

ORIGINAL ARTICLE

Positive reactions to gold sodium thiosulfate in patch test panels (TRUE Test) in Japan: A multicentre study

Kayoko Suzuki¹  | Akiko Yagami¹ | Akiko Ito^{2,3} | Atsuko Kato⁴ | Hitoshi Miyazawa⁵ | Hiromi Kanto⁶ | Kayoko Matsunaga^{1,3}

¹Department of Allergology, Fujita Health University Second Educational Hospital, Aichi, Japan

²Department of Dermatology, Nagata Clinic, Niigata, Japan

³Department of Integrative Medical Science for Allergic Disease, Fujita Health University School of Medicine, Aichi, Japan

⁴Department of Dermatology, Osaka Kaisei Hospital, Osaka, Japan

⁵Department of Dermatology, Nishi-Sapporo Skin and Allergy Clinic, Sapporo, Japan

⁶Department of Dermatology, School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan

Correspondence

Associated Professor, Dr Kayoko Suzuki, Department of Allergology, Fujita Health University Second Educational Hospital, 3-6-10 Otobashi, Nakagawa-ku, Nagoya 454-8509, Japan.
Email: kayokos@fujita-hu.ac.jp

Background: The proportion of positive test results with gold sodium thiosulfate included in a patch test panel (P-GST) had been found to be greater than that with gold sodium thiosulfate 0.5% pet. by allergEAZE (A-GST).

Objectives: To compare positive reactions to P-GST and A-GST, and to evaluate late reactions after the day (D) 7 reading.

Methods: A retrospective analysis was performed of 588 patients at participating departments (119 males; 469 females) who were patch tested with P-GST and A-GST in May 2015 to March 2016.

Results: Positive test reactions to P-GST and A-GST were observed in 15% and 6% of patients, respectively. Three patients reported a positive reaction occurring after the D7 reading.

Conclusions: Gold sodium thiosulfate often gives a positive reaction after 2 to 3 weeks, and, in such cases, the positive reaction may be sustained, so it is recommended to assess the reaction for up to 1 month after application.

KEYWORDS

active sensitization, gold sodium thiosulfate, late reaction, patch test

1 | INTRODUCTION

Patch testing is the standard method for determining the cause of contact dermatitis. The test is performed by placing a hapten sample on an investigator-loaded patch test chamber such as a Finn Chamber on Scanpor tape (SmartPractice, Phoenix, Arizona), and applying this on the back or the upper arm for 2 days. However, this method has the following disadvantages: (1) considerable time is required for preparing; (2) the amount of patch test preparation placed on the chamber is not consistent; and (3) in Japan, very few haptens used are covered by insurance.¹

To overcome the first 2 disadvantages, Fischer et al² proposed performing a patch test by applying a sample contained in a hydrophilic base onto a polyester support and applying this to adhesive tape. Thus, the Thin-layer Rapid Use Epicutaneous Test (TRUE Test) was developed. This product was subsequently put into clinical use,

and has been sold as a ready-to-use allergen patch test in Sweden since 1987 and in the United States since 1994; it is now available worldwide from SmartPractice. The current TRUE Test comprises 3 panels in total, with 12 different haptens in 1 panel.

In Japan, the TRUE Test contains allergens corresponding to the Japanese baseline series compiled in 2008 by the Japanese Society for Contact Dermatitis.³ It was approved as Patch Test Panel (S), and released by Sato Pharmaceutical (Tokyo, Japan) in May 2015. Subsequently, it was observed that more positive reactions occurred with Patch Test Panel (S) containing gold sodium thiosulfate (P-GST) than with gold sodium thiosulfate 0.5% pet. by allergEAZE (A-GST). Moreover, cases of late positive reactions to P-GST after the day (D) 7 reading were seen.

In the present study, we compared positive reactions to P-GST and A-GST, and we present 3 cases (cases 1–3) with late reactions to P-GST after the D7 reading. We also present another case (case 4) in

whom positive reactions to P-GST at D3 and D4 had disappeared by D7, but a flare-up granulomatous reaction at 3 months after patch testing was observed.

2 | PATIENTS AND METHODS

We retrospectively analysed 588 patients at participating departments (119 males; 469 females) who underwent P-GST patch testing from May 2015 to March 2016, involving readings until D7. Of these 588 patients, 406 (81 males; 325 females) were also patch tested with A-GST. Hence, 588 cases were analysed regarding patch test reactions to P-GST, and 406 cases were analysed to compare the reactions with A-GST.

The following 14 departments participated in this study: Osaka Kaisei Hospital, Kariya Toyota General Hospital, Kyoto Prefectural University of Medicine Graduate School for Medical Sciences, Showa University Fujigaoka Hospital, Joy Dermatological Clinic, Daiichi Clinic, Chigasaki Municipal Hospital, Chihiro Dermatological Clinic, Toho University Omori Medical Centre, Nagata Clinic, Nishi-Sapporo Skin and Allergy Clinic, Fujita Health University, Yokosuka General Hospital Uwamachi, and Yokohama City University.

Patch Test Panel (S) containing gold sodium thiosulfate 0.075 mg/cm² (P-GST), corresponding to 0.061 mg gold per patch in a hydroxypropyl cellulose gel vehicle, was used along with the allergEAZE patch test preparation gold sodium thiosulfate 0.5% pet. by SmartPractice (A-GST), and the Trolab patch test reagent (SmartPractice) gold sodium thiosulfate 0.25% pet. (Trolab-GST). Patch Test Panel (S) consists of 22 Japanese baseline series allergens. Finn Chambers on Scanpor tape (SmartPractice) were used to apply A-GST and Trolab-GST on the upper back for 2 days. P-GST and A-GST were patch tested simultaneously. We evaluated the reactions according to ICDRG criteria on D3, D4, and D7. A positive reaction was diagnosed if a + or stronger reaction was observed on D3/D4 or D7.

3 | RESULTS

3.1 | Overall results

Between May 2015 and March 2016, 588 patients (119 males, aged 17–86 years [average 52.4 ± 17.6 years]; 469 females, aged 8–86 years [average 50.9 ± 17.1 years]) underwent P-GST patch testing, and 406 were also patch tested with A-GST. Concerning the comparison of positive reactions in those cases in which P-GST and A-GST were applied simultaneously, Table 1 shows the patch test reactions to A-GST and P-GST on D3, and Table 2 shows the patch test reactions to A-GST and P-GST on D7. Positive test reactions to P-GST and A-GST were seen in 15% and 6% of cases, respectively; of P-GST-positive cases, 37% (22/59) were also A-GST-positive, and of A-GST-positive cases, 92% (22/24) were also P-GST-positive.

On comparison of reactions on D3 and D7 in cases in which P-GST and A-GST were applied simultaneously, regarding P-GST, 110 of 406 cases (27.1%) showed a weaker reaction on D7 than on

TABLE 1 Patch test reactions to gold sodium thiosulfate 0.5% pet. by allergEAZE (A-GST) and Patch Test Panel (S) containing gold sodium thiosulfate (P-GST) on day 3

		A-GST				Total
		–	?+	+, ++	IR	
P-GST	–	232	0	1	1	234
	?+	24	0	0	0	24
	+, ++	61	6	17	4	88
	IR	57	0	0	3	60
	Total	374	6	18	8	406

Abbreviation: IR, irritant reaction.

TABLE 2 Patch test reactions to gold sodium thiosulfate 0.5% pet. by allergEAZE (A-GST) and Patch Test Panel (S) containing gold sodium thiosulfate (P-GST) on day 7

		A-GST				Total
		–	?+	+, ++	IR	
P-GST	–	321	0	2	0	323
	?+	12	0	0	1	13
	+, ++	35	1	22	1	59
	IR	11	0	0	0	11
	Total	379	1	24	2	406

Abbreviation: IR, irritant reaction.

TABLE 3 Patch test reactions to gold sodium thiosulfate 0.075 mg/cm² in Patch Test Panel (S) on days 3 and 7

		Day 7						Total
		–	?+	+	++	+++	IR	
Day 3	–	227	2	4	0	0	1	234
	?+	16	4	3	0	0	1	24
	+	28	6	34	5	0	1	74
	++	2	1	7	6	0	0	16
	+++	0	0	0	0	0	0	0
	IR	47	1	2	0	0	8	58
Total		320	14	50	11	0	11	406

Abbreviation: IR, irritant reaction.

D3 (Table 3). Moreover, 30 cases showed a + reaction or stronger on D3, and a negative result on D7. In contrast, for A-GST, only 11 of the 406 cases (2.7%) showed a weaker reaction on D7 than on D3. Also, none of the cases showed a response stronger than + on D3 and became negative on D7 (Table 4).

Regarding late reactions in terms of positive P-GST reactions occurring after D7, 3 of the 588 patients (0.5%) reported a positive reaction occurring after D7 (Table 5: cases 1–3). Moreover, we encountered an interesting case (case 4) with a + reaction to P-GST on D2 and D3 that completely disappeared by D7, but flared up 3 months later. We present details of these 4 cases below.

3.2 | Case reports

3.2.1 | Case 1

A 40-year-old woman underwent patch testing for contact dermatitis of the face. She had no clinical symptoms associated with gold

TABLE 4 Patch test reactions to gold sodium thiosulfate 0.5% pet. by allergEAZE on days 3 and 7

		Day 7					IR	Total
		–	?+	+	++	+++		
Day 3	–	370	1	5	0	0	0	374
	?+	4	0	2	0	0	0	6
	+	0	0	13	2	0	0	15
	++	0	0	1	2	0	0	3
	+++	0	0	0	0	0	0	0
	IR	5	0	1	0	0	2	8
Total		379	1	22	4	0	2	406

Abbreviation: IR, irritant reaction.

allergy, but had a metal dental implant. Initial patch testing with P-GST showed an erythematous reaction (?+) on D3 that became negative on D7. However, a + reaction was observed at the same site after 1 month. Repeat patch testing 3 months after the first patch test showed a + P-GST reaction starting on D2, whereas A-GST applied at the same time showed a positive reaction on D7. The patient later had the gold-palladium alloy dental implant removed, and reported that her facial dermatitis improved after removal. However, it was not possible to ascertain whether the dental metal was the actual cause of her symptoms, because she also showed a positive reaction to her hair conditioner, and had stopped using it after the patch test. She did not experience any symptoms of gold allergy after showing positive patch test reactions to gold preparations. Her late positive reaction to P-GST was suspected to represent active sensitization.

3.2.2 | Case 2

A 51-year-old woman was patch tested for metal allergy as a possible cause of uncomfortable sensations in the mouth and tongue. She had no clinical symptoms associated with gold allergy. She had a metal dental implant and had never worn earrings. Initial patch testing with P-GST, A-GST and Trolab-GST gave negative results until D7. Three months later, a weak erythematous reaction (?+) was observed in the P-GST area, whereas A-GST and Trolab-GST were negative. Repeat patch testing 5 months later showed P-GST to be positive starting on D2, A-GST to be positive starting on D3, and Trolab-GST to be positive starting on D7. Despite the reported uncomfortable feelings in the mouth and tongue, the patient did not remove the dental implant after patch testing. Furthermore, she did not show any symptoms of gold allergy after the positive reactions to gold sodium thiosulfate.

TABLE 5 Patch test results of 4 cases for Patch Test Panel (S) containing gold sodium thiosulfate (P-GST), gold sodium thiosulfate 0.5% pet. by allergEAZE (A-GST), and Trolab gold sodium thiosulfate (Trolab-GST)

Case No.	First patch test							Second patch test												
	P-GST			Late reaction	A-GST			Trolab-GST			Duration	P-GST			A-GST			Trolab-GST		
D2	D3	D7	D2		D3	D7	D2	D3	D7	D2		D3	D7	D2	D3	D7	D2	D3	D7	
1	–	?+	–	1 mo, +	NT	NT	NT	NT	NT	NT	3 mo	+	+	+	–	–	+	NT	NT	NT
2	–	–	–	3 mo, +	–	–	–	–	–	–	5 mo	+	+	+	+	+	+	+	+	+
3	–	–	–	D21, +	–	–	–	–	–	–	3 wk	NT	NT	NT	+	+	+	–	–	–
4	+	+	–	3 mo, +	–	–	–	NT	NT	NT	10 mo	+	+	+	?+	?+	?+	?+	?+	?+

Abbreviations: D, reading day; mo, month(s); NT, not tested.

Her doctor diagnosed the late positive P-GST reaction after the first patch test as active sensitization.

3.2.3 | Case 3

A 34-year-old man was patch tested as part of an assessment for burning mouth syndrome. He had no clinical symptoms associated with gold allergy, but had a metal dental implant. He had never had his ears pierced. Initial patch testing with P-GST, A-GST and Trolab-GST gave negative results up to D7. After 3 weeks, positive reactions were observed at the P-GST and A-GST patch sites, whereas the Trolab-GST site was negative. Repeat patch testing was performed after 3 weeks. Only A-GST and Trolab-GST, and not P-GST, were applied. A-GST was positive starting on D2, whereas Trolab-GST remained negative at the second patch test. As the primary focus in this case had been to investigate the burning mouth syndrome, the dental implant was removed after patch testing. However, no change in symptoms was observed until 10 months after removal. The attending physician suspected that the positive P-GST reaction represented active sensitization; however, the patient did not experience any symptoms of gold allergy after a positive reaction to gold-containing materials.

3.2.4 | Case 4

A 72-year-old woman with contact dermatitis of the face and ear was patch tested. She had no clinical symptoms of gold allergy, but had a metal dental implant in place. She had never worn earrings. Patch testing with P-GST showed erythema and infiltration on D2 and D3, which became negative on D7. Three months later, a + reaction was observed at the same site. The site of A-GST testing remained negative. A skin biopsy of the P-GST late-positive site showed no epidermal changes. However, nodular dermatitis with lymphocyte infiltration in the upper dermis was observed. Repeat patch testing 10 months after the first patch test showed a + P-GST reaction starting on D2. A-GST and Trolab-GST applied at the same time showed ?+ reactions starting on D2. The face and ear symptoms improved over time, although she did not have the dental implant removed.

4 | DISCUSSION

Allergic reactions to metallic gold are thought to be extremely rare, although they have been reported since the 1960s.⁴ However, in the 1990s, many cases of gold sensitization were reported, including a few reports of allergic contact dermatitis caused by gold. There are

several gold patch test preparations, including gold sodium thiosulfate, chloroauric acid, and gold sodium thiomalate. From the perspective of irritancy, false-positive reactions and the persistence of positive reactions, gold sodium thiosulfate in pet. is a recommended patch test preparation⁵ and is widely used.

In Japan, Aihara⁶ reported an evaluation of gold sodium thiosulfate (1%, 0.5%, and 0.25%), gold acid chloride trihydrate (0.4%, 0.2%, and 0.1%), and gold acid chloride tetrahydrate (0.4%, 0.2%, and 0.1%), all in pet. As optimum gold patch test preparation, gold sodium thiosulfate 0.5% pet. was identified. Furthermore, Bruze et al⁷ reported that false-negative reactions are more frequent with gold sodium thiosulfate 0.5% pet., and that gold sodium thiosulfate 2% pet. is more sensitive in gold-sensitized humans. Nevertheless, in Japan, there have been no further studies on the optimal concentration of gold sodium thiosulfate for testing since the report by Aihara.⁶ Because the TRUE Test and P-GST do not use pet. as a vehicle, investigations concerning the optimal concentration were performed on gold-sensitized individuals.⁸ In that study, the concentration of gold sodium thiosulfate was set to be equivalent to 2% pet., so it is conceivable that P-GST showed a higher yield of positive reactions than A-GST 0.5% pet.

Sensitization is one of the complications of patch testing. According to textbooks on contact dermatitis, such as *Fisher's Contact Dermatitis* 6th edition⁹ and *Contact Dermatitis* 5th edition,¹⁰ sensitization by patch testing is characterized by no reaction until D7, a flare-up response on D10 to D14, and, at repeat patch testing, a positive reaction on D2 to D4. Considering this definition, cases 1, 2 and 3 showed negative reaction up to D7 of the initial patch test, with a flare-up afterwards, and then had positive reactions in re-patch testing from D2. Thus, it is considered that sensitization was caused by patch testing with gold sodium thiosulfate in each of these cases.

On the other hand, Bruze et al⁷ patch tested serial dilutions of gold sodium thiosulfate in 10 known cases of gold allergy. At lower concentrations, a positive reaction occurred only 1 week after application. It has also been reported that gold sodium thiosulfate is an exception to the general textbook rule mentioned above.⁹ Positive test reactions up to 3 weeks after application do not represent active sensitization. In the present study, positive reactions to both A-GST and P-GST were seen in 17 cases on D3, and in 22 cases on D7 (Tables 1 and 2). Positive reactions to A-GST on D3 were seen in 18 cases, increasing to 24 cases on D7 (Table 4). Also, positive reactions to P-GST occurred in 88 cases on D3, decreasing to 59 cases on D7. Conversely, 7 cases with a ?+ or – reaction on D3 showed positive reactions on D7 (Table 3). Therefore, in the patch test for gold sodium thiosulfate, it is essential to perform readings until D7.

Regarding the positive reactions to gold sodium thiosulfate observed >1 week after application of the patch test in the 4 cases presented, the attending physician diagnosed case 2 as active sensitization, and cases 1 and 3 as suspected active sensitization. In case 4, erythema with infiltration was seen on D2 and D3, and there was no sensitization from patch testing. There was also an interesting feature whereby the reaction disappeared by D7 and was followed by a flare-up granulomatous reaction 3 months later. If, in the repeat patch test, a concentration 10–100 times lower than that in the first patch test elicits a positive reaction within 1 week, active sensitization by

the patch test is usually suspected.⁷ We did not perform the re-patch test in the 3 aforementioned cases with lower concentrations. As they showed positive reactions from D2 in the repeat patch test, we still suspect that their late reactions represented active sensitization. Generally, no consensus has been reached, and patch testing with gold is still being debated overseas, including the association between positive reactions and clinical symptoms.¹¹

In conclusion, further detailed investigation is necessary to determine whether the observed positive reactions are late reactions in pre-sensitized individuals or active sensitization by patch tests. Gold sodium thiosulfate often gives a positive reaction after 2 to 3 weeks, and, in such cases, the positive reaction may be sustained. Therefore, assessment is recommended up to 1 month after application. The association between positive gold sodium thiosulfate reactions and clinical symptoms is an important issue, and will be investigated in the future.

Conflict of interests

The authors declare no potential conflict of interests.

ORCID

Kayoko Suzuki  <https://orcid.org/0000-0001-8367-1034>

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How to cite this article: Suzuki K, Yagami A, Ito A, et al. Positive reactions to gold sodium thiosulfate in patch test panels (TRUE Test) in Japan: A multicentre study. *Contact Dermatitis.* 2019;80:114–117. <https://doi.org/10.1111/cod.13105>