LETTERS TO THE EDITOR

Indapamide-Associated Stevens-Johnson Syndrome

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To the Editor:

Indapamide is a non-thiazide sulfonamide derivative with an indole ring. It belongs to the diuretic group of drugs and is widely used in antihypertensive therapy. The most frequent side effects are electrolyte imbalances and prerenal acute renal failure. Several types of occupational cutaneous exanthemas have also been described, among which Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis stand out due to their severity.

We present the case of a 62-year-old man, with no known drug allergies, admitted with a fever of 39°C, acute renal failure with oliguria/anuria, anasarca, and cutaneous lesions.

Physical examination showed erythematous maculopapular lesions, some of which had a ring-like shape and a tendency to merge. They were located on the trunk, head, palms, and soles, as well as the oral, nasal, and genital mucosa (Figures 1 and 2).

Seven days before admission he had begun treatment with indapamide for recently diagnosed hypertension; he did not report taking any other medication. Skin biopsy showed a lymphohistiocytic perivascular infiltrate in the superficial dermis, along with eosinophils, foci of lymphocytic exocytosis, vacuolation of basal cells, and cellular necrosis in the epidermis and hair follicles.

Treatment was begun with intravenous corticosteroids (methylprednisolone 60 mg every 6 hours) and topical corticosteroids, and indapamide was withdrawn. The cutaneous lesions completely resolved, without scarring, and renal function returned to normal. Three months later he underwent patch tests using the Spanish Contact Dermatitis Research Group (Grupo Español de Investigación en Dermatitis de Contacto) standard battery, with negative results at 48 hours and 96 hours. Patch tests with indapamide (1:1000 in petrolatum) produced a positive reaction (++) at 48 hours and 96 hours.

The incidence of SJS is estimated to be between 1 and 3 cases per million inhabitants per year, and mortality among those affected is approximately 5%. In the case series analyzed by Laguna et al., mortality due to SJS was 0%. It is clinically characterized by erythematous or purpuric macular target lesions and vesiculobullous lesions—either disseminated or predominating on the trunk—that lead to detachment affecting less than 10% of the body surface, and it is frequently associated with mucosal and visceral lesions.

It is currently thought that SJS is unrelated to exudative erythema multiforme from a clinical, etiologic, or histopathologic standpoint. The mechanism by which a drug is capable of inducing epidermal necrosis is partly understood. First, there seems to be individual susceptibility to develop this type of cutaneous drug reaction. It has also been suggested that these patients metabolize the drug in an anomalous way, giving rise to the active metabolites affecting less than 10% of the body surface, and it is frequently associated with mucosal and visceral lesions.

Figure 1. Crusted lesions on the nasal pyramid and chin with mildly affected lips and nostrils.

Figure 2. Erythematous, maculopapular, ring-like semi-confluent lesions on the trunk.
responsible for the epidermal damage. Immunologic mechanisms appear to be more relevant; it is thought that the suspect drug behaves like a hapten that, in conjugation with epidermal proteins, acts as an antigen to elicit the cytotoxic cellular immune response, leading to epidermal cell necrosis that apparently takes place in the form of apoptosis. It is currently accepted that many cases of SJS are due to drug reactions, although in 4% of cases no obvious causal factor has been identified. The drugs that most frequently trigger it are sulfonamides, anticonvulsants, nonsteroidal anti-inflammatory drugs, and allopurinol.

Indapamide has been reported as the cause of SJS on 1 occasion; the diagnosis was established by observing how the symptoms developed over time and no patch tests were performed. Two cases of indapamide-associated toxic epidermal necrolysis have been described. Other cutaneous reactions to indapamide described in the literature include erythema multiforme, exanthema and fever, secondary pigmented pemphigus foliaceus lesions, and drug-induced exanthema.

The usefulness of patch tests has been well documented in the diagnosis of delayed hypersensitivity drug reactions, which are the main mechanism responsible for some forms of cutaneous drug reaction, such as exanthemas, erythema multiforme, and lichenoid and lupus-like reactions. In the case of SJS, they are of limited value as the multifactorial mechanisms are difficult to reproduce, and although they are highly specific, with few false-positive results, their sensitivity is low, around 9%, as reported in the literature. Other tests used in the etiologic diagnosis of cutaneous drug reactions are the in vitro tests (radioallergosorbent test, lymphocyte transformation test, lymphocyte toxicity tests, etc). These are more complex to perform and are not available in all centers. The importance of diagnosis by patch testing is emphasized, as it provides etiologic confirmation and avoids the risks of oral challenge tests. Patch testing should be adopted as a routine technique, while taking all the precautions necessary when performing any type of skin test.

References