Fixed Drug Eruption Due to Nabumetone in a Patient With Previous Fixed Drug Eruptions Due to Naproxen

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Nabumetone is a nonacidic nonsteroidal anti-inflammatory drug (NSAID) formulated as a pharmacologically inactive prodrug that becomes active only after absorption, predominantly in the small intestine, and through hepatic conversion to its active metabolite, 6-methoxy-2-naphthylacetic acid (6-MNA). This metabolite is structurally similar to naproxen, and is a potent inhibitor of prostaglandin synthesis, preferentially via the cyclooxygenase-2 (COX-2) pathway [1]. Nabumetone has been recommended as a safe alternative in most patients with hypersensitivity reactions to NSAIDs [2].

A 52-year-old woman complained of various episodes of itching, burning, and erythematous plaques—one on her forehead (1-2 cm diameter) and the other in the intraclavicular area (5 cm diameter)—in the previous 2 years. The plaques became red-brown and disappeared within 1 week without treatment. With time, the infraclavicular lesion persisted as brown pigmentation. After various episodes the patient noticed that the eruption might be related to the intake of naproxen tablets, but she was not sure. The last episode had occurred 1 year before consultation and she had subsequently tolerated ibuprofen, paracetamol, and naproxen. The tests were performed on the back (normal skin) and previous lesions with naproxen and on the face, and the neck [4]. False negative results are common when testing topical naproxen on both normal skin and previous FDE lesions, and oral provocation is still the most reliable method for the diagnosis of FDE [5,6]. Although cross-reactivity between drugs with similar molecular structures is possible, in a previous study, we did not find cross-reactivity between naproxen and other propionic acid derivatives [6]. However, in the case reported here, the administration of nabumetone (a naphthylalkanone NSAID) was positive. In our opinion, the similarity of the chemical structure of naproxen and the active metabolite of nabumetone could be the reason for this reaction. Because there are no references in the literature to nabumetone intolerance in patients with FDE to naproxen, we believe that our case is interesting as it might help to prevent such reactions in the future.

References

Hand Contact Dermatitis Made a Patient Blind for the Second Time!

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Keywords: Exotic wood, wood contact dermatitis. Quercus robur, Fagus sylvatica. Gossweilerodendron balsamiferum.


Wood contact dermatitis is a rare condition, but it is frequently reported in occupational contexts, especially in association with tropical woods [1]. Sensitization in such cases is related to direct or airborne exposure to wood dust [1]. There have been only a few reports of sensitization to solid wood and finished wood products such as instruments, wooden jewelry, and knife handles [1].

We report the case of a 38-year-old woman, blind since the age of 15 years due to retinal detachment, who developed contact dermatitis after exposure to wood. In the previous 14 months, she had developed erythema on both hands, as well as severe lesions consisting of erythematous lichenified plaques alternating with vesicles, particularly affecting the tips of the fingers. The lesions resulted in dreadful itching and a progressive loss of sensitivity that prevented the patient from reading Braille. No other lesions were observed at any other skin sites. Symptoms were only partly controlled with local and systemic corticosteroid treatment, with incomplete remission of skin lesions. Allergic persistent moderate/severe rhinitis to Dermatophagoides pteronyssinus had been previously diagnosed. The patient underwent patch testing with the European baseline series (Chemotechnique Diagnosis, Vellinge, Sweden). Allergens were applied on the upper back using 8 mm Finn Chambers (Epitest, Oy, Finland). The readings were noted on days 2 and 4 according to International Contact Dermatitis Research Group criteria. All the results were negative.

A careful evaluation of the patient’s routine revealed the use of wood in writing equipment (Jugulans nigra, Fagus sylvatica), a walking stick (Swietenia mahogani), door handles (Quercus robur, Pinus monticola), a working desk (Chlorophora excelsa) and a piano used daily for teaching (Swietenia mahogani, Gossweilerodendron balsamiferum). We performed patch tests with natural dust from these woods (10% in petrolatum). The patches were left in place for 48 hours and readings recorded at 48 hours (1 hour after removal) and 72 hours. The results were positive for G balsamiferum, F sylvatica, and Q robur (+++, strong reaction for all) at 48 hours, with persistence of lesions at 72 hours. The same tests carried out in 2 healthy individuals and 2 patients with nickel contact dermatitis were negative.

The exhaustive investigation of less common potential contact allergens was essential for the diagnosis of contact dermatitis to wood in our patient, with results showing sensitization to 1 exotic wood (G balsamiferum) and 2 nonexotic woods (F sylvatica and Q robur) through exposure to finished articles.

Contact dermatitis to exotic wood has been reported in the past [2,3], but we found no recent reports. Sensitization to F sylvatica, in contrast, has been rarely reported in the past, but there have been some recent cases described in occupational settings [4,5]. Q robur seems to be less likely to induce contact dermatitis, with only 1 report of 3 patients in the literature [6]. The negative results to allergens from the European baseline series used in the preparation of wood varnishes, resins, and preservatives corroborate exclusive sensitization to wood.

Complete avoidance of the objects made with the woods to which our patient was sensitized resulted in the remission of skin lesions. The specific diagnosis was essential in this particular case as it allowed us to propose specific measures to help the patient, who was blind, to recover her ability to read braille and therefore regain quality of life.

References


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Urticaria Due to Articaine

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Key words: Amide. Articaine. Local anesthetic. Urticaria.

Local anesthetics are very common drugs. Although usually well tolerated, they can precipitate adverse reactions of different types and severity. These reactions can be directly related to the anesthetic (allergic reaction/idiosyncratic), to the doses administered (toxic reaction or overdosage), or to psychogenic/vasovagal factors (fear and anxiety).

We report the case of a 25 year-old woman with a personal history of rhinoconjunctivitis due to pollen sensitivity, who, 30 minutes after the subcutaneous administration of Ultracain (articaine and epinephrine) for a dental procedure, developed generalized pruritus, facial edema, and hives on the face, neck, and thorax. The symptoms were treated with parenteral antihistamines and corticosteroids. She had previously tolerated Ultracain and had never had urticaria before.

The patient was referred to our allergy department, where she underwent an allergy study after giving her informed consent.

Prick tests with aeroallergens were positive to house dust mites, dog and cat dander, and pollen. A latex prick test was negative. Prick and intradermal tests performed with Ultracain and epinephrine were negative. Subsequently, a graded-dose subcutaneous challenge with Ultracain (articaine without epinephrine was not available) up to 2 mL was performed. Twenty minutes after the administration of a cumulative dosage of 0.6 mL, the patient developed pruritus and urticarial lesions on the neck, trunk, and forehead. She was treated with parenteral antihistamines and corticosteroids and the lesions cleared in an hour.

A cross-reactivity study was performed in order to identify an alternative local anesthetic. Skin prick and intradermal tests with mepivacaine, lidocaine, and bupivacaine were negative, and subcutaneous challenge tests with mepivacaine, lidocaine, epinephrine, and bupivacaine were all well tolerated. Preservatives were ruled out as the etiologic agent because the patient tolerated other drugs containing the same excipient as that used in Ultracain (bisulfite).

The literature shows that immediate allergic reactions to local anesthetics are rare, with a reported prevalence of less than 1% [1-3]. Articaine is one of the most widely used anesthetics in dental procedures but there are few cases published in the literature of allergy to this drug. Warrington and McPhillips [4] reported the case of a 35-year-old woman who developed generalized giant hives 5 minutes after an injection of Ultracain. Skin prick and intradermal tests performed with prilocaine and bupivacaine were positive, and a subcutaneous challenge test performed with procaine was also well tolerated.

Figure. Local anesthetics from the amide group.
El-Qutob et al [1] described the case of a 51-year-old woman who experienced erythema and facial edema after the administration of Ultracain. Skin prick tests were negative for epinephrine, lidocaine, mepivacaine, and bupivacaine, and positive for articaine. A subsequent subcutaneous challenge test with mepivacaine was negative. On the basis of the allergy study, the authors concluded that there was no cross-reactivity between articaine and the other anesthetics in the amide group. Our patient developed an adverse reaction after a subcutaneous challenge with articaine, but the cross-reactivity study showed tolerance of the other local anesthetics in the amide group, as reported by El-Qutob et al. One possible explanation is that although articaine is an amide, it has a substitute thiophene ring instead of a methylated phenyl ring (Figure) [5]. We believe that our patient is sensitized to this thiophene ring. The difference in the ring of the chemical structure may explain the lack of cross-reactivity between articaine and other amide local anesthetics [1,3].

In conclusion, although skin prick and intradermal tests were negative in our patient, her history and the positive subcutaneous challenge test strongly suggest that she did experience an immediate sensitivity reaction to articaine. We have demonstrated the lack of cross-reactivity with lidocaine, mepivacaine, and bupivacaine by challenge testing. To the best of our knowledge this case is one of the few cases of articaine allergy that has been reported in the literature.

References


Global Research Productivity in Allergy

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Key words: Allergology. Bibliometric analysis. Impact factor. Medical journals. Worldwide trends in research.


The term allergy is used to describe a variety of human disorders that manifest as symptomatic responses of the immune system to otherwise harmless environmental triggers [1,2]. The prevalence of allergic disorders has increased considerably over the last few decades, generating a considerable economic burden for society [3-5] and leading to increased production of related research, which aims to provide better screening methods and improved therapeutic modalities. The goal of the present study was to assess the quantitative and qualitative contribution of different geographical regions to research activity in the field of allergy.

We used a methodology similar to that of other authors [6,7] and were able to identify 23 journals listed in the Allergy category of the 2009 Science Citation Index Expanded-Journal Citation Reports database [8]. We finally included 15 journals that were also listed in the PubMed database [9] and had an impact factor. A total of 28 050 articles produced during the period 1995-2008 were retrieved; 99.74% of these contained sufficient data to classify them according to their place of origin (Table).

Our results show that Western Europe and the USA are the leading regions in terms of quantity (total production of articles); however, other regions, such as Canada and Oceania, are the leaders in terms of quality. When we consider the population and annual gross domestic product of each region, both Canada and Oceania improve their rank considerably; this is a direct effect of the high quality of articles produced in these regions. The developing countries of Eastern Europe, Latin America and the Caribbean, Asia (excluding Japan), and Africa generally account for a small portion of research productivity.

Interestingly, in all categories, Western Europe is the leading region in the field of allergy. Closer consideration of the contribution of individual countries in Western Europe reveals that, in terms of the total number of articles produced, the United Kingdom, Italy, and Germany rank in the first 3 places. When we take into account economic criteria, the leading countries are Finland, Sweden, and Denmark.

Our results demonstrate that developed countries, which invest more money in biomedical research, have a high quantity and quality of research production.

Although it provides a representative illustration of general trends in global allergy research, our study has certain
Table. Global Research Productivity Indexes in the Field of Allergy During the Period 1995-2008

<table>
<thead>
<tr>
<th>World area</th>
<th>Total Number of Articles</th>
<th>Mean Impact Factor</th>
<th>Total Product</th>
<th>Total Product According to Population</th>
<th>Total Product According to GDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Europe</td>
<td>13,602</td>
<td>4.53</td>
<td>61,440</td>
<td>35.4</td>
<td>11.5</td>
</tr>
<tr>
<td>Iceland</td>
<td>12</td>
<td>5.90</td>
<td>71</td>
<td>38.0</td>
<td>17.6</td>
</tr>
<tr>
<td>Ireland</td>
<td>47</td>
<td>3.85</td>
<td>181</td>
<td>7.9</td>
<td>3.3</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>2301</td>
<td>4.54</td>
<td>10,506</td>
<td>36.6</td>
<td>12.5</td>
</tr>
<tr>
<td>Spain</td>
<td>1727</td>
<td>4.12</td>
<td>7121</td>
<td>50.5</td>
<td>12.7</td>
</tr>
<tr>
<td>Portugal</td>
<td>139</td>
<td>3.69</td>
<td>513</td>
<td>22.1</td>
<td>3.5</td>
</tr>
<tr>
<td>France</td>
<td>987</td>
<td>4.78</td>
<td>4714</td>
<td>16.7</td>
<td>5.4</td>
</tr>
<tr>
<td>Netherlands</td>
<td>859</td>
<td>4.74</td>
<td>4071</td>
<td>50.6</td>
<td>18.1</td>
</tr>
<tr>
<td>Belgium</td>
<td>374</td>
<td>4.61</td>
<td>1724</td>
<td>32.6</td>
<td>11.5</td>
</tr>
<tr>
<td>Switzerland</td>
<td>487</td>
<td>4.92</td>
<td>2395</td>
<td>48.8</td>
<td>23.2</td>
</tr>
<tr>
<td>Germany</td>
<td>1794</td>
<td>4.65</td>
<td>8351</td>
<td>21.9</td>
<td>7.3</td>
</tr>
<tr>
<td>Italy</td>
<td>1948</td>
<td>4.38</td>
<td>8530</td>
<td>36.0</td>
<td>10.5</td>
</tr>
<tr>
<td>Denmark</td>
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<td>4.39</td>
<td>2646</td>
<td>77.0</td>
<td>35.2</td>
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<tr>
<td>Norway</td>
<td>172</td>
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<td>852</td>
<td>21.7</td>
<td>13.5</td>
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<tr>
<td>Finland</td>
<td>608</td>
<td>4.75</td>
<td>2890</td>
<td>115.8</td>
<td>39.8</td>
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<tr>
<td>Sweden</td>
<td>1033</td>
<td>4.59</td>
<td>4744</td>
<td>103.2</td>
<td>37.8</td>
</tr>
<tr>
<td>USA</td>
<td>7336</td>
<td>4.63</td>
<td>33,989</td>
<td>21.4</td>
<td>8.4</td>
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<tr>
<td>Canada</td>
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<td>4804</td>
<td>32.0</td>
<td>10.9</td>
</tr>
<tr>
<td>Japan</td>
<td>2031</td>
<td>3.92</td>
<td>7961</td>
<td>14.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Oceania</td>
<td>769</td>
<td>4.76</td>
<td>3664</td>
<td>33.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Asia (excluding Japan)</td>
<td>1910</td>
<td>3.15</td>
<td>6009</td>
<td>7.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>990</td>
<td>3.18</td>
<td>3149</td>
<td>10.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Latin America and the</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caribbean</td>
<td>481</td>
<td>3.17</td>
<td>1525</td>
<td>4.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Africa</td>
<td>113</td>
<td>4.01</td>
<td>453</td>
<td>3.5</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Abbreviation: GDP, gross domestic product.

The mean impact factor is an index of quality.

The total product of articles is an integrated index of quantity and quality (number of articles × impact factor).

limitations. First, the PubMed search engine did not include all the journals listed in the Journal Citation Reports database, with the result that we had to exclude 2 journals that did not have an impact factor. This raises another controversial issue, namely, whether impact factor is a credible and useful means of indexing quality, even though no other generally acceptable alternative has been proposed [10]. Furthermore, we cannot exclude the presence of journals not listed in the Institute for Scientific Information database and local journals, which also contribute to total research production. Finally, as PubMed provides only the address of the first author, we were unable to take account of the many articles that are the result of multinational cooperation.

In summary, the present study is the first attempt to analyze worldwide trends in research productivity in the field of allergy for the period 1995-2008. Western Europe is the leading region. Other developed countries, such as the USA, Canada, and Oceania rank high, especially if we take into account economic criteria. Developing countries, on the other hand, provide only a small contribution to research productivity.

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Chironomids are nonstinging insects belonging to the Nematocera suborder of the Diptera order. They are found in wetlands and are a frequent cause of environmental allergy in countries where Chironomus thummi is used, with positive results in the skin prick test, specific IgE determination, and basophil activation test. To our knowledge, this is the first report of an allergy to Chironomus in which the basophil activation test [5] was performed as part of the allergy workup. Given the risk not only of serious local reactions [6], but also of severe systemic reactions [4] when a prick-prick test with Chironomus is used, we believe that the basophil activation test is a highly useful tool in the diagnosis of allergy to C thummi.

**References**

Figure. Basophil activation test with Chironomus thummi extract (6 mg/mL). Results of the different concentrations tested.


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Anaphylaxis Due to Olive Fruit After Pollen Immunotherapy

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Keywords: Food allergy. Immunotherapy. Subcutaneous nodules. Olive pollen. Olive fruit.


Olive pollen (Olea europaea) is considered to be one of the main causes of allergic respiratory disease in Mediterranean countries [1]. However, despite the high prevalence of allergy to olive pollen presenting as seasonal rhinoconjunctivitis or asthma and the high consumption of olive fruit, only 2 cases of olive fruit allergy have been reported [2,3].

We present the case of a 16-year-old boy with a history of seasonal rhinoconjunctivitis and asthma that had been successfully treated over a 5-year period with subcutaneous immunotherapy (SCIT) based on a pollen extract vaccine (40% O. europaea pollen, 30% Lolium perenne pollen, 30% Salsola kali pollen) at 1500 UBE/mL. He developed pruritic wheals on the arms and upper part of the thorax associated with oppressive retrosternal pain and moderate dyspnea 20 minutes after eating olives. Skin prick testing (SPT) performed with olive fruit extract (0.8 μg/mL) was positive for olive pollen, 6.46 kUA/L for olive seed (1.6 μg/mL), and partial inhibition with extracts from Artemisia vulgaris pollen, 0.76 kUA/L for S. kali pollen, 0.51 kUA/L for O. europaea pollen, and <0.35 kUA/L for profilin. Likewise, specific IgE determined using the enzyme allergosorbent test (HYTEC, HYCOR Biomedical Ltd, UK) was positive for olive fruit (1.0 kUA/L), olive seed (1.6 kUA/L), and peach LTP (1.0 kUA/L; 100 μg/mL Ole e 1). An immunoblot-inhibition study (Figure) with olive fruit extract in the solid phase showed almost complete inhibition with olive pollen extract, less intense inhibition with grass pollen extract, and partial inhibition with extracts from Russian thistle pollen and olive fruit. An oral challenge test with olive fruit induced urticaria and mild bronchospasm 20 minutes after eating 7 units.

SPT, specific IgE, and a challenge test with olive fruit confirmed the food allergy. The original aspect of this case is that the urticarial lesions developed only in the areas in which the aluminium-adsorbed SCIT had been administered. This type of SCIT slowly releases allergens that can persist for several months in the area of administration, causing a foreign-body reaction to aluminium hydroxide and an immunological interaction with the administered antigen [4]. The location of the lesions at the previous sites of SCIT suggests activation of immunological memory after exposure to a different antigen (olive fruit) that has common allergenic structures with the pollens. Maximum inhibition of blotting was observed with the O. europaea pollen extract.

In contrast to the case reported by Azofra [2], our patient was also allergic to pollens; therefore, sensitization to olive fruit could therefore be due to cross-reactivity between the pollen and the fruit of the same tree, as has been reported for grape and vine pollen [5] and for hazelnut and hazel pollen [6]. Ünsell et al [3] described a patient in whom primary sensitization to O. europaea pollen occurred 3 years before developing allergy to olive fruit. However, in our case, we extended the study with an immunoblot-inhibition test, which...
showed the IgE binding bands responsible for the tree-pollen cross-reactivity, and we performed an oral challenge test with the implicated fruit.

Hyposensitized patients develop persistent subcutaneous nodules at the injection site in 0.5%-6% of cases. These nodules are usually painful and pruritic and may last for several years. In our region, *O. europaea* allergy is very common (60% of patients attending the clinic), as is eating olive fruit. Consequently, we are surprised not to have detected more cases. We believe that this phenomenon could occur with SCIT for other pollens and their corresponding fruits and that it could provide the basis for several publications.

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