

Excipient and Dose per Unit Area Affect Sensitivity When Patch Testing With Gold Sodium Thiosulfate

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Background: Dose/area and reading paradigms for gold patch testing are controversial and not standardized worldwide.

Objectives: The aims of this study were to determine the optimum patch test dose of gold sodium thiosulfate (GST) in a hydrogel (HYD) and to establish GST HYD safety/efficacy and further characterize normal morphology and time course of GST reactions.

Methods: Twenty gold-allergic patients were patch tested with a dilution series of GST HYD and with GST 2% petrolatum (pet). Furthermore, this previously determined optimal dose was compared with GST 0.5% pet in 19 known-allergic and 216 consecutive subjects.

Results: The optimal GST HYD dose was 0.075 mg/cm², not statistically different from GST 2% pet ($P = 0.4795$). Gold sodium thiosulfate HYD outperformed GST 0.5% pet in both known-allergic subjects (79% vs 63%, $P = 0.2482$) and consecutive subjects (30% vs 9%, $P < 0.0001$). Late reactions were common in consecutive patients with both HYD and pet. Significantly more persistent reactions were associated with GST HYD than with GST 0.5% pet.

Conclusions: Gold sodium thiosulfate HYD 0.075 mg/cm² is the optimal dose for diagnosis of gold contact allergy with GST. Gold sodium thiosulfate 0.5% pet yielded false-negatives in some patients, suggesting inadequate dose per centimeter squared. Late reads are normal, expected, and necessary for diagnosis of gold contact allergy in this cohort.

Gold patch test positivity in referred patients ranges from approximately 8% to 20% but may be as high as 71% in certain symptomatic individuals.^{1–4} Nevertheless, gold is a controversial allergen and has been dropped from many standard screening series worldwide because of disparate prevalence rates and difficulty assessing the clinical relevance of gold patch test positivity.⁵

In most of the world, the preferred compound for patch testing to diagnose gold contact allergy is gold sodium thiosulfate (GST) because of its reliability and availability. Gold sodium thiosulfate used for patch testing is formulated in 1 of 3 excipients: petrolatum (pet),

water, or hydrogel (HYD). Petrolatum is the most commonly used excipient worldwide. Water formulations are more typically used in Japan and parts of Europe, and HYD formulations are used in pre-made patch test products such as the T.R.U.E. Test.

To help clarify the use of gold patch testing and broaden the basis for comparing the performance of different tests, we performed 2 studies with the following 2 objectives: (1) determine the optimum patch test dose of GST in an HYD and (2) establish GST HYD safety/efficacy and further characterize normal morphology and time course of GST reactions.

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are his sons but have no ownership or other interests to declare. K.E.A. is the medical advisor for SmartPractice Denmark. M.B. has lectured at a patch test course arranged by SmartPractice. J.F.F. is a consultant for SmartPractice.

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METHODS

Study 1: Dose Response

A multicenter, blinded, phase 2 clinical trial was conducted to establish the optimum dose of GST HYD for patch testing. The protocol was approved by the local ethics committee of the investigator (M.B.), and written informed consent was obtained from all participants before initiation of the study.

Twenty subjects (19 women and 1 man) with known gold contact allergy, based on a previous positive patch test reaction to GST within 5 years, participated in the study. Patients were 18 years or older (mean age, 52.2 years; age range, 23–69 years). Exclusion criteria are shown in Supplementary Table 1, <http://links.lww.com/DER/A11>.

All patients were patch tested with a reference allergen (20 mg of GST 2% pet dispensed in Finn Chambers with an internal area of 0.503 cm² for a total dose per unit area of 0.80 mg GST/cm²) and with a dilution series of GST HYD at the following doses: 0.075, 0.025, 0.0083, 0.0028, 0.00093, and 0 mg/cm² (negative control). The investigator was aware of the doses being used, but patch placement was double blinded. Patches were worn for 2 days, and the results were read at day 3 or 4 (visit 3) and again at day 7 (visit 4).

The optimum dose was defined as the lowest dose associated with a positive reaction (1+ or 2+) in 70% to 90% of the 20 subjects allergic to GST 2% pet. A McNemar test with Bonferroni adjustment was used to compare the paired results of the GST dilution series with the negative control and between paired results of the lowest nonzero dose (0.00093 mg/cm²) and the highest dose (0.075 mg/cm²). $P < 0.0125$ was considered significant. The associations between paired reactions to the doses of 0.075 mg/cm² GST HYD and GST 2% pet were analyzed by a McNemar test with $P < 0.05$ considered significant. Statistical analysis was performed with GraphPad QuickCalcs software (GraphPad Inc, La Jolla, CA).

RESULTS

Study 1: HYD Dose Response

Three of the 5 doses of GST HYD (0.0083, 0.025, and 0.075 mg/cm²) performed significantly better than did the negative control GST HYD ($P = 0.016$, 0.0019, and 0.0004, respectively). The GST dilution series elicited more positive reactions with increasing doses, and the 0.075 mg/cm² was the most sensitive dose (Table 1, Fig. 1).

Patch test positivity with GST 2% pet was slightly higher than GST HYD 0.075 mg/cm² at both visit 3/visit 4 (95%/100% vs 80%/90%). However, the agreement between GST 2% pet and GST HYD was 90%, and there was no statistically significant difference between the 2 tests ($P = 0.4795$). Gold sodium thiosulfate HYD at 0.075 mg/cm² was the most sensitive HYD test dose and produced the most optional diagnostic reactions (+ or++) when using HYD excipient to diagnose gold contact allergy.

METHODS

Study 2: Safety and Efficacy

An open-label, prospective, multicenter (4 sites in the United States and 1 in Denmark) clinical trial was conducted to evaluate the diagnostic performance and safety of 0.075 mg/cm² GST HYD. The protocol was approved by the local ethics committee or institutional review board of the investigators, and written informed consent was obtained from all participants before initiation of the study. The exclusion criteria were identical to the dose-response study (Supplementary Table 1, <http://links.lww.com/DER/A11>).

Of the 235 total subjects, 19 (17 women and 2 men; mean age, 49.6 years; age range, 20–76 years) had previous positive patch tests to GST within the prior 5 years. The remaining 216 subjects were considered our consecutive cohort. All subjects were patch tested with 0.075 mg/cm² GST HYD and with a reference allergen (20 mg GST

TABLE 1. Summary of Number of Reactions to GST 2% Pet and GST HYD Dilution Series by Visit in 20 GST-Sensitive Subjects in Dose-Response Study (Visit 3: 72–96 Hours; Visit 4: Day 7)

Reaction	GST											
	2% Pet (0.80 mg/cm ²)		HYD 0.00093 mg/cm ²		HYD 0.0028 mg/cm ²		HYD 0.0083 mg/cm ²		HYD 0.025 mg/cm ²		HYD 0.075 mg/cm ²	
	Visit 3, No. (%)	Visit 4, No. (%)	Visit 3, No. (%)	Visit 4, No. (%)	Visit 3, No. (%)	Visit 4, No. (%)	Visit 3, No. (%)	Visit 4, No. (%)	Visit 3, No. (%)	Visit 4, No. (%)	Visit 3, No. (%)	Visit 4, No. (%)
Negative	0	0	14 (70)	12 (60)	13 (65)	6 (30)	7 (35)	6 (30)	3 (15)	2 (10)	2 (10)	1 (5)
?/IR	1 (5)	0	5 (25)	7 (35)	4 (20)	5 (25)	8 (40)	5 (25)	7 (35)	5 (25)	2 (10)	1 (5)
+	10 (50)	9 (45)	1 (5)	1 (5)	0	7 (35)	0	7 (35)	4 (20)	5 (25)	4 (20)	2 (10)
++	6 (30)	9 (45)	0	0	3 (15)	2 (10)	3 (15)	2 (10)	4 (20)	8 (40)	7 (35)	14 (70)
Optimal diagnostic reaction (+ or ++)	16 (80)	18 (90)	1 (5)	1 (5)	3 (15)	9 (45)	3 (15)	9 (45)	8 (40)	13 (65)	11 (55)	16 (80)
+++	3 (15)	2 (10)	0	0	0	0	2 (10)	0	2 (10)	0	5 (25)	2 (10)
Total positive	19 (95)	20 (100)	1 (5)	1 (5)	3 (15)	9 (45)	5 (25)	9 (45)	10 (50)	13 (65)	16 (80)	18 (90)

?/IR, doubtful or irritant.

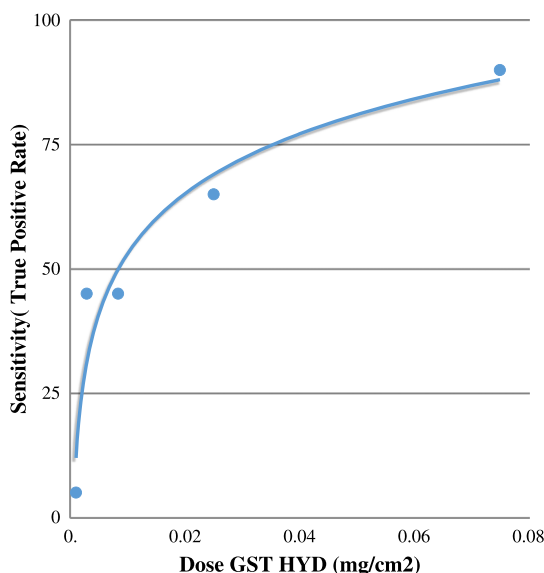


Figure 1. Dose-response curve for GST in HYD dilution series.

0.5% pet, which is equivalent to approximately 0.20 mg/cm^2) dispensed in Finn Chambers. The GST 0.5% pet was selected because it is the most commonly used screening preparation. Patch testing was conducted as in the dose-response study with the exception that reactions were also read at day 21 (visit 5). Timing of reaction debut and reaction severity was recorded. Pair responses between 0.075 mg/cm^2 GST HYD and 0.5% GST pet were assessed with a 2-sided McNemar test. Comparing positive response ratios was assessed with a Fisher exact test. Statistical analysis was performed with GraphPad QuickCalcs software (GraphPad Inc).

RESULTS

Study 2: Safety and Efficacy

Previously GST-Allergic Subjects

Among the 19 previously GST-allergic subjects, 15 (79%) patients had positive reactions (1+, 2+, or 3+) to GST 0.075 mg/cm^2 HYD and 12 (63%) patients had positive reactions to GST 0.5% pet (Table 2). This difference did not reach statistical significance ($P = 0.2482$). For both GST HYD and GST pet, all positive reactions debuted on day 3 (Supplementary Table 2, <http://links.lww.com/DER/A12>). At visit 5 (day 21), there were 7 persistent positive reactions to GST HYD, significantly more than 1 persistent positive reaction observed to GST 0.5% pet at day 5 ($P = 0.0412$). Gold sodium thiosulfate HYD produced more reactions with a highest grade of 3+ ($n = 8$ [42%]) compared with GST 0.5% pet ($n = 1$ [5%]; McNemar test, $P = 0.023$), and GST 0.5% pet produced more reactions with a highest grade of 1+ ($n = 9$ [47%]) compared with GST HYD ($n = 1$ [5%]; McNemar test, $P = 0.013$). There was no significant difference between GST 0.5% and GST HYD in reaction with a highest grade of 2+.

TABLE 2. Safety and Efficacy Study: Summary of Reactions in 19 Gold-Allergic and 216 Consecutive Patients to GST 0.5% Pet and GST HYD*

Patients	Reaction	GST 0.5% Pet (0.20 mg/cm^2)					HYD 0.075 mg/cm^2				
		Visit 3 (Day 3 or 4), No. (%)	Visit 4 (Day 7), No. (%)	Visit 5 (Day 21), No. (%)	Final Read, No. (%)		Visit 3 (Day 3 or 4), No. (%)	Visit 4 (Day 7), No. (%)	Visit 5 (Day 21), No. (%)	Final Read, No. (%)	
Previously GST-allergic patients ($n = 19$)	Neg	7 (37)	6 (32)	16 (84)	7 (37)		2 (11)	3 (16)	12 (63)	4 (21)	
	?/IR	0	1 (5)	2 (11)	0		2 (11)	1 (5)	2 (11)	0	
	+	10 (53)	9 (47)	1 (5)	9 (47)		5 (26)	2 (11)	7*	1 (5)	
	++	1 (5)	3 (16)	0	2 (11)		5 (26)	5 (26)		7 (37)	
	+++	1 (5)	0	0	1 (5)		5 (26)	8 (42)		7 (37)	
Total positive		12 (63)	12 (63)	1 (5)	12 (63)		15 (79)	15 (79)	7 (37)	15 (79)	
Consecutive patients ($n = 216$)	Neg	196 (91)	194 (90)	202 (94)	197 (91)		144 (67)	153 (71)	198 (92)	152 (70)	
	?/IR	10 (5)	11 (5)	5 (2)	0		18 (8)	12 (6)	0	0	
	+	5 (2)	6 (3)	9 (4)	14 (6)		27 (13)	20 (9)	18†	25 (12)	
	++	2 (1)	2 (1)	0	2 (1)		17 (†)	21 (10)		23 (11)	
	+++	3 (1)	3 (1)	0	3 (1)		10 (5)	10 (5)		11 (5)	
Total positive		10 (5)	11 (5)	9 (4)	19 (9)		54 (25)	51 (24)	18 (8)	64 (30)‡	

*Positives but no grades available.

†Positives but no grades available (13 persistent and 5 late positive reactions).

‡Includes the 5 unscored positive late reactions (none of these had preceding positive reactions).

Consecutive Subjects

Of the consecutive subjects, 30% (64/216) had a positive reaction to GST 0.075 mg/cm² HYD, significantly more than 9% of the subjects (19/216) who had positive reactions to GST 0.5% pet (McNemar test, $P < 0.0001$) (Table 2). Gold sodium thiosulfate 0.075 mg/cm² HYD produced 45 positive reactions that were negative to GST 0.5% pet. Gold sodium thiosulfate 0.5% pet did not produce any positive reactions among patients negative to GST 0.075 mg/cm² HYD but had 45 false-negatives. Among the consecutive subjects, positive reactions to both GST 0.075 mg/cm² HYD (54/64 [84%]) and GST 0.5% pet (10/19 [53%]) most often debuted on visit 3 (Supplementary Table 2, <http://links.lww.com/DER/A12>). Patients with positive reactions to GST pet were more likely to have a positive reaction debut after week 1 compared with GST HYD patients (8% vs 32%; $P = 0.015$).

DISCUSSION

Main Findings

Gold sodium thiosulfate HYD at 0.075 mg/cm² is the optimal dose when using HYD to diagnose gold contact allergy—comparable with using 2% GST in pet. Gold sodium thiosulfate HYD 0.075 mg/cm² had higher sensitivity for gold contact allergy than GST 0.5% pet among consecutively patch-tested subjects. The dose per unit area when using GST 0.5% pet produces false-negative results in some patients. Late reactions were common among our consecutively tested patients using both HYD and pet preparations, and late readings are required to avoid a false-negative patch test.

Dose Response of GST in HYD

Gold sodium thiosulfate HYD at 0.075 mg/cm² was the most sensitive test dose and produced the most optimal positive reactions (+ or ++).

Lower doses of HYD had much lower sensitivity (Table 1). Gold sodium thiosulfate HYD elicited positive patch test reactions in a dose-response manner (Fig. 1). A far smaller dose of GST HYD (0.075 mg/cm²) performed comparably with GST 2% pet (0.80 mg/cm²). This approximate 10-fold difference in GST effective dose per unit area between HYD (0.075 mg/cm²) and pet (using 2.0% delivered dose = 0.80 mg/cm²) is in line with data on other allergens and cutaneous drug delivery.^{6–8}

Optimal Doses of GST in All Excipients

Gold sodium thiosulfate 0.075 mg/cm² HYD produced more reactions than GST 0.5% pet (0.20 mg GST/cm²), but comparable with GST 2% pet (0.80 mg GST/cm²). Over the past 30 years, more than 6 different gold salts and 2 dozen different combinations of concentrations/doses of GST with pet, water, and HYD excipients have been used for patch testing.^{3,9–22} The American Contact Dermatitis Society included GST 2% pet when it introduced its Core Allergen Series in 2011²³; however, many clinicians test with GST 0.25% or 0.5% pet.²⁴ In this study, GST 0.5% pet (0.20 mg/cm²) showed lower sensitivity, producing 45 false-negative results.

Timeline of Reactions/Delayed Reactions

Among consecutively tested subjects, reactions appearing on day 7 or later were common for GST HYD (10/64 [16%]) and GST 0.5% pet (9/19 [47%]). Reactions appearing only on day 21 were also common for GST HYD (5/64 [8%]) and GST 0.5% pet (6/19 [32%]). This is consistent with previous studies; Schaffran et al¹⁷ reported that 53% of positive reactions to gold occurred on day 7 or later, and Koch and Bahmer²² found that positive reactions to GST 0.5% pet debuted at day 10 or 17 in 46% of the patients. We here demonstrate that late positive reactions are not only common when testing consecutive patients but also necessary for diagnosis.

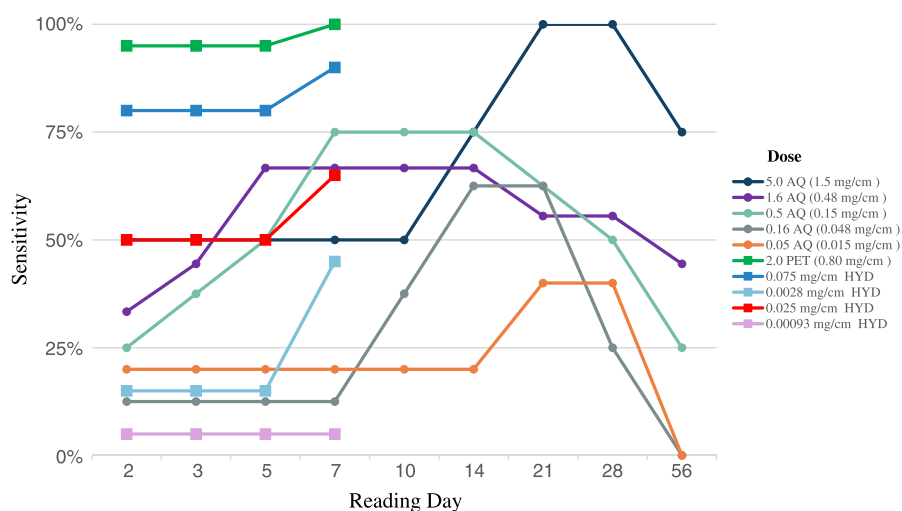


Figure 2. True-positive rate (sensitivity) of patch tests in known gold-allergic patients. Based on data from this dose-response study (indicated by squares; no reading times available beyond day 7) and from Bruze et al¹⁴ (indicated by circles). Note the similarity in the curves for 0.80 mg/cm² (GST 2% pet) and GST HYD 0.075 mg/cm² and the significant delays in debut among preparations with lower dose per centimeter squared.

Without late reads, GST 0.075 mg/cm² HYD would have had a false-negative rate of 15.6%, and GST 0.5% pet would have had a false-negative rate of 84.4%.

There is concern among some dermatologists that late reactions to gold may potentially represent patch test active sensitization, particularly if the positive reaction debut is earlier on retesting.²⁵ However, a late reaction to GST is a well-described exception to the general definition of active sensitization.²⁶ Notably, delayed reactions are common in known GST-allergic subjects who are incapable of being actively sensitized (Fig. 2).¹⁴ It is somewhat unexpected that we did not see late reactions in our known gold-allergic patients, as has been common in previous studies.

Patch Test Grade/Strength

As GST HYD (0.075 mg/cm²) performed comparably with GST 2% pet (0.80 mg/cm²) in our dose-response study and there is typically a 10-fold difference in diagnostically effective dose/unit area between HYD and pet, the GST 0.075 mg/cm² HYD represents a “higher” apparent dose compared with the GST 0.5% pet (0.20 mg/cm²). Gold sodium thiosulfate 0.075 mg/cm² HYD produced stronger reactions compared with GST 0.5% pet (Supplementary Table 3, <http://links.lww.com/DER/A13>). Patch testing with higher doses of GST provoked earlier and stronger reactions for some patients in a previous study.¹⁴

Continued Patch Testing Is Needed to Better Understand Gold Hypersensitivity

Gold sodium thiosulfate is almost universally included in supplemental metal patch test panels; however, its utility as a standard screening agent is more controversial. Although some studies do demonstrate low relevance of GST patch testing, the literature is far from conclusive. For example, in the 2 largest studies that included GST from the North American Contact Dermatitis Group, clinical relevance ranged from 10% to 15%, which is comparable with the relevancy rates of nickel (11.9%–16.2%) and greater than that of cobalt (7.7%–12.5%).^{2,27} It seems inconsistent to accept low rates of relevance associated with other baseline allergens while questioning the comparable or higher relevancy rates associated with gold.²⁸ Nevertheless, a detailed discussion of clinical relevance is beyond the scope of this study, but dermatologists who do decide to test with GST should be aware of the potential false-negatives/lower sensitivity when using GST 0.5% pet and should be encouraged to use GST 2% pet or GST HYD (0.075 mg/cm²).

CONCLUSIONS

Gold sodium thiosulfate HYD at 0.075 mg/cm² is the optimal dose when using HYD excipient to diagnose gold contact allergy. The dose per unit area when using GST 0.5% pet is too low for some patients and causes false-negative results. Late reactions to GST are common and normal—and they are required for the diagnosis of gold contact allergy in many patients. International consensus on

GST dosing and the definitions of late reactions, persistent reactions, and active sensitization are needed. Many questions about gold as a sensitizer are unlikely to be answered without continued patch testing and a multidisciplinary approach to understand the clinical relevance of this metal allergen.^{28,29}

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