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Topical Ketoconazole does not Potentiate Oral Cyclosporin A in Allergic Contact Dermatitis

JANET McLELLAND and SAM SHUSTER

University Department of Dermatology, Royal Victoria Infirmary, Newcastle, UK

Cyclosporin A is an effective drug but its use is limited by its side effects. Since oral ketoconazole inhibits the metabolism of oral cyclosporin, we set out to find out whether topical ketoconazole would enhance the effect in the skin of oral cyclosporin. Five patients with contact allergic dermatitis (CAD) were given a 6-day course of cyclosporin (1 mg/kg/day) and applied 2% ketoconazole cream to an area on one arm and the inert base to the other. Serial dilutions of the relevant allergen were aplied to the arms at 3 days for 48 hours, and the responses were measured objectively a day later. There was no significant difference between responses at the two sites, indicating that topical ketoconazole does not enable the dose of oral cyclosporin to be reduced in CAD.

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J. McLelland, Dermatology Department, Royal Infirmary, New Durham Road, Sunderland SR2 7JE, UK.

Cyclosporin A is a very effective treatment for many skin disorders including allergic contact dermatitis (1), but its oral use is limited by dose-related unwanted effects, particularly nephrotoxicity, and it has been ineffective topically, presumably because of poor penetration. Cyclosporin is metabolised in the liver by the microsomal mixed function mono-oxygenase system, which can be inhibited by oral ketoconazole (2). Since this enzyme system is also active in the skin (3), we wondered whether its inhibition by topical ketoconazole, which has been shown to penetrate the epidermis (4), would enhance the concentration of cyclosporin in the skin and allow a greater effect from a lower oral dose. We therefore set out to study whether topical ketoconazole would enhance the effect of oral cyclosporin on the allergic contact dermatitis reaction.

MATERIALS AND METHODS

Five patients with contact allergic dermatitis and a positive response using conventional patch testing to one of a variety of common allergens (including nickel, chromate, and thiurams) were studied, using our quantitative method for patch testing to dilutions of common allergens (5). Patients were commenced on a 6-day course of 1 mg/kg/day of cyclosporin A and given 2% ketoconazole cream to apply twice daily to an outlined area on one upper inner arm and inert cream to a symmetrical area on the other arm for 72 h in a single blind design. The dose of 1 mg/kg/day was chosen because we have shown that this suppresses the contact dermatitis response only partially (1). We measured patch test responses quantitatively as previously described (5), using four doubling dilutions of the allergen as supplied for routine patch testing (Trolab) which were made in white soft paraffin and loaded in 5 ml syringes. At 72 h a 5 mm length of allergen of each concentration was applied to a Finn chamber on Scanpor adhesive (Epitest Ltd) and placed symmetrically on both arms within the areas to which ketoconazole or placebo had been applied. The patches were removed after 48 h, and 24 h later the responses were measured as change in skin thickness using Harpenden callipers with one spring removed (6). Results were analysed by analysis of variance.

In eight control patients who were not given oral cyclosporin, patches were applied as above.

RESULTS

We have previously shown a good correspondence between the measured reaction and clinical assessment of response (5). The size of the response to common contact allergens measured as skin thickness showed a direct relationship to the dose of allergen applied ($p < 0.05$). There was no significant difference between the size of the responses at each concentration at sites to which ketoconazole had been applied and sites to which inert cream had been applied. In the eight control patients there was no difference between the ketoconazole- and the placebo-treated sites.

DISCUSSION

Our present findings are in keeping with our previous observation that whereas cyclosporin at a dose of 2.5 mg/kg/day almost completely inhibits the contact allergic response to topically applied allergens (1), at doses of 1 mg/kg/day responses occurred to a range of doses of allergen. Thus topical ketoconazole did not enhance the inhibitory effect of cyclosporin on contact allergic responses, although the dose of cyclosporin we chose would have allowed its detection. We therefore conclude that metabolism of cyclosporin by mixed function mono-oxygenases in human skin is not critical to its effects on the skin, which could be because either the specific sub-group of enzymes responsible for the metabolism of cyclosporin is not present to a significant level in the skin or because cyclosporin has a central, and not a peripheral site of action. Concomitant administration of topical ketoconazole does not permit a reduction in the dose of oral cyclosporin for the treatment of skin disease.

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