

2008

RE: Use With Immunosuppressive Therapies

Dear Health Care Professional;

Thank you for your recent request for information regarding the T.R.U.E. Test® Allergen Patch Test. We hope the following provides you with the information you require.

Systemic Glucocorticoids: Overall, it is best to avoid the systemic administration of immunosuppressive steroids prior to and during patch testing. As you are probably aware, these potent therapeutic agents (when equivalent to 10 mg or more of prednisolone) can suppress positive patch test reactions and increase the risk of false negatives. This overall recommendation is based on historical studies demonstrating reduced patch test reactions in patients receiving 20-40 mg prednisone daily.

Moreover, a recent study (Anveden et al., *Contact Dermatitis* 2004) confirmed suppression of positive patch tests in nickel-allergic patients receiving 20 mg prednisone daily. Therefore, for optimal test results it is recommended that systemic glucocorticoids or other immunosuppressive steroids be suspended for 2 weeks prior to patch testing. Because the biological half-life of these drugs varies from hours to days, circulating plasma levels may require days to weeks to diminish sufficiently.

Drug manufacturers may provide guidance on minimal clearance times. When absolutely necessary to patch test patients early, it is suggested that immunosuppressant therapy be suspended for a minimum of 1 week. For patients in which systemic glucocorticoids cannot be discontinued, patch testing may be performed if required and if the oral dose does not exceed 10 mg prednisolone (or its equivalent). However, under these conditions diminished patch test reactivity and false negatives must be considered when evaluating test results.

Systemic Antihistamines: The effect of systemic antihistamine administration during patch testing with T.R.U.E. TEST is unknown. Although many physicians believe these drugs have little effect on patch test results, conclusive data is limited.

Grob et al. (*Acta Dermato-Venereologica* 1998) reported that oral cetirizine reduced positive reaction intensity, but not clinical interpretation. In contrast,

Motolese et al. (*Contact Dermatitis* 1995) found that oral loratadine reduced reaction intensity and impacted patch test clinical significance. Oral cinnarizine was shown to similarly influence patch test reactions in over onethird of treated patients (Lembo et al., *Contact Dermatitis* 1985). While the applicability of these findings to other antihistamines or to patch testing with T.R.U.E. TEST is unknown, it may be prudent to minimize the potential influence of systemic antihistamines on test results.

Systemic Cyclosporins: Cyclosporins have been shown to inhibit T cell-mediated delayed allergic reactions (Higgins et al., *British Journal of Dermatology* 1990, and *Journal of Dermatological Science* 1991). However, the effect of systemic cyclosporin administration during or prior to patch testing with T.R.U.E. TEST is unknown. Two clinical studies suggest that brief treatment with oral cyclosporins does not impact true positive reactions in patients with widespread eczema (Flori and Andreassi, *Contact Dermatitis* 1994) or excited skin syndrome (Vena et al., *Contact Dermatitis* 1994). It has been suggested that cyclosporins may help distinguish false-positive from true-positive patch test reactions, and as such may be helpful in these patients.

Topical Immunosuppressants: In general, it is best to avoid topically administered glucocorticoids, antihistamines or other immunosuppressants on patch test sites during testing. In addition, the use of topical steroids or immunosuppressants at or near potential test sites should be avoided for at least 1 week prior to patch testing. In contrast, topically applied steroids, antihistamines and immunosuppressants may be used on non-test areas as needed. In a recent study (Alomar et al., *Contact Dermatitis* 2003), treatment of conventional patch test sites with a topical immunosuppressive macrolactam (i.e., tacrolimus ointment) reduced skin responses to test allergens. Similarly, an earlier study (Lembo et al., *Contact Dermatitis* 1989) demonstrated suppression of patch test reactions with a topical steroid (i.e., dexamethasone). In contrast, conventional patch test reactions were not suppressed by the administration of a topical cyclosporin. However, the impact of topical cyclosporins on T.R.U.E. TEST patch test reactions is unknown.

Please let us know if we can provide any further information about patch testing with T.R.U.E. TEST that may be helpful to you or your patients.
Sincerely,



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REFERENCES

1) Clin Exp Immunol. 1986 Dec;66(3):582-9.

Topical cyclosporin A in nickel contact hypersensitivity: results of a preliminary clinical and immunohistochemical investigation.

Aldridge RD, Sewell HF, King G, Thomson AW.

Four out of eighteen (22%) patients with nickel contact sensitivity showed inhibition of skin patch test responses to the allergen in the presence of topical cyclosporin A (CsA; 5% v/v). No systemic drug absorption or side effects were detected. The clinical response to CsA was accompanied by marked diminution of the T cell infiltrate, although no alteration in the helper/suppressor cell ratio was observed. Expression of the Leu 6 marker on epidermal Langerhans cells and of major histocompatibility complex (MHC) class II antigens (HLA-DR, DQ and DP) on lymphocytes and Langerhans cells was unaffected by topical CsA. The incidence of IL-2 receptor positive lymphocytes in all biopsies was too small to ascertain the influence, if any, of CsA. The prospective use and method of application of CsA in immune contact dermatitis and other immunologically-based skin disorders warrants further evaluation.

2) Arch Dermatol Res. 1990;282(6):408-11.

Effects of topical cyclosporin A on guinea-pig toxic contact dermatitis.

Yokoo M, Oka D, Nakagawa S.

Department of Dermatology, Kawasaki Medical School, Japan.

It is known that the topical application of cyclosporin A (CsA) has a significant suppressive effect on allergic contact dermatitis. In this study, we investigated the effect of topical CsA on toxic (non-allergic) contact dermatitis. Topical CsA significantly suppressed the toxic contact reaction to croton oil. This suppressive effect was short-lived and reversible. Significant inhibition of the reaction to croton oil persisted for 3 days after stopping the CsA. The toxic reaction was blocked when CsA was applied within 6 h of the croton oil application, but when application of CsA was delayed until 12 h after the oil application there was no significant suppressive effect. Topical administration of CsA could become a valuable tool for treating toxic and allergic contact dermatitis without producing the adverse reactions caused by systemic therapy.

3) Contact Dermatitis. 1989 Jan;20(1):10-6.

Topical cyclosporine: effects on allergic contact dermatitis in guinea pigs.

Biren CA, Barr RJ, Ganderup GS, Lemus LL, McCullough JL.

Department of Dermatology, University of California, Irvine.

Cyclosporine (CSA) is an effective immunosuppressive agent and is used in tissue transplantation. The present investigation was undertaken to determine the effect of topical delivery of CSA on allergic contact dermatitis in guinea pigs. Topical 15% CSA in an azone (1-dodecylazacycloheptan-2-one)-containing vehicle blocked local elicitation in previously dinitrochlorobenzene (DNCB) sensitized animals that received a single topical application just prior to elicitation. Elicitation was not blocked at a distant site, indicating a local effect of topical CSA. In contrast, topical CSA when applied twice daily for a total of 5 applications during sensitization only, did not block subsequent elicitation. These experiments suggest that cyclosporine may be beneficial in the therapy of human contact dermatitis, as well as other T cell mediated dermatoses.

4) Skin Pharmacol. 1991;4(1):21-8.

Topical application of liposomally entrapped cyclosporin evaluated by in vitro diffusion studies with human skin.

Egbaria K, Ramachandran C, Weiner N.

College of Pharmacy, University of Michigan, Ann Arbor.

The kinetics and extent of uptake of cyclosporin (CSA) in various strata of human cadaver skin upon topical application of several CSA formulations were determined by in vitro diffusion cell experiments. The CSA formulations tested included an oil-in-water emulsion and four liposomal systems. The accumulation of CSA in the stratum corneum at 24 h is in the order: 'skin lipid'

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multilamellar liposomes (MLV) greater than phospholipid MLV approximately 'skin lipid' large unilamellar liposomes (LUV) greater than phospholipid LUV much much greater than emulsion. The total amount of drug in the deeper stratum corneum and deeper skin strata at 24 h is in the order: phospholipid MLV greater than 'skin lipid' MLV greater than phospholipid LUV greater than 'skin lipid' LUV greater than emulsion. Whereas 'skin lipid' liposomes were more effective than phospholipid-based liposomes in depositing drug in deeper skin strata for rodent species (mouse and guinea pig), the opposite effect was observed for human cadaver skin. More importantly, all the liposomal formulations tested were far more effective than the emulsion formulation in depositing CSA into the skin.

5) Arch Dermatol. 1969 Apr;99(4):380-9.

Influence of oral prednisone on eczematous patch test reactions.

O'Quinn SE, Isbell KH.

6) Br J Dermatol. 1972 Jan;86(1):68-71.

A study of the effect of prednisone and an antihistamine on patch test reactions.

Feuerman E, Levy A.

Contact Dermatitis. 2004 May;50(5):298-303.

Oral prednisone suppresses allergic but not irritant patch test reactions in individuals hypersensitive to nickel.

Anveden I, Lindberg M, Andersen KE, Bruze M, Isaksson M, Liden C, Sommerlund M, Wahlberg JE, Wilkinson JD, Willis CM.

Department of Medicine, Karolinska Institutet and Stockholm Centre for Public Health, Stockholm, Sweden.

A multicentre, randomized, double-blind, crossover study was designed to investigate the effects of prednisone on allergic and irritant patch test reactions. 24 subjects with known allergy to nickel were recruited and patch tested with a nickel sulfate dilution series in aqueous solution, 5% nickel sulfate in petrolatum and 2 dilution series of the irritants nonanoic acid and sodium lauryl sulfate. The subjects were tested x2, both during treatment with prednisone 20 mg oral daily and during placebo treatment. The total number of positive nickel patch test reactions decreased significantly in patients during prednisone treatment. The threshold concentration to elicit a patch test reaction increased and the overall degree of reactivity to nickel sulfate shifted towards weaker reactions. The effect of prednisone treatment on the response to irritants was divergent with both increased and decreased numbers of reactions, although there were no statistically significant differences compared with placebo. It is concluded that oral treatment with prednisone suppresses patch test reactivity to nickel, but not to the irritants tested.

7) Arch Dermatol. 1973 Apr;107(4):540-3.

Influence of oral prednisone on patch-test reactions to Rhus antigen.

Condie MW, Adams RM.

8) Contact Dermatitis. 1981 Jul;7(4):180-5.

Influence of topically applied corticosteroids on patch test reactions.

Sukanto H, Nater JP, Bleumink E.

Four commercially available corticosteroid preparations were assayed for their capacity to suppress patch test reactions with contact allergens (nickel sulfate, nitrofurazone, potassium dichromate, epoxy resin, wood tars and Maneb) in sensitized individuals (n=14). Beta-methasone valerate, betamethasone dipropionate, hydrocortisone-17-butyrate and triamcinolone acetonide (0.05-0.7% solutions in isopropanol or ethanol) were applied under occlusion in amounts of 0.01, 0.02 and 0.04 ml, respectively. Patch tests were performed on the pretreated skin sites. The patches were removed 24 h after application and the reactions were read 15 min and 24 h later. The intensity of the reactions and the size of the infiltrated areas of the pretreated sites were measured and compared with those of a control patch test. Topical application of corticosteroids was found to have a suppressive effect both on the intensity as well as on the size of the epicutaneous reactions. No marked difference in the suppression effect of the four corticosteroids could be observed.