Reaction to Teicoplanin With Tolerance to Vancomycin

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Key words: Teicoplanin. Vancomycin. Cross-reactivity. Hypersensitivity.

Palabras clave: Teicoplanina. Vancomicina. Reactividad cruzada. Hipersensibilidad.

Teicoplanin is a glycopeptide antibiotic that has proven very effective in the treatment of severe infections caused by gram-positive bacteria [1]. The most common adverse effects are hematological disorders, ototoxicity, and nephrotoxicity; red man syndrome appears in rare cases [2]. Hypersensitivity reactions, generally delayed, have been described [3-6], in most cases involving cross-reactivity with vancomycin (figure). We present the case of a patient with exanthemata in reaction to teicoplanin and good tolerance of vancomycin.

A 54-year-old man with a febrile syndrome was admitted by the hematology department. He was diagnosed with T-cell lymphoma and received treatment with cefepime, teicoplanin, and co-trimoxazole. Two days later he presented a slightly pruriginous maculopapular exanthema on the trunk and arms that spread over the next 3 days. Cefepime treatment was suspended on the third day and replaced with ciprofloxacin, but the exanthema still spread. After 7 days co-trimoxazole and teicoplanin were also discontinued and treatment with parenteral corticosteroids and antihistamine was initiated. The clinical manifestations disappeared within 1 week.

The patient had previously tolerated cefepime and teicoplanin, and he had received prophylactic treatment with co-trimoxazole twice a week for several months. He was examined in our department 4 weeks after the reaction appeared. Skin prick and intradermal tests were performed with teicoplanin and -lactam antibiotics, including penicilloyl-polylysine, minor determinant mix penicillin G, amoxicillin, ampicillin, cefazolin, cefonicid, ceftriaxone, cefuroxime, ceftazidime, and cefepime. All of them were negative. Patch tests with penicillin G, amoxicillin, ampicillin, cefazolin, cefonicid, ceftriaxone, cefuroxime, ceftazidime, cefepime, teicoplanin, and trimethoprim–sulfamethoxazole were negative at 48- and 96-hour readings. A challenge test with intravenous cefepime up to the therapeutic dose was negative. An oral provocation test with trimethoprim–sulfamethoxazole was also negative. A provocation test with intravenous

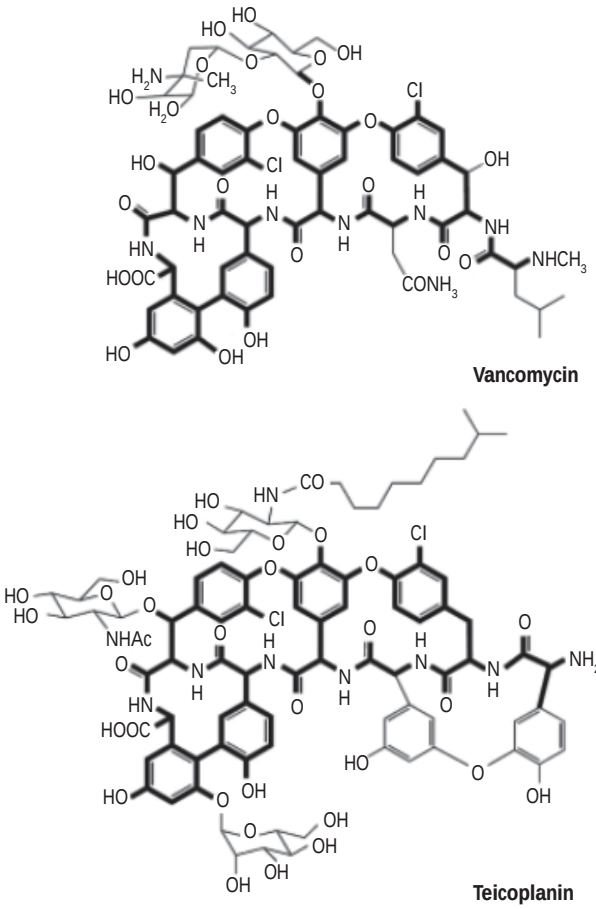

Figure. Chemical structures of vancomycin and teicoplanin. The common core of these molecules is shown in bold.

teicoplanin was performed and the patient presented pruritic erythematous-papular exanthemata on elbows, forearms and abdomen 1 hour after administration of a 400-mg dose. He received treatment with dexchlorpheniramine and methylprednisolone. Pruritus improved during the first hour and lesions disappeared in less than 24 hours. For clinical reasons, and after informed consent had been obtained, the patient underwent a controlled challenge with vancomycin up to the therapeutic dose. Tolerance was good.

This patient suffered from maculopapular exanthemata 2 days after starting treatment with teicoplanin. Skin prick, intradermal, and patch tests were negative and the challenge test reproduced the reaction.

The main skin reaction to glycopeptide antibiotics is red man syndrome in relation to the administration of vancomycin. This reaction is very unusual with teicoplanin, however, because this compound does not cause histamine release, even at faster infusion rates than those of vancomycin [2]. Hypersensitivity reactions to teicoplanin are infrequent, although there are some documented cases of immunoglobulin-E–mediated reactions [7,8].

Hypersensitivity reactions to teicoplanin and vancomycin involving cross-reactivity between the 2 drugs have

been reported [3,4,9]. Maculopapular exanthemata [3], vasculitis [4] and, more rarely, DRESS syndrome (drug rash with eosinophilia and systemic symptoms) and acute generalized exanthematous pustulosis [5,6] have also been described. We found only 1 case of hypersensitivity to teicoplanin with tolerance to vancomycin [10], as occurred in our patient, when we reviewed the literature. Although most published cases show cross-reactivity between 2 drugs, the selectivity of the response to teicoplanin is not surprising, as it has been described in other nonimmediate drug reactions. These reactions are usually mediated by T cells and the response can be directed to the entire molecule [11].

In summary, the hypersensitivity reaction to teicoplanin diagnosed by clinical history and provocation tests that we have reported occurred in a patient who tolerated vancomycin. Our findings suggest an immune mechanism, although the underlying mechanisms involved have yet to be fully elucidated.

References

1. Eitel F, Bauernfeind A, Lang E. Teicoplanin in the therapy of bone and joint infections. Curr Ther Res Clin Exp. 1992;51:197-211.
2. Polk RE. Anaphylactoid reactions to glycopeptide antibiotics. J Antimicrob Chemother. 1991;27:17-29.
3. McElrath MJ, Goldberg D, Neu HC. Allergic cross-reactivity of teicoplanin and vancomycin. Lancet. 1986;1:47.
4. Marshall C, Street A, Galbraith K. Glycopeptide-induced vasculitis cross-reactivity between vancomycin and teicoplanin. J. Infect. 1998;37:82:3.
5. Hyouk-Soo Kwon. A case of hypersensitivity syndrome to both vancomycin and teicoplanin. J Korean Med Sci. 2006;21:1108-10.
6. Perret CM, Mc Bride SR. Teicoplanin-induced drug hypersensitivity syndrome. BMJ. 2004;328:1292 .
7. Asero R. Teicoplanin-induced anaphylaxis Allergy. 2006;61:1370-2.
8. Knudsen JD, Pedersen M. IgE-mediated reaction to vancomycin and teicoplanin after treatment with vancomycin. Scand J Infect Dis. 1992;24:395-6.
9. Grek V, Andrien F, Colignon J, Fillet G. Allergic cross-reaction of teicoplanin and vancomycin. J Antimicrob Chemother. 1991;28:476-7.
10. De Vries E, van Weel-Sipman MH, Vossen JM. Comparative safety of teicoplanin and vancomycin. Pediatr Infect Dis J. 1994 Feb;13(2):167.
11. Depta JP, Pichler WJ. Cross-reactivity with drugs at the T cell level. Curr Opin Allergy Clin Immunol. 2003 Aug; 3(4):216-7.

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Moxifloxacin-Associated Drug Hypersensitivity Syndrome With Drug-Induced Hypersensitivity Pneumonitis

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Key words: Moxifloxacin. Drug hypersensitivity.

Palabras clave: Moxifloxacino. Hipersensibilidad a medicamentos.

Drug-associated hypersensitivity syndrome is a rare and potentially fatal drug reaction characterized by fever, skin rash, and internal organ abnormalities [1]. Moxifloxacin is a new-generation fluoroquinolone antibiotic that has broad-spectrum activity against many organisms [2]. Although there have been reports of moxifloxacin-associated side effects such as interstitial nephritis [3], recurrent tendonitis [4], and anaphylactoid reaction [5], moxifloxacin-associated hypersensitivity syndrome is very rare [6]. We report the case of a 50-year-old woman who, following moxifloxacin treatment, developed hypersensitivity syndrome associated with hypersensitivity pneumonitis.

The patient was referred to our allergy department because of high fever and a generalized maculopapular rash after taking moxifloxacin for 7 days for an upper respiratory infection. She was previously healthy and had a known drug allergy to -lactam antibiotics. On admission, her temperature was 39.8°C, blood pressure 90/50 mm Hg, pulse 120 beats/min, and respiratory rate 16 breaths/min. On physical examination, a generalized, diffuse, maculopapular erythematous rash was noted over her face, trunk and extremities. The laboratory findings revealed mild thrombocytopenia. (white blood cell count, 4000/mm^3; 1.0% eosinophils; platelets 109 000/mm^3). Liver function tests revealed aspartate aminotransferase 71 IU/L (normal 10-35 IU/L) and alanine aminotransferase 46 IU/L (normal 0-35 IU/L). Serology for a small selection of autoantibodies, viral markers, and infectious organisms were all negative. There was accentuation of bronchovascular marking and mild haziness in the left lower portion of her chest x-ray film. A high-resolution chest computed tomography (CT) scan showed diffuse areas of interlobular septal thickening and ground glass opacities in both lower lobes of the lung. Seven days after discontinuation of moxifloxacin without other specific treatment, the fever resolved and the skin lesions improved. The follow-up chest x-ray showed complete resolution of the lesions in both lower lobes.

Two weeks after complete resolution of her symptoms and biochemical abnormalities, skin prick and intradermal tests were performed using serial dilutions of moxifloxacin. The skin prick test showed no positive responses to moxifloxacin at any concentration. However, the intradermal test resulted in a positive response to a 1:10

dilution of moxifloxacin, giving a wheal measuring 9 mm × 6 mm and erythema measuring 17 mm × 17 mm). Enzyme-linked immunosorbent assay (ELISA) to detect specific immunoglobulin (Ig) E antibodies to moxifloxacin in serum was negative.

The patient in this report presented with a febrile skin eruption with systemic involvement including hepatitis, hypersensitivity pneumonitis, and thrombocytopenia following moxifloxacin intake. A diagnosis of drug-associated hypersensitivity syndrome is made based on a history of drug exposure and clinical manifestations, while withdrawal of the suspicious drug and subsequent improvement of clinical manifestations support the diagnosis [1]. The diagnosis of hypersensitivity pneumonitis in this case was based on exposure to the drug preceding the development of new infiltrates on chest radiographs, exclusion of infection or alternative pulmonary disease, CT findings consistent with drug-induced lung disease, and clinical and radiological improvement after withdrawal of the drug. These features are consistent with the criteria advocated for the diagnosis of drug-induced pulmonary hypersensitivity [7].

Immediate hypersensitivity reactions to quinolones are not common [5]. Considering the result of ELISA, the positive response to the intradermal test with a 1:10 dilution of moxifloxacin might be a nonspecific irritant reaction. In this case, the results of the skin prick tests, intradermal tests, and ELISA suggest that factors other than an IgE-mediated mechanism may be associated with this syndrome. Many studies have shown the usefulness of the lymphocyte transformation test and patch testing in the diagnosis of drug-associated hypersensitivity syndrome [8,9]. Unfortunately, these studies were not performed in this case because the patient did not consent.

Further studies are required to evaluate the mechanisms of moxifloxacin-associated hypersensitivity syndrome. In conclusion, this case suggests to us that moxifloxacin might be a new candidate to consider as the cause of drug-associated hypersensitivity syndrome.

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References

1. Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among hypersensitivity and antiviral and antidrug immune response. Allergo Int. 2006;55:1-8.
2. Zahnel GG, Fontaine S, Adam H, Schurek K, Mayer M, Noreddin AM. A review of new fluoroquinolone: focus on their use in respiratory tract infections. Treat Respir Med. 2006;5:437-65.
3. Argirov M, Ricken G, Zecher D, Fischereder M. Acute interstitial nephritis associated with moxifloxacin. Clin Ther. 2005;27:1260-3.
4. Burkhardt O, Kohnlein T, Pap T, Welte T. Recurrent tendinitis after treatment with two different fluoroquinolones. Scand J Infect Dis. 2004;36:315-6.
5. Aleman AM, Quirce S, Cuesta J, Novalbos A, Sastre J. Anaphylactoid reaction caused by moxifloxacin. J Investig Allergol Clin Immunol. 2002;12:67-8.
6. Nori S, Nebesio C, Brashear R, Travers JB. Moxifloxacin-associated drug hypersensitivity syndrome with toxic epidermal necrolysis and fulminant hepatic failure. Arch Dermatol. 2004;140:1437-8.
7. Henry MT, Newstead CG. Sirolimus: another cause of drug-induced interstitial pneumonitis. Transplantation. 2001;72:773-4.
8. Knowles SR, Shapiro LE, Shear NH. Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. Drug Saf. 1999;21:489-501.
9. Schnid DA, Depta JP, Pichler WJ. T cell-mediated hypersensitivity to quinolones: mechanisms and cross-reactivity. Clin Exp Allergy. 2006;36:59-69.

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Allergic Rhinoconjunctivitis Caused by *Cannabis sativa* Pollen

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Key words: *Cannabis sativa* pollen. Immunoglobulin-mediated allergy. Immunoblotting. Rhinoconjunctivitis.

Palabras clave: Polen de *Cannabis sativa*. Alergia mediada por inmunoglobulina E. Inmunodetección. Rinoconjuntivitis.

Hemp (*Cannabis sativa* L), a plant of Asian origin in the Cannabaceae family, is well-known for its fibers, fruit, and narcotic properties. Although it is usually cultivated, it can grow wild in some places. *C sativas* is an anemophilous plant, and its very light pollen can be transported over long distances. It pollinates during summer (June-July), and its allergenic capability is mild to high. We present the case of a 27-year-old Moroccan woman who developed intense perennial rhinoconjunctivitis over a period of 2 years while working with the material before consulting our clinic.

The patient's symptoms began in Spain, where she worked in a research laboratory and was in contact with *C sativa* pollen. She reported that symptoms worsened in spring, that she was not a user of marijuana, and that she did not present symptoms when exposed to marijuana smoke or fumes. Skin prick tests were performed with common commercially available inhalants, including latex (ALK-Abelló, SA, Madrid, Spain), and *C sativa* pollen extract. The results were positive (wheal diameter larger than 3 mm) for the pollen extracts of *C sativa* (6 mm) and *Olea europaea* (4 mm). Serum specific immunoglobulin (Ig) E was determined using a radioallergosorbent test and a cutoff value of 0.35 kU/L was used. The hemp pollen allergen extract (pollen obtained from the patient) was prepared at 2% (wt/vol) in phosphate-buffered saline (PBS), at 5ºC and subjected to magnetic stirring for 90 minutes. After centrifuging, the supernatant was dialyzed against PBS and filtered through a 0.2 m membrane. The extract was 50% glycerinated for prick testing. Cyanogen-bromide–activated paper disks were sensitized with *C sativa* pollen extract and incubated with the patient's serum; disks sensitized with *Lolium*

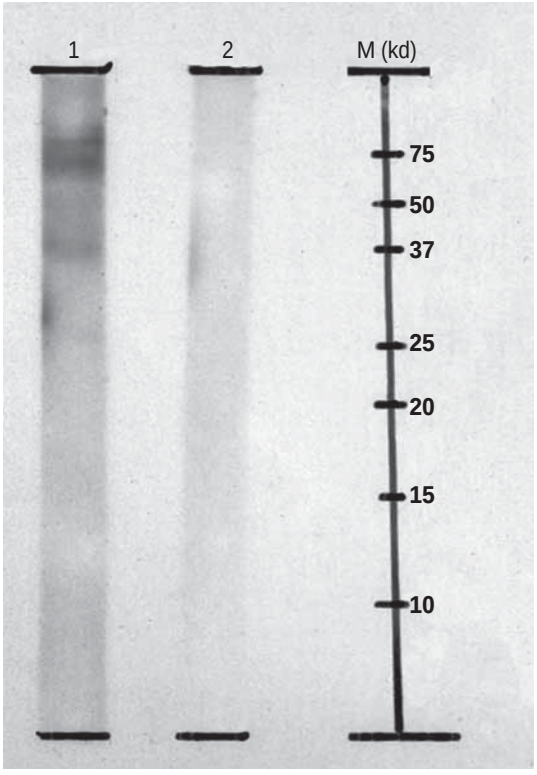

Figure. IgE-immunoblotting with *Cannabis sativa* pollen extract. Lane 1, patient's serum. Lane 2, buffer control. M indicates molecular weight.

perenne were used as a reference along with a pool of sera from grass-allergic patients previously calibrated in kU/L. We found IgE antibodies against *C sativa* pollen (11.0 kU/L) and olive tree pollen (0.4 kU/L). IgE-immunoblotting experiments after sodium dodecyl sulfate polyacrylamide gel electrophoresis (figure) showed that the patient's IgE recognized 37 kd and 70-80 kd protein bands in the hemp pollen extract.

Although the allergic potential of hemp has been known for more than 60 years, few studies have established the clinical significance of its pollen as an aeroallergen. In this sense, Stokes and colleagues [1] carried out a study in Nebraska, in the United States, where hemp was cultivated and grew spontaneously. They observed that hemp pollen accounted for 36% of the total pollen count. In a sample of pollen-allergic patients, 78% were sensitive to *C sativa* pollen and 73% presented symptoms during the pollination season. However, they called for additional studies to assess the clinical relevance of this sensitization, since the patients had concomitant sensitizations to other pollens. Exposure to hemp at an industrial level has been related to a deleterious effect on the respiratory function of workers [2].Other cases of allergy to hemp have been ascribed to the manipulation of the leaf, the ingestion of the seed as a spice, or injection [3-5].

In this report of a case of IgE-mediated allergic rhinitis and conjunctivitis due to *C sativa* pollen, the patient's symptoms began after close, direct contact with the pollen. We do not rule out the possibility of a previous sensitization in the patient's country of origin, where she had lived in a region dedicated to hemp cultivation.

We detected the presence of hemp pollen allergenic proteins of about 37 kd and 70-80 kd, in agreement with other studies carried out with nonpollen materials from *C sativa* [3,5], although those studies also described other allergens with smaller molecular weights (6 kd and 14-16 kd) which might be absent from the pollen material.

References

1. Stokes JR , Hartel R, Ford LB, Casale TB. Cannabis (hemp) positive skin tests and respiratory symptoms. Ann Allergy Asthma Immunol. 2000;85:238-40.
2. Zuskin E, Mustajbegovic L, Schachter EN. Follow-up study of respiratory function in hemp workers. Am J In Med. 1994;26:103-15.
3. Pajarón MJ, Bartolomé B, Orts D, CarneroL, Canto E, Alcolea MD. Alergia a planta de marihuana. Alergol et Inmunol. 2005;20:186.
4. Perez JA. Allergic reaction associated with intravenous marijuana use. J Emerg Med. 2000; 18:260-1.
5. Stadtmauer G, Beyer K, Bardina L, Sicherer SH. Anaphylaxis to ingestion of hempseed (Cannabis sativa). J Allergy Clin Immunol. 2003;112:216-7.

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A Case of Hypersensitivity Syndrome Due to Phenytoin

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Key words: Anticonvulsant. Cross-reactivity. Hypersensitivity syndrome. Phenytoin.

Palabras clave: Anticonvulsivante. Reactividad cruzada. Síndrome de hipersensibilidad. Fenitoína.

Hypersensitivity syndrome, also known as DRESS syndrome (drug rash with eosinophilia and systemic symptoms), is a potentially life threatening, idiosyncratic drug reaction that consists of rash, fever, multiorgan involvement, and hematologic abnormalities [1]. The syndrome can be caused by aromatic antiepileptic drugs (phenytoin, carbamazepine, phenobarbital, and primidone), sulfonamides, dapsone, minocycline, terbinafine, azathioprine, and allopurinol [2].

The incidence of antiepileptic hypersensitivity syndrome is between 1 in 1000 and 1 in 10000 exposures [3], and the rate of cross-reactivity among aromatic anticonvulsant agents is

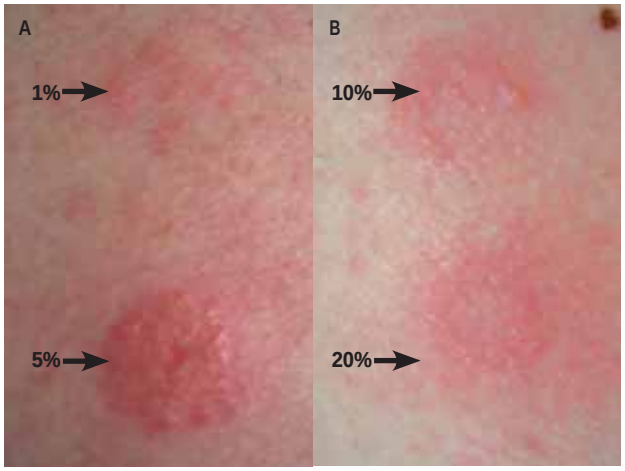

Figure. Patch tests with (A) phenytoin at 1% and 5% and (B) phenobarbital at 10% and 20%.

greater than 80% [4]. This is also described between aromatic anticonvulsant agents and lamotrigine [5] and for tricyclic antidepressant agents [4]. Early diagnosis is very important because the syndrome is associated with a mortality rate of about 10% and specific treatment may be required [1].

A 23-year-old man, with no history of atopy or allergy, was treated with phenytoin 100 mg 3 times a day for a seizure disorder. One month later, he presented with fever, pruritus, and progressive generalized maculopapular rash. Physical examination revealed enlarged cervical lymph nodes and petechiae on the soft palate. The results of laboratory tests were normal except for a slight eosinophilia (864 cells/ L; 13% eosinophils in differential white cell count). For the last 3 days the patient had also received ibuprofen and diazepam for a muscle contracture. The 3 drugs were withdrawn and the patient's symptoms cleared in a week with corticosteroids. The patient began treatment with levetiracetam and currently shows good tolerance to the drug.

Six months later he was referred to our outpatient allergy unit. Informed consent to further tests was provided and patch tests were performed on the patient's upper back with 1% and 5% phenytoin, 60% ibuprofen, and 1% diazepam in saline solution. Test results were assessed at 48 and 96 hours. As we strongly suspected anticonvulsant hypersensitivity syndrome, and to investigate cross-reactivity to other aromatic antiepileptic drugs, we also performed patch tests with carbamazepine at 0.1%, 1%, 10%, 20%, and 100% and phenobarbital at 10% and 20% in saline solution. Patch tests were positive with 1% (++) and 5% (+++) phenytoin and with 10% (+++) and 20% (+++) phenobarbital. (Figure). Patch tests with carbamazepine, ibuprofen, and diazepam were negative. Patch tests were performed in 10 control subjects, 5 atopic and 5 nonatopic, with negative results.

Single-blind oral challenges with ibuprofen and diazepam were negative. Positive patch tests with phenytoin and phenobarbital demonstrated cross-reactivity between these drugs. Due to the high cross-reactivity between phenytoin and carbamazepine, we did not perform an oral challenge with carbamazepine despite a negative patch-test result. It was recommended that the use of aromatic anticonvulsant drugs be avoided in this patient, and that these be replaced by levetiracetam, which is currently well tolerated. Other alternative drugs might be gabapentin or vigabatrin.

Anticonvulsant hypersensitivity syndrome was first described in 1959 with the use of phenytoin [6]. Phenytoin and carbamazepine are the most common causes of the syndrome, followed by phenobarbital and primidone [2]. Valproic acid, benzodiazepines, and gabapentin are structurally and metabolically different, and have been used as alternative drugs [4]. Our patient is currently receiving levetiracetam without any side effects.

The symptoms of anticonvulsant hypersensitivity syndrome usually develop 2 to 8 weeks after initiating therapy with the drug [1]. In our case, the patient had been taking phenytoin for 1 month. The reaction usually starts with fever and, over the next 24 to 48 hours, lymph node enlargement, cutaneous manifestations, and multiorgan involvement become apparent.

The complete pathogenesis of anticonvulsant hypersensitivity syndrome is unknown. One hypothesis is that all aromatic anticonvulsant drugs are metabolized by the enzyme cytochrome P-450 to a common arene oxide metabolite. A defect in the epoxide hydrolases, critical for the detoxification of arene oxides, could lead to the accumulation of reactive metabolites and might predispose to toxicity of anticonvulsant drugs [7].

In summary, we report a hypersensitivity syndrome due to phenytoin with cross-reactivity to phenobarbital that was confirmed by a positive patch test. Avoidance of all aromatic antiepileptics was recommended in this patient because of the high rate of cross-reactivity among this group of drugs.

References

1. Kaur S, Sarkar R, Thami GP, Kanwar AJ. Anticonvulsant hypersensitivity syndrome. Pediatr Dermatol. 2002;19:142-5.
2. Schlienger RG, Shear NH. Antiepileptic drug hypersensitivity syndrome. Epilepsia. 1998;39: suppl 7:S3-7.
3. Gennis MA, Vemuri R, Burns EA, Hill JV, Miller MA, Speilberg SP. Familial occurrence of hypersensitivity to phenytoin. Am J Med. 1991;91:631-4.
4. Seitz CS, Pfeuffer P, Raith P, Brocker EB, Trautmann A. Anticonvulsant hypersensitivity syndrome: cross-reactivity with tricyclic antidepressant agents. Ann Allergy Asthma Immunol. 2006;97:698-702.
5. Galindo PA, Borja J, Gómez E, Mur P, Gudin M, García R, Encinas C, Romero G, Garrido JA, Cortina P, Feo F. Anticonvulsant drug hypersensitivity. J Investig Allergol Clin Immunol. 2002;12:299-304.
6. Saltzstein S, Ackerman L. Lymphadenopathy induced by anticonvulsant drugs and mimicking clinically and pathologically malignant lymphomas. Cancer. 1959;12:164-82.
7. Maquiera E, Yanez S, Fernández L, Rodríguez F, Picans I, Sánchez I, Jerez J. Mononucleosis-like illness as a manifestation of carbamazepine-induced anticonvulsant hypersensitivity syndrome. Allergol Immunopathol. 1996;24:87-8.

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Occupational Allergic Contact Dermatitis to 2-N-octyl-4-isothiazolin-3-one

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Palabras clave: Alergia. Isotiazolinonas. Dermatitis de contacto ocupacional.

2-N-octyl-4-isothiazolin-3-one (OIT) is a preservative belonging to the isothiazolinone group. It was developed specifically for use in latex and oil-based paints, adhesives, wood preservatives, and metal-working fluids [1]. Chloromet hylisothiazolinone/methylisothiazolinone (MCI/MI) is a well-known sensitizer [2] that has been widely used as a preservative in cosmetics and is still in use in various industrial areas. Benzisothiazolinone (BIT) is used as a preservative in paints, varnishes, and glues, and less frequently in metal-working fluids. Contact allergy to BIT is rare [3,4].

In order to study the significance of OIT contact allergy, we carried out a retrospective analysis of patient records for the period from 2002 to 2007. Five cases were identified. In all cases OIT had been patch tested at a concentration of 0.1% in petrolatum. Data from patients with allergic reactions to OIT are shown in the table. A standard commercial series of patch test allergens (True Test, Pharmacia, Hillerod, Denmark) had also been assessed in all patients.

Two patients reacted simultaneously to all isothiazolinones (MCI/MI, BIT, and OIT). Those patients worked in paint manufacture and presented dermatitis on their arms. The remaining patients had dermatitis on the hands and 1 exhibited facial dermatitis. A third patient reacted to MCI/MI and OIT but not BIT. Thus, a total of 3 out of 5 patients reacted to MCI/MI, the isothiazolinone contained in the commercial series, indicating that the clinical efficiency of patch test with the standard series to diagnose occupational allergic contact dermatitis to isothiazolinones is 60%. In 2 patients, the manufacturer confirmed that metal-working fluids and an anti-woodworm product contained MCI and OIT, and MCI/MI and OIT, respectively. These cases show that a unique sensitization to OIT is possible and that there is no cross-reactivity with MCI/MI. Consequently, we suspect that cosensitization rather than cross-reactivity may be responsible in cases 2, 3, and 4.

The ranking in frequency of sensitization described in the literature is MCI/MI >BIT>OIT [2]. The leading position of MCI/MI is clearly not only due to its allergenic potential, but also due to its widespread use [2]. Simultaneous sensitization to these 3 isothiazolinones is extremely rare. The lack of cross-reactivity between MCI/MI, BIT, and OIT [1] shows that chemical similarity does not necessarily induce an allergenic relationship. Thus, multiple sensitization rather than immunological cross-reactivity is probably responsible for some cases of simultaneous reactions. Therefore, we must consider that sensitization to OIT may be implicated in contact dermatitis despite negative results in patch tests with MCI/MI from a standard series.

In summary, OIT is a rare sensitizer and contact allergy mainly occurs in paint manufacturing. OIT is used in some metal-working fluids and may sensitize machinists. Manufacturers could reduce the amount of preservatives, particularly isothiazolinones, in paint, putties, and glues by

Table. Patients With Occupational Allergic Contact Dermatitis to 2-N-octyl-4-isothiazolin-3-one.

Patient	Sex	Age, y	Occupation	Patch Tests						Exposure	Diagnosis
				MCI/MI		OIT		BIT			
				48 h	96 h	48 h	96 h	48 h	96 h		
1	Male	58	Metal machinist	-	-	++	++	NT	NT	MWF	OACD from MWF
2	Male	40	Paint manufacture	+	++	++	++	++	++	Biocides in paints	OACD from biocides
3	Male	50	Painter	+++	+++	++	++	NT	NT	Biocides in paints	OACD from preservatives in paint
4	Male	42	Operator in paint manufacture	+	+	++	++	++	++	Water-based paints	OACD from biocides
5	Female	46	Railway conductor	-	-	++	++	NT	NT	Anti-woodworm	OACD from biocides

Abbreviations: BIT, benzisothiazolone; MCI, 5-chloro-2 methyl-4-isothiazolin-3-one; MI, 2-methyl-4-isithiazolin-3-one; OIT, 2-N-octyl-4-isothiazolin-3-one; MWF, metal-working fluid; OACD, occupational allergic contact dermatitis; NT, not tested.

using sterile production methods and a smaller package size so that the material must be used within a short period of time after unpacking [5].

References

1. Aalto-Korte K, Alanko K, Henriks-Eckerman M, Kuuliala O, Jolanki R. Occupational allergic contact dermatitis from 2-N-octyl-4-isothiazolinone-3-one. Contact Dermatitis. 2007;56:160-3
2. Geier J, Schnuch A. No cross-sensitization between MCI/MI, benzisothiazolinone and octylisothiazolinone. Contact Dermatitis. 1996;34:148.
3. Nielsen H. Occupational exposure ti isothiazolinones: a study based on a product register. Contact Dermatitis. 1994;31:18-21.
4. Rodriguez A, Ano García MA. Occupational contact allergy to Kathon R WT. Allergy. 2002; 57:307.
5. Fischer T, Staffan B, Edling C, Rystedt I, Wieslander G. Skin disease and contact sensitivity in house painters using water-based paints, glues and putties. Contact Dermatitis. 1995;32:39-45

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