing and Challenge Data in All Groups Combined

Drug tested	No. of patients with negative skin tests and challenges	No. of patients with positive skin tests	No. of patients with positive skin tests challenged without adverse reactions
Lidocaine	80	2	2
Procaine	4	5	1
Mepivacaine	6	2	1
Pontocaine	0	1	0

Table 8
Conclusions from Study of Skin Testing and Incremental Dose Challenges in 90 Patients with Local Anesthetic Reactions

1. False positive skin tests occurred when full-strength (FS) local anesthetics were injected intradermally
2. False positives were not seen with prick tests of FS local anesthetics or 1:100 dilutions intradermally
3. The presence of paraben made no difference in skin-test results in any patient
4. Skin testing as part of an incremental challenge protocol is useful in patient management
5. Positive skin tests with dilute solutions of local anesthetic are rare and may suggest immunologic sensitivity
6. Most patients labeled allergic to local anesthetics are not allergic

skin test to mepivocaine was challenged without difficulty, and one patient had a positive skin test to full-strength drug intradermally, but was not challenged.

CONCLUSIONS OF THE STUDY

It was evident from this experience, as seen in Table 8, that false-positive skin tests occurred when full-strength local anesthetics were injected intradermally even in 0.02-mL vol. These false-positive reactions did not occur with prick test of full-strength local anesthetics or intradermal injection of 1:100 dilutions. Since all positive skin tests to paraben containing local anesthetics occurred to

the same anesthetics without paraben, it appeared that paraben played no part in either the clinical reactions or the skin test results in any of the patients studied.

On the basis of this data, we conclude that skin testing appears useful as part of a progressive challenge protocol for patient management. Since positive skin tests that occur with dilute solutions of local anesthetics are rare, positive tests with this protocol may suggest the possibility of real immunologic sensitivity. In one patient, a positive skin test with 1:100 local anesthetic was observed. In another, a positive prick test to full strength was noted. Unfortunately, these patients could not be challenged to find out if they were truly hypersensitive. Finally, and perhaps most importantly, these data point out that most patients labeled allergic to local anesthetics in fact are not.

OTHER STUDIES

Incaudo, Schatz, and associates also reported their experience with puncture and intradermal skin testing in a progressive challenge protocol (23). They concluded that skin tests were less informative. Five of their 59 patients had positive puncture skin tests with local anesthetics as dilute as 1:10,000. All positive skin tests were to agents to which the patients were not historically reactive. Three of these patients were uneventfully challenged with the drug to which they were skin-test positive. In two of their skin test positive patients in whom skin tests with increasing concentrations of drug were performed, initially positive skin tests became smaller or failed to increase in size with increasing concentrations of drug. In addition, four of the five patients had positive skin tests to local anesthetics from both ester and amide groups. These data suggested that the dermal reactions to dilute local anesthetic solutions observed occurred on a nonimmunologic basis or, less probably, represented reactions to paraben present in their solutions. However, the presence or absence of paraben in their solutions was not noted.

Subsequently, Schatz and Fung reviewed their experience and that in the literature up to 1986 on this topic (29). Their review included a total of 257 subjects in whom a negative skin test to a local anesthetic was followed by challenge to that drug without reaction. They concurred that skin testing was useful as part of an

incremental dose challenge protocol. They suggested that the skin testing phase be limited to three skin tests: prick or puncture with 1:100, and full-strength drug and intradermal injection of a 1:100 dilution of drug. This is a reasonable suggestion since (as discussed above) skin testing with full-strength drug has a low probability of providing useful information.

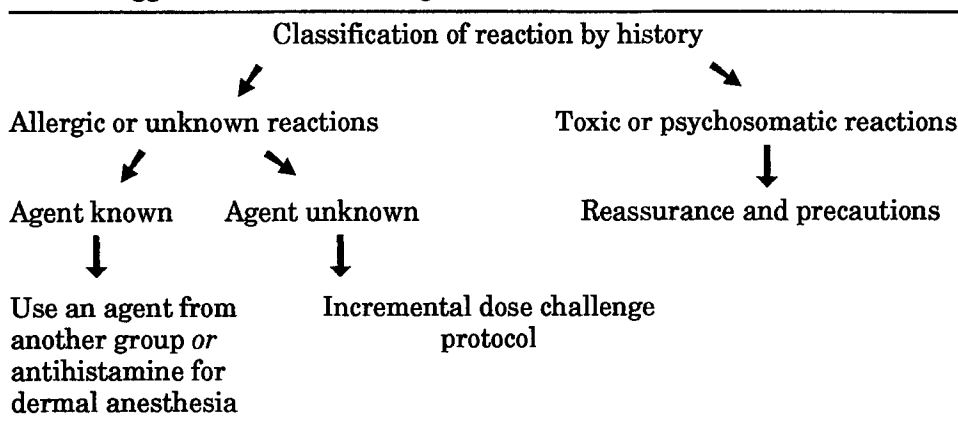
Chandler and colleagues reviewed a similar experience with 59 patients using a five-step skin-test provocative dose challenge protocol (30). This protocol used a single prick skin test with undiluted local anesthetics prior to subcutaneous challenges. The investigators suggested, however, that additional skin tests with 1:10 and 1:100 dilutions of local anesthetics be used in patients with histories of particularly severe reactions. Their experience included two patients who had experienced apparent anaphylactoid reactions to oral antiarrhythmic drugs of the lidocaine class, but who tolerated iv lidocaine subsequent to an incremental dose challenge protocol.

MANAGEMENT OF PATIENTS WITH HISTORIES OF REACTIONS TO LOCAL ANESTHETICS

The usual approach to management of patients with histories of reactions to ester local anesthetics has been to recommend a nonester compound. This approach apparently came about by using very limited patch-test data from one patient studied in 1945 (31) and another in 1955 (32), showing crossreactivity between ester local anesthetics. Similarly, esters have been used for patients with historical amide sensitivity. Although without scientific rationale, clinical experience seems to have proved this approach to be a useful one. It is said that crossreactivity does not occur between Group 2 local anesthetics, although data to support this are not available since immunologic reactions appear to be rare or nonexistent.

Another option is the use of an injectable antihistamine, such as benedryl, as a local anesthetic. It has been our observation that local anesthetics, although useful for dermal local anesthesia, such as that required for suturing, are not adequate for dental anesthesia.

Table 9
Suggested Practical Management of Local Anesthetic Reactions



The sum total of these observations has led to the management scheme presented in Table 9. In individuals who have reactions with allergic characteristics or with reactions that are difficult to characterize, determination of the agent provoking the reaction is useful. Obviously, if the agent is an ester, an amide local anesthetic may be used. Questions about paraben may be avoided by using paraben-free local anesthetics. Similarly, if an amide, such as lidocaine, is incriminated, one may use procaine. We have never provoked a hypersensitivity reaction in any patient where this has been done. Bisulfites are now known to be triggers of anaphylactoid reactions in a small subpopulation of asthmatics. Avoidance of local anesthetic solutions containing bisulfite is the most reasonable approach in such patients.

If the agent is unknown, or circumstances otherwise warrant, skin test and challenge to an epinephrine-free, paraben-free agent is the most useful approach in our hands. We obtain informed consent from the patient for this procedure. This approach is outlined in Table 10. If intradermal reactivity occurs at local anesthetic dilutions of 1:100 or greater or on prick testing, the possibility an immediate hypersensitivity reaction may exist. Challenge of such individuals is a research procedure that must be done with caution. If prick tests and intradermal tests are negative, the patient may be carefully challenged with increasing volumes of anesthetic. We are not aware of any patient with a negative challenge who reacted on

Table 10
Recommended Skin Testing and Incremental Challenge Protocol for
Subjects with Histories of Prior Adverse Reactions to Local Anesthetic Agents

Step	Route	Vol (cc)	Dilution ^a
Skin testing			
1 ^b	Prick	—	1:100
2	Prick	—	Undiluted
3 ^b	Intradermal	0.02	1:100
Incremental challenge			
4 ^b	Subcutaneous	0.1	Undiluted
5	Subcutaneous	0.5	Undiluted
6	Subcutaneous	1.0	Undiluted

^a1% local anesthetic without epinephrine and paraben preservative is used.

^bPrick, intradermal, and subcutaneous injections with phosphate buffered saline as placebo may be introduced at these points.

later clinical administration of the drug. Such an occurrence would be worthy of a report in the medical literature. If patients have histories of delayed reactions, skin-test sites are best observed over time and challenge deferred until skin tests are read.

Subsequent to these initial studies, we have found that initial prick and intradermal skin testing with saline diluent at the beginning of the skin-test challenge protocol can frequently save time and trouble. Hysterical individuals frequently have reactions to either prick or intradermal diluent injections prior to testing with local anesthetics. This initial testing is useful in screening patients prone to such reactions prior to undertaking the actual management procedure.

Some medical writers have published skin testing and challenge protocols to be used by dentists and other medical professionals (33). We believe that considerable care must be taken in the use of such protocols. Moreover, individuals with training and experience in the use of skin testing and challenge and in the treatment of anaphylactic-type reactions should be involved in such activities.

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