Research Journal of Biological Sciences 4 (8): 899-904, 2009
ISSN: 1815-8846

Is Allergy to Local Anesthetics in Dentistry Possible?

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Abstract: It has been estimated that half a million administrations of local analgesics are given each day in the USA and that around 70 million cartridges of dental local analgesic are given annually in the UK. It is widely claimed that adverse reactions to local analgesics are uncommon. It has additionally been estimated that true allergic reactions account for <1% of all adverse reactions to local analgesic agents. Thus, true allergic reactions to local analgesics are extremely rare. The majority of adverse reactions to local anesthetics seems to be psychogenic in nature and related to fear.

Key words: Allergy, local anesthetic, dentistry, oral surgery, type 1, type 4, hypersensitivity

INTRODUCTION

True allergy to local analgesics may be either type 1 immediate, anaphylactic reactions, mediated by IgE antibodies or type 4 delayed hypersensitivity reactions mediated by sensitized lymphocytes. The latter type is most commonly expressed as a contact dermatitis and accounts for approximately, 80% of all true allergic responses to local analgesics. Type 2 responses are the result of IgE and IgM interactions with complement, causing a cytotoxic reaction and type 3 immune reactions result in vascular or connective tissue oedema and inflammation. Type 2 and 3 hypersensitivity responses have not been observed with local analgesic agents (Ball, 1999). The objectives of the present study are:

- To assess the incidence of immediate allergic reactions among adverse events in subjects who required local anesthesia during a dentist therapy
- To learn how to avoid these reactions and how to treat true allergies to local analgesic agents

Type 1 hypersensitivity: The first exposure to allergen is the sensitizing dose. It causes Immunoglobulin E (IgE) antibody production from type B lymphocyte cells and these antibodies bind to basophils and mast cells. On exposure to a second dose of the agent, allergic disorders develop. The expression of allergic disorders is due to the interaction of specific allergen with allergen-reactive IgE bound to high-affinity receptors on mast cells and basophils. This interaction leads to activation of these target cells and their release of preformed, granule-associated mediators (exemplified by histamine), synthesis of lipid mediators from membrane lipids (sulfidopeptide leukotrienes) and the transcription and secretion of cytokines including tumor necrosis factor-a and interleukines 4, 5 and 13. These mediators induce smooth muscle contraction, vascular dilatation and endothelial leakage; cause vascular adhesion molecule expression and attract and activate inflammatory leukocytes, particularly CD4 + T-lymphocytes, basophils and eosinophils. It is important to recognize that allergy is a systemic immune disorder and thus its expression can be multi-systemic (Goldman and Ausiello, 2004).

Type 4 hypersensitivity: Type 4 (delayed-type hypersensitivity) reactions are the most common with local anesthetics. Type T lymphocyte cells are sensitized to the local anesthetic during first exposure (no antibodies are formed). On a secondary exposure, the memory T cells release lymphokines that cause inflammatory reactions and activate macrophages to release mediators of inflammatory reactions. Symptoms of type 4 reactions are similar to those of type 1. These include erythema, swelling and urticaria. However, these are generally localized to the region of injection (Campbell *et al*., 2000).

Diagnosis of allergic disorders-history: Quite often the diagnosis of allergic disorders is straightforward after asking about the nature of the patient's complaints, when and where reactions occur, what exposures the patient believes are relevant to symptom induction and/or exacerbation and his response to medical treatment. The coexistence of allergic symptoms, such as rhino-conjunctivitis, asthma, drug or food allergy, urticaria, contact dermatitis and eczema is characteristic to patients with allergy. There is a high degree of heritability of allergic disease and the risk of expressing allergic

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disorders is highest if both parents are atopic. The seasonal appearance of symptoms can be caused by exposure to pollen or fungi sporule, whereas exposure to allergens that can be found all over the year such as home dust mites or insects, furred animals and mold at home, school, workplace causes chronic symptoms. All these should be included in the history of the patient additionally to description of pillows, carpets, curtains etc. (Goldman and Ausiello, 2004).

Classification of adverse reactions: Adverse systemic reactions to analgesics fall into 4 categories: toxic (drug overdose, rapid absorption intravascular injection), psychogenic, idiosyncratic, or allergic (Ball, 1999).

Allergic and toxic reactions can be traced directly to the pharmacological properties of the local anesthetic. Idiosyncratic reactions may in the vast majority of cases, be unrelated to the drug being possibly psychogenic in origin or having some unrelated patho-physiological underlying cause. Adverse reactions caused by fear or anxiety, inadvertent intravascular administration of local anesthetic, overdosage, intolerance and idiosyncrasy could be mistaken for a true hypersensitivity reaction.

The consequence of such a misdiagnosis could be serious for the patient. Many patients have been denied dental treatment with local anesthesia on the basis of a history of reactions that are not truly allergic. Less than 1% of adverse reactions to local anesthetics are truly allergic in nature. A proper understanding of the various potential adverse reactions to local anesthetics would avoid misdiagnosis of allergy, which can result in unnecessary dental consequences (Selcuk *et al*., 1996).

Clinical findings of allergic or toxic reactions

Anaphylactic allergic shock: Signs and symptoms of type 1 allergy tend to occur within minutes of giving the injection. The lips and periorbital areas swell; the patient becomes agitated and there is widespread itching, particularly of the hands and feet. Tightness of the chest, with wheezing and difficulty in breathing, may occur with a fall in blood pressure and a rapid pulse causes pallor. A true anaphylaxis would cause laryngeal oedema, bronchospasm and hypotension. Other distinctive signs and symptoms include urticaria, angioedema, sneezing and pruritus (Ball, 1999).

Anaphylactic shock is the least common, yet most serious, of the allergic reactions which can occur from the administration of a local anesthetic agent (Giovannitti and Bennett, 1979). It is characterized by a sudden circulatory and respiratory collapse, loss of consciousness, laryngeal oedema and urticaria. The blood pressure falls, the pulse becomes weak or imperceptible and respiration is impaired due to bronchospasm (respiratory difficulty is an important distinguishing factor between anaphylaxis and syncope). Anaphylaxis must be dealt with promptly to avoid loss of life (Laskin, 1984).

Milder allergic reactions: Milder allergic reactions to local anesthetics are most frequently manifested in such conditions as urticaria, rash, angioneurotic oedema, rhinitis and asthma (Giovannitti, 1981). These reactions generally occur soon after injection, although, oedema at the injection site may occur 12-24 h later. Usually, the allergic response is to the anesthetic itself but it can also be to the methylparaben that some anesthetic solutions contain as a preservative (Luebke and Walker, 1978; Johnson and DeStigter, 1983; Laskin, 1984).

Toxic reactions: Toxic reactions result from an overdose of a local anesthetic. With the quantities and concentrations generally used in dentistry, such levels in the brain generally can only be approached when the anesthetic solution is rapidly injected into a blood vessel (Aldrete *et al*., 1977). By aspirating before injecting, toxic reactions from this source should be avoided. Routine aspiration is essential because studies have shown that the incidence of accidental intravascular insertion of the needle ranges from 3-12% (Bishop, 1983).

It is also possible, for a toxic overdose to occur because, the drug undergoes slow biotransformation or elimination. The amide types of local anesthetics are slowly broken down by hydrolysis and metabolized in the liver. Patients with advanced liver disease may not be able to metabolize amide compounds adequately or completely, so a normal dose may become a toxic dose. All local anesthetics, or their degradation products, are excreted in the urine. Patients with decreased renal function may not be able to excrete these substances adequately and this can also lead to a toxic accumulation of the local anesthetic or its metabolic by-products. It is therefore, important to take a careful medical history if such situations are to be avoided (Laskin, 1984).

Management of adverse reactions: The mainstay of treatment, which must be immediate, is adrenaline. The dose is 0.01 mL kg^{-1} body weight up to a maximum of 1 mL of 1:1000 adrenaline solution (usually between 0.3 and 0.5 mL), which may be injected submucosally beneath the tongue so that rapid systemic absorption is assured from this highly vascular area, or alternatively intramuscularly. This is supplemented by antihistamine treatment with agents such as 10-20 mg chorpheniramine,

or 50 mg hydroxyzine hydrochloride, or 50 mg promethazine hydrochloride given slowly by intravenous injection. Hydrocortisone 100 mg may also be given by intravenous injection.

During these procedures the airway must be secured and oxygen administered continuously to compensate for compromised ventilation. If the patient continues to deteriorate, immediate medical help must be summoned, as cardiac massage and intravenous infusion of plasma expanders may be required. One should record all drugs given, routes of administration and times of clinical signs and symptoms for future reference.

Although, extremely rare, generalized anaphylaxis is rapid and life threatening, with sudden onset of syncope, hypotension, respiratory failure and cardiac arrest and death can occur within minutes of exposure to an insignificant amount of a drug (Ball, 1999).

In mild cases of allergy, an oral antihistaminic drug such as diphenhydramine (Benadryl) 50 mg or chlorpheniramine maleate (Chlor-Trimeton, Piriton) 4 mg is given 4 times a day. The more severe immediate reactions should be treated by the subcutaneous administration of 05 mg of 1:1000 epinephrine or an intramuscular injection of an antihistamine such as Benadryl 50 mg, or Chlor-Trimeton 10 mg every 6 h. In the delayed form of allergic oedema, antihistamines taken orally are helpful in relieving the swelling and itching. Warm moist applications are also beneficial in reducing the oedema (Laskin, 1984).

Differential diagnosis of adverse reactions: Most reactions to local anesthetics are not true allergies; rather, they are autonomic or toxic adverse effects. It may be difficult to distinguish between immediate allergic reactions and autonomic adverse effects. However, autonomic effects are short-termed and usually require minimal treatment. Toxic reaction occur when excessive amounts of a local anesthetic are given or an inadvertent intravascular injection has occurred. Symptoms of systemic toxicity include dizziness, muscle twitching, diplopia, tremor, bradycardia. If the practitioner cannot discern whether the reaction was autonomic, toxic, or a true allergy, skin testing should be performed. Many medications can modify an allergic response to skin testing. These include anti-histamines, cough and cold medications, tricyclic antidepressants and steroids, all of which should be discontinued for several days prior to testing (Campbell *et al*., 2000).

Anaphylactic and anaphylactoid reactions are differentiated by their mechanism, with the anaphylactic reaction being immunologically mediated, whereas the anaphylactoid reaction cannot be immunologically mediated. Psychogenic reactions to local anesthetics are common and may manifest in numerous ways, some of which can mimic anaphylaxis. Idiopathic anaphylaxis is diagnosed when no inciting agent can be identified, whether or not immunologic in nature, after a thorough investigation. Factitious anaphylaxis is a feigned reaction and should be suspected in patients who have recurrent episodes of inspiratory stridor, collapse and wheezing-when vital signs and objective criteria are normal and psychiatric disturbance is probable (Bosco *et al*., 1993).

CASE REPORTS

In a study, with a sample of 5,018 patients most of the adverse reactions (22/25) were mild quickly spontaneously (not requiring medication) reversed, psychogenic starting immediately within 30 min after the anesthetic injection. None of the adverse reactions in this study was due to an allergy. Findings are similar to those of other authors who think that the most frequent adverse reactions are the psychic reactions that follow the local anesthetics injections and that allergic hypersensitivity to local anesthetic is rare.

Paterson state that in >30 years of specialty practice in the Norwest of the United States, there has never been verified an immediate allergic reaction using their diagnostic methodology (Baluga, 2003). Another study was carried out in order to investigate patients considered to have experienced allergic reactions to local anesthetics administered for dental treatment. The procedure included skin and intra-oral challenge tests. The results were that no patients were found to be allergic to lignocaine or prilocaine. The most likely causes of the adverse reactions were found to be psychog enic (Rood, 2000). Allergic hypersensitivity to lidocaine hydrochloride, the most widely used and examined local anesthetic is rare. Only four acceptable cases have been found in the literature in the past 10 years. The symptoms range from urticaria to bronchospasms and hypotension with syncope. The symptoms usually are reversible with epinephrine and antihistamines. Skin testing with plain lidocaine has been useful in some patients but may be dangerous and is not recommended. Patients who are allergic to lidocaine have been found to tolerate procaine, prilocaine, or mepivacaine (Chin and Felner, 1980).

The Committee on Safety of Medicines (CSM) records a total of 702 reported cases showing an adverse reaction to both single and multi-constituent products containing lignocaine from June 1964 until November 1997 (33 years). In relation to single constituency lignocaine products the CSM lists 8 nonspecific allergic reactions, 13 anaphylactic reactions including 2 fatalities; 10 anaphylactoid reactions and one type I hypersensitivity

reaction during this period, a total of 32 true allergic responses. For multi-constituent products containing lignocaine the CSM reports a total of 41 reactions for the same disorders during the same period. Because, the Committee lists all the reactions include each report, the total number of reactions usually exceeds the number of reports, i.e., patients. The Committee on Safety of Medicines points out that... in most situations there is considerable under-reporting of reactions and it has been estimated from various surveys that only 10-15% of serious adverse reactions are reported: it should be mentioned that the corresponding figures for prilocaine are 217 reported cases with no fatal outcomes for both single and multi-constituent products during the same period. Twenty-seven came into the category of disorders of the immune system: 9 for single constituency products, 18 for multi-constituency products (Ball, 1999).

Management of «allergic» patients: After an adverse reaction has occurred, an easy and convenient explanation is frequently requested. An allergic reaction to the local anesthetic should not be suggested by the dentist. The term, allergic, given by the clinician is easily recognized by patients and is readily adopted as the explanation of the case.

Experience has shown that the outcome of testing reassures some patients, but many remain committed to the original suggestion (and repeat the 'diagnosis' to the next practitioner they consult/resulting in another referral and reinforcement of their belief). Local anesthesia is the mainstay of pain control during dental treatment, so that an adverse reaction must not be misdiagnosed as caused by an allergy, thereafter denying the patient access to safe pain control. Despite the numerous publications demonstrating that allergy is rare, practitioners still appear to suggest this frequently as a cause for untoward events.

When signs and symptoms develop, which are genuinely suggestive of an allergic response, it is more likely to have resulted from contact with more common allergens (eg latex), so again the local anesthetic should not be suggested as the probable cause. Where, doubt exists or where, the patient gives a 'definite history', it is important to refer the patient, but to inform them that the tests will be undertaken to confirm the safety of local anesthesia and, if possible, to identify the true cause of the reaction. In the very rare cases where, a patient is found to be allergic to one of the anesthetic agents or to one of the other contents of a commercial preparation, a suitable alternative can usually be identified.

Most adverse reactions to local anesthetic injections can be avoided if the following procedures are adopted:

- Confident, caring management; (for extremely anxious patients, pre-medication or sedation maybe required)
- Supine positioning of patients (this will prevent the majority of faints)
- Aspiration (to avoid intravascular injections)
- Using preparations which do not contain methylparaben
- Slow injections (reduce discomfort and improve localization of solution)
- Restricting total dose (for example, do not exceed 300 mg of lignocaine with or without adrenaline - for a healthy adult male of 70 kg, i.e., 7 dental 2.2 mL cartridges) (Rood, 2000)

Prevention and treatment of anaphylactic shock: As anaphylactic shock is a major medical emergency, it is wise to prevent it.

History: Before giving any injection, inquire about previous exposure to the drug and any reaction, however mild.

Allergic disease: Drug reactions are more common to individuals with atopic diseases or who are predisposed to asthma.

Oral medication: Oral administration should be used in preference to injections because symptoms are usually milder if a reaction occurs.

Sensitivity testing: This is helpful in a limited sense on not at all. It may cause a severe or fatal reaction in sensitive individuals unless carefully performed.

One may apply any of the ester-type drugs of the local anesthetics in 25 or 50% dilution intranasally with an applicator. If the patient is allergic, local oedema will develop. Should the hypersensitivity remain questionable, one can inject subcutaneously 10% of the normal dosage with epinephrine at 15 min intervals and increase the dosage until the desired dose is attained. However, the danger of anaphylaxis developing is ever-present and proper precautions should be taken (Seskin, 1978).

Allergy tests

The test procedure: The patient is seated in the dental chair, which is then tilted so that the patient is semi-reclined. Baseline recordings of the patient's pulse rate, blood pressure and oxygen saturation are obtained. The pulse oximeter remains in position during the tests. In cases, where the history cannot exclude an allergic reaction, venous access is secured. The intra-dermal direct challenge tests are undertaken in the skin of the

flexor surface of the forearm (which is cleaned using sterile saline). The test consists of intra-dermal injections of 0.1 mL of 0.5% lignocaine and 0.5% prilocaine (both plain without vasoconstrictor and without preservative) and normal saline (as a control). Although, skin testing has been criticized (as false positive and negative reactions occur), they remain valuable as part of the testing procedure. The site of the injections and the patient's general condition are observed closely for the first 15 min and then at 15 min intervals up to 1 h. In the absence of an immediate response, the second stage of the procedure is conducted. A 'dental' challenge test is undertaken. The dental chair is positioned so that the patient is fully reclined. A 1.0 mL of 2% lignocaine with adrenaline (Xylocaine, Astra) is administered as a maxillary buccal infiltration adjacent to the second premolar. The patient is then monitored for a further hour, which includes re-examination of the skin test sites. At the completion of the observation period, the patient is discharged, but is requested to contact, or to return to hospital, on the following day (or later) if he has any concerns and, in particular, if he has any swelling, itch or a rash (Rood, 2000).

If the suspect local anesthetic is known, skin testing should be performed with a non cross-reacting drug; if unknown, an amide-usually lidocaine-can be used. If preservatives are suspected, one should request that these are tested separately. Vasoconstrictors are omitted as they can mask a positive test result. Dilutions and doses are based on those, for which systemic reactions to skin tests or false results have been reported. If the patient demonstrated a previous delayed allergic reaction to a local anesthetic, challenge tests should be delayed 24-48 h. If a positive test is encountered, another agent should be tested. Once, a negative agent is identified by skin testing, incremental subcutaneous challenge is performed to confirm a safe and tolerable drug. Obviously, this procedure should be performed in a facility capable of treating an adverse reaction. Given a negative challenge-test result, the agent should be acceptable for clinical use. Again, if the patient's history is suggestive of a delayed reaction, clinical use should be delayed 24-48 h to ensure a delayed test reaction has not occurred (Bosco, 1993).

CONCLUSION

Many investigations shown that adverse reactions to local analgesics can mimic symptoms characteristic of allergic responses, but on subsequent investigation proved not to be caused by true allergies to local analgesic agents. Allergic reactions to amide type local anesthetics agents are extremely rare. Ester local anesthetics produce para-amino benzoic acid as a metabolite and it is a known allergen. Methylparaben is also a known allergen and it is used occasionally as a preservative in commercial preparations of some amide local anesthetics. The majority of reactions is either psychosomatic or a consequence of intravenous administration. A small portion may also be generally dermatologic when they occur and rarely are systemic or anaphylactoid. Recommendations for screening suspect patients can be found in the study and generally involve skin tests.

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