CASE REPORT

Type IV Reaction Due to Phenylephrine Administered Nasally With Cross-reactivity With Ethylephrine

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Abstract

Type IV hypersensitivity eye reactions have been described after the administration of the sympathomimetic agent phenylephrine.
We report the case of an atopic woman who developed nasal congestion and discharge, dysphagia, and dyspnea 1 hour after the administration of Stopcold pills and Disneumon Pernasal nasal spray for otitis. The same symptoms reappeared after the accidental administration of Rinobanedif ointment in the nasal mucosa.
Skin patch tests were performed with a standard True Test panel, preservatives, Disneumon Pernasal, pseudoephedrine, eyedrops (tropicamide, cyclopentolate, and phenylephrine), and other sympathomimetic agents. The patient also underwent oral, ocular, and nasal controlled challenges with the same drugs. Finally, patch tests were performed in 11 controls with phenylephrine and ethylephrine. Our patient had a positive outcome in patch testing with nickel sulphate, fragrance mix, phenylephrine, and ethylephrine.
To our knowledge, this is the first report of a type IV reaction to nasally administered phenylephrine with cross-reactivity with ethylephrine detected by patch testing.

Key words: Phenylephrine. Hypersensitivity. Cross-reactivity. Sympathomimetic. Ethylephrine.

Resumen

La fenilefrina es un agente simpaticomimético. Se han descrito reacciones de hipersensibilidad tipo IV vía ocular tras su administración.
Presentamos el caso de una mujer atópica que presentó congestión nasal, rinorrea, disfagia y disnea una hora después de administrarse Stopcold comprimidos y Disneumon Pernasal spray nasal por otitis. Este cuadro clínico se desarrolló de nuevo tras administración accidental de Rinobanedif pomada vía nasal.
Se realizaron tests epicutáneos con batería estándar True Test, conservantes, Disneumon Pernasal, pseudoefedrina, colirios tropicamida, ciclopentolato y fenilefrina, y otros simpaticomiméticos. Llevamos a cabo provocación oral, ocular y nasal controladas con dichos fármacos. También realizamos epicutáneas en 11 controles con fenilefrina y etilefrina. Nuestra paciente presentó positividad en parches con sulfato de níquel, mezcla de perfumes, fenilefrina y etilefrina.
La fenilefrina puede causar reacciones tipo IV vía nasal y presentar reactividad cruzada con etilefrina en tests epicutáneos. Que nosotros conozcamos estos dos hechos no han sido referidos anteriormente.

Palabras clave: Fenilefrina. Hipersensibilidad. Reactividad cruzada. Simpaticomimético. Etilefrina.

Introduction

Phenylephrine is a sympathomimetic agent extensively used as a mydriatic and a topical or nasal decongestant. Type I and especially type IV hypersensitivity eye reactions have been reported following the administration of this drug. The pattern of cross-reactivity with other sympathomimetic agents has not yet been well defined.

We present a rare case of type IV hypersensitivity following the nasal administration of phenylephrine, and show, for the first time, using patch testing, cross-reactivity with ethylephrine, which is homologous to phenylephrine but used as a hypotensive agent.

Case Description

We report the case of a 53-year-old woman with a personal history of physical urticaria, rhinoconjunctivitis, and allergic bronchial asthma, with sensitization to grass and *Artemisia* pollen, dog dander, and *Anisakis*. She came to our department after taking Stopcold pills (cetirizine 5 mg, pseudoephedrine 120 mg, saccharose, lactose) and Disneumon Pernasal nasal spray (phenylephrine 500 mg, sodium saccharin, sodium propionate, menthol, eucalyptol) to treat otitis in January 2009. An hour after the first dose of each drug, she developed intense bilateral nasal congestion and nasal discharge, dysphagia, and dyspnea. Her symptoms improved with oral corticosteroids and dexchlorpheniramine within 4 days. Following diagnosis, the patient applied Rinobanedif ointment (phenylephrine 250 mg, antazoline, bacitracin, chlorobutanol, neomycin, prednisolone, cineol, gomenol) to the nasal mucosa, and developed the same symptoms, albeit less severe, as previously.

It is interesting to note that in 2007, during a right eye examination, the patient also developed erythema on the right side of the face and intense inflammation of the right eye several hours after the administration of mydriatic eyedrops (tropicamide, cyclopentolate, and a third unknown eyedrop).

Patch tests were performed with a standard True Test panel (Upjohn-Pharmacia, Uppsala, Sweden) and preservatives (benzalkonium chloride 0.1% in aqueous, polyethylene glycol 100% and EDTA 1% in petrolatum), with positive results for nickel sulphate and the fragrance mix. We then performed patch tests with the drugs involved in the reaction, namely unaltered Disneumon Pernasal, pseudoephedrine 10% in petrolatum prepared by the hospital pharmacy, and the commercial eyedrops tropicamide 1%, cyclopentolate 1%, and phenylephrine 10% (Table 1). The test patches were applied to the patient´s back and removed after 48 hours, with readings performed at 48 and 96 hours according to the recommendations of the European Contact Dermatitis Research Group [1]. The reactions at 48 and 96 hours were strongly positive for Disneumon Pernasal and the phenylephrine eyedrops (Figure 1).

To investigate possible cross-reactivity with other sympathomimetic agents and offer the patient treatment alternatives for the future, we also performed patch tests with commercial preparations containing ephedrine 5%, adrenaline 1/1000, noradrenaline 1 mg/mL, eyedrops (atropine 1%, tetryzoline 0.05%, naphazoline 0.1%, and brimonidine 0.2%), nasal sprays (xylometazoline 0.1%, tramazoline 1.18 mg/mL, and oxymetazoline 0.05%), and ethylephrine 7.5 mg/mL (Table 1). The results were positive only for ethylephrine 7.5 mg/mL (at 48 and 96 hours).

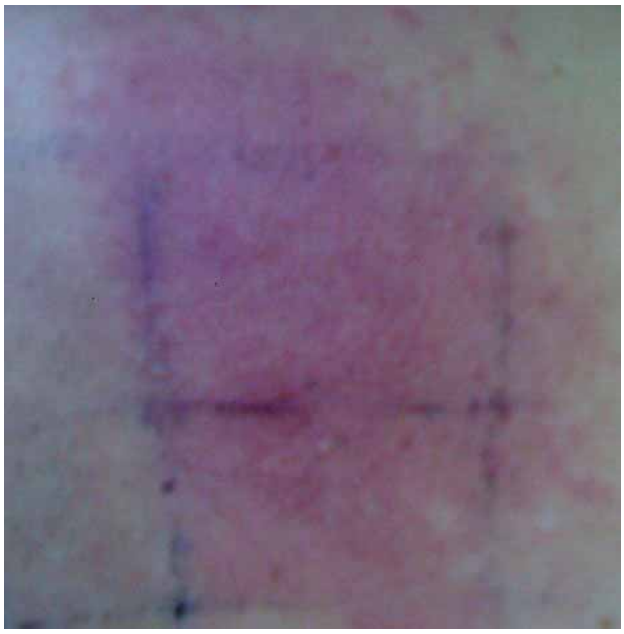

Figure. Epicutaneous tests with Disneumon Pernasal and Phenylephrine eyedrops.

Table 1. Patch Tests With Implicated Drugs, Eyedrops, and Sympathomimetic Agents

Patch Tests	48 h	96 h
Disneumon Pernasal (phenylephrine 500 mg)	+++	+++
Pseudoephedrine 10% in petrolatum	–	–
Eyedrops		
• Tropicamide 1%	–	–
• Cyclopentolate 1%	–	–
• Phenylephrine 10%	+++	+++
Ephedrine 5%	–	–
Adrenaline 1/1000	–	–
Noradrenaline 1 mg/mL	–	–
Ethylephrine 7.5 mg/mL (Efortil)	++	++
Eyedrops		
• Atropine 1%	–	–
• Tetryzoline 0.05% (Vispring)	–	–
• Naphazoline 0.1% (Zolina)	–	–
• Brimonidine 0.2% (Alphagan)	–	–
Nasal sprays		
• Xylometazoline 0.1% (Idasal)	–	–
• Tramazoline 1.18 mg/mL (Rhinospray)	–	–
• Oxymetazoline 0.05% (Utabon)	–	–

We also carried out a controlled oral challenge with Stopcold; an ocular challenge with tropicamide, cyclopentolate, tetryzoline, naphazoline, and brimonidine; and a nasal challenge with xylometazoline, tramazoline, and oxymetazoline. All the results were negative.

Finally, patch tests were performed, with negative results, with phenylephrine and ethylephrine in 11 atopic and nonatopic controls.

We did not perform a challenge with phenylephrine due to the marked positivity of the patch tests with Disneumon Pernasal and the phenylephrine eyedrops, and the repetition of the symptoms after the self-administration of Rinobanedif (which also contains this drug). Ethylephrine was not tested either for ethical reasons (the patient did not need treatment with this drug at the time of the tests).

Discussion

Phenylephrine is a powerful vasoconstrictor with both direct and indirect sympathomimetic effects (mainly α-agonist), although in high doses it can activate cardiac ß-adrenergic receptors [2]. It is formed by a benzene ring with an OH-radical in position 3 and a lateral chain of ethylamine [3,4]. It is used nasally to fight nasal congestion, orally together with other drugs to treat different diseases of the upper respiratory tract, and in ophthalmology as a diagnostic mydriatic during eye examinations. It is also found in ear preparations and in rectal and vascular ointments [1]. The most frequent side effects in eye administration are blurred sight, burning sensation, tearing, conjunctival irritation, liberation of iris pigment into the anterior chamber, and corneal edema. Systemic reactions, mainly hypertensive crisis, are much less frequent [1].

Ethylephrine is homologous to phenylephrine but it has an additional carbon atom [2]. It is a direct sympathomimetic agent with affinity for α-1, ß-1 and ß-2 receptors. It is used orally as a hypertensive agent [2].

Both ethylephrine and phenylephrine belong to the phenylamine family, which is divided into phenylpropanolamine-derived agents (ephedrine, pseudoephedrine, norephedrine) and phenylethanolamine-derived agents (phenylephrine, epinephrine) [5]. Despite similarities in chemical structure, the cross-reactivity pattern between different sympathomimetic agents is not well defined (Table 2) [1,3,5-9]. Moreno-Ancillo et al [1] reported several cases of ocular allergic dermatitis due to phenylephrine with tolerance of ephedrine in 2 out of 3 patients and of pseudoephedrine in all 3 patients. Rodríguez et al [7] described 14 patients who developed ocular reactions due to phenylephrine, with cross-reactivity with pseudoephedrine in 80% of the cases and with ephedrine in 50%. Some authors have suggested that the central structure might be the sensitizing part of the drug [1] from its active metabolite hydroquinone, which enhances the production of interleukin 4 (IL-4) in $CD4^+$ T cells and increases immunoglobulin E levels in murine sera [10,11].

The first case of allergic contact dermatitis to phenylephrine was recorded in 1979 [1,5]. Despite its widespread use, phenylephrine is a well-known sensitizing agent but it only causes between 54% and 96% of all reported eye reactions [4].

To our knowledge, we have presented the first case of a type IV reaction following the nasal administration of phenylephrine and identified cross-reactivity with its homolog ethylephrine in patch testing. This cross-reactivity has not been previously

Table 2. Cross-reactivity Between Sympathomimetic Agents

Reaction	Implicated Agent	Cross-reactivity	Tolerance	Reference
Ocular allergic contact dermatitis	Phenylephrine	Ephedrine (1/3 patients)	Epinephrine Pseudoephedrine Ephedrine	Moreno-Ancillo et al [1]
Generalized erythema	Pseudoephedrine		Ephedrine	Soto-Mera et al [6]
Ocular allergic contact dermatitis	Phenylephrine	Pseudoephedrine (80%) Ephedrine (50%) Oxymetazoline (50%)		Rodríguez et al [7]
Ocular allergic contact dermatitis	Phenylephrine		Epinephrine Ephedrine Naphazoline	Almeida et al [3]
Generalized dermatitis	Pseudoephedrine	Ephedrine	Phenylephrine Epinephrine	Moreno-Escobosa et al [8]
Erythrodermia	Pseudoephedrine	Phenylephrine	Ephedrine Norephedrine Epinephrine	Gonzalo-Garijo et al [5]
Anaphylaxis	Phenylephrine		Epinephrine Pseudoephedrine Ephedrine	Rojas-Hijazo et al [9]

reported because ethylephrine has not been tested in previous studies. We believe that our patient was already sensitized to phenylephrine and that the unknown eyedrops that had been used together with tropicamide and cyclopentolate during the right eye examination 2 years earlier had probably been phenylephrine. Moreover, we suggest that the positive patch test result to the fragrance mix was due to cross-reactivity with phenylephrine as the benzene ring is similar in both molecules.

Our patient presented dyspnea due to upper airway involvement. The symptoms began quickly (within an hour of administration of the drug, probably due to a high level of sensitization) and reached a peak within 12 to 24 hours. Findings that rule out an irritant contact dermatitis and confirm a type IV reaction due to phenylephrine are 1) the intensity of the patch test results, 2) the persistence of cutaneous positivity for several days, and 3) the negative results in the controls. Patch testing is considered an essential diagnostic tool in such cases [1,3]. It is less invasive than both skin prick and intradermal tests, which according to some authors, are not sufficient for the diagnosis of delayed hypersensitivity eye reactions [1]. There is no widely accepted procedure for performing patch tests with phenylephrine [4,12], although the most commonly reported concentration is 10% [1,3]. Many publications defend the use of just eyedrops because the concentrations are not irritating [1,13]. Another important point to bear in mind when performing patch tests with commercial preparations is that all the components should be tested individually in order to prevent sensitization to preservatives [1].

A challenge with phenylephrine was not indicated in the case of our patient because the patch tests with this drug were highly positive, and because the patient developed the same symptoms after the self-administration of an ointment containing less concentrated phenylephrine.

In summary, it should be borne in mind that phenylephrine may cause type IV hypersensitivity reactions when administered not only in eyedrops but also in nasal preparations. Because there is a potential for cross-reactivity with the homologous agent ethylephrine, we recommend that patch tests be performed in all cases. There are no immunohistological differences between eye and nasal mucosa (as mastocytes, plasmatic cells, lymphocytes, and dendritic cells can be found in both cases), and we do not know why type IV reactions are much more frequent after the use of eyedrops, particularly considering that phenylephrine is used in higher concentrations and for longer periods when administered nasally. More studies are needed to investigate this further.

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References

1. Moreno-Ancillo A, Muñoz-Robles ML, Cabañas R, Barranco P, López-Serrano MC. Allergic contact reactions due to phenylephrine hydrochloride in eyedrops. Ann Allergy Asthma Immunol. 1997;78:569-72.
2. Fenilefrina. Etilefrina. In: Vademecum. Updated 2004, 2008. Available from: http://www.iqb.es/cbasicas/farma/farma04/e035.htm.
3. Almeida L, Ortega N, Dumpierrez AG, Castillo R, Blanco C, Navarro L, Carrillo T. Conjunctival allergic contact hypersensitivity. Allergy. 2001;56:785.
4. Botelho C, Rodríguez J, Castel-Branco MG. Allergic contact blepharoconjunctivitis with phenylephrine eyedrops – the relevance of late readings of intradermal tests. Allergol et Immunopathol. 2007 July-Aug;35(4):157-8.
5. Gonzalo-Garijo MA, Pérez-Calderón R, de Argila D, Rodríguez-Nevado MI. Erythrodermia to pseudoephedrine in a patient with contact allergy to phenylephrine. Allergol et Immunopathol. 2002 Jul-Aug;30(4):239-42.
6. Soto-Mera MT, Filgueira JF, Villamil E, Días MT, Cidrás R. Eritema generalizado por pseudoefedrina con tolerancia de efedrina. Alergol Inmunol Clin. 1999;14(6):404-6.
7. Rodríguez A, Trujillo MJ, Herrero T, de Frutos C, Barranco R, Rubio M, Tornero P, de Barrio M. Reactividad cruzada con fármacos alfa-adrenérgicos. Alergol Inmunol Clin. 2000;15(3):68-9.
8. Moreno-Escobosa MC, de las Heras M, Figueredo E, Umpiérrez A, Bombin C, Cuesta J. Generalized dermatitis due to pseudoephedrine. Allergy. 2002;57:753.
9. Rojas-Hijazo B, Garcés MM, Segura N, Ferrer L, Sobrevía M. Anaphylactic reaction after intake of phenylephrine and tolerance of other sympathomimetic drugs. J Investig Allergol Clin Immunol. 2007;17(6):413-23.
10. Lee MH, Chung SW, Kang BY, Kim KM, Kim TS. Hydroquinone, a reactive metabolite of benzene, enhances interleukin-4 production in CD4+ T cells and increases immunoglobulin E levels in antigen-primed mice. Immunol. 2002;106:496-502.
11. Youl-Cho J. Suppressive effect of hydroquinone, a benzene metabolite, on in vitro inflammatory responses mediated by macrophages, monocytes, and lymphocytes. Mediators Inflammation. 2008;298010:1-11.
12. Singal A, Rohatgi J, Pandhi D. Allergic contact dermatitis to phenylephrine. Indian J Dermatol, Venereol Leprol. 2008 May-Jun;74(3):298.
13. Resano-Lizaldre A, Esteve-Cornejo C, Fernández-Benítez M. Blefaroconjuntivitis alérgica de contacto debida a colirio de fenilefrina. Rev Esp Alergol Inmunol Clin. 1998;13(1):208-9.

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