TITLE:

TWO CASE REPORTS OF DELAYED-ALLERGIC REACTIONS TO CLINDAMYCIN CONFIRMED WITH A POSITIVE LYMPHOCYTE TRANSFORMATION TEST.

AUTHORS:

Francisca Vílchez Sánchez[1], Javier Domínguez-Ortega[1, 3], Miguel González Muñoz[2], David Loli-Ausejo[1], Rocío Heredia-Revuelto[1], Ana Fiandor Román[1], Santiago Quirce[1, 3]

AFFILIATIONS:

1. Department of Allergy, Hospital La Paz Institute for Health Research (IdiPaz), Madrid. Spain
2. Department of Immunology, Hospital La Paz, Madrid.
3. CIBER de Enfermedades Respiratorias, Ciberes, Madrid Spain.

INSTITUTION: Hospital Universitario La Paz. Paseo de la Castellana, 261. 28046 Madrid, Spain.

CORRESPONDING AUTHOR:

Francisca Vílchez Sánchez.

Servicio de Alergología. Hospital Universitario La Paz.

Paseo de la Castellana, 261. 28046 Madrid, Spain.

E-mail: franvilsan@gmail.com

SUMMARY:

Clindamycin is widely used in the prophylaxis and treatment of infections due to its broad spectrum of antimicrobial activity. Its hypersensitivity seems to be not very common (less

than 1% of drug-allergic reactions) and it mostly appears as delayed T-cell mediated. For the diagnosis, skin testing is considered to be highly sensitive and rather safe but cutaneous and systemic reactions have been described. Provocation test is considered the "gold standard". However, it includes the possibility of severe reactions. We reported two cases of delayed allergic reaction to clindamycin confirmed with a positive lymphocyte transformation test showing this in vitro test like a promising diagnostic method because of its usefulness and safety.

Keywords: Clindamycin· Allergy· Delayed reaction· Lymphocyte transformation test· Diagnosis.

Introduction.

Clindamycin is a lincosamide antibiotic that binds exclusively to the 50s subunit of bacterial ribosomes and suppresses intracellular protein synthesis. It is widely used in the prophylaxis and treatment of infections due to its broad spectrum of antimicrobial activity. Hypersensitivity to clindamycin seems to be not very common (less than 1% of drug-allergic reactions [1]) which are mostly non-immediate or delayed ones: Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) [2], Symmetric drug-related intertriginous and flexural exanthema (SDRIFE) [3], drug-induced hypersensitivity syndrome (DIHS) [4], generalized maculopapular exanthema [5], anaphylaxis [6] and acute generalized [7] and localised exanthematous pustulosis [8] have been described.

The diagnostic approach includes a detailed medical history, clinical examination, and skin testing and/or oral challenge with clindamycin. Lymphocyte transformation test (LTT) in general has been shown to be more sensitive than skin testing for non-immediate reactions diagnosis [9,10,11], although there are only few studies that analyze the LTT in

allergy to betalactams or quinolones, so its diagnostic value for other antibiotics remains uncertain [12].

We present two different cases of delayed allergic reaction to clindamycin with maculopapular exanthema in which LTT confirmed clindamycin as the culprit agent.

Clinical cases.

Case 1: A 64-year-old woman who came to the allergy department from the emergency department to be studied for a possible allergy to clindamycin. She denied any past history of urticarial episodes or adverse reactions to the ingestion of food or medication. In September 2013 she took clindamycin for a dental infection. After the fifth dose she developed a cutaneous eruption that began in the thighs, with erythematous pruritic plaques that spread through her back and trunk day by day in spite of the clindamycin discontinuation. She was treated with high doses of prednisone for several weeks. She had no fever or systemic symptoms. Laboratory studies did not find leukocytosis, eosinophilia, kidneys failure or elevated liver enzymes. Skin prick test (150 mg/ml) and intradermal test (1.5mg/ml and 15 mg/ml) [13, 14, 15] with clindamycin results were negative after 30 minutes, 24 and 48 hours. Patch testing of skin with 10% clindamycin in petrolatum at 48 and 96 h according to the Spanish Society of Allergy and Clinic Immunology criterion was also negative [13]. As the patient refused to undergo any other in vivo tests, an oral challenge with the culprit drug was not performed.

Case 2: A 56-year-old man, who came to the allergy department from his general practitioner to study a possible allergy to clindamycin. He had not allergic background. His medical history was significant for hypertension, type 2 diabetes and hyperlipidemia. His long-term drug therapy consisted of metformin, acetylsalicylic acid, olmesartan/amlodipine and simvastatin. In January 2018 he had dermatitis in his legs by

the application of hydrocortisone with broponol. He received clindamycin as treatment and three days after the cutaneous eruption spread through his body, except the head, with desquamation in his lower limbs. He was studied in dermatology being diagnosed with toxicodermia. He improved with systemic prednisone but he went worse after prednisone discontinuation. Laboratory studies found leukocytosis and eosinophilia (2100/ μL) but no kidney failure or elevated liver enzymes. Cutaneous biopsy was not performed. In March 2018 he arrived to allergy department being asymptomatic. Patch testing of skin with 1% clindamycin in petrolatum was negative at 48 and 96 hours.

Material and methods.

In an attempt to clarify the underlying mechanism, 3 months after the reaction, we performed the LTT with clindamycin in both patients. The LTT using 6 different concentrations of clindamycin (0.01-250 μg/ml) was performed.

Briefly, proliferation of lymphocytes from the allergic patients was measured as previously described [16, 17, 18]. Mononuclear cells were separated over a density gradient (Histopaque-1077, Sigma-Aldrich) from fresh peripheral blood and were incubated for 6 days at 10^6 cells/mL in triplicate with 6 different concentrations of clindamycin. Phytohemagglutinin (5 μg/mL) was used as a positive control. For the final 18 hours of the incubation period, proliferation was determined by the addition of [^{3}H] thymidine (0.5 μCi/well). Stimulation index (SI), defined as the ratio between the mean values of counts per minute in cultures with antigen and those obtained without antigen, calculate the proliferative responses. The positive response is defined as an SI ≥2.

Results.

In both patients, the result of the LTT was positive, with a SI of 5.9 at a concentration of 0.01 μg/ml and with SI of 13.1 at a concentration of 250 μg/ml, respectively (table I).

LTT with clindamycin in four controls showed no proliferative responses. From this finding, we diagnosed maculopapular rash as delayed hypersensitivity to clindamycin.

Discussion.

In drug hypersensitivity, the diagnostic approach usually includes a detailed clinical history, which is not always possible and can be unreliable. This is usually followed by appropriate in vivo test (skin and/or drug provocation test). Although skin testing with this drug is considered to be highly sensitive and rather safe, cutaneous and systemic reactions have been described [19]. Moreover, patch testing sensitivity in contact allergy is between 60-80%. They are also helpful for the study of some non-immediate adverse drug reactions, although they suffer from a lack of standardization. Sensitivity in non-beta-lactam antibiotics is low and there is also a high rate of false positive results due to irritation [9]. Provocation test is considered the "gold standard" to establish or exclude the diagnosis of allergy to a certain substance, however, it includes the possibility of severe reactions.

Given the limitations of in vivo tests, in vitro tests can be helpful for diagnosis, and they are the only alternative method when in vivo tests are not recommended. They are essential to clarify drug allergy status, despite having suboptimal sensitivity. The most widely employed technique for diagnosing non-immediate reactions is LTT. Its main disadvantage is that an in vitro proliferation of T cells to a drug is difficult to transfer to the clinical situation and that the test *per se* is rather cumbersome and technically demanding. In addition, its sensitivity is limited (for β-lactam allergy it is in the range of 60-70%), although it is higher than that of other test for drug hypersensitivity diagnosis [9]. LTT in general has been shown to be more sensitive than skin testing for non-immediate reactions diagnosis [9, 12].

In 2012, Nakamura et al [4] reported a case of delayed DIHS/DRESS due to clindamycin intake with a positive LTT (stimulation index of 17.5 the tenth day after the DRESS start) but also with a positive skin patch test.

To our knowledge, these are the first cases reported of maculopapular rash induced by clindamycin with a positive LTT and negative skin tests and since then, no other positive results have been published. However, further studies are needed to assess the validity of the LTT in allergic reactions to clindamycin.

Conflict of interest.

The authors declare that they have no conflict of interest.

Acknowledgments

References:

1. Doña I, Blanca-López N, Torres MJ, García-Campos J, García-Núñez I, Gómez F, et al. Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. J Investig Allergol Clin Immunol. 2012;22:363-71.
2. Miller Quidly A, Bookstaver PB, Gainey AB, Gainey MD. Fatal clindamycin-induced drug rush with eosinophilia and systemic symptoms (DRESS) syndrome. Pharmacotherapy. 2012; 32:e387-92.
3. Tan SC, Tan Jw. Symmetrical drug-related intertriginous and flexural exantema. Curr Opin Allergy Clin Immunol. 2011 Aug;11(4):313-8.
4. Nakamura Y, Wakamatsu K, Muto M. Drug-induced Hypersensitivity Syndrome Induced by Clindamycin. Acta Derm Venereol. 2013;93:83-4.
5. Monteagudo B, Cabanillas M, Iriarte P, Ramírez-Santos A, León-Muinos E et al. Clindamycin-induced maculopapular exantema with preferential involvement of

striae distensae: a Koebner phenomenon? Acta Dermatovenerol Croat. 2018 Apr;26(1):61-3.

6. Bulloch MN, Baccas JT, Arnold S. Clindamycin-induced hypersensitivity reaction. Infection. 2016 Jun;44(3):357-9.
7. Alniemi DT, Wetter DA, Bridges AG, el-Azhary RA, Davis MD et al. Acute generalized exanthematous pustulosis: clinical characteristics, etiologic associations, treatments, and outcomes in a series of 28 patients at Mayo Clinic, 1996-2013. Int J Dermatol. 2017 Apr;56(4):405-14.
8. De Cruz R, Ferguson J, Wee JS, Akhras V. Acute localized exanthematous pustulosis (ALEP) induced by clindamycin in pregnancy. Australas J Dermatol. 2015 Aug;56(3):e55-8.
9. Doña I, Torres MJ, Montañez MI, Fernández TD. In vitro diagnostic testing for antibiotic allergy. Allergy Asthma Immunol Res. 2017;9:288-98.
10. Monge-Ortega OP, Cabañas R, Fiandor A, Domínguez-Ortega J, González-Muñoz et al. Overlap between DRESS syndrome and exantema induced by sulfadiazine in a patient treated with suflamethoxaxole: utility of the lymphocyte transformation test for identification of the culprit drug. J Investig Allergol Clin Immunol 2018; 28:132-4.
11. Antolin-Amerigo D, Sánchez-González MJ, Barbarroja-Escudero J, Ayuso-Peralta L, Bellón-Heredia T et al. Delayed hypersensitivity reaction to oral dimethyl fumarato. J Investig Allergol Clin Immunol 2018; 28:201-3.
12. Mayorga C, Celik G, Rouzaire P, Whitaker P, Bonadonna P et al. *In vitro* test for drug hypersensitivity reactions: an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2016;71:1103-34.

13. Dávila González IJ, Jáuregui Presa I, Olaguibel Rivera JM, Zubeldia Ortuño JM. Tratado de Alergología. 2a Ed. Majadahonda (Madrid): Ergon; 2016.
14. Empedrad R, Darter AL, Earl HS, Gruchalla R. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. J Allergy Clin Immunol. 2003;112:629-30.
15. Gonzalo-Garijo MA, De Argila D. Erytrodermia due to Aztreonam and Clindamycin. J Investig Allergol Clin Immunol. 2006; 16:210-1.
16. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. Allergy. 2004; 59:809-20.
17. Domínguez-Ortega J, Entrala A, Pola-Bibian B, González-Muñoz M, Fiandor A, Quirce S. Delayed allergic reaction to acenocoumarol with a positive lymphocyte transformation test. J Investig Allergol Clin Immunol. 2016; 26:273-4.
18. González-Cavero L, Domínguez-Ortega J, González-Muñoz M, Mayor-Ibarguren A, Tomás M, Fiandor A, et al. Delayed allergic reaction to terbinafine with a positive lymphocyte transformation test. J Investig Allergol Clin Immunol. 2017; 27:136-7.
19. Papakonstantinou E, Müller S, Röhrbein JH, Wieczorek D, Kapp A, Jakob T, Wedi B. Generalized reactions during skin testing with clindamycin in drug hypersensitivity: a report of 3 cases and review of the literature. Contact Dermatitis. 2018 Apr;78(4):274-280. doi: 10.1111/cod.12956. Epub 2018 Jan 22.

Table I.

Stimulation index with different concentrations of clindamycin, in our two patients (1 and 2), and in four **non-allergic to clindamycin** controls.

	Stimulation index					
Clindamycin	0.01 µg/ml	0.1 µg/ml	1 µg/ml	10 µg/ml	100 µg/ml	250 µg/ml
Patient 1	5.9	2.4	1.8	1.2	2.3	–
Patient 2	–	–	2.8	1.1	6.4	13.1
Controls (n=4) mean±SD	–	–	0.8±0,2	0.9±0.5	0.8±0.3	0.8±0.2

SD: standard deviation µg/ml: micrograms/milliliter