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Contact Allergy to Gold and Gold Therapy in Patients with Rheumatoid Arthritis

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Patients with rheumatoid arthritis were investigated for contact allergy to gold in connection with treatment with gold preparations. There were 57 patients with rheumatoid arthritis previously treated with gold, with or without cutaneous side-effects, as well as 20 patients intended for such treatment; all were exposed to patch and intradermal tests with gold sodium thiosulfate, gold sodium thiomalate and auranofin. Contact allergy to gold was demonstrated in 8 out of 77 patients (10.4%). In the retrospective material, gold allergy was found in 1.8%, in the prospective material in 35.0%.

Contact allergy to gold is very frequent among patients with rheumatoid arthritis before gold therapy. In order to avoid early hypersensitivity reactions skin tests should be carried out before gold therapy is instituted. ***Key words: gold sodium thiosulfate; gold sodium thiomalate; auranofin; patch test; intradermal test.***

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Gold salts have for many decades constituted an important group of drugs for the treatment of patients with rheumatoid arthritis (RA). Within the last two decades auranofin, oral gold triethylphosphin, has also been introduced. Side-effects often occur, however, with all gold preparations, and with regard to cutaneous reactions they take a leading position if frequency of use is taken into account (1). Traditionally, the cutaneous side-effects are named "gold dermatitis", although no uniform clinical entity has been described. Under this heading there are reports on lichenoid dermatitis, reactions similar to seborrhoeic dermatitis and pityriasis rosea as well as various rashes and cases of non-specific dermatitis (2–7). Nor is there any agreement on a typical histopathological picture of this side-effect (8, 9).

In recent clinical-experimental studies (10, 11) we have found that patients with contact allergy to gold react within hours with a rise of body temperature and a vigorous flare-up of healed patches of contact dermatitis if given gold sodium thiomalate (GSTM), even in a so-called test dose of 10 mg i.m. The relationship between these early hypersensitivity reactions and the much later appearing "gold dermatitis" is at present unknown.

Contact dermatitis to metallic gold is extremely rare, mainly because contact allergy to the metal or to gold salts has been difficult to demonstrate. Recent data with the use of proper allergens and test concentrations show, however, a high frequency of contact allergy to gold in patients investigated for eczematous disease (12–14). Contact allergy to gold may thus be demonstrated by patch-testing with gold sodium thiosulfate (GSTS) and/or GSTM, as well as by intradermal testing with these salts (15).

With this new test procedure we found it warranted to perform skin tests for cell-mediated gold allergy in patients with RA after treatment with gold salts and auranofin, with or without side-effects. We also wanted to look for presence of contact allergy to gold in patients intended for gold therapy, i.e. as a prospective study.

MATERIAL AND METHODS

Patients

The study was carried out during the years 1994–1996 in collaboration between dermatologists and rheumatologists in Kristianstad and Malmö, two cities in southern Sweden. In Kristianstad all patients diagnosed with RA in the department of rheumatology were invited to participate in the study, if they had previously been treated with gold preparations or were intended to be. In Malmö, the same type of patients were recruited, not only, however, from the department of rheumatology but also from private practice.

In this study, a patient who for some reason at any time had been treated with a gold compound was referred to the retrospective group. All patients who were intended for such treatment were referred for skin testing before it was started. This prospective group comprised patients who had never been given treatment with a gold preparation.

In total, 79 patients with RA were invited to the study but 2 refused skin testing. Therefore, 77 patients were studied: 56 females, aged 18–78 years, and 21 males, aged 34–77 years. The classification criteria of the American Rheumatism Association (16) were followed.

Before test applications the patients answered a questionnaire about subjective sensitivity to metallic gold. Pharmacological treatment at the time of testing was also noted. The patients gave informed consent, and permission for the study was obtained from the ethics committee of the Medical Faculty, Lund University.

Test material and procedure

All 77 patients were patch-tested with the Swedish standard series, supplemented with GSTS 0.5% and 2.0% in petrolatum (pet) from Chemotechnique Diagnostics and GSTM (Myocrisin® Rhône-Poulenc Rorer) 36.0% pet (3 patients with 11.5% only). Auranofin (Ridaura® SmithKline Beecham) was tested 47.5% pet (the highest dispensable concentration) in 61 patients. In addition, 27 and 7 patients were patch-tested with GSTS 5.0 and 10.0% pet, respectively. The testing was performed with Finn chambers® and Scanpor® on the back, with an application time of 48 h. In 58 patients intradermal tests were carried out on the volar aspect of the forearm, using 0.55 mM saline solutions of GSTS and GSTM, in 27 cases also with auranofin. The varying test protocols among the patients were due to different availability of the test materials.

All tests were read 3 and 7 days after application. The ICDRG criteria (17) were followed when reading the patch test reactions. For the intradermal tests, an inflammatory reaction with an infiltration ≥ 5 mm was required to be considered positive.

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Side-effects

Mucocutaneous reactions which appeared after introduction of gold therapy and for which no other causes could be held responsible were regarded as possible adverse reactions to gold. If the reaction disappeared with dose reduction or discontinuation of gold therapy, it was classified as a probable adverse reaction. A definite side-effect was assigned when a rechallenge with a gold compound was positive. All patients instituted on gold therapy after testing were followed for at least 2 months in order to register any cutaneous side-effects.

Statistics

Statistical calculation was performed with Fisher's exact two-sided test.

RESULTS

Skin testing for contact allergy to gold was thus performed in 77 patients with RA. The test battery contained three gold compounds in different concentrations, and the epicutaneous as well as the intradermal route was used for the tests. Hereby, 8 patients (10.4%) with contact allergy to gold were found in the material. The test results of these patients are presented in detail in Table I. Evidence of gold allergy was based on epicutaneous tests with GSTS in 7 cases, with GSTM in 6 cases, with auranofin in 2 cases, and by intradermal testing in 5 cases. In 3 patients the positive tests were delayed about 2 weeks from application.

Gold allergy was observed in 1/57 patients in the retrospective group (1.8%) and in 7/20 patients in the prospective group (35.0%). This difference was highly significant ($p<0.001$).

Gold dermatitis, possible or ascertained, had occurred in 7/57 patients in the retrospective group (12%), by definition in no case in the prospective group. Gold dermatitis and a positive skin test to gold were observed in one patient (no. 2). A subjective sensitivity to metallic gold was reported by 3 other patients (nos. 7 and 19 in the prospective group with positive gold tests and no. 63 in the retrospective group with negative gold tests).

Contact allergy to one or more allergens in the standard series was found in 20/57 patients in the retrospective group (35%) and in 4/20 patients in the prospective group (20%).

Many patients were treated with remission-inducing drugs at the time of skin testing, primarily with prednisolone (2.5–10 mg daily), methotrexate, or gold preparations (GSTM or auranofin), as well as various analgetics and non-steroidal anti-inflammatory drugs. Prednisolone was taken by 23/69 gold-negative patients (33%) and by 4/8 gold-positive ones (50%). Methotrexate was taken by 6/69 gold-negative patients and by none (0/8) in the gold-positive group.

Among the 27 patients on prednisolone, contact allergy to one or more standard allergens was demonstrated in 7 cases. And *vice versa*: among the 24 patients with such an allergy, 7 were on prednisolone, 17 were not. There were 16 patients treated with gold preparations. Contact allergy to standard allergens occurred in 6/11 patients given GSTM, and in 1/5 patients on auranofin.

DISCUSSION

In the present material of patients with RA many individuals complained of skin reactions, in some cases attributed to their medical treatment. Among our 77 patients we found 10.4% positive skin tests to gold, which is about the same frequency as that demonstrated in our patients with suspected allergic contact dermatitis. These latter patients were, however, tested only with a standard preparation of GSTS 0.5% pet (in cases with a doubtful test result also intradermally with GSTS). Since we have noticed that a higher frequency of positive tests may be obtained with a higher test concentration, without increasing the risk of irritant reactions (to be published), we sought in the present study to improve the technique by using higher concentrations of GSTS, by adding other gold substances, and by supplementing with the intradermal method. If only our regular test procedure had been used, the frequency of contact allergy to gold in our rheumatic patients would have been 5.2%. On the other hand, if our extended test battery had been used in all 77 patients, the incidence of contact allergy to gold would probably have exceeded the 10.4% actually observed. Obviously, it would be of great interest to know the frequency of contact allergy to gold in the healthy population; such a study has not, to the best of our knowledge, been published.

The mechanism of the mucocutaneous side-effects to gold is unknown, but there are indications that these effects may have toxic as well as allergic origins (7). Reinstitution of gold therapy after healing of mucocutaneous signs has shown different results. Thus, 9 of 12 patients who were rechallenged (7) experienced a second episode of mucocutaneous reactions. These were similar to the first episode but appeared earlier, speaking in favour of an allergic mechanism. The outcome of

Table I. *Patients with rheumatoid arthritis with contact allergy to gold*

Pat No	Patch tests						Intradermal tests			Notes
	GSTS %				GSTM	Auranofin	GSTS	GSTM	Auranofin	
	0.5	2.0	5.0	10.0						
R 2	?	?	+	+	+	–	–	–	–	
P 7	–	+	++	++	++	nt	(+)	(+)	nt	Delayed
P 8	–	?	+	+	?	nt	(+)	(+)	nt	Delayed
P 15	?	(+)	(+)	nt	(+)	+	+	+	+	
P 19	–	–	–	nt	–	–	–	+	+	
P 29	++	++	++	++	++	nt	++	++	nt	Delayed
P 65	+	+	nt	nt	+	–	nt	nt	nt	
P 77	+	++	nt	nt	++	+	nt	nt	nt	

R = retrospective, P = prospective. Test results indicated according to ICDRG. nt = not tested; Delayed = the tests took 2 weeks to become positive. GSTS: gold sodium thiosulfate; GSTM: gold sodium thiomalate.

a second course seems, however, also to be a question of dosage. Thus, Klinefelter (2) reported a successful reinstitution of gold therapy in 28 of 30 patients with mucocutaneous reactions. Here, the therapy started with a low dose of 1–10 mg GSTM and was gradually increased at each injection to a maximum of 50 mg. Seven patients had a flare of their dermatitis which was controlled with dose adjustment and, in some cases, specific treatment.

In the present material, only one case of contact allergy to gold was observed among patients previously given gold preparations, which seems to speak against such a mechanism being of pathogenetic importance for the majority of skin complications in the case of gold therapy. There were, however, very few cases of ascertained "gold dermatitis" in the present material. The majority of skin diseases observed in our rheumatic patients were given other dermatologic diagnoses and were considered to be independent of the gold therapy.

The low frequency of contact allergy to gold in our retrospective material is probably not explained by other drugs given at the time of skin testing. True, patients were treated with anti-inflammatory drugs, which theoretically might diminish or abolish positive skin tests. They were, however, given in low doses, e.g. prednisolone in doses less than 20 mg per day, which is considered not to influence the development of skin tests (18). Furthermore, many previously gold-treated patients had positive patch tests to allergens in the standard series, actually more than in the prospective material. Apparently, they had no "immunoparalysis" with regard to cell-mediated allergy, which has been suggested to prevail in RA (19). The low frequency of delayed hypersensitivity seems to hold true for the gold compounds in particular. Interestingly, Goldermann et al. (6), when patch-testing patients with gold dermatitis, found no reactions to different gold salts but a few positive tests among the controls. Also patch testing with low concentrations of potassium dicyanoaurate was negative in patients with gold dermatitis (5).

In a paper published in 1935, Lichtenstein (20) reported on patch test findings in tuberculosis patients treated with gold preparations. He used GSTS 33% in lanolin and found a high number of positive tests after gold treatment, particularly in patients with cutaneous adverse reactions, while patients without such treatment were always test-negative. Lichtenstein also noted that 10 of 27 patients, patch-tested every week, developed positive patch tests to gold during the treatment course. These test results, albeit open to critic from methodological aspects, are certainly interesting since our findings were quite the opposite and most surprising: a high frequency of contact allergy to gold in our prospective material, 35% of tested patients. Even if our multiple test procedure is taken into account, gold allergy was more frequent than in patients routinely investigated for eczematous disease. Most probably, our patients had been sensitized by contact with metallic gold, e.g. in jewelry (21).

As indicated in Table I, the test reaction in 3 of our gold-positive patients was delayed up to 2 weeks after application. This phenomenon is not unusual when patch-testing with gold salts (22) and might lead to mistakes: first, a positive test may be missed if read only during the first week; second, a late reaction might be interpreted as active sensitization. Nevertheless, the possibility of such active sensitization in these 3 cases cannot entirely be ruled out. A delayed positive test is indicated by redness and itching. Therefore, it is highly improbable that more patients than these 3 had late – and consequently false negative – test reactions.

There is immunohistochemical evidence that cell-mediated hypersensitivity mechanisms are activated during therapy with gold preparations (9), and gold-specific T-cells are obviously generated (23, 24). In this light, it is difficult to comprehend the almost non-existing gold allergy in our rheumatic patients after long-term administration of gold compounds by the intramuscular or oral route. The negative test results might possibly be explained by a hyposensitization phenomenon. This has been demonstrated to occur in contact allergy to urushiol and nickel sulphate after repeated oral administration of the allergen (25, 26).

If possible, the early cutaneous and general hypersensitivity reactions occurring frequently in patients with contact allergy to gold given gold injections (10, 11) should be avoided. We therefore conclude that patients intended for treatment with gold preparations should probably first be properly skin-tested. With present experience a simple patch test with GSTS 0.5% is obviously not sufficient.

A positive skin test to gold may not necessarily contraindicate further treatment with gold preparations. Two of our gold-allergic patients (P 65, P 77 in Table I) were given a starting dose of only 5 mg GSTM i.m., which was then gradually increased. Here, no mucocutaneous complications occurred. This seems to indicate that contact allergy to gold may be disregarded using carefully selected doses. Nevertheless, pretreatment skin testing is recommended.

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REFERENCES

1. Swanbeck G, Dahlberg E. Cutaneous drug reactions. An attempt to quantitative estimation. Arch Dermatol Res 1992; 284: 215–218.
2. Klinefelter HF. Reinstitution of gold therapy in rheumatoid arthritis after mucocutaneous reactions. J Rheum 1975; 2: 21–27.
3. Gibbons RB. Complications of chrysotherapy. A review of recent studies. Arch Intern Med 1979; 139: 343–346.
4. Thomas I. Gold therapy and its indications in dermatology. A review. J Am Acad Dermatol 1987; 16: 845–854.
5. Svensson Å, Theander J. Skin rashes and stomatitis due to parenteral treatment of rheumatoid arthritis with sodium aurothiomalate. Ann Rheum Dis 1992; 51: 326–329.
6. Goldermann R, Schuppe H-C, Gleichmann E, Kind P, Merk H, Rau R, et al. Adverse immune reactions to gold in rheumatoid arthritis: lack of skin reactivity. Acta Derm Venereol (Stockh) 1993; 73: 220–222.
7. van Gestel A, Koopman R, Wijnands M, van de Putte L, van Riel P. Mucocutaneous reactions to gold: a prospective study of 74 patients with rheumatoid arthritis. J Rheum 1994; 21: 1814–1819.
8. Penneys NS, Ackerman AB, Gottlieb NL. Gold dermatitis. A clinical and histopathological study. Arch Dermatol 1974; 109: 372–376.
9. Ranki A, Niemi K-M, Kanerva L. Clinical, immunohistochemical, and electron-microscopic findings in gold dermatitis. Am J Dermatopathol 1989; 11: 22–28.
10. Möller H, Larsson Å, Björkner B, Bruze M, Hagstam Å. Flare-

up at contact allergy sites in a gold-treated rheumatic patient. Acta Derm Venereol (Stockh) 1996; 76: 55–58.
11. Möller H, Björkner B, Bruze B. Clinical reactions to systemic provocation with gold sodium thiomalate in patients with contact allergy to gold. Br J Dermatol 1996; 135: 423–427.
12. Björkner B, Bruze M, Möller H. High frequency of contact allergy to gold sodium thiosulfate. An indication of gold allergy? Contact Dermatitis 1994; 30: 144–151.
13. McKenna KE, Dolan O, Walsh MY, Burrows D. Contact allergy to gold sodium thiosulfate. Contact Dermatitis 1995; 32: 143–146.
14. Sabroe RA, Sharp LA, Peachey RDG. Contact allergy to gold sodium thiosulfate. Contact Dermatitis 1996; 34: 345–348.
15. Bruze M, Björkner B, Möller H. Skin testing with gold sodium thiomalate and gold sodium thiosulfate. Contact Dermatitis 1995; 32: 5–8.
16. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315–324.
17. Fregert S. Manual of contact dermatitis. 2nd edn. Copenhagen: Munksgaard, 1981: 71–76.
18. Wahlberg JE. Patch testing. In: Rycroft RJG, Menné T, Frosch P, Benezra C, eds. Textbook of contact dermatitis. Berlin: Springer Verlag, 1992: 258.
19. Smith MD, Smith A, O'Donnell J, Ahern MJ, Roberts-Thomson PJ. Impaired delayed type cutaneous hypersensitivity in rheumatoid arthritis reversed by chrysotherapy. Ann Rheum Dis 1989; 48: 108–113.
20. Lichtenstein MR. The patch test for gold hypersensitivity. J Allergy 1935; 6: 460–463.
21. Bruze M, Edman B, Björkner B, Möller H. Clinical relevance of contact allergy to gold sodium thiosulfate. J Am Acad Dermatol 1994; 31: 579–583.
22. Bruze M, Hedman H, Björkner B, Möller H. The development and course of test reactions to gold sodium thiosulfate. Contact Dermatitis 1995; 33: 386–391.
23. Schuhmann D, Kubicka-Muranyi M, Mirtschewa J, Günther J, Kind P, Gleichmann E. Adverse immune reactions to gold. I. Chronic treatment with an Au(I) drug sensitizes mouse T cells not to Au(I), but to Au(III) and induces autoantibody formation. J Immunol 1990; 145: 2132–2139.
24. Romagnoli P, Spinas GA, Sinigaglia F. Gold-specific T cells in rheumatoid arthritis patients treated with gold. J Clin Invest 1992; 89: 254–258.
25. Epstein WL, Byers VS, Frankart W. Induction of antigen specific hyposensitization to poison oak in sensitized adults. Arch Dermatol 1982; 118: 630–633.
26. Sjövall P, Christensen OB, Möller H. Oral hyposensitization in nickel allergy. J Am Acad Dermatol 1987; 17: 774–778.