LETTER TO THE EDITOR

Tacrolimus toxicity following topical treatment of perianal Crohn's disease: An admonitory anecdote

Dear Sir,

A 23 year old female with a 12 year history of Crohn's disease had received a variety of systemic and biologic therapies, all of which were either of poor efficacy or had been poorly tolerated. Most recently an end ileostomy and rectal stump had been formed, with a view to ileal pouch formation at a later date. However, our patient continued to develop deep ulceration of the anal verge and distal rectum, despite daily application of superpotent topical corticosteroid ointment. A trial of once daily topical application of 1 g tacrolimus ointment (Protopic®, Fujisawa USA, 0.1%) proximal to and on the anal verge resulted in amelioration of symptoms within days. Four weeks later, during routine clinic review, the patient complained of nausea, paraesthesia and light-headedness. Serum tacrolimus level was drastically elevated at (14.7 ng/ml), well above the therapeutic range expected of renal transplant recipients, and remained elevated on repeat testing one week later. Although renal function, electrolytes and blood pressure were unaltered, topical tacrolimus therapy was stopped and levels normalised within one week. Tacrolimus is a calcineurin inhibitor, used as a systemic immunosuppressive agent following solid organ transplantation. Side effects of tacrolimus toxicity include hypertension, renal impairment, gastrointestinal symptoms and central nervous system symptoms. Long-term considerations include a predilection to malignancy, particularly non-melanoma skin cancer and lymphoproliferative disorders. Topical tacrolimus is licensed for use in atopic dermatitis for children and adults over the age of two years with a low risk of systemic toxicity. Furthermore, it is deployed off-license for a variety of other inflammatory dermatoses by dermatologists, including perianal Crohn's disease. Amongst the original case series of 8 children with oral and perianal Crohn's disease, in which 0.05% tacrolimus ointment was used twice daily, tacrolimus levels were undetectable; 7 of 8 patients showed marked improvement within 6 weeks. A subsequent randomised controlled trial of 0.1% twice daily tacrolimus ointment in patients with fistulating or ulcerating perianal Crohn's disease reported undetectable levels in 7 patients applying tacrolimus and levels well below the therapeutic range in two patients (4.2 and 3.6 ng/ml). Three of four patients with ulcerating disease and no patients with fistulating disease responded clinically to the tacrolimus.

Toxicity with complicating varicella infection has been reported following twice daily liberal application of 0.05% tacrolimus in orabase for orofacial Crohn's disease. The toxicity observed in this and our case is likely due to enhanced absorption across the gastrointestinal mucosal surface. To our knowledge, this is the first reported case of tacrolimus toxicity following topical application for perianal Crohn's disease. Clinicians should be wary of the potential for toxicity, particularly in off-label uses of the topical formulation, and carefully consider the need for serial drug level monitoring.

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References

1. BNF. British National Formulary; March 2013.

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