

performed with mepivacaine which turned positive after the challenge test. It could be because of, as it has been reported with other drugs, the loss of immunologic memory, because it had occurred 1 year earlier. Thus, although skin test is useful in the diagnosis, a negative result should be cautiously interpreted when the reaction had not occurred recently.

We encourage the study and reporting of IgE-mediated reactions to LAAG for a better knowledge of cross-reactivity among these drugs (6).

*Servicio de Alergia
Hospital General Universitario Gregorio
Marañón
C/Dr. Esquerdo, 46
28007 Madrid
Spain
Tel: 91 5868268
Fax: 91 5868018
E-mail: jmdmiguél@i4con.com

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Hypersensitivity to local anaesthetics

R. B. Jacobsen, J. E. Borch*, C. Bindslev-Jensen

Key words: amide; drug allergy; local anaesthetics; skin testing.

Our aim was, through comparison of history and investigation, to characterize observed reactions, and thereby facilitate decision making on predictability of allergy to local anaesthetics.

Thirty-eight females, median age 40.5 (7–72) years; 10 males, median age 41 (12–62) years referred during the period January 1994 to January 2003. The majority of patients were referred by dentists and the

Hypersensitivity to local anaesthetics (LA) are frequently reported by patients but rarely confirmed upon investigation.

remainder from GPs, and hospital departments. Reactions ranged from dizziness and fainting to manifest anaphylaxis (Table 1). Immediate reactions were reported in 112 of 118 reactions, occurring within 24 h after administration of LA. Forty-five patients experienced the adverse reaction during dental procedures.

In 29, 1, 13 resp. 7 cases, the suspected drug was lidocaine, bupivacaine, prilocaine and mepivacaine. All patients were tested by skin prick test (SPT), intradermal test (IDT) and subcutaneous challenge (SCC) with lidocaine, irrespective of the drug previously administered. Patch testing with LAs were only performed in selected cases of delayed reactions on IDT (patient no. 8). Patch testing was performed with concentrations of LAs of 5 and 15% pet.

Three patients representing four case histories tested positive on IDT (eight controls). None tested negative by SPT and IDT reacted to SCC. Histories in these cases were two of local swelling and two of a general rash. One patient

Table 1. Reported reactions in 48 patients. Figures in brackets are number of reactions, reported for patients, tested positive

Reaction	Number of reactions in history: all/ (test positive)	Reaction occur within 24 h	Reaction occur after 24 h
Local			
Rash	7 (0)	6	1
Swelling	14 (2)	13 (2)	1 (0)
Generalized			
Rash	10 (2)	8 (2)	2 (0)
Swelling	1 (0)	1	0
Astmalike	10 (0)	8	2
Gastrointestinal	7 (0)	7	0
Anaphylactic	5 (0)	5	0
Unspecific*	64 (0)	64	0

* Unspecific reactions:

Rash: urticaria, itching, wheal, flare and rash.

Swelling: swelling, angioedema, swelling of throat/mucous membrane and Quinckes oedema.

Local is defined as delimited to the face, neck or hands (not to the injection site).

Gastrointestinal: nausea and vomiting.

Astmalike: difficulty in breathing and dyspnoea.

Palpitations (5), fainting (6), claustrophobia (1), 'blood ran out of head' (1), cold sweat (7), dizzy (7), discomfort (9), Constricting feeling/a weight on the chest (4), tingling/pricking sensation (5), quivering (2), hyperventilation (2), confusion (1), restlessness (1), distant (3), extreme tiredness (2), burst into tears (1), amnesia (2), weak pupil reaction (1), blisters on tongue (1), fever (1), elevated blood pressure (1).

Table 2. History, sex, age and test results for test-positive patients

Patient no.	Sex	Age	History	Reactions at tests
5	F	27	No known allergies. Lidocaine: two cases swelling of face and hands	Lidocaine: IDT 1:1: Positive Tolerates Bupivacaine
8	F	45	Contact allergy to Colofony. Lidocaine: Local oedema, general rash and vesicles.	Lidocaine: IDT 1 : 1: Positive after 4 h, Patchtest 5 & 15% (pet): Positive (+ 3) Carbocaine (Octapressin) 30 mg/ml: IDT 1 : 1: Positive after 2–3 h Bupivacaine 5 mg/ml: IDT: Doubtful positive test (delayed) Tolerates Citanest (Octapressin) 30 mg/ml at IDT
39	F	29	No known allergies. Citanest (Octapressin) (1.8 mg): Flare and itching of the face. Flare on arms and abdomen. Reactions disappeared in 1 h. Described as urticaria	Citanest (Octapressin): IDT: Positive at 1 : 10 Tolerates Lidocaine

experienced swelling at the site of IDT 2–3 h after testing. Patch testing with lidocaine was positive (+ + +).

Twelve reacted with local swelling; eight with general rash ($P > 0.05$).

Patients described a range of anamnestic reactions, ranging from dizziness to anaphylaxis, categorized as either local or systemic (Table 1). Sixty-four of 118 reactions were of subjective nature. Neither five anamnestic cases of anaphylaxis referred by dentists nor one case of asthma were tested positive. All test-positive patients were women (Table 2). None of the test-positive patients were atopic.

Four of 77 tests were positive. We found a safe alternative LA in all cases.

We found no statistical significant difference in reported reactions between patients tested positive and patients tested negative ($P > 0.05$). Sixty-four of 118 (54%) reported reactions were unspecific. No test-positive patients presented unspecific reactions. We found no parameter in the case history predicting a positive test outcome.

Blood is aspirated in between 2 and 30% of injections of LA (1, 2) and thus contains a risk of accidental i.v. administration. Dental injections are the most feared experience in college students, and reactions resembles reactions to experimental i.v. administration of epinephrine

(1). Between 59 and 77% of reactions has been described as psychogenic (1). Psychogenic reactions usually present as dizziness, pallor, nausea, palpitations, fainting, sweating or other autonomic nervous system responses, including vasovagal syncope, with an onset usually within 1–2 min.

Toxic reactions are depression of the CNS and heart, fainting, suppression of respiration, seizures and visual or auditory disturbances.

Investigation should be initiated with a thorough case history of the adverse reaction. Whether SPT, IDT or SCC is the more reliable and correct test for diagnosing true immediate allergy is a matter of controversy.

No clear pattern regarding cross reactions among amide LAs has been established, and is to our knowledge only described for delayed type hypersensitivity (3, 4).

Allergy to parabens present in the commercially available LA formulations should be investigated routinely. Patient 8 had a negative patch test to parabens, whereas patient 5, who had an immediate reaction, was not tested. Other allergies, such as allergy to latex (5) or chlorhexidine (6, 7) should also be considered when appropriate.

It is important to monitor blood pressure and pulse rate in patients reacting to

LA administration; it may be impossible to differentiate initial signs of anaphylaxis from other causes of fainting: anaphylaxis is virtually always associated with hypotension and compensatory sinus tachycardia, whereas bradycardia or rhythm disturbances are common in vasovagal and cardiac syncope respectively.

In 2001–2002, 2910 patients underwent procedures involving LA administration in our department. The only adverse reactions observed were vasovagal syncope with bradycardia which recovered promptly in a supine position.

The anxious patient should be guided through the planned procedure in advance. Instructions in coping techniques of hyperventilation might be helpful.

*Allergy Center
Department of Dermatology
Odense University Hospital
29 Sdr Boulevard
DK 5000 Odense C
Denmark
E-mail: jakob.borch@allergi.sdu.dk

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A 54-year-old man, with a previous history of myocardial ischemia in treatment with acetylsalicylic acid 200 mg, ticlopidine and atenolol 50 mg for the previous 4 years, was referred to our department after suffering, 3 years ago, an erythematous and itching eruption in the hands and arms and later in the abdomen and groins, that was started 20 min after administration a tablet of acetylsalicylic acid and a tablet of chlorazepate. The episode resolved within 60 min, with no specific treatment. Acetylsalicylic acid was straight afterwards removed. Later he noticed a similar episode of erythematous and itching eruption on his hands, 15 min after the administration a new tablet of chlorazepate.

We performed intradermal tests with acetylsalicylate of lysine up to a concentration of 18 mg/ml, and with diazepam, midazolam and chlorazepate according to the pharmaceutical concentration commercialized; all these tests were negative both in immediate and in the late readings. We also performed patch testing with chlorazepate, the results of which were also negative.

An oral challenge with 100 mg of acetylsalicylic acid was negative, but

10 min after the oral administration of 2.5 mg of chlorazepate intense pruritus and erythema was noted, which resolved with the administration of 10 mg of cetirizine. One week later, 60 min after the oral challenge with 5 mg of diazepam, a similar episode to the previous one was observed, which also resolved after the administration of 10 mg of cetirizine. Finally, the oral provocation with 25 mg of bentazepam was negative.

Chlorazepate is a long-acting benzodiazepine used for preoperative anxiolysis and sedation. It is metabolized in the microsome oxidases of the liver, across the N-desalkylation and hydroxylation pathways, via the cytochrome p450 (CYP450) (CYP3A4) complex (3). The resulting product is an active metabolite called N-desmethyldiazepam or nordiazepam, common to other benzodiazepines such as chlordiazepoxide, diazepam, ketazolam, medazepam, pinazepam and prazepam. N-desmethyldiazepam mediates all the pharmacological effects.

In the literature we have reviewed we have only found a case of delayed hypersensitivity to the chlorazepate dipotassium (3), which described a

Hypersensitivity to chlorazepate dipotassium

R. C. Aznar, M. D. Calatayud, M. A. Martín, D. E.-Q. López, A. P. Hernández*

Key words: chlorazepate dipotassium; drug allergy; immediate hypersensitivity.

The benzodiazepines can produce several types of adverse reactions inclusive hypersensitivity reactions. Until now hypersensitivity reactions have been described following the use of the following benzodiazepines: diazepam (1), tetrazepam (2, 4), clobazam, oxazepam, alprazolam, etizolam (5), nitrazepam, midazolam, temazepam and chlorazepate (3).

Immediate hypersensitivity to chlorazepate dipotassium.

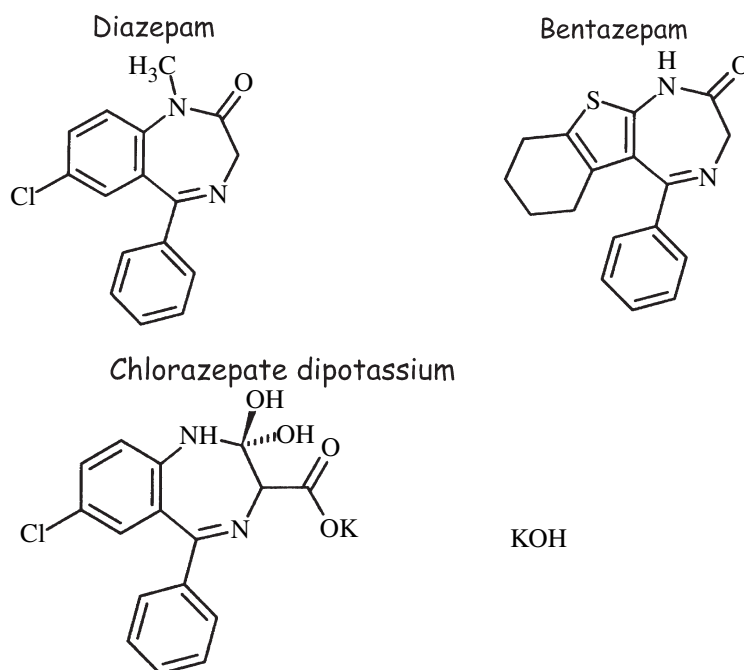


Figure 1. Diazepam, bentazepam and chlorazepate dipotassium.