

CLINICAL CASE

Allergy to dexchlorpheniramine. Study of a case

O. Cáceres Calle and M. Fernández-Benítez

Department of Allergology and Clinical Immunology. University Clinic of Navarra. School of Medicine. University of Navarra. Pamplona. Spain.

ABSTRACT

Introduction: Dexchlorpheniramine (DH) is a classical or first generation antihistamine belonging to the ethanolamine group.

Adverse effects related to these antihistamines are frequent, but the hypersensitivity reactions described in the literature since 1940 are exceptional.

We report the case of a 32-year-old woman who experienced two episodes of acathisia secondary to intravenous (i.v.) dexchlorpheniramine administration for a possible hypersensitivity reaction to local anesthetics.

Material and methods: Allergological study consisted of the following tests: skin prick tests with routine allergens, with a negative result; skin prick and intradermal tests with local anesthetics and DH, with a positive result to DH in the intradermal skin test (+ +); serum specific IgE, which was within normal levels; histamine release test with DH with a negative result, and the basophil activation test (BAT) with local anesthetics and DH, which was positive for DH and weakly positive to Lidocaine®.

Conclusion: BAT is proving to be a highly useful tool in the field of drug allergy, with a higher sensitiv-

ity and specificity than other *in vitro* tests. Because it avoids the need for provocation tests, this is especially important in drug-induced allergic reactions in which *in vivo* tests are repeatedly negative despite a clear clinical history.

Key words: Dexchlorpheniramine. Hypersensitivity to dexchlorpheniramine. Antihistamines. Allergy to antihistamines. Acathisia. Basophil activation test.

RESUMEN

Introducción: La Dexclorfeniramina es un antihistamínico clásico o de 1.ª generación perteneciente al grupo químico de las Etanolaminas.

Son frecuentes los efectos adversos relacionados con estos antihistamínicos pero las reacciones de hipersensibilidad descritas en la literatura desde 1940 son excepcionales.

Presentamos a una mujer de 32 años que tuvo en dos ocasiones un cuadro de acatisia secundario a la administración de dexclorfeniramina endovenosa (e.v.) para tratar una posible reacción de hipersensibilidad a anestésicos locales.

Material y métodos: En el estudio alergológico realizado se efectuaron pruebas cutáneas (Prick) a los alérgenos habituales con resultado negativo; pruebas cutáneas a medicamentos (Prick e intradermo) con anestésicos locales y dexclorfeniramina con resultado positivo en intradermo a dexclorfeniramina + + ; IgE sérica total que resultó dentro de la normalidad, Test de Liberación de Histamina (TLH) a dexclorfeniramina con resultado negativo y Test de Activación de Basófilos (TAB) frente a anestésicos locales y dexclorfeniramina con resultado positivo

Correspondence:

O. Cáceres Calle
Department of Allergology and Clinical Immunology
University Clinic of Navarra
Apartado 4209
31080 Pamplona, Spain
Tel.: 34 948 255400 - Fax: 34 948 296500
E-mail: ocaceres@unav.es

para dexclorfeniramina y levemente positivo para Lidocaína®.

Conclusión: El TAB está demostrando ser una herramienta muy útil en el campo de la alergia a medicamentos, donde cuenta con una sensibilidad y especificidad superior a otras técnicas *in vitro*, siendo especialmente importante en aquellas reacciones alérgicas medicamentosas en donde a pesar de los datos anamnésticos claros, las pruebas *in vivo* son repetidamente negativas, evitando así la realización de pruebas de provocación.

Palabras clave: Dexclorfeniramina. Hipersensibilidad a dexclorfeniramina. Antihistamínicos. Alergia a antihistamínicos. Acatisia. Test de activación de basófilos.

INTRODUCTION

The Dexchlorpheniramine (DH) is a classic or first generation antihistamine belonging to the chemical group of the Ethanolamines. Alike the rest of antihistamines, it inhibits the H1 receptors in a non-selective way, antagonising the effects of histamine and competing with it for these receptors. Its action is not selective and it frequently inhibits also peripheral and central colinergic receptors, serotonergic receptors, etc. And it also exerts other pharmacological actions with therapeutic use.

To be highlighted among its actions:

- As antihistamine: it increases the capillary permeability, inhibits the pruritus, the bronchoconstriction, etc.

- On the central nervous system it exerts a sedative hypnotic action, especially for the ethanolamines. In children, and sometimes in adults, it can produce excitement and agitation. At toxic dosages, it usually produces an intense stimulation that could even cause convulsions and activate epileptic foci. It has some antikinetic action avoiding the symptoms caused by the abnormal stimulation of the labyrinth.

- Its anticolinergic action produces dryness of mouth and hands, miction difficulty and other dosage-dependent effects.

- As local anaesthetic, at high dosages, it blocks the sodium channels, decreasing the excitability of the cells.

The side effects related with these antihistamines are frequent¹, but the hypersensitivity reactions described in the literature since 1940 are exceptional:

disease associated with immunocomplexes attributed to Diphenhydramine + Pyridylidione (Peroben®)², allergic dermatitis and photodermatitis induced by Diphenhydramine³ and DH⁴, contact dermatitis induced by DH⁵, fixed drug eruption⁶ and cross sensitivity with DH in subjects allergic to Paraphenylenediamine⁷. As immediate hypersensitivity reactions, an anaphylactic reaction attributed to hyoscine + Diphenhydramine⁸, and another one to Diphenhydramine⁹ are described.

CASE REPORT

We report the case of a 32 year old woman with no allergic background who visits us in order to rule out drug sensitisation. In the first labor in July 1997, two hours after administration of epidural anaesthetics of Lidocaine® and Fentanil (Fentanes®), she starts with generalised pruritus, especially in cervical area and upper limbs with no skin lesions. The patient is administered DH i.v. (Polaramine®) starting with immediate hypotension, dizziness, feeling of lack of air, tinnitus and uncontrolled movements of both lower limbs. The symptoms yielded after administration of Diazepam i.v. (Valium®).

The second labor took place with no incidences avoiding administration of Lidocaine® and Fentanes® in the epidural anaesthetics.

In the third labor, after administration of Lidocaine® and Fentanes®, the patient started with similar symptoms in a more immediate way, ten to fifteen minutes after administration of the anaesthetics, reason why an ampoule of DH i.v. (Polaramine®) was administered. The patient starts almost immediately with dizziness, difficulty to breath and paresthesias in lower limbs together with involuntary movements impossible to stop that extended upwards until reaching higher members and accompanied by lateral movements of the neck. No loss of consciousness or hypotension. In spite of the administration of 80 mg of Methylprednisolone i.v. (Urbason®) the patient needed admission in the Intensive Care Unit, yielding the symptoms with Midazolam i.v.

During the visit the patient related that six years before, at the dentist', thirty minutes after administration of Lidocaine®, she presented a subjective feeling of hypotension and dizziness that yielded without medication. She did not report clinic with latex.

As personal background, she was diagnosed of an antiphospholipid syndrome.

The patient had been studied at the Department of Neurology, discarding the existence of an organic pathology that could explain the reaction reported, and being diagnosed of pharmacological acathisia



Figure 1.—Intradermal test: positive result to DH in intradermal tests.

and secondary rhabdomyolysis manifested at the moment of the reaction induced by the increase of PCK.

The physical examination was within normal levels.

Complementary examination

Prick skin tests performed with fish, shell-fish, fruits, nuts, legumes, wheat flour, egg, milk, dog, cat and horse dander, Dermatophagoides pt, Alternaria, Cladosporium, Aspergillus, grass pollen, tree pollen, weed pollen, olive pollen, latex, Anisakis and Blattella were negative.

Prick and intradermal skin tests performed with local anaesthetics (Mepivacaine, Procaine, Lidocaine, Bupivacaine and Fentanil) and with DH, were positive to Polaramine in intradermal (+ +) (fig. 1).

Serum specific IgE was 8.75 kU/l, and the Histamine Release Test was negative (Basal 3.98 ng/ml; anti IgE 20.83 %; total histamine 38.42 ng/ml; Polaramine 1st dilution 0.00 %).

The Basophil Activation Test (BAT) was positive for DH (Polaramine®) and weakly positive to Lidocaine (Positive 85.4 %; Negative 1.9 %; Lidocaine first dilution 6.3 %, second dilution 3.6 %; Procaine first dilution 0.3 %, second dilution 0.5 %; Fentanil® first dilution 1.2 %, second dilution 0.4 %; Dexchlorpheniramine first dilution 16.9 %, second dilution 16.3 %).

Once these diagnostic tests had been performed and considering the unexpected results obtained in the intradermal and in the Basophil Activation Tests, we decided to contrast them performing four controls for the intradermal test with Polaramine, and eight controls for BAT, being all of them negative.

The patient was suggested to complete the study by means of challenge test with Lidocaine and provo-

cation-tolerance with other antihistamines but she did not give her consent. She was diagnosed of probable drug sensitisation to the amida group of local anaesthetics and sensitisation to DH, advising her to avoid the administration of both drugs until the study was completed.

DISCUSSION

It has been described that DH can produce excitement and agitation in some adults¹. Our patient, staying completely conscious at all moment, had a reaction compatible with acathisia after administration of this drug in the first and third labors, although in the third one the symptoms started before and were more severe clinically.

It also seems clear the positivity to local anaesthetics of the amida group, that together with the clinical history of the patient suggest a more than probable hypersensitivity reaction to Lidocaine, which induced to the administration of DH i.v. in the first and third labors in order to control the reaction.

The study performed by the Department of Neurology in order to rule out any cause justifying the symptoms was negative which supports that the reaction, even though unknown until that moment, was produced by some immunological mechanisms to DH.

It is important to develop new *in vitro* techniques that facilitate the diagnosis of allergic reactions to drugs in patients with repeated negative *in vivo* tests in spite of a clearly positive clinical history. Understandably, many patients do not give their consent to undergo challenge tests with drugs after having suffered complicated or severe clinical reactions, and it is then when these new diagnostic techniques become more important. Basophil Activation Test is being proven to be a very useful tool in the field of drug allergy with a higher sensitivity and a specificity than other *in vitro* tests¹⁰.

REFERENCES

1. Estelle F, Simons R. Antihistamines. In: Franklin Adkinson Jr N, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Estelle F, Simons R, eds. Middleton's Allergy: Principles and Practice, Volume 2, 6th Edition. Mosby, 2003;51:834-69.
2. Van Neste D, Pierad GE, Hermanns JF. Immune complex disease associated with Peroben® intake. Dermatologica 1979; 158:417-26.
3. Demoly P, Messaad D, Benahmed S, Sahla H, Bousquet J. Hypersensitivity to H1-antihistamines. Allergy 2000;55:679-80.
4. Horio T. Allergy and photo-allergic dermatitis from diphenhydramine. Arch Dermatol 1976;112:1124-6.
5. Cusano F, Capozzi M, Errico G. Contact dermatitis from dexchlorpheniramine. Contact Dermatitis 1989;21(5):340.
6. Dwyer CM, Dick D. Fixed drug eruption caused by diphenhydramine. J Am Acad Dermatol 1993;29:496-7.

7. Sorning De Laysat C, Boone M, Blondeel A, Song M. Two cases of Cross-sensitivity in subjects allergic to Paraphenylenediamine following ingestion of Polaronil®. *Dermatology* 2003;206(4):379-80.
8. Watanabe T, Funayama M, Morita M. Fatal anaphylactic shock to hyoscine and diphenhydramine. *J Toxicol Clin Toxicol* 1994; 32:593-4.
9. Barranco P, Lopez-Serrano MC, Moreno-Ancillo A. Anaphylactic reaction due to diphenhydramine. *Allergy* 1998;53:814.
10. Sanz ML, Gamboa PM, Antépara I, Uasuf C, Vila L, García-Avilés MC, Chazot M, de Weck AL. Flow cytometric basophil activation test by detection of CD63 expression in patients with immediate-type reactions. *Clin Exp All* 2002;32: 277-86.