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ORAL PROVOCATION IN ECZEMATOUS CONTACT ALLERGY TO NEOMYCIN AND HYDROXY-QUINOLINES

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Introduction

Most important in the prophylaxis and treatment of contact eczematous dermatitis is to eliminate the suspected or proven allergen. Even if the patient is thoroughly shielded from such exposure repeated flare-ups and chronicity is a common clinical experience. Recurrences have frequently been reported following accidental ingestion of the particular contact allergen (3, 4).

The aim of the present study was to obtain answers to the following questions: Should ingested contact allergens be considered of any quantitative significance in patients with eczematous contact dermatitis? When oral provocation is positive, do the patients react with a flare-up of the original dermatitis, or do they show some other, specific type of skin eruption?

Patients with a eczematous contact dermatitis were orally provoked with the respective allergen when the original dermatitis and the patch test response had subsided. To obtain the least possible reactions, and, hopefully, on typical and most sensitive skin sites, patients with a contact allergy to neomycin and to hydroxy-quinolines were selected, since these drugs are generally considered to be absorbed from the intestinal tract in minute amounts only. Because of this poor intestinal absorption the danger of producing "systemic eczematous contact-type dermatitis medicamentosa" with neomycin is considered rare (3).

Material and Methods

Twelve hospitalized patients with a contact allergy to neomycin and nine with a contact allergy to hydroxy-quinolines were selected for the study. There were five males and sixteen females, the most common diagnosis being ulcus et ezcema venosum cruris (stasis dermatitis). Contact allergy was established with patch tests applied for 48 hours (neomycin sulfate 40 % in petrolatum; hydroxy-quinolines as 5 % each of cliochinol and of chlorchinaldol in petrolatum). The tests were read after a further 24–48 hours and considered positive when erythema with infiltration, papules or vesicles occurred on the test site.

When the original dermatitis and the test reaction had subsided, patients were given tablets of neomycin sulfate[1] 0.5 g, cliochinol[2] 0.25 g or chlorchinaldol[3] 0.1 g, respectively. Dosage schedule was: first day, one tablet; second day, no tablet; third and fourth days, one tablet three times a day; fifth and sixth days two tablets three times a day. The provocation was interrupted if and when a skin reaction appeared.

The identical provocation schedule was applied to a control group of nine hospitalized patients of similar age and diagnosis. In these patients there was no contact allergy to neomycin or hydroxy-quinolines as confirmed by patch tests. Six patients were given neomycin sulfate, and three were given hydroxy-quinolines.

[1] Neomycin®, Upjohn.
[2] Entero-Vioform®, Ciba.
[3] Sterosan®, Geigy.

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The oral provocation was considered positive when one or more of the following signs were observed: flare-up of original dermatitis, flare-up of patch test reaction, a more or less generalized eruption.

Results

The oral provocation was positive in sixteen of the 21 patients studied. In the control group no skin reaction was observed.

Positive results were obtained in ten of the twelve neomycin patients, and in six of the nine hydroxy-quinoline patients (Tables 1–2). The original dermatitis exacerbated in ten of the sixteen positive patients from both groups. When any other skin eruption occurred this did not show a typical localization or character. There was no essential difference in the reaction pattern between the two patient groups, with one exception: Among the ten patients positive at provocation with neomycin six reacted with a flare-up of the patch test; in the hydroxy-quinoline group there was no such reaction.

In most cases more than one tablet was required to elicit a positive reaction. However, some type of skin reaction was obtained in five of the sixteen positive patients after the ingestion of only one tablet. All of these five belonged to the hydroxy-quinoline group.

Discussion

In the present study frequent cutaneous reactions were observed during oral provocation with neomycin and hydroxy-quinolines in patients with a contact allergy to these compounds. Toxic and allergic skin eruptions during oral therapy with neomycin and hydroxy-quinolines are rare (14), and thus do not explain the positive results. The figures obtained are comparable with those of other authors. Baer and Leider (1), feeding azo-dyes to p-phenylene-diamine-sensitive subjects found five patients with objective skin reactions among twenty studied. Sidi and Melki (12) gave 0.5 g of sulfamide to fourteen patients with a contact allergy to this substance and produced a dermatitis in twelve. Schleiff (11) administered potassium dichromate to twenty patients with a chromate contact allergy and the skin disease recurred in most cases. Consequently, the possibility of inducing disease by ingestion of a contact allergen is considerable. Since the high frequency of contact allergy to neomycin and hydroxy-quinolines is a clinical reality, and especially hydroxy-quinolines are commonly used as intestinal antiseptics, the chance of meeting skin eruptions due to oral intake of these compounds should be considerable.

In several patients where the provocation was positive there was a flare-up of the original dermatitis. Since no regular pattern of other skin reaction was observed every cutaneous eruption occurring during the course of a contact dermatitis should be suspected to be elicited by an oral allergen.

In four of the sixteen positive patients a toxiderma-like rash appeared. It is thus possible that non-explained "drug reactions" in clinical practice may be the expression of a contact allergy. Consequently, it might be worthwhile to consider epicutaneous testing in that patient category.

In their feeding experiments Baer and Leider (1), and Sidi and Melki (12) worked with the para-amino group of contact allergens, Schleiff (11) with chromate. Concerning low-absorbable neomycin and hydroxy-quinolines no systematic provocation has been made previously. Pirilä and Rantanen (9) reported, however, one case of positive oral provocation with neomycin in a case of contact allergy to this substance, and the corresponding result was obtained by Leifer and Steiner (6) in one patient with contact allergy to a hydroxy-quinoline. Sidi and Melki (12), as well as Schleiff (11), stated that only small amounts of oral allergens were needed to evoke a skin reaction. The present systematic study—with frequent positive results using a small dose of a low-absorbable agent—confirms these earlier isolated findings.

In the treatment of hepatic cirrhosis and in preparative therapy for bowel surgery neomycin is given in daily doses of 6–8 g. With a good renal function 1–3 % of oral neomycin is excreted in the urine and

Table 1. *Provocation with neomycin*

Patients			Diagnosis	Result of provocation	Flare-up of original dermatitis	Flare-up of test	Other skin reaction	Other reaction
No.	Age	Sex						
1	73	F	Ulcus venosum crur.	+	−	+	−	Nausea
2	58	F	Eczema crur. amb.	+	+	+	Vesicular eruption of palms	−
3	82	F	Ulcus et eczema venosum crur.	+	−	+	−	Nausea, general itching
4	68	M	Ulcus et eczema venosum crur.	+	+	+	Papular rash of back and groins	General itching
5	66	F	Ulcus et eczema venosum crur.	+	−	+	Scattered papules of back	Itching of legs
6	77	F	Ulcus et eczema venosum crur.	+	−	−	Vesicular eruption of palms	−
7	68	M	Ulcus et eczema arteriale crur.	+	+	−	−	Nausea, vomiting
8	59	F	Ulcus venosum crur.	+	−	−	Vesicular eruption of palms	General itching
9	54	F	Eczema crur. amb.	+	+	+	General dermatitis	General itching
10	78	F	Ulcus et eczema venosum crur.	+	+	−	−	−
11	66	F	Ulcus et eczema venosum crur.	−	−	−	−	−
12	68	F	Eczema ped. amb.	−	−	−	−	Itching of soles

plasma values are usually non-measurable (5, 15). Hydroxy-quinolines are probably absorbed from the intestinal tract in a somewhat higher degree than is usually assumed. These compounds are metabolized and to a certain extent excreted in the urine as conjugates, which explains the low urinary levels obtained with regular methods (2, 7). Plasma levels of neomycin and of hydroxy-quinolines in our patients may nevertheless be deduced to be very low considering the low dosage schedule.

The potency of a circulating antigen to elicit a focal contact eczematous reaction, even a generalized rash, was early established in the experimental animal by Sulzberger (13). The mechanism by which this effect is mediated is unknown. Mayer (8), feeding guinea-pigs highly sensitive to p-phenylene-diamine with huge amounts of this substance, had only negative results. The assumption that flare-up reactions after systemic administration of contact allergens was mediated through cell-bound antibodies was recently challenged by Polák and Turk (10). Considering the histologic picture, the non-inhibitory effect of anti-lymph node permeability serum factor, the inhibitory effect of antipolymorphonuclear leukocyte serum and the short eliciting time in these provocation experiments, they concluded that humoral antibodies were of greater importance. A short eliciting time—a matter of hours—found in some of our patients is compatible with the hypothesis of the flare-up reaction as essentially different in pathogenesis compared with the original dermatitis.

Table 2. *Provocation with hydroxy-quinolines*

Patients			Diagnosis	Result of provocation	Flare-up of original dermatitis	Flare-up of test	Other skin reaction	Other reaction
No.	Age	Sex						
1	73	F	Ulcus et eczema venosum crur.	±	±	—	—	—
2	77	F	Ulcus et eczema venosum crur.	±	—	—	Scattered papules on arms	—
3	58	M	Eczema palpebrarum	±	+	—	General papular dermatitis	—
4	68	M	Ulcus et eczema venosum crur.	±	±	—	—	Itching of legs
5	68	F	Ulcus et eczema venosum crur.	±	+	—	Scattered papules on right thigh	Itching of legs and test
6	66	F	Ulcus et eczema venosum crur.	±	±	—	—	—
7	60	M	Ulcus et eczema venosum crur.	—	—	—	—	—
8	76	F	Ulcus venosum crur.	—	—	—	—	—
9	84	F	Ulcus et eczema venosum crur.	—	—	—	—	—

SUMMARY

Twenty-one patients with contact allergy to neomycin or hydroxy-quinolines were challenged orally with these allergens respectively. Positive results were obtained in sixteen patients: flare-up of original dermatitis, flare-up of test reaction, and/or some other cutaneous eruption. The clinical implication and possible pathogenetic mechanism is discussed.

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