'Delayed-type hypersensitivity to subcutaneous lidocaine with tolerance to articaine: confirmation by in vivo and in vitro tests

Andreas J. Bircher, Sabine Langauer Messmer, Christian Surber and Th. Rüfli
Allergy Unit, Department of Dermatology, University Hospital, Basel, Switzerland

A 43-year-old woman suffered from recurrent localized swellings and an eczematous dermatitis starting 1 day after an injection of lidocaine. Intradermal, patch and lymphocyte transformation tests revealed sensitization to lidocaine and cross-reactivity to the other aminoacylamlide local anesthetics bupivacaine, mepivacaine and prilocaine, but not to articaine. Contact allergy to the ester local anesthetics benzocaine, procaine and tetracaine, the quinoline or aminoalkylamide cinchocaine, and the preservatives methylparaben and metabisulfite, was excluded. A subcutaneous challenge with articaine was well tolerated.

Key words: delayed-type hypersensitivity; aminoacylamlide local anesthetics; lidocaine; articaine; cross-reactivity; patch tests; intradermal tests; subcutaneous challenge; lymphocyte transformation test. © Munksgaard, 1996.

Accepted for publication 27 November 1995

Contact allergy to amide local anesthetics is rare, whereas ester local anesthetics are common cutaneous sensitizers. For lidocaine, the use in the topical treatment of pruritus ani is the most common cause of sensitization (1). Delayed-type allergy to locally-injected lidocaine is exceptional (2, 3). Since lidocaine is a widely used local anesthetic and an important anti-arrhythmic drug, such patients should be investigated with appropriate tests including subcutaneous challenges to identify a safe alternative anesthetic drug. We report a patient with a delayed-type hypersensitivity to lidocaine. Skin tests and lymphocyte transformation tests revealed sensitization to all aminoacylamlide derivatives with the exception of articaine.

Case Report

A 43-year-old woman was referred by her dentist with a history of localized angioedematous swellings and eczematous eruptions beginning 24 h after local anesthetics for dental surgery and excision of nevi. A similar eruption had occurred after the use of a topical OTC-lotion to treat sunburn, and once oropharyngeal pruritus had been present after the use of an unidentified anesthetic spray for bronchoscopy. She did not have a personal or family history of atopy, but contact allergy to nickel and p-phenylenediamine had been diagnosed by patch tests 10 years ago. Her skin did not show any eczematous lesions when she was first examined.

Laboratory analyses, including a full red and white blood cell count, serum chemistry, total immunoglobulin E, levels of serum cholinesterase, complement C3, C4 and total complement hemolytic activity, were all within the normal range.

Prick and intradermal tests (injected volume 0.05 to 0.1 ml) were performed with a series of local anesthetics and preservatives (Table 1). Readings at 20 min were negative. Readings at day 2 showed positive (2+) reactions to the acylamides lidocaine, mepivacaine and prilocaine, but not to articaine and bupivacaine, and also not to ester derivatives. Patch tests were performed with a standard series, a preservative series including methylparaben and metabisulfite, and local anesthetics. Positive reactions were observed to nickel, p-phenylenediamine, and strongly positive reactions (3+) to the amides lidocaine, mepivacaine, bupivacaine and prilocaine, but negative to articaine, the ester local anesthetics benzocaine, procaine and tetracaine, and the quinoline or alkylamide local anesthetic cinchocaine, which is also called dibucaine (Table 1).

A lymphocyte transformation test (LTT) was performed with several acylamide local anesthetics and preservatives. An increased stimulation index
Table 1. Test results with local anesthetics

<table>
<thead>
<tr>
<th>Substances</th>
<th>concentration (%)</th>
<th>Test techniques</th>
<th>Patch tests</th>
<th>Subcutaneous challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Prick tests</td>
<td>Intradermal tests</td>
<td>concentration (%)</td>
</tr>
<tr>
<td>Amide derivatives</td>
<td></td>
<td>20 min</td>
<td>20 min/D2</td>
<td></td>
</tr>
<tr>
<td>articaine</td>
<td>4.0</td>
<td>-</td>
<td>-</td>
<td>4.0</td>
</tr>
<tr>
<td>bupivacaine</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
</tr>
<tr>
<td>lidocaine</td>
<td>1.0</td>
<td>-</td>
<td>++</td>
<td>1.0</td>
</tr>
<tr>
<td>mepivacaine</td>
<td>0.5</td>
<td>-</td>
<td>++</td>
<td>0.5</td>
</tr>
<tr>
<td>prilocaine</td>
<td>1.0</td>
<td>-</td>
<td>++</td>
<td>1.0</td>
</tr>
<tr>
<td>Ester derivatives</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>procaine</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
<td>2.0</td>
</tr>
<tr>
<td>oxybuprocaine</td>
<td>0.2</td>
<td>-</td>
<td>-</td>
<td>1.0</td>
</tr>
<tr>
<td>tetracaine</td>
<td>na</td>
<td>nd</td>
<td>nd</td>
<td>2.0</td>
</tr>
<tr>
<td>Quinoline derivative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cinchocaine (dibucaine)</td>
<td>na</td>
<td>nd</td>
<td>nd</td>
<td>5.0</td>
</tr>
<tr>
<td>Preservatives</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>methylparaben</td>
<td>0.13</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>propylparaben</td>
<td>0.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>sodium metabisulfite</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
<td>1.0</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>histamine vehicle</td>
<td>prick 1 mg, id 0.1 mg/ml</td>
<td>+/++/na</td>
<td>+/++/na/na</td>
<td>nd</td>
</tr>
</tbody>
</table>

nd: not done; na: not applicable.

(cpm drug/cpm negative control, positive >2.0) was found for all tested agents with the exception of articaine (Fig. 1) and the preservatives (data not shown).

A subcutaneous provocation test with 0.5 ml 0.125% bupivacaine was negative, but with 0.5 ml 0.5%, it resulted in an infiltrated erythematous reaction at day 2. A subcutaneous challenge with articaine (2.0 ml, 4%) was negative and several local anesthetics with this agent were subsequently well tolerated.

Discussion

A similar case with delayed type hypersensitivity to subcutaneous mepivacaine with cross-reactivity to lidocaine and tolerance of articaine has been reported (3). Other acylamides have not been tested in this patient. In other patients with contact allergy to topically applied lidocaine, articaine has not been tested. Cross-reactivity to other aminoacylamides such as mepivacaine, prilocaine and bupivacaine (2, 4-6) has been repeatedly shown on the basis of positive patch tests.

In our patient, the delayed positive intradermal and patch tests to the aminoacylamide local anesthetics suggest a delayed-type hypersensitivity reaction. The intradermal test had a lower sensitivity than the patch test, since it did not identify the sensitization to bupivacaine. The sensitization to lidocaine was probably induced by its earlier topical or subcutaneous application. There was no evidence that the other aminoacylamides bupivacaine, mepivacaine and prilocaine have ever been used in this patient. The sensitization to these compounds is therefore most likely the expression of cross-reactivity. With the exception of articaine, which has a substituted thiophen ring, all aminoacylamides have a methylated phenyl ring (Fig. 2). This difference may explain the lacking cross-reactivity of articaine, and suggests that the allergenic structure is associated with the lipophilic aromatic ring. Fregert et al.
Aminoacylamides

Aromatic part lipidophilic Intermediate chain Amino group hydrophilic

Lidocaine

\[
\begin{align*}
\text{CH}_3 & - \text{N} - \text{C} - \text{CH}_2 - \\
& \text{O} & \text{O} & \text{N} - \text{C}_2 \text{H}_5
\end{align*}
\]

Mepivacaine

\[
\begin{align*}
\text{CH}_3 & - \text{N} - \text{C} - \text{O} & \\
& \text{O} & \text{O} & \text{N} - \text{C}_2 \text{H}_5
\end{align*}
\]

Prilocaine

\[
\begin{align*}
\text{CH}_3 & - \text{N} - \text{C} - \text{CH} & \\
& \text{O} & \text{O} & \text{N} - \text{C}_2 \text{H}_5
\end{align*}
\]

Bupivacaine

\[
\begin{align*}
\text{CH}_3 & - \text{N} - \text{C} & \\
& \text{O} & \text{O} & \text{N} - \text{C}_2 \text{H}_5
\end{align*}
\]

Atricaine, Carticaine

\[
\begin{align*}
\text{CH}_3 & - \text{N} - \text{C} - \text{CH} & \\
& \text{O} & \text{O} & \text{N} - \text{C}_2 \text{H}_5
\end{align*}
\]

Fig. 2. Chemical structure of amide local anesthetics.

Aminoalkylamide

Cinchocaine, Dibucaine

\[
\begin{align*}
\text{O} & - \text{C} - \text{N} - \text{C}_2 \text{H}_5 & \\
\text{O} & \text{N} - \text{C}_2 \text{H}_5
\end{align*}
\]

of adverse drug reactions, including local anesthetic reactions (7). It has often been applied to immunologically (8) and non-immunologically mediated reactions (9) to local anesthetics and therefore had a low sensitivity. In delayed-type allergic reactions, T-lymphocytes are involved in the induction and the elicitation of the pathogenetic cascade. Therefore, the LTT is well suited to identify contact allergens and can be used to reproduce the clinical reaction in vitro. However, caution is required, since technical pitfalls may result in false-negative test results (10), and patients should be additionally evaluated with in vivo techniques. If no severe reactions have occurred or have to be expected, the subcutaneous challenge test is the gold standard and should be performed.

References


Address:
Andreas J. Bircher
Department of Dermatology
Kantonsspital
CH-4051 Basel
Switzerland
This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.