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Clinical Response to Gold as a Circulating Contact Allergen*

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In order to study the flare-up of contact allergy, 35 patients with a contact allergy to gold were given an intramuscular injection of 10 mg gold sodium thiomalate, i.e. the anti-rheumatic drug Myocrisin®. Clinical reactions comprised an eczematous flare-up of previously positive patch tests to gold and of a previous dermatitis, which occurred in 80% and 26%, respectively; a toxicoderma-like rash in 46%; and a transient fever in 60%. With the antigen rapidly reaching the blood-stream, the technique provides an experimental human model for studying flare-up mechanisms in contact allergy. ***Key words: contact allergy; systemic provocation; gold sodium thiomalate; flare-up; fever; toxicoderma.***

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An allergic contact dermatitis is often more widely distributed than might be explained by direct exposure to the eliciting antigen. This fact has been particularly well documented in nickel dermatitis (1–4), and the clinical features are often similar to those of "allergids" occurring in hypostatic dermatitis (5). The entity has been named "endogenous contact dermatitis" (6). During the past 30 years, many provocation studies with different antigens have been carried out to elucidate the pathogenesis of endogenous contact dermatitis (7). In these studies, protocols have implied systemic exposure by an oral route. During the last decade of the 20th century gold has emerged as a frequent contact allergen, demonstrated by introducing gold sodium thiosulphate (GSTS) in a standard patch test series (8). The high frequency of gold allergy in patients with eczematous disease has been confirmed by several test laboratories around the world.

Patients with contact allergy to GSTS are also allergic to other monovalent gold salts, among them gold sodium thiomalate (GSTM) (9). This compound happens to be a drug (Myocrisin®), which is frequently used for rheumatoid arthritis and usually given in weekly intramuscular injections. Such treatment is often started with a "test dose" of 10 mg in order to avoid unnecessary side-effects, which, nevertheless, sometimes do occur (10). The systemic exposure to GSTM in patients with contact allergy to gold has been used as an experimental model for endogenous contact dermatitis, for the first time by a parenteral route. In the following, the experience from 35 such provocations is presented.

MATERIAL AND METHODS

The patient material was collected from 4 experimental studies (11–14). The patients had earlier been investigated with standard patch testing because of eczematous disease and found to be positive to GSTS 0.5% pet. The test material was Finn chambers® on Scanpor®. After obtaining permission from the ethics committee of Lund University Medical Faculty and informed consent from the patients they volunteered to participate in the study.

In order to ascertain the contact allergy the patients were once again tested with GSTS, now in an aqueous dilution series in 9 steps from 5.0% with a dilution factor of $\sqrt{10}$. All tests were read on day 7 only, the optimal reading time for GSTS (15). One week to 2 months after test application the patients were given a single intramuscular injection of 0.5 ml 20 mg/ml GSTM (Myocrisin®, Rhône-Poulenc Rorer, Helsingborg, Sweden).

RESULTS

Patch testing with a dilution series of GSTS in the 35 patients showed a varying strength of hypersensitivity, with a positive test threshold from 5.0% down to 0.016%, the most frequent endpoint being 0.5%.

Clinical reactions to the systemic provocation with GSTM are presented in Table I. There were 3 types of reaction: eczematous flare-up, toxicoderma and fever. The most common reaction type was a flare-up of healing, positive patch tests (Fig. 1), whereas a reactivation of a previous dermatitis occurred in every fourth case only.

A toxicoderma-like eruption was observed in about half the patients, usually in the form of a maculo-papular rash (Fig. 2), in a few cases as oedema of hands and fingers or urticaria. The rise in body temperature, sometimes accompanied by widespread muscle ache, was noted a couple of hours after the injection, reached a maximum of 38–39°C after 10–12 h, and was usually normalized after 24 h. A

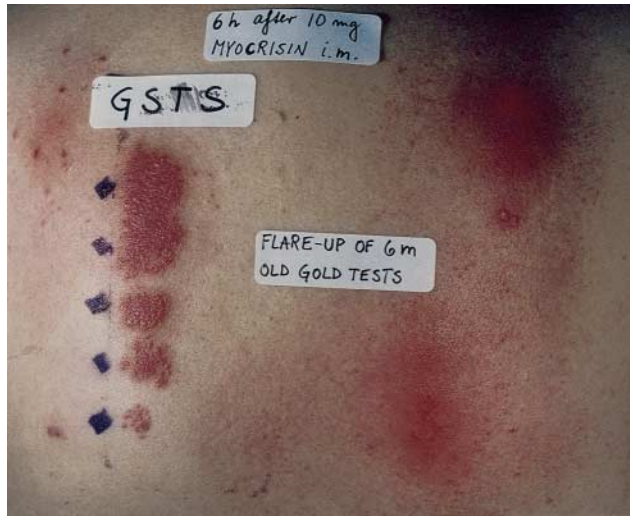

Fig. 1. Flare-up of positive patch tests (*left*) and intradermal tests (*right*) to gold sodium thiosulfate 6 h after i.m. injection of gold sodium thiomalate. Patch tests and i.c. tests had been applied 1 month and 6 months, respectively, before the provocation.

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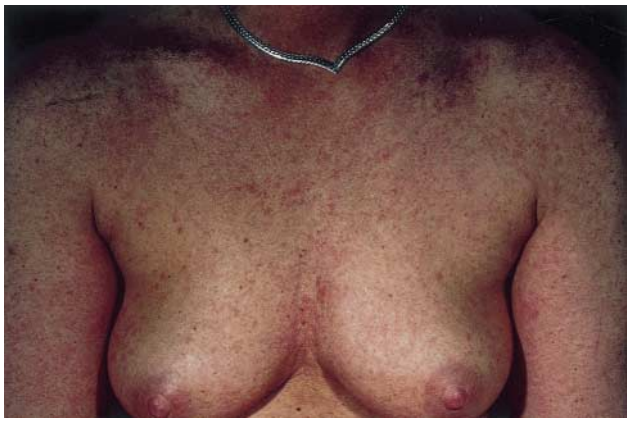

Fig. 2. Toxicoderma: papular exanthema 24 h after systemic provocation in a patient with contact allergy to gold.

combination of toxicoderma and fever occurred in 13/35 patients, 3 patients having toxicoderma only and 8/35 fever only of these 2 signs.

DISCUSSION

An eczematous flare-up after systemic provocation occurred in 80% of healed or subsiding patch tests, only in 26% of a previous dermatitis (Table I). This might be explained by the fact that the patients' dermatitis had different lengths of history and, furthermore, may have been caused by another disease process (nummular eczema, other concomitant allergens, etc.). However, a varying degree of cross-reactivity may also play a role. The flare-up is clearly specific in nature; an irritant dermatitis is not reactivated by a circulating allergen (16), and only the particular allergen given systemically can reactivate the eczematous process (11, 16).

A toxicoderma-like eruption occurred in about half the patients with clinical features similar to an endogenous dermatitis. Eczematous flare-up reactions as well as general rashes have also been described in patients with nickel allergy ingesting nickel sulphate capsules. For the flare-up reactions after nickel provocation in patients with a nickel allergy there is a dose-response relationship (16–21, present study).

The time lapse between application of the GSTS patch tests and the systemic provocation varied from 1 to 8 weeks. In spite of findings to the contrary with oral provocations in nickel allergy (17), there was no correlation between the length of this lapse and the occurrence of clinical reactions. Nor was there any correlation between the strength of contact allergy to GSTS and the occurrence or intensity of clinical reactions.

A vigorous, but transient, rise in body temperature was a noteworthy and frequent event, accompanied by an influenza-like feeling, during the first 24 h after provocation. Although many patients with rheumatoid arthritis have a gold allergy (22), such events have not been reported when these patients are treated with GSTM in 10–50 mg doses. The fever might be compared to the Jarisch-Herxheimer reaction frequently observed when starting penicillin therapy in secondary syphilis, and a release of C-reactive protein has been demonstrated in both conditions (12, 23).

Table I. *Clinical reactions to systemic GSTM provocation in 35 patients with contact allergy to gold*

Number of patients with			
Eczematous flare-up of previous		Toxicoderma	Fever
Test site	Dermatitis		
28 (80%)	9 (26%)	16 (46%)	21 (60%)

Fever has not been reported after systemic provocation in nickel allergy. A possible explanation might be a more protracted bioavailability, instead of a peak, after oral provocation. A rise of body temperature has, however, been documented after oral provocation in contact allergy to sulphonamides (24) and to synergistins (25). Similar phenomena have been reported after handling lauryl ether sulphate (26); in this case a percutaneous resorption of the allergen had to be surmised.

The flare-up of healed positive patch tests can be visualized within the first hour after intramuscular provocation and reaches a maximum with strongly increased cutaneous blood flow after 6–8 h (14). A reactivation of epicutaneous as well as intradermal tests has been observed up to 2 years after the original application (11), which is evidence for a local immunological memory after the previous allergic contact dermatitis (27). A significant part of this tissue priming seems to comprise memory T-cells and endothelial leukocyte adhesion molecules; in the reactivation process, mast cells and blood-borne monocytes seem to play essential roles (28).

In conclusion, parenteral provocation in contact allergy to gold provides an easily monitored, experimental human model for studying the pathogenesis of endogenous contact dermatitis with special reference to clinical, biochemical and immunohistochemical aspects of the flare-up mechanism. If, during the course of an allergic contact dermatitis, the clinical picture resembles the reactions observed after the present provocations, a circulating contact allergen should be suspected.

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