

## ABNORMAL CUTANEOUS REACTIONS TO A NICOTINIC ACID ESTER

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**Abstract.** The reaction to a locally applied ointment with an ester of nicotinic acid (Trafuril) was studied in various dermatoses. The immediate reddening caused by Trafuril was diminished in patients with psoriasis, whereas the one-hour erythema in those with chronic urticaria was increased. Abnormal reactions to Trafuril were observed in most patients with pustular psoriasis, allergic purpura, pemphigoid and dermatitis herpetiformis. In these disorders Trafuril induced lesions within the test area which were typical of each disorder. The reactions occurred as a delayed phenomenon which was maximal about 24 hours after the application of Trafuril. The strength of the immediate reaction did not differ from that in healthy subjects. In dermatitis herpetiformis the delayed response with its blisters was more pronounced on the extensor side of the arms than on the flexor side. In purpura the test reaction was strongest on the lower legs. When the patient's condition improved after treatment or spontaneously, the delayed Trafuril reaction was diminished. The mechanism for the delayed Trafuril responses is unknown. They may be of help in the diagnosis of these disorders.

Application of 5% tetrahydrofurfurylester of nicotinic acid in an ointment (Trafuril®, Ciba, Basel) on the skin of healthy subjects causes erythema and, in some, also edema. The erythema usually persists for 1 to 3 hours, but may be evident after 24 hours. An increased dermographic response and/or reddening after gentle rubbing is often seen in the treated area for 48 hours (12). The erythematous response to Trafuril is postponed by pretreatment with aspirin (13). An abnormal blanching of the skin is often seen in atopic dermatitis (4).

When studying vascular behaviour in various dermatoses we found some unusual reactions to Trafuril in patients with dermatitis herpetiformis, bullous pemphigoid, pustular psoriasis and allergic purpura. They have therefore been investigated further.

## METHODS

With a syringe 30 to 35 mg of the Trafuril ointment was applied on a 9 cm<sup>2</sup> area of the skin on the volar side of the forearm. Before application, the skin of the test area was always of normal appearance. In patients with purpura, the ointment was also applied on the lower leg and, in patients with dermatitis herpetiformis, also on the dorsal side of the arm just distal to the elbow. It was left on without covering for 10 min and then gently removed with a dry cotton swab. The area was then cleaned with 60% ethyl alcohol. The reaction was observed at 20 and 60 min, 2, 5 and 24 hours after application of the ointment. The intensity of erythema was graded 1 to 3: clearly visible erythema = 1, strong erythema = 2, very strong erythema = 3.

All subjects tested were carefully asked about drugs taken the days prior to the test. With the exception of those with pemphigoid, no patients using antihistamines, immunosuppressive drugs, corticosteroids, salicylates and other antiphlogistics were included.

## PATIENTS

**Controls:** 21 healthy subjects between 20 and 44 years of age.

**Eczema:** 28 patients 20 to 60 years old with contact dermatitis and nonspecific eczematous dermatitis. None of them had atopic dermatitis.

**Psoriasis:** 33 patients 18 to 66 years old with psoriasis of slight or moderate severity. Some of them used ointments with salicylic acid and dithranol.

**Pustular psoriasis:** 3 patients 31, 58 and 75 years old.

**Palmoplantar pustulosis:** 12 patients 22 to 62 years old without any typical signs of psoriasis.

**Chronic urticaria:** 26 patients 20 to 60 years old with urticaria for more than 4 months.

**Purpura:** 49 patients 7 to 85 years old. Four of them had a thrombocytopenia and one a thrombasthenia. In 4 others cryoglobulins were found. One of them had a myelomatosis and moderate purpura of the legs, and one a purpura with a pronounced vasculitis and superficial ulcerations. In the 2 other patients with cryoglobulins, the purpura was considered to be of the Schamberg type. One patient with a probable systemic lupus erythematosus had an elevated ESR. No blood

Table I. Intensity of erythema 20 and 60 minutes after application of Trafuril

	No.	Mean of reaction intensity ± S.E. of the Mean	
		20 min	60 min
Healthy subjects	21	1.17 ± 0.18	1.24 ± 0.20
Eczema	28	0.97 ± 0.16	1.43 ± 0.17
Psoriasis	33	0.64 ± 0.12 <sup>a</sup>	1.00 ± 0.15
Palmar plantar pustulosis	12	0.96 ± 0.24	1.13 ± 0.19
Chronic urticaria	26	1.19 ± 0.12	1.96 ± 0.15 <sup>b</sup>

<sup>a</sup>  $P < 0.02$  when compared with healthy subjects.

<sup>b</sup>  $P < 0.01$  when compared with healthy subjects.

abnormalities were found in the remaining patients. In 24 patients the purpura was considered to be of the pigment purpura types (Schamberg, Majocchi, Gougerot and Blum). In 7 patients the diagnosis was purpura simplex and in 8 patients it was interpreted as allergic purpura, e.g. Schönlein-Henoch or drug-induced purpura.

*Dermatitis herpetiformis*: 30 patients 22 to 86 years old. The intensity and duration of their disorders varied. The diagnosis of all patients had been confirmed by a biopsy. With the exception of one new case, all patients were being treated with 4,4'-diaminodiphenylsulphone (dapsone). The doses varied between 0.1 g once or twice weekly and 0.2 g daily. Sixteen patients had been requested not to take the drug the day before and the day of the test while the others continued with their normal doses.

*Pemphigoid*: 8 patients. One patient was 18 years old and had blisters especially on the trunk. Repeated biopsies showed a histological picture of pemphigoid. The other patients were 48 to 82 years old. Four patients were tested both before and during prednisone administration and 4 only during steroid treatment.

*Various disorders*: 19 patients with the following diseases: Panniculitis (7), scleroderma (2), discoid lupus erythematosus (2), epidermolysis bullosa (1), erythema multiforme (3), sacoidosis (2), porphyria cutanea tarda (1) and drug reaction (1). The patient with a drug reaction had an erythematous papular reaction on the trunk, hands and feet caused by ampicillin.

## RESULTS

The erythema was diminished after 20 min in the normal-appearing skin of patients with psoriasis and increased after 1 hour in patients with chronic urticaria (Table I). One of the patients with chronic urticaria who occasionally had a bullous urticaria had a normal initial reaction to Trafuril, but after 24 hours an intense edematous reaction with confluent pea-sized blisters was observed.

Three patients with a pustular psoriasis devel-

oped many small, superficial pustules after 24 to 36 hours at the site where Trafuril had been applied (Fig. 1). When the lesions of the patients had disappeared, the reaction to Trafuril became normal.

In 8 patients with allergic purpura or a recent history of it, the Trafuril-treated skin first showed a normal erythema which did not differ from that seen in controls. About 5 to 7 hours after application of Trafuril, the area began to become purpuric. The purpura was best seen after 24 hours and was sharply limited to the treated area. In some cases it was spotted (Fig. 2) and in others the purpura covered the whole test area (Fig. 3). The purpuric reaction was more pronounced on the leg than on the arm. When the patients' conditions had improved, the purpuric Trafuril reaction first became negative on the arm, whereas it still could be seen on the legs. Positive reactions were seen in 4 patients several months after the disappearance of their purpuric reaction. The same type of purpura after Trafuril was present in the patient with systemic lupus erythematosus and also in 1 patient with cryoglobulinemia and a pronounced vasculitis. Three other patients with cryoglobulinemia showed normal reactions. Normal reactions to Trafuril were also seen in all patients with pigmented purpuric dermatosis and in patients with thrombocytopenic or thrombasthenic purpura.

In 4 untreated patients with pemphigoid, a normal initial reaction to Trafuril was present. After 12 to 20 hours, 3 of them developed an edematous and sometimes papulous reaction. Subsequently blisters developed, being most evident 24 to 48 hours after application of Trafuril. The blisters were tense, often pea size, and nonconfluent (Fig. 4). When corticosteroid treatment was given, Trafuril caused no or only a few small blisters. Four other pemphigoid patients were treated with 10 to 20 mg prednisone for several weeks. One of them developed blisters in the test area after 24 hours and a delayed papular reaction was seen in 2 of them. One had a normal reaction.

In patients with dermatitis herpetiformis the initial reaction to Trafuril varied in strength and did not differ from that seen in healthy subjects. Only 4 patients had an initial edematous reaction. These reactions always disappeared in the same way as those in control subjects. After 5 hours,

however, an itching erythema with papules and often also edema developed within the test areas in 29 of the 30 patients tested. In the following hours, the reaction became more pronounced with the formation of distinct papules and often also vesicles with diameters of 2 to 4 mm. The changes were strictly limited to the test areas, and were most pronounced 24 hours after application of Trafuril (Figs. 5-6). They were more intense on the dorsal side of the arm near the elbow than on the volar side of the forearm. If the dose of dapsone was increased, the degree of the abnormal reactivity to Trafuril decreased. The one patient who had not yet been treated with dapsone showed the strongest reaction to Trafuril. There seemed to be no connection between the type of initial reaction and the intensity of the late reaction. Biopsies from the test area of 4 patients revealed a histological picture consistent with dermatitis herpetiformis.

#### DISCUSSION

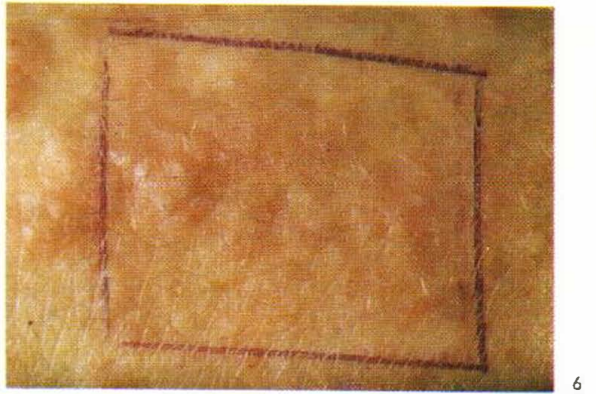
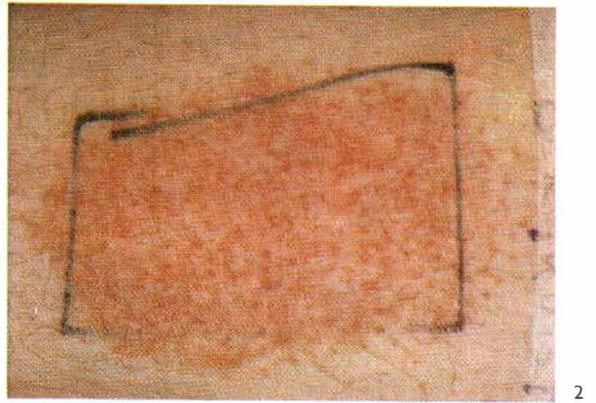
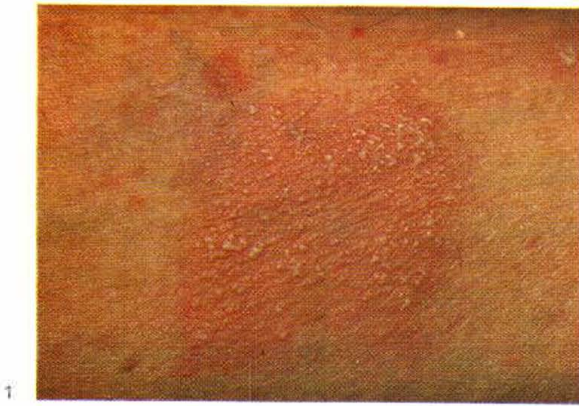
The reaction occurring in the skin 15 min after application of Trafuril was studied by Engelhardt (2) in various skin disorders including psoriasis. Normal reactions were observed at that time in all patients except those with atopic dermatitis. Decreased reactions to Trafuril have been reported in patients with diabetes and scleroderma (10, 11). In patients with psoriasis, decreased reactions to Trafuril, histamine (3) and kallikrein (8) have been reported. In the present study we could confirm that patients with psoriasis have diminished reactions to Trafuril. The significance of this weak response, as well as of other reduced vascular responses in psoriasis, is still obscure. The increased reactions to Trafuril seen after 1 hour in patients with chronic urticaria is consistent with the increased reactivity to kallikrein and prostaglandin E<sub>1</sub> often observed in this disorder (5, 9).

The abnormal delayed reactions to Trafuril in patients with purpura, dermatitis herpetiformis, pemphigoid and pustular psoriasis have not previously been reported. They have the same appearance as the lesions typical of the patient's disorder. It therefore seems evident that Trafuril can provoke the lesions within the test area. The strength of the initial reactions did not seem to influence the late response. The mechanism for

the formation of pustules, purpura, and blisters after Trafuril is obscure. It cannot be explained only as an effect of initial vasodilation since intradermal injections of strong vasodilators such as histamine, prostaglandin E and kallikrein do not give rise to any such delayed reactions (6).

Patients with various types of pigment purpura, e.g. Schamberg's disease, etc., had a normal reaction of Trafuril, whereas those with "allergic purpura" responded with purpura in the test area. The cause of this difference is not known. It might be associated both with the mechanism of the reaction and the type of vessels engaged. In pigment purpura, the inflammatory reaction which is located in the superficial small vessels, mainly the capillaries, is usually mild. In allergic purpura, the vasculitis is often more intense with involvement of both capillaries and arterioles (7). Little is known about the mechanism of allergic purpura and Trafuril-induced reactions, but it seems likely that Trafuril in some way activates the vasculitis.

The papular erythema and the blisters seen after Trafuril in patients with dermatitis herpetiformis have not been observed in other skin disorders. In dermatitis herpetiformis the blisters seen in the test area are, as a rule, more vesicular and more confluent than in pemphigoid where they are larger and more elevated. The fact that the reaction in dermatitis herpetiformis is stronger near the elbow than on the volar side of the forearm is compatible with the distribution of the lesions in this disorder. The iodide patch test is commonly positive in patients with dermatitis herpetiformis. When strong concentrations of iodide (30%) are used, irritant reactions also occur in one-third of the patients with other skin disorders (1). It is uncertain if iodide causes an irritation which induces a delayed reaction in the same way as Trafuril. We have not yet been able to reproduce the lesions with various vasoactive drugs such as histamine, compound 48/80, kallikrein, bradykinin and prostaglandin E (6). Vesiculobullous reactions have, however, been observed after intradermal injections of various bacterial antigens (12 for ref.). They have usually been regarded as an expression of bacterial hypersensitivity. Pretreatment with fluocinolone 0.2% cream under plastic covering for 24 hours is the only way in which we hitherto have been able to diminish the reaction. The inhibition by fluocinolone might be explained by its known suppressive



*Fig. 1.* Pustular psoriasis. Reaction appearing 36 hours after application of Trafuril.

*Fig. 2.* Allergic purpura, spotted reaction to Trafuril on lower leg at 24 hours.

*Fig. 3.* Allergic purpura, intensive reaction to Trafuril on forearm at 24 hours.

*Fig. 4.* Pemphigoid. Bullous reaction to Trafuril on forearm at 24 hours.

*Figs. 5-6.* Dermatitis herpetiformis. Reactions to Trafuril near elbow at 24 hours.

action both of the normal Trafuril reaction and the lesions of dermatitis herpetiformis.

The Trafuril test may become a valuable diagnostic test especially in dermatitis herpetiformis where the lesions nearly always could be produced by application of Trafuril. This test may also be used as an indicator of the efficiency of the treatment. The same may be valid for patients with allergic purpura where the diagnosis sometimes can be obtained from the test reaction even when the skin lesions have disappeared.

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