

Prevention of nickel-induced allergic contact reactions with pentoxifylline

H. SARICAOĞLU¹, Ş. TUNALI¹, E. BÜLBÜL¹, I. R. WHITE² AND Z. PALALI¹

¹Department of Dermatology, University of Uludağ, Faculty of Medicine Bursa, Turkey

²St John's Institute of Dermatology, St Thomas Hospital, London SE1 7EH, UK

In this study, we investigated the effect of pentoxifylline, an inhibitor of TNF- α , on the contact sensitivity response induced by nickel. For induction, open epicutaneous sensitization by NiSO₄·6 H₂O (25% aq.) solution was applied on the backs of 38 albino guinea pigs 5 days a week for 4 weeks. NaCl (0.9%) solution was applied epicutaneously to 10 albino guinea pigs as a control group. 19 were sensitized by nickel and developed positive patch test reactions. Patch tests were repeated after 10 of the sensitized pigs were given pentoxifylline 20 mg/kg/day orally. At the end of this study, only 2 positive patch test reactions were observed in the pentoxifylline-treated group, while 7/9 of the untreated guinea pigs developed positive reactions. These results suggest that pentoxifylline inhibits the contact sensitivity response induced by nickel only during drug administration.

Key words: pentoxifylline; experimental nickel sensitization; guinea pigs; inhibition elicitation phase.
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Pentoxifylline is a phosphodiesterase inhibitor drug derived from methylxanthine, which has been used for more than 20 years in patients with microcirculatory disturbance (1). The increase in leucocyte chemotaxis; decrease in endothelial adhesion of leucocytes, neutrophil degranulation and superoxide secretion, monocyte derived tumor necrosis factor (TNF) production; decreased activation of T and B lymphocytes and natural killer activity of cells; and decreased response of leucocytes to IL-1 and TNF are examples of its effects on the immune system (1, 2).

In the effector phase of contact dermatitis, which is a typical example of cellular hypersensitivity (CHS), effector cells in the lymph nodes produce lymphokines, the many pharmacological properties of which give rise to the inflammatory reaction, erythema and oedema characterizing the delayed skin reaction observed on contact with allergen (3). Recently, it has been showed that TNF- α is a critical mediator in the effector phase of contact hypersensitivity. Pentoxifylline inhibits the effector phase of contact dermatitis. Many studies are carried out to treat allergic contact der-

matitis and prevent CHS reactions (5, 6). Nickel is the most common contact sensitizer in the general population worldwide and it is possible to induce contact sensitization experimentally (7–9).

In this study, we investigated the effects of pentoxifylline on CHS response on the experimentally nickel-sensitized pigs.

Materials and Methods

Experimental animals

38 albino guinea pigs weighting 300–600 g (mean: 430 g) were used. They were housed in groups of 5 in small chambers. At the beginning of the study, each guinea pig was numbered by punching their ears with a machine. The animals were fed with standard animal food supplemented with some fresh vegetables each day. The room temperature was 20±3°C, relative humidity rate was 55%. The test area of 2×4 cm over the scapulae was shaved with electric shaver on the 1st day and shaved manually every other day in the course of sensitization.

Sensitization procedure

25% $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ aqueous was used for open epicutaneous sensitization. The control group comprised 10 albino guinea pigs. During the sensitization process of 4 weeks, only saline solution was applied topically to the control group weighing 350–600 g (mean: 450 g). The shaved back skin of experimental animals was painted with nickel sulfate aqueous solution 5 days a week. Control animals were also painted with saline solution. Topical challenge test by 5% NiSO_4 in pet. was performed 2 weeks after the sensitization procedure. For control petrolatum was used for challenge test. The allergen was applied in Leucotest, additionally attached with Scanpor tape. The tests were removed after 24 h and read at 48 h and 72 h. The same test was performed in the control group. The test reactions were evaluated by visual assessment and graded with 0: no reaction; 1+ = slight, diffuse erythema; 2+ = intense, confluent, palpable ery-

thema; 3+ = erythematous strongly palpable induction.

Pustular reactions without erythema were assessed as irritant reactions (IR), only + reactions were recorded as "negative".

Desensitization procedure

1 week after the test, 10/19 of sensitized animals, established by topical challenge test, were given pentoxifylline 20 mg/kg/day p.o. by gavage (suspension in water was prepared from capsular contents). Patch testing was repeated in 6 h. The tests were removed after 24 h and read at 48 h and 72 h. Pentoxifylline administration continued in the test evaluation period. The test was also repeated in 9/19 of sensitized pigs without pentoxifylline administration. 1 week after we stopped the pentoxifylline administration, patch testing was repeated in both groups to assess the action period of pentoxifylline.

Statistics

Data was evaluated statistically with the Fisher χ^2 test in the Biostatistics Department of Uludağ University.

Results

Table 1 shows the results of topical challenge tests in both control and experimental groups performed 2 weeks after the sensitization procedure. Since it was summer, irritant pustular reactions were observed in high numbers. The sensitization rate was 50% in the experimental and 10% in the control group. This result was statistically significant (Table 2). A positive result was recorded in 2/10 of pigs (experimental group) whose tests were repeated during pentoxifylline treatment. This result was also statistically significant (Table 3). When the same tests were performed 1 week after we stopped drug administration, an increase in the number of positive reactions was observed. When compared with the results of the 1st challenge test, there was no statistically significant difference (Table 4).

Discussion

Contact dermatitis, having an incidence of 2% in the population, is an important social and medical problem and it comprises 4–7% of all dermatoses (7, 10). Nickel, the most important sensitizer, also sensitizes albino guinea pigs. It is more difficult to induce experimental contact sensitization by nickel than by other substances (9, 11). Different procedures or different studies of the same procedure

Table 1. Skin reactions to topical challenge

Topical challenge response	Sensitized guinea pigs (n: 38)	Control (n: 10)
3+	4	–
2+	15	1
1+	3	1
(–)	10	4
IR	6	4

Table 2. Comparison of topical challenge results

Nickel sensitization			
experimental group	n: 38	19 (+)	19 (–)
control	n: 10	1 (+)	9 (–)
$p < 0.05$			

Table 3. Effect of pentoxifylline on topical challenge test

	Sensitized guinea pigs	Topical challenge	
		positive	negative
pentox (+)	10	2	8
pentox (–)	9	7	2
$p < 0.05$			

Table 4. Topical challenge response 1 week after pentoxifylline treatment

	Sensitized guinea pigs	Topical challenge	
		positive	negative
pentox (+)	10	5	5
pentox (–)	9	6	3
$p > 0.05$			

bring out different rates of sensitization (9, 12, 13). Contact sensitization of guinea pigs is the most similar experimental model of human contact sensitization both histologically and morphologically (14). There are many methods for induction of contact sensitization in pigs by nickel sulfate. The guinea pig maximization test (GPMT), open epicutaneous sensitization (OE), intradermal method (ID), injection of Freund's complete adjuvant (FCA), OE+FCA, intraperitoneal injection (IP) are all examples of such methods (9, 12–14). Although OE sensitization is a time-consuming and laborous procedure, a 50% sensitization rate and similarity to the afferent phase of clinical human contact dermatitis makes it an appropriate method for experimental induction of sensitization in guinea pigs (14). For this reason, in our study we tried to induce nickel sensitization in pigs by the OE method. We achieved a 50% positive sensitization rate, which is compatible with that of Lammintausta et al. (9). Zissu et al. (13) report 63–80% sensitization rates with NiSO_4 1% in lanolin applied open epicutaneously and injecting potassium alum 0.1% i.d. every week. When Rohold et al. (12) compared OE sensitization by NiSO_4 0.25–10% with i.d. injection of NiSO_4 3%, they showed that i.d. injection was a superior method (sensitization rate 40%).

In the last decade, beyond corticosteroids, new therapy alternatives have been studied in the therapy of contact dermatitis, which is a typical model of cellular hypersensitivity (15). Clonidine, Ca channel blockers, IL-10, and Cyc A are examples of such drugs (16–20). Besides its main use for vasodilatation and regulation of the microcirculation, pentoxifylline has also been studied in many other diseases. There are reports showing successful results in Schamberg's disease, Behçet's disease and various vasculitic disorders (21–24). The concept that pentoxifylline inhibits the elicitation phase of contact dermatitis by inhibiting $\text{TNF-}\alpha$ has brought about new studies (1, 2, 5, 6). Schwarz et al. (5) observed a significant decrease in the severity of patch test reactions in 2 volunteers, who were known to have nickel contact sensitization, by giving 600 mg pentoxifylline p.o. every 6 h. In a different study, they also showed inhibition of the contact hypersensitivity reaction in sensitized guinea pigs by intraperitoneal pentoxifylline injection. We observed that no reaction developed in 9/10 of sensitized cases during pentoxifylline treatment. When we repeated the patch test 1 week after we stopped the therapy, 3 of the cases developed positive reactions.

We conclude that pentoxifylline inhibits the afferent phase of nickel contact sensitivity significantly, but only during the therapy. Besides $\text{TNF-}\alpha$ inhibition, pentoxifylline has other biologic ef-

fects, particularly regulation of the microcirculation, which could possibly be responsible for the prevention of nickel-induced allergic contact reactions.

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Address:

Hayriye Sarıcaoğlu
Uludağ Üniversitesi Tıp Fakültesi
Dermatoloji Anabilim Dalı
16059 Görükle-Bursa
Turkey