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Systemic Absorption of Topical Tacrolimus in Metastatic Crohn Disease With Skin Ulcers☆

Absorción sistémica de tacrolimus tópico en enfermedad de Crohn metastásica con úlceras cutáneas

To the Editor:

We present the case of a 54-year-old woman with colonic Crohn disease with metastatic Crohn lesions affecting the perianal region and skin folds. During an exacerbation she presented ulcerated intertrigo in the intergluteal, inguinal, and abdominal folds (measured surface area of ulceration of 155 cm^2, done with ImageJ software). After the administration of fentanyl and lorazepam for analgesia and anxiolysis, daily lavage was performed with soap and water and normal saline, and 60 g of topical 0.1% tacrolimus was applied using an impregnated swab. After 15 days, the nursing staff developed a new method for the daily application of the cream, emptying the contents of the tube into a pressure-lavage syringe and applying the preparation directly to the ulcers. Ten days later a moderate kidney failure was detected (elevation of creatinine from 1.4 mg/dL to 2.4 mg/dL and of urea from 69 mg/dL to 110 mg/dL). This was interpreted as prerenal failure and was treated by increasing fluid intake and intravenous fluids administration. However, suspecting the possible implication of tacrolimus in the deterioration of renal function, blood tests were performed and tacrolimus levels of 9.7 ng/mL were detected in whole blood (the therapeutic range after solid organ transplant is 5-20 ng/mL). The application of the cream was interrupted for 24 hours, and the level fell to 5.3 ng/mL. The concentration of the topical tacrolimus formulation was then reduced to 0.03%. Subsequent controls showed almost undetectable tacrolimus concentrations, and the serum creatinine fell to previous values.

Discussion

Cutaneous manifestations of CD occur in 9% to 23% of patients.[1] Perianal fissures and fistulas are probably the most common lesions (17%-43% of patients).[2] Metastatic CD is defined as the presence of compatible granulomatous lesions in skin that is not contiguous with the digestive tract.[3]

Topical tacrolimus administered once a day has shown a limited effect on the clinical course of fistulas and ulcers, achieving remission in 36% of patients and some response in 29%.[4] Regarding its side effects, Shah et al.[5]considered the most common to be mild pruritus at the site of application; they added that absorption through skin lacking the epidermal barrier or through the mucosas is usually low, giving rise to low or undetectable blood levels. Other authors have described elevated blood concentrations of tacrolimus after its application to the skin. Faisal[6] reported a level of 14.7 ng/mL associated with nausea, paresthesia, and dizziness, which he attributed to absorption through the gastrointestinal mucosa in a case of perianal CD. Russell et al.[7]described a patient with orofacial involvement in whom the application of 0.05% tacrolimus to an area of 1-2 cm^2 produced blood concentrations of 9 ng/mL and the patient developed thoracolumbar herpes zoster. Olson et al.[8] defined a series of risk factors for increased transcutaneous absorption of tacrolimus: the surface area involved, the absence of the skin barrier, and the use of occlusive dressings. Neuman et al.[9] added a further 2 factors: young age and warm skin due to increased circulation. They recommended monitoring tacrolimus blood levels in patients with 1 or more of these factors.

In our patient, the application of topical tacrolimus directly over the skin fold ulcers coincided temporaly matched with a deterioration in her renal function. Other causative factors may be implicated, but tacrolimus blood concentrations of 9.7 ng/mL could certainly have

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contributed to this deterioration; the effect may have been more intense in this patient as she had underlying kidney disease (serum creatinine, 1.4 mg/dL). Dose adjustment and the falling blood levels coincided with the improvement in renal function.

In our patient, absorption of the topical preparation was high as it was applied to ulcers (absent stratum corneum) and to skin folds (occlusive dressing). The progressive fall in tacrolimus blood levels in our patient may be explained not only by the dose reduction (topical 0.03% tacrolimus), but also by the improvement in the lesions and in the barrier properties of the skin.

In summary, we have presented a case of systemic absorption of tacrolimus after topical application, with a deterioration of renal function (a common adverse effect of this drug). This coincided with the direct application of tacrolimus to ulcerated areas (altered skin barrier) and the use of occlusive dressings (skin folds and moist areas). Monitoring tacrolimus blood levels is recommended to avoid side effects associated with unexpectedly high concentrations, particularly in patients with underlying kidney disease. A rational regimen would be to monitor levels weekly for the first month and every 2 weeks or every month thereafter, and at any time that complications are detected.[7]

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Quinacrine: A Treatment Option That Should Not Be Overlooked☆

Quinacrina, un escalón terapéutico que no debemos obviar

To the Editor:

Quinacrine, or mepacrine as it is also known, is a synthetic quinine analog that was the drug of choice for malaria prevention during World War II.[1] It was during this period that its effectiveness in the treatment of connective tissue diseases became obvious, when many soldiers taking the drug to prevent malaria experienced improvements in the symptoms of lupus and rheumatoid arthritis. With the advent of hydroxychloroquine and chloroquine, both of which proved to be more effective antimalarial agents, quinacrine fell into disuse.

Clinical Cases

The patient, a 45-year-old woman (nonsmoker), had been diagnosed with cutaneous lupus erythematosus (CLE) when she was 38 years of age. Six years later her condition met the criteria for systemic lupus erythematosus (SLE). Clinically, her condition was characterized by photosensitivity, malar eruption, scattered erythematous papules (Fig. 1a), and aphthous mouth ulcers. Laboratory test results revealed chronic lymphocytopenia and a positive antinuclear antibody titer of 1:640. Despite treatment with several different topical and systemic agents (prednisone, hydroxychloroquine, methotrexate, and colchicine), the patient never achieved optimal control of the disease. Seven months ago, after quinacrine 100 mg/d was added to her treatment regimen (colchicine 1 mg/d and hydroxychloroquine 200 mg/d), the patient experienced marked

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