Topical Pentoxifylline with A Concentration of 5%, 7,5% and 10% Does Not Suppress Allergic Patch Test Responses¶

TOPİKAL PENTOKSİFİLİNİN %5, %7,5 VE %10'LUK KONSANTRASYONLARI ALLERJİK YAMA TESTİ SONUÇLARINI BASKILAMAZ

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Summary

Purpose: Pentoxifylline has been shown to inhibit the formation of tumor necrosis factor-alpha which is an important mediator in the effector phase of allergic contact dermatitis. In this study we aimed to evaluated possible effects of topical pentoxifylline on allergic patch test reactions in twelve female patients with a history of contact hypersensitivty against nickel.

Material and Method: At first visit, patch test with European standart series was performed on the back of the patients and evaluated on both 48 and 72 hours. In all of the 12 patients, a positive reaction to nickel sulfate 5% (baseline reaction) was obtained. At second visit (2 weeks later) the patients were advised to apply a base cream and topical pentoxifylline creams with a concentration of 5%, 7.5% and 10% to 4 different points on inner aspects of their arms twice daily for one week. At the end of one week of application (third visit), patch test with nickel sulfate was reperformed on points where topical pentoxifylline creams and base cream had been applied and evaluated on both 48 and 72 hours.

Results: No statistically significant difference was found between baseline reactions and reactions obtained after one week of topical pentoxifylline creams / base cream application.

Conclusions: According to this study results, it has been concluded that topical pentoxifylline, one week application of used concentration, does not suppress allergic patch test responses.

Key Words: Topical pentoxifylline, Contact dermatitis

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Özet

Amaç: Pentoksifilinin allerjik kontakt dermatitin efektör fazında önemli bir medyatör olan tümör nekrotizan faktör alfayı inhibe ettiği bilinmektedir. Bu çalışmada nikele karşı aşırı duyarlılık hikayesi olan 12 kadın hastada topikal pentoksifilinin allerjik yama testleri üzerindeki muhtemel etkisinin değerlendirilmesi amaçlandı.

Materyal ve Metod: İlk görüşmede hastaların sırtlarına Avrupa Standart Serisi ile yama testi uygulanarak sonuçlar 48 ve 72'nci saatlerde değerlendirildi. Hastaların tümünde %5'lik nikel sülfat ile pozitif reaksiyon elde edildi ve sonuçlar hastaların baz değerleri olarak kabul edildi. İki hafta sonra yapılan ikinci görüşmede hastalara, her iki kol iç kısımlarında işaretlenen 4 farklı bölgeye %5, %7,5, %10'luk konsantrasyonlarda hazırlanan topikal pentoksifilin ve baz kremi bir hafta süreyle günde 2 kez uygulamaları öğütlendi. Bu bir haftalık uygulamanın ardından yapılan üçüncü görüşmede, ilaçların sürüldükleri bölgelere %5'lik nikel sülfat ile yama testi tekrarlandı ve sonuçlar 48 ve 72'nci saatlerde değerlendirildi.

Bulgular: İstatistiksel olarak karşılaştırılan baz değerleri ve bir haftalık topikal pentoksifilin / baz krem uygulamasını takiben yapılan yama testi sonuçları arasında anlamlı bir farklılık olmadığı görüldü.

Sonuç: Çalışmanın sonucunda elde edilen verilere göre topikal pentoksifilinin, kullanılan konsantrasyonlarda bir haftalık uygulamasının, allerjik yama testi sonuçlarını baskılamadığı sonucuna varıldı.

Anahtar Kelimeler: Topikal pentoksifilin, Kontakt dermatit

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Allergic contact dermatitis (ACD) is a common inflammatory skin disease (1) mediated by antigen-specific T lymphocytes (2). Certainly, avoidance of the offending allergens is the first-line treatment for ACD. But this is not always possible; in such cases major treatment strategy is based upon topical or systemic corticosteroids with some possible long term side effects (3). Therefore there is in great need for topical or systemic agents to prevent the occurence of ACD when allergen

avoidance is not possible in sensitized patients and identification of new therapeutic regimens would be of great importance. Pentoxifylline which is mainly used in the treatment of vascular disorders has been shown to inhibit the formation of tumor necrosis factor-alpha (TNF-α), a critical mediator in the effector phase of contact dermatitis (1, 3-5). Recent reports have shown the efficacy of systemic pentoxifylline on nickel-induced allergic reactions in animal models (6, 7). In humans after the demonstration of systemic pentoxifylline suppresses allergic patch test reactions by Schwarz et al. (3), there are not sufficient studies about the effects of either topical or systemic pentoxifylline on patch test reactions in the literature. Therefore we planned this study to evaluate the effects of topical pentoxifylline on allergic patch test reactions in humans known to be allergic to nickel.

Materials and Methods

Preparation of test creams

Pentoxifylline creams were prepared in a base cream (Elobaz® cream, Schering-Plough) with a concentration of 5%, 7,5% and 10% in pharmacology department of our university. The base cream itself was also used as placebo. All test creams (pentoxifylline creams with 3 different concentrations and base cream) were put in identical boxes and labelled.

Study design

Twelve female patients with a history of contact hypersensitivity against nickel were enrolled in this open, placebo-controlled, double-blinded study between September 1998 - May 1999. Ethical approval was obtained and all patients gave written informed consent before including the study. The patients were instructed not to use any topical or systemic medication including antihistamines, corticosteroids and not to expose to nickel containing substances during the whole study period.

At first visit, patch test with European standart series (supplied by Brial, Hal Allergenen Laboratorium B.V., Netherlands) was performed on the back of the patients by the first investigator. After 48 hours the patches were removed and read. The patch sites were reevaluated and read on 72 hours.

Grading of positive test reactions were evaluated as follows: ±: only erythema; 1+: erythema and infiltration, non or few papules; 2+: erythema, intensive infiltration, many papules, occasional vesicles; 3+: densely aggregated papules and vesicles.

After a 2 weeks of wash-out period, the second investigator marked two different test areas separeted from each other by at least 2 cm on inner aspect of the each arm (each 1 cm in diameter, total 4 test sites) and advised the patients to apply test creams (base cream and topical pentoxifylline creams with a concentration of 5%, 7,5% and 10%) on marked areas. The order in which the four creams were applied to the marked areas on the subjects inner arm had randomized. The patients were instructed to use the respective creams on the same arm and on the same area as marked by second investigator twice daily for one week The first investigator and patients did not know which cream was used to which area.

At the end of one week of application (third visit), patch test with nickel sulfate 5% was reperformed by the first investigator on points where test creams had been applied by the patients. The patch tests were read on both 48 and 72 hours.

The patch test reactions obtained on 48 and 72 hours after the one week application of 5%, 7,5% and 10% topical pentoxyfilline creams and base cream were compared with baseline reactions.

Statistics

Friedman's two-way analysis of variance test was used to analyze statistical differences in the baseline reactions and reactions obtained after one week of topical pentoxifylline creams and base cream application on both 48 and 72 hours.

Five % was set as the significance level of the study and the power of the study was set at 80%.

Results

In all of the 12 patients a positive patch test reaction with nickel sulfate 5% was obtained on both 48 and 72 hours before (baseline reactions) and after one week of application of test creams. There was no statistically significant difference

between the baseline reactions and reactions obtained after one week of 5%, 7,5% and 10% topical pentoxifylline creams and base cream application neither on 48 hours (x^2: 4,250, p: 0,373) nor on 72 hours (x^2: 4,667, p: 0,323) among the treatment groups.

Discussion

A complex cytokine network in the skin is involved in the pathogenesis of ACD. One of these cytokines, TNF-α which is produced by Th 1 and Th 2 cells, activated keratinocytes and Langerhans cells, is a critical one in the effector phase of ACD. It induces the expression of intercellular adhesion molecule (ICAM)-1 and HLA-DR on keratinocytes which might be important in T-cell migration to epidermis. It also induces degranulation of human dermal mast cells, eventually leading to the release of many other cytokines including interleukin (IL)-1, IL-2, IL-6, granulocyte-macrophage colony stimulating factor (GM-CSF) and interferon (IFN)-γ all of which might contribute to the inflammatory cascade of ACD (2).

Although TNF-α is believed to have an important role in the cellular events of ACD (2), in an immunohistologic study Oxholm (8) et al. showed that TNF-α expression by keratinocytes was not significantly altered in the allergic patch test reactions induced by nickel sulfate when compared with non-tested skin in humans.

Pentoxifylline, a xanthine derivative, is an effective treatment agent used in peripheral vascular disease, cerebrovascular disease and conditions involving a defective microcirculation (9). Althuogh its primary action is on red blood cell deformability, blood viscosity and platelet aggregation (9) it has also some immune functions (1,5,10) which led it to be used in a number of other conditions with encouraging preliminary results (5,10).

Inhibition of the formation of TNF-α mRNA is one of the most commonly known effects of pentoxifylline on immune functions (1,3,9). Schwarz (3) et al. were the first authors who suggested that inhibition of TNF-α by pentoxifylline might be effective in suppression of ACD. They showed that intraperitoneal pentoxifylline injection can suppress contact hypersensitivity reactions on animal models (7). Sarıcaoğlu (6) et al. also demonstrated the inhibitory effects of systemic pentoxifylline on contact sensitivity responses in nickel-sensitive albino guinea pigs only during the drug administration period. In a different study Schwarz (3) et al. observed a significant reduction in the severity of patch test reactions in 2 patients with documented nickel allergies 1 week after ingestion of pentoxifylline (600mg orally every 6 hours). On the other hand, Brehler (4) et al. found that 6% pentoxifylline cream had no significant prophylactic and therapeutic effects on allergic patch test reactions with nickel sulfate 5%. We did not also observed a significant difference on the results of patch test reactions with nickel sulfate 5% obtained before and 1 week after topical pentoxifylline creams with a concentration of 5%, 7,5% and 10% and placebo.

According to our study results topical pentoxyifylline does not suppress allergic patch test responses although our study group comprised only 12 subjects. The contraversial results of pentoxifylline on contact hypersensitivity reactions might be explained as follows: 1) Topical pentoxifylline is not absorbed from skin since there are a few studies in which a therapeutic effect of systemic pentoxyifylline was shown on patch test reactions both in human and animal studies (3,6). 2) The concentration of topical pentoxyifylline we used is not high enough to suppress contact allergic reactions. 3) TNF-α expression by keratinocytes is not significantly altered in the allergic patch test reactions in humans as shown by Oxholm (8) et al. previously. Therefore further studies are needed to explain whether topical pentoxyifylline should be regarded as a potential candidate for the treatment of ACD.

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