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Fixed drug eruption induced by indapamide. Cross-reactivity with sulfonamides

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SUMMARY

Indapamide is a nontiazidic sulfonamide diuretic which has not been previously reported as a cause of fixed drug eruption. We describe a patient who experienced several episodes of fixed drug eruption during treatment with indapamide. The diagnosis was confirmed by positive controlled oral challenge test. The possible existence of cross-reactivity with other sulfonamide derivatives was investigated by controlled oral challenge test with sulfamethoxazole, sulfadiazine and furosemide, with the tests with sulfamethoxazole and sulfadiazine resulting positive.

Key words: Fixed drug eruption - Indapamide - Cross-reactivity paraamine group - Antiinfectious sulfonamides

INTRODUCTION

Fixed drug eruption (FDE) is a peculiar dermatosis, which is mainly considered pathognomonic of drug allergy. Sulfonamides are one of the most frequent causes of FDE (1-3), but indapamide, a nontiazidic sulfonamide diuretic, has never been involved in its etiology. We report a patient with relapsing episodes of FDE with indapamide also reproduced by controlled oral challenge test with antiinfectious sulfonamides.

MATERIALS AND METHODS

Case report

A 68-year-old woman without any previous history of allergic diseases was referred for several episodes of FDE while she was under treatment with indapamide for hypertension. The first time, she had a single painful burning oval erythematous-violaceous lesion located on the back of the left hand. Months later, she suffered a similar lesion in the same area. Three months later she presented a comparable picture but with several lesions on both forearms, lower lip and left leg. The eruptions always cleared up spontaneously within days, leaving no residual lesions. The patient denied the intake of other drugs and declared that the eruption appeared few hours after the administration of indapamide. In spite of this, she had been tolerating the hypotensor drug between episodes until the last stage. At this point her dermatologist ordered the withdrawal of the drug because of a clinical suspicion of FDE induced by indapamide. Since then she has not presented any new FDE.

Controlled oral challenge test

A single-blind controlled oral challenge test was carried out following the method suggested by Kaupinen (4). We started with an eighth of the therapeutic dose of the drug in question and a quarter of the other drugs (sulfamethoxazole, sulfadiazine and furosemide). A new dose was administrated every 48 h. When the test was positive, the challenge was performed with another drug at least 2 months later in order to avoid a supposed refractory period.

RESULTS

The controlled oral challenge test with furosemide was negative. The lesions of FDE were elicited after the administration of sulfamethoxazole (back of the left hand and both forearms), sulfadiazine (forearms, left leg and lower lip) and indapamide (back of the left hand, forearms and lower lip).

DISCUSSION

Fixed drug eruption is characterized by the appearance of one or several erythematous or erythematous-violaceous lesions with well defined borders a few hours after the administration of the responsible drug. Blister formations within the lesions are relatively frequent. A grey-brown pigmented spot usually remains after healing and may often persist for months or years (1). After an additional dose of the etiological drug, the eruption may appear at the same sites and sometimes together with new lesions of similar morphology (1), even though the exanthema might not reappear (2, 5). On the other hand, chemically related compounds to the responsible drug can also induce the recurrence of the FDE (1, 2, 6).

In our patient, indapamide was the only drug involved, and the patient did not present new signs of FDE after its withdrawal. The fact that she tolerated indapamide between the FDE episodes might however question its etiological responsibility. Nevertheless, as also found in other allergic clinical pictures, in FDE the existence of a refractory period that could last for months (2, 5), during which the involved drug could be administered without the reappearance of the exanthematic lesions, either totally (2, 5) or partially (7), has been previously described. Moreover, in our patient, the lesions were reproduced by controlled oral challenge test with sulfonamides and indapamide. Several types of exanthema caused by indapamide, most of them mild (8), have been published, though erythema multiform and toxic epidermal necrolysis have also been expressed (8-10). This is not surprising for a compound chemically related to sulfonamides. However, to our knowledge, indapamide had never been previously described as a cause of FDE, with diuretics showing an exceptional etiology of this dermatosis (3).

In the pathogenesis of FDE the cross-sensitivity among drugs of similar chemical structure can be observed but less frequently than in other kinds of drug allergy (1). Cross-reactivity has been demonstrated among different antiinfectious sulfonamides (11), but not between these and other paraamino compounds, furosemide (11) among them. Our patient tolerated furosemide; in other exanthemas induced by indapamide, the patients tolerated both furosemide and other related diuretics (8), in spite of the similar chemical structure among them.

This suggests that the reaction would not be directed against the lateral sulfonamide chain but, possibly, against a metabolite of the drug (8). Although the cross-reactivity among paraamino compounds has only been clearly established in contact dermatitis, from a practical point of view, it would be advisable, in any kind of allergic eruption to avoid all the drugs that belong to the para-aminobenzene-sulfonamide group in order to prevent relapses. A case of toxic epidermal necrolysis by indapamide in a patient with an allergic history to sulfonamides has been published (10), which would emphasize the great importance of always considering the possibility of cross-reactivity amongst drugs in allergic drug dermatosis.

RESUMEN

La indapamida es un diurético no tiazídico perteneciente al grupo de los compuestos para aminosulfonamida. Se han descrito diversos tipos de exantemas cutáneos relacionados con su empleo, sin embargo no se ha comunicado ningún caso de exantema fijo producido por este fármaco. Presentamos el caso clínico de una mujer de 68 años que sufrió varios cuadros de exantema fijo mientras seguía un tratamiento hipotensor mantenido con indapamida. La enferma toleró dicho medicamento entre los distintos brotes del exantema, lo que podría atribuirse a la administración del fármaco durante el periodo refractario inducido tras las agudizaciones del exantema, hecho descrito previamente en esta dermatosis. El exantema fijo remitió definitivamente al suspender el fármaco. El diagnóstico etiológico se confirmó mediante la prueba de provocación oral controlada a simple ciego con indapamida, reproduciéndose las lesiones de exantema fijo en los lugares referidos por la paciente en la historia clínica. Para evaluar la existencia de reactividad cruzada entre indapamida y otros compuestos del grupo para amino, se realizaron pruebas de provocación oral controlada, a simple ciego, con sulfametoxazol, sulfadiazina y furosemida, resultando positivas con ambas sulfonamidas antiinfecciosas y negativa con furosemida. Estos resultados sugieren la existencia, en el exantema fijo, de sensibilidad cruzada entre indapamida y sulfamidas antiinfecciosas, pero no entre ambos diuréticos a pesar de la similitud química estructural existente entre ellos. No obstante, estos hallazgos deberían ratificarse estudiando amplias series. En conclusión, aunque la reactividad cruzada entre diversos compuestos del grupo para amino sólo haya sido establecida claramente en la dermatitis de contacto –y a pesar de que en el exantema fijo no se haya encontrado previamente sensibilidad cruzada entre sulfamidas antiinfecciosas y otros fármacos del grupo–, los resultados del estudio realizado en esta paciente sugieren que en esta dermatosis se deberían evitar todos los componentes del grupo, salvo que se demostrara su tolerancia en aquellos casos en que fuera imprescindible su empleo terapéutico.

Palabras clave: Exantema fijo - Indapamida - Reactividad cruzada grupo paraamino - Sulfonamidas antiinfecciosas

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