

Long-lasting patch reactions to gold sodium thiosulfate occurs frequently in healthy volunteers

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In a skin irritancy study in healthy volunteers with 3 metal salts, aqueous gold sodium thiosulfate (GSTS) in a dilution series caused unexpectedly frequent and strong patch test reactions on volar forearm skin in 22 of 31 participants (71%). The reactions showed morphological features consistent with a contact allergic reaction, and the crescendo type of the response speaks in favour of an allergic nature. Further, 8 of the 31 (26%) developed long-lasting test reactions. A follow-up interview among 28/31 participants 10 years later showed that none had experienced long-term consequences in the form of skin and/or mucosal complaints related to exposure to gold items. The results indicate that inclusion of GSTS in routine patch testing may cause problems regarding interpretation and clinical relevance of positive GSTS patch tests, which fulfil the clinical criteria of a contact allergy.

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Patch tests with some metal salts, including various gold salts, may provoke in eczema patients positive test reactions, which are unexplainable from a clinical point of view. Positive patch test reactions to gold sodium thiosulfate (GSTS) most often show clinical reaction patterns consistent with contact allergic reactions, and they have been reported to occur with a frequency of up to 8–10% in consecutive eczema patients. However, the clinical relevance is difficult to ascertain, and most patients with a positive reaction to GSTS are able to wear gold jewellery and have gold teeth without any skin problems. Further, positive GSTS reactions may persist for weeks or months (1–5). The possible explanations for long-lasting test reactions include slow elimination of the allergen at the reaction site or a tendency to elicit chronic inflammation (1, 6). Gold salts have been used in pathology to stain Langerhans' cells, and gold salts like aurothiomalate are also used as immunosuppressants and modulators mainly in the treatment of rheumatoid arthritis. Ionic gold, contrary to metallic gold, is chemically very reactive, which probably contributes to the skin reaction characteristics of gold salts.

In 1995, we designed a trial to evaluate in healthy volunteers the skin irritant properties of 3 metal salts: GSTS, thimerosal and nickel chlo-

ride. GSTS has been reported to have a low frequency of irritant reactions compared with other gold salts (7, 8).

Materials and methods

A total of 31 healthy volunteers, 23 women and 8 men, aged 20–45 years, without previous skin disease or known allergy to test chemicals were recruited. The study was performed according to the Helsinki Declaration II and approval was obtained from the local ethical committee (no. 95/11). All the test substances were of analytical grade and were mixed in isotonic saline solution in suitable test concentrations. GSTS was >99% pure and obtained from Pfaltz & Bauer, Waterbury, CT, USA. The participants were patch tested with 5 patches on the volar aspect of each forearm. The total of 10 patches included isotonic saline as control and the 3 substances, each in 3 concentrations. Hill Top Chambers[®] (19 mm) (Hilltop, Cincinnati, OH, USA) HillTon Chambers[®] (19 mm) with Webril[®] pads (Hill-Ton, Cincinnati, OH, USA) were used for application of the patch tests and fixed with Scanpor[®] tape (Norgesplaster A/S, Oslo, Norway). 100 µl test solution was applied to the chambers using a micro pipette.

A double-blind test design was used so the order of the test materials was unknown to the investigator and the volunteer until the study was completed. The test sites on the arms were rotated between subjects to counteract the regional variation in skin reactivity. The chambers were removed after 2 days and read on day (D) 2, D4, and D7. The reactions were scored in descriptive terms, by registration of subjective complaints as itching, burning, and stinging, and by using a visual ranking scale: –, no reaction; +?, spotty erythema; +, uniform erythema; ++, erythema and infiltration; +++, vesiculo-papular erythematous infiltration.

Aqueous solutions of 0.5%, 1%, and 2% GSTS were applied to the first 20 subjects, but due to strong test reactions, the remaining 11 subjects were tested with 0.25%, 0.5%, and 1% GSTS. Aqueous thimerosal was applied in concentrations of 0.025%, 0.05%, and 0.1%, and aqueous nickel chloride in concentrations of 0.25%, 0.5%, and 1%.

Results

22 of 31 participants (71%) had within 7 days a skin reaction to at least one of the GSTS concentrations ranging in strength from spotty erythema to an infiltrated papulo-vesicular, crescendo type reaction consistent with an allergic reaction (Table 1). Eight of the 31 individuals (26%) developed strong, long-lasting test reactions to GSTS. Six of these had a spotty erythema as the highest score during the first week. The study design concentrated on skin irritancy, and late readings were not planned in advance.

Based on the initial findings, 12 subjects were called back between 14 and 33 days after for a late reading, and in 8 of them we found a delayed, crescendo-pattern positive reaction. One was read D99 and still had an infiltrated erythematous reaction (no. 22). Based on the unexpected high frequency of strong test reactions in healthy volunteers compatible with allergic reactions, the study was terminated.

10 years later (in 2005), 28 of the 31 participants were contacted by phone and interviewed regarding the possible consequences of the GSTS patch test reactions. All reported that the skin reactions disappeared after few to several weeks and they had not had any skin and/or mucosal problems since. However, as the trial was performed 10 years previously, some had difficulties remembering in detail the course of their reactions. None of the subjects reported any problems with gold items in contact with skin or oral cavity. An association between the strength of the patch test reac-

tion to GSTS and persistence of the reaction was not seen.

Skin biopsies from late reactions from two of the participants showed identical features of superficial and deep dense perivascular lymphocytic infiltrates composed of both B and T cells. The infiltrates also contained many CD68+ histiocytes, focally in a granulomatous pattern. Only a few eosinophils were seen, and the epidermis was completely normal, in particular, without spongiogenesis. The overall features were those of an early pseudolymphoma, as described before (9).

The results of thimerosal and nickel chloride will not be discussed in detail. Nickel generated only mild irritation in a few subjects, but produced allergic reactions in 3. Thimerosal produced very strong reactions in 5 volunteers and was evaluated as allergic reactions related to previous childhood vaccinations. Alleged irritative responses were seen in 11 subjects.

Discussion

GSTS in concentrations up to 5% in aqueous solution is reported to be non-irritant when tested in ordinary Finn Chambers containing 20 μ l (1). It was considered whether the large Hill Top Chambers used for patch testing in this experiment contributed to the generation of frequent and strong reactions to gold in the healthy volunteers. Stronger irritant and allergic patch test reactions with larger compared with smaller chambers have been described (10–13). However, it is suggested that the volume of test agent per square millimetre of chamber surface is decisive (10). In this study, the amount of test material per area was comparable with the routine test procedure, 2.8 μ l/mm² (100 μ l applied to 283 mm² in Hill Top chamber) versus 3.3 μ l/mm² (15 μ l applied to 50 mm² in Finn Chamber). Also, Löffler et al. (14) compared transepidermal waterloss (TEWL) values when the irritant sodium lauryl sulfate (SLS) was applied in different volumes and in different chamber sizes and did not find any significant difference.

The vehicle used may also influence the reactivity of GSTS. In this experiment, GSTS was diluted in an aqueous solution. In a Swedish study testing with aqueous GSTS resulted in weaker patch test reactions than with equivalent concentrations in petrolatum (15).

Incidentally, the mothers of two of the subjects with strong and persistent reactions to GSTS had been treated with gold salts for rheumatoid arthritis and had developed a gold-induced cutaneous drug reaction. It is tempting to speculate whether gold reactivity is regulated by genetic factors (16), but it may as well be purely coincidental.

Table 1. Test results of the participants in the study who had a skin reaction to at least 1 of the GSTS concentrations within 7 days

No.	Concentration (%)	D2	D4	D7	Late reading	No.	Concentration (%)	D2	D4	D7	Late reading
1	0.25	NT	NT	NT		12	0.25	NT	NT	NT	
	0.5	–	–	–			0.5	++	+	++	
	1	–	–	+			1	+	+	+	
	2	++	+	+			2	++	+	+	
2	0.25	NT	NT	NT		13	0.25	NT	NT	NT	NT
	0.5	–	–	–			0.5	+	–	–	++ (D23)
	1	–	–	–			1	+	+	+	++
	2	–	–	++			2	–	–	–	++
3	0.25	NT	NT	NT		14	0.25	+	++	+	+
	0.5	–	–	–			0.5	+++	+++	++	++
	1	+	–	–			1	+++	+++	++	++
	2	+	+	+			2	NT	NT	NT	NT
4	0.25	NT	NT	NT		15	0.25	–	–	–	–
	0.5	–	–	–			0.5	–	–	–	–
	1	–	–	–			1	++	+	+	++
	2	++	+	+			2	NT	NT	NT	NT
5	0.25	NT	NT	NT	NT	16	0.25	–	–	–	–
	0.5	–	–	–	– (D12)		0.5	+	–	–	–
	1	+	+	+	–		1	+	–	–	–
	2	+	+	+	++		2	NT	NT	NT	NT
6	0.25	NT	NT	NT	NT	17	0.25	–	–	–	–
	0.5	+	+	–	++ (D33)		0.5	–	+	+	–
	1	+	+	–	++		1	–	+	+	–
	2	++	+	+	++		2	NT	NT	NT	NT
7	0.25	NT	NT	NT	NT	18	0.25	+	–	–	–
	0.5	–	–	–	++ (D12)		0.5	+	–	–	–
	1	–	+	–	++		1	–	–	–	–
	2	–	+	–	++		2	NT	NT	NT	NT
8	0.25	NT	NT	NT		19	0.25	+	–	–	++ (D14)
	0.5	+	+	–			0.5	++	+	–	+
	1	–	–	–			1	++	++	–	++
	2	+	+	–			2	NT	NT	NT	NT
9	0.25	NT	NT	NT		20	0.25	+	–	–	–
	0.5	+	+	++			0.5	+	+	–	–
	1	+	++	++			1	+	+	–	–
	2	+	++	+++			2	NT	NT	NT	NT
10	0.25	NT	NT	NT		21	0.25	+	–	–	–
	0.5	+	–	–			0.5	–	–	–	–
	1	+	+	+			1	+	–	–	–
	2	++	+	–			2	NT	NT	NT	NT
11	0.25	NT	NT	NT		22	0.25	–	–	N/A	–
	0.5	–	+	+			0.5	–	–	N/A	–
	1	+	+	+			1	+	+	N/A	++
	2	+	+	+			2	NT	NT	NT	NT

NT, not tested.

However, patch testing with gold salts is still a scientific task because of deficient understanding of the nature of the many positive GSTS patch tests in eczema patients as well as in healthy volunteers. Inclusion of GSTS in a routine patch test series is of concern and gives rise to problems regarding interpretation and clinical relevance of positive GSTS patch tests fully compatible with contact allergic reactions.

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