

Desensitization to Co-trimoxazole in a Patient With Fixed Drug Eruption

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■ Abstract

Although co-trimoxazole is a major cause of fixed drug eruption, there are no reports in the literature of desensitization protocols for co-trimoxazole in such patients. We present the case of an 85-year-old woman with a fixed drug eruption to co-trimoxazole. Since she needed co-trimoxazole therapy for treatment of infection of a prosthetic hip by *Staphylococcus aureus*, she underwent allergy testing with co-trimoxazole and its components sulfamethoxazole and trimethoprim. Allergy tests were all negative and a diagnosis of nonallergic hypersensitivity reaction to co-trimoxazole was made. Based on previous experience, we decided to attempt a desensitization protocol with co-trimoxazole. After 10 days, the patient could receive 800 mg of sulfamethoxazole and 160 mg of trimethoprim twice a day and no adverse reactions were observed. We suggest that desensitization protocols with co-trimoxazole be considered in patients with fixed drug eruption, especially when there are no alternative drugs.

Key words: Fixed drug eruption. Nonallergic drug hypersensitivity. Co-trimoxazole. Oral desensitization.

■ Resumen

A pesar de que el cotrimoxazol es la principal causa de erupción fija inducida por fármacos no existe información en la literatura sobre los protocolos de desensibilización de cotrimoxazol. Presentamos el caso de una mujer de 85 años de edad con erupción fija inducida por cotrimoxazol. Puesto que la mujer necesitaba tratamiento con cotrimoxazol para tratar una infección por *Staphylococcus aureus* de una prótesis de cadera, se le practicaron pruebas alergológicas con cotrimoxazol y sus componentes: sulfametoxazol y trimetoprima. Las pruebas alergológicas fueron todas negativas y se le diagnosticó una reacción de hipersensibilidad no alérgica al cotrimoxazol. Basándonos en nuestra experiencia previa, decidimos intentar llevar a cabo un protocolo de desensibilización con cotrimoxazol. Pasados 10 días, fue posible administrarle a la paciente 800 mg de sulfametoxazol y 160 mg de trimetoprima dos veces al día sin que se observaran reacciones adversas. Por lo tanto, sugerimos que se practiquen protocolos de desensibilización con cotrimoxazol a los pacientes con erupción fija inducida por los medicamentos, y en particular en aquellos casos en los que no existan fármacos alternativos.

Palabras clave: Erupción fija inducida por fármacos. Hipersensibilidad a los fármacos no alérgica. Cotrimoxazol. Desensibilización oral.

Introduction

Fixed drug eruption (FDE) is characterized by recurrent round, erythematous or violaceous plaques measuring 2 to 10 cm in diameter and with well-defined borders that appear in the same location each time the culprit drug is taken and resolve after discontinuation of the drug [1]. It can be caused by many different drugs (mainly sulfonamides, tetracyclines, naproxen, and salicylates) [1-3] and chemically unrelated drugs can cause FDE in the same patient [2].

The pathogenic mechanisms of FDE are still not well defined, but CD8⁺ T cells seem to play a major role in initiating epidermal injury by producing interferon γ and interacting with other inflammatory cells. Even if a drug is responsible for

activation of CD8⁺ T cells, it does not seem to be the antigen recognized by CD8⁺ T cells [1]. The reason for recurrence of lesions at the same site may be explained by the persistence in situ of CD8⁺ memory T cells [1]. The involvement of CD8⁺ T cells may suggest a role for cell-mediated hypersensitivity in the pathogenesis of FDE.

Co-trimoxazole (trimethoprim plus sulfamethoxazole) is one of the most commonly prescribed sulfonamide drugs. It is effective against gram-positive and gram-negative bacteria and various opportunistic pathogens. Unfortunately, adverse reactions such as erythematous rashes, urticaria, fever, neutropenia, thrombocytopenia, Lyell syndrome, Stevens-Johnson syndrome, and on rare occasions anaphylactic shock occur during its use and co-trimoxazole is a major cause of FDE [1,3].

When a drug hypersensitivity reaction occurs and use of the culprit drug is necessary, various desensitization protocols have been carried out successfully. In the literature, there are reports of desensitization to allopurinol in patients with FDE [4-6] but there are none of desensitization protocols to co-trimoxazole in such patients.

Case Description

An 85-year old woman developed a round violaceous plaque on the volar surface of the right forearm during co-trimoxazole therapy prescribed several years previously. The plaque disappeared following discontinuation of the drug, but symptoms reappeared at a later date following administration of co-trimoxazole. A diagnosis of FDE to co-trimoxazole was made by a dermatologist and the patient was forbidden to take the drug again.

The patient was seen in our allergy department in May 2007 since she needed co-trimoxazole therapy for infection of a hip prosthesis with *Staphylococcus aureus*. An oral antibiotic was needed since the patient had to undergo chronic antibiotic therapy, and according to the antibiotic assay, co-trimoxazole was the only oral drug available.

The patient underwent allergy testing with co-trimoxazole and with its components, sulfamethoxazole and trimethoprim. Skin prick tests (SPT) were performed using powdered co-trimoxazole tablets and sulfamethoxazole and trimethoprim powders (Sigma-Aldrich, Steinheim, Germany) dissolved in saline, according to the recommendations of the European Network for Drug Allergy (ENDA), the interest group on drug hypersensitivity of the European Academy of Allergology and Clinical Immunology [7]. Readings were taken after 20 minutes. Histamine was used as a positive control and saline as a negative control. Immediate reactions with a diameter at least 3 mm larger than negative controls were considered positive for SPT.

Patch tests were performed using the same drugs as for SPT according to ENDA recommendations [7]. Patches were applied to the interscapular region and evaluated at 48 and 72 hours according to the recommendations of the American Academy of Dermatology [8]. The co-trimoxazole tablet powder and the sulfamethoxazole and trimethoprim powders were used at a concentration of 20% (weight by weight) in petrolatum. Commercially available self-adhesive hypoallergenic gauze strips (Curatest, Lohmann, Neuwied, Germany) were used as supports.

The results of patch tests and SPT were all negative, leading to a diagnosis of nonallergic hypersensitivity reaction to co-trimoxazole.

Desensitization protocols to allopurinol have already been successfully carried out in patients with FDE to this drug [4-6]. Because of these successful reports, we decided to attempt a previously successful desensitization protocol with co-trimoxazole [9]. After informed consent was obtained from the patient, oral desensitization treatment was begun (Table).

On the first day, the patient received 0.2 µg of sulfamethoxazole and 0.04 µg of trimethoprim, and on the tenth day we reached the final dose of 1600 mg of sulfamethoxazole

Table. Protocol for Oral Desensitization to Co-trimoxazole

Day	Doses	Cumulative Daily Dose
1	0.02 µg SS + 0.004 µg TR 0.04 µg SS + 0.008 µg TR 0.06 µg SS + 0.012 µg TR 0.08 µg SS + 0.016 µg TR	0.2 µg SS + 0.04 µg TR
2	0.2 µg SS + 0.04 µg TR 0.4 µg SS + 0.08 µg TR 0.6 µg SS + 0.12 µg TR 0.8 µg SS + 0.16 µg TR	2 µg SS + 0.4 µg TR
3	2 µg SS + 0.4 µg TR 4 µg SS + 0.8 µg TR 6 µg SS + 1.2 µg TR 8 µg SS + 1.6 µg TR	20 µg SS + 4 µg TR
4	20 µg SS + 4 µg TR 40 µg SS + 8 µg TR 60 µg SS + 12 µg TR 80 µg SS + 16 µg TR	200 µg SS + 40 µg TR
5	200 µg SS + 40 µg TR 400 µg SS + 80 µg TR 600 µg SS + 120 µg TR 800 µg SS + 160 µg TR	2 mg SS + 400 µg TR
6	2 mg SS + 400 µg TR 4 mg SS + 800 µg TR 6 mg SS + 1.2 mg TR 8 mg SS + 1.6 mg TR	20 mg SS + 4 mg TR
7	20 mg SS + 4 mg TR 40 mg SS + 8 mg TR 60 mg SS + 12 mg TR 80 mg SS + 16 mg TR	200 mg SS + 40 mg TR
8	40 mg SS + 8 mg TR 80 mg SS + 16 mg TR 160 mg SS + 32 mg TR 320 mg SS + 64 mg TR	600 mg SS + 120 mg TR
9	200 mg SS + 40 mg TR 200 mg SS + 40 mg TR 400 mg SS + 80 mg TR	800 mg SS + 160 mg TR
10	800 mg SS + 160 mg TR 800 mg SS + 160 mg TR	1600 mg SS + 320 mg TR

Abbreviations: SS, sulfamethoxazole; TR, trimethoprim.

and 320 mg of trimethoprim. From the first to the ninth day, each dose was administered every 30 minutes, while on the tenth day each dose was administered every 3 hours. No adverse reactions were observed during the desensitization protocol and at the time of writing the patient is undergoing therapy with co-trimoxazole with no side effects after a period of 60 days.

Discussion

Desensitization protocols have been carried out successfully with co-trimoxazole in cases in which an adverse reaction to the drug would otherwise preclude its use for prophylaxis or treatment of specific infections [9], especially in patients infected with the human immunodeficiency virus [10,11]. The oral route is preferable, since it is reported to be associated with a lower incidence of adverse reactions during penicillin desensitization [12].

The exact mechanism of tolerance induction is still poorly understood. It is hypothesized that low, continuous incremental doses of antigen may result in univalent occupancy of receptors, so that antibodies or immune cells cannot be crosslinked by higher doses of co-trimoxazole. Such a mechanism has been demonstrated in other situations [13].

It has recently been shown that CD8⁺ cells are the final effector of epidermal injury in FDE [1] and that CD25⁺ CD4⁺ T cells may play a role in the induction of desensitization to FDE [14].

Desensitization protocols have been successfully used for IgE-mediated allergy to penicillins [12,13], but it is very difficult to desensitize cell-mediated allergy. Since it is possible to desensitize patients with FDE, cell-mediated hypersensitivity may not play a major role in the pathogenesis of the disease. However, further studies are needed to clarify this point.

This is the first reported case of tolerance induction to co-trimoxazole in a patient with FDE. Our results with this patient suggest that desensitization protocols with co-trimoxazole should also be considered in patients with FDE, especially when there are no alternative oral drugs.

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