

Patch test materials for mercury allergic contact dermatitis

TOKIO NAKADA^{1,3}, NAOTAKA HIGO¹, MASAFUMI IJIMA¹, HIDEO NAKAYAMA² AND
HOWARD I. MAIBACH³

¹Department of Dermatology, Showa University School of Medicine, 1-5-8, Hatanodai,
Shinagawa-ku, Tokyo 142, Japan

²Nakayama Dermatology Clinic, 3-3-5, Kamiohsaki Shinagawa-ku, Tokyo 141, Japan

³Department of Dermatology, University of California, School of Medicine, Box 0989, Surge 110,
San Francisco, California 94143-0989, USA

The objective of this study was to define adequate patch test materials to evaluate mercury allergic contact dermatitis. We applied 0.1% and 0.05% mercuric chloride, and 0.5% and 0.2% mercury in petrolatum to systemic eczematous contact-type dermatitis (baboon syndrome), and gold-dermatitis patients. All baboon-syndrome patients reacted not only to mercuric chloride but also to metallic mercury. In gold-dermatitis patients, significantly more patients reacted to mercuric chloride than to metallic mercury (21 of 35, 60%, versus 2 of 19, 10.5%, $p < 0.0005$). We speculated that sensitization to mercury may be of 2 types: one a reaction to ionized mercury only, the other to both ionized mercury and non-ionized mercury. The possibility that the phenomenon is caused by differences in bioavailability or percutaneous penetration between ionized and non-ionized mercury cannot be ruled out, but could be explored by penetration measurement. For the evaluation of mercury hypersensitivity, it may be more reliable to apply both ionized and non-ionized mercury, rather than only mercuric chloride or ammoniated mercury.

Key words: ionized mercury; non-ionized mercury; baboon syndrome; patch testing technique; gold; allergic contact dermatitis; cross-sensitivity. © Munksgaard, 1997.

Accepted for publication 31 December 1996

Mercury occurs in 3 chemical forms: metallic, mercury salts, and organic; all may cause both immediate and delayed contact allergies in man (1). Systemic eczematous contact-type dermatitis due to mercury, known as a characteristic exanthema and called "baboon syndrome" (2, 3), is seen more commonly in Japan and Korea than in the Western world, presumably because of higher rates of mercury sensitization (1, 4, 5). A conceivable reason for the higher sensitization rate in Japan may relate to earlier extensive use of Mercurochrome (4, 6).

In evaluating mercury delayed hypersensitivity, 0.05% mercuric chloride or 1~2% ammoniated mercury or 0.5% metallic mercury in petrolatum have commonly been used (7, 8). For mercury patch testing, mercury metal 1% pet. (ICDRG) and ammoniated mercury 1% pet. (ICDRG) are recommended. As ear piercing has become increasingly popular in Japan, we have encountered 21 cases of clinical gold dermatitis in women with pierced earlobes, who developed edematous erythema followed by intracutaneous nodules on the earlobes (March 1989 to October 1992) (9). These

patients, patch-test-positive to gold chloride, had a tendency to cross-hypersensitivity to mercuric chloride and not to metallic mercury (9-11). Although it is stated that exposure to mercury is common in Japan, only 3 patients had an overt history of breaking thermometers.

Here, we compared the patch-test-positive rate to mercuric chloride and metallic mercury in 5 baboon-syndrome patients. In addition, we have encountered 14 more cases of gold dermatitis (April 1992 to June 1995), and have re-examined the phenomenon described above. Comparing the positive rates to mercurial materials in the baboon syndrome to those in gold-dermatitis patients, we attempt to define adequate patch test materials for mercury hypersensitivity.

Patients and Methods

5 baboon-syndrome patients (women ranging in age from 25 to 27 years) were patch tested at Showa University Hospital from October 1991 to April 1994. We applied 0.1% and 0.05% mercuric chloride and

0.2% gold chloride (Torii Pharmaceutical CO., LTD. Japan, purity ~100%, all in aq. solutions) with vinyl plaster (Mini-plaster®, Torii Pharmaceutical CO., LTD. Japan) to avoid chemical reaction between aluminum and mercuric chloride (12). In addition, 0.5% and 0.2% mercury in pet. (provided by Dr. Nakayama, purity ~100%) were patch tested utilizing Finn Chambers. These patch test materials were applied on the back for 2 days. The results were read with the ICDRG scoring system 3 days after application (13). Reactions of + to +++ were regarded as positive.

Additionally, 35 patients with gold dermatitis due to ear piercing (women ranging in age from 17 to 39, mean 22.8, S.D. ± 5.1 years) were patch tested with gold chloride and mercuric chloride from March 1989 to June 1995 using the above methodology. 19 of the 35 were also patch tested with 0.5% and 0.2% mercury in pet. The 19 were patients who were retested after we observed cross-hypersensitivity between gold and mercuric chloride, or were those patients identified when we simultaneously tested mercuric chloride and metallic mercury.

Differences of positive rates between mercuric chloride and mercury in petrolatum with gold-dermatitis patients were analyzed with the χ^2 test. Differences were considered significant when $p < 0.05$.

Results

Table 1 shows the contrast of positive rates to mercurial materials and gold chloride between patients with baboon syndrome and gold dermatitis. All 5 patients with baboon syndrome reacted to mercury in petrolatum as well as mercuric chloride, but none to gold chloride (Table 1).

Among the gold-dermatitis patients, all reacted to gold chloride, and 60% (21/35) of them also reacted to mercuric chloride. 19 of the 35 were also patch tested with 0.5% and 0.2% mercury in pet.;

13 reacted and 6 did not react to mercuric chloride. Of 13 patients reactive to mercuric chloride, 2 patients were also positive to mercury in petrolatum. All 6 patients negative to mercuric chloride did not react to mercury in petrolatum. There were significantly more patients reacting to mercuric chloride than to metallic mercury (21 of 35, 60%, versus 2 of 19, 10.5%; $p < 0.0005$, Table 1) among gold-dermatitis patients.

Discussion

This study indicates that it is more reliable to apply non-ionized as well as ionized mercury than ionized mercury alone for evaluation of mercury hypersensitivity. Evidence for this is the difference in positive rates between ionized mercury, mercuric chloride, and to non-ionized mercury, mercury in pet. with gold-dermatitis patients (21 of 35, 60%, versus 2 of 19, 10.5% $p < 0.0005$, Table 1). The positive reactions to ionized mercury may be regarded as sensitization because of the following. (i) Positive reactions were not considered as irritant reactions because the concentration of mercuric chloride was adequate (7, 8), and these reactions were not weaker at 3 days than at 2 days. (ii) Contamination was ruled out utilizing electron microprobe analysis of patch test materials (10). (iii) The reactions were not likely due to "excited skin syndrome" (15, 16); 3 gold-dermatitis patients showing positive reactions both to gold chloride and to mercuric chloride were retested individually at a later date; we still noted positive reactions to both (10). It was unlikely that positive reactions to mercuric chloride were related to ear piercing, since "18K" earrings (75% gold and 25% other metals, not including mercury) are commonly used in Japan (14).

We speculate that sensitization to mercury seems to be of 2 types: one is a reaction only to ionized mercury, the other is to non-ionized as well as ionized mercury. Applying only ionized mercury, the 2 types of sensitization cannot be differentiated. With non-ionized mercury alone, we failed to observe positive reactions to mercuric chloride among gold-dermatitis patients. Nordlind et al. (17) reported 2 cases of lichenoid mucosal lesions associated with amalgam, revealed to be patch-test positive to mercuric chloride and negative to metallic mercury. Our data suggests that baboon syndrome is of the latter type. Furthermore, most reported cases of baboon syndrome reacted not only to ionized but also to non-ionized mercury (3, 4, 18–22). However, Vena et al. (23) reported 6 cases reacting to 1% ammoniated mercury and not to metallic mercury. Handley et al. (24) recommended patch testing with both metallic mercury and am-

Table 1. Positive rates to mercurial materials and gold chloride

Materials	Baboon-syndrome patients		Gold-dermatitis patients	
0.1% mercuric chloride	100 (%)	(5/5)	60.0 (%)	(21/35)
0.05% mercuric chloride	100	(5/5)	60.0	(21/35)
0.5% mercury in pet.	100	(5/5)	10.5	(2/19)
0.2% mercury in pet.	100	(5/5)	10.5	(2/19)
0.2% gold chloride	0	(0/5)	100	(35/35)
			$p < 0.0005^a$	

^a There were significantly more patients reacting to mercuric chloride than to mercury in pet. (21 of 35, 60% versus 2 of 19, 10.5%; $p < 0.0005$, Table 1) among gold-dermatitis patients.

moniated mercury in patients with suspected mercury allergy. We do not have data to correlate the reactivity to mercuric chloride and ammoniated mercury.

We speculate that those who were sensitized by gold may have a tendency to react to ionized mercury. Evidence for this is that the positive rate to mercury in petrolatum is only 10.5% with gold-dermatitis patients, which resembles the mercury sensitization rate reported in Japan (25). Another possibility is that those sensitized by mercury had a genetic tendency toward sensitization to gold (10, 26). However, most gold-dermatitis patients (32/35, 91.4%) had no overt history of mercury sensitization, and all the baboon-syndrome patients did not react to gold. Those who were originally sensitized by mercury seemed to have had a different form of determinant derived from mercury or ionized-mercury that did not cross-react to gold ions. As to the background of such cross-hypersensitivity, we speculated that similarities of electron structure between gold and mercury might play an important rôle (11, 12). In the table of elements, gold is no. 79, and mercury is no. 80. Au^{3+} is ionized with an outermost free electron lost on the 6s orbit. Hg^{2+} is ionized with a pair of outermost free electrons lost there as well. Conversely, non-ionized mercury has the free electrons preserved on the 6s orbit.

Our speculation described above is based on the assumption that the dissociation was caused by differences in the quality of allergic reaction. Another possibility relates to the difference of quantity of absorbed allergen. If so, higher concentrations of metallic mercury might be necessary in cases reacting to ionized and not to non-ionized mercury, because of differences in bioavailability and penetration between mercuric chloride and metallic mercury.

In conclusion, it may be more reliable to apply not only ionized but also non-ionized mercury than either alone for the evaluation of mercury hypersensitivity.

References

- Hostynek J J, Hinz R S, Price M, Guy R H: Metals and the skin. *Critical Reviews in Toxicology* 1993; 23: 171–235.
- Fisher A A. Systemic eczematous "contact-type" dermatitis medicamentosa. *Annals of Allergy* 1966; 24: 406–420.
- Anderson K E, Hjirih N, Menné. The baboon syndrome: systemically-induced allergic contact dermatitis. *Contact Dermatitis* 1984; 10: 97–100.
- Nakayama H, Niki F, Shono M, Hada S. Mercury exanthem. *Contact Dermatitis* 1993; 9: 411–417.
- Kim H J, Pyo H C. Three cases of allergic contact dermatitis (mercury exanthem) due to mercury inhalation from a broken thermometer. *Hifu* 1987; 29 (suppl 3): 51–55.
- Inoue M, Nakayama H. Dentistry and metal allergy. Tokyo: Dental Diamond Co., 1993: 128–129 (in Japanese).
- Rietschel R L, Fowler, Jr. J F. *Fisher's contact dermatitis*, 4th edition. Baltimore: Williams & Wilkins, 1995: 978, 1017.
- De Groot A C. *Patch testing*. Amsterdam, Elsevier Science Publishers BV, 1986: 159.
- Nakada T, Iijima M, Fujisawa R. The dissociation of results of patch test to ionized/ non-ionized mercury between SCD due to mercury and gold dermatitis. *Jpn J Dermatol-lergol* 1994; 1: 237–241 (in Japanese).
- Nakada T, Iijima M, Fujisawa R, Nakayama H. A clinical, histopathological, immunohistological study on gold dermatitis due to ear piercing. *Jpn J Dermatol* 1992; 102: 815–825 (in Japanese).
- Nakada T, Iijima M, Fujisawa R, Nakayama H. Cross hypersensitivity to ionized mercury and not to non-ionized mercury with gold dermatitis patients caused by ear piercing (abstract from The Second Tricontinental Meeting of the JSID, SID, and ESDR). *J Invest Dermatol* 1993; 101: 473.
- Kubo Y, Nonaka S, Yoshida H. False positive reaction to patch testing with aqueous mercuric chloride in an aluminum Finn Chamber®. *Contact Dermatitis* 1992; 26: 136–137.
- Wilkinson D S, Fregert S, Magnusson B, Bandmann H J, Calnan C D, Cronin E, Hjorth N, Maibach H J, Malten K E, Maneghini C L, Pirilä V. Terminology of contact dermatitis. *Acta Dermato-venereologica* 1970; 50: 287–292.
- Nakada T, Iijima M. Metal allergy. *Japan Medical Journal* 1996; 3756: 37–42 (in Japanese).
- Mitchell J C. The angry back syndrome: eczema creates eczema. *Contact Dermatitis* 1975; 1: 193–194.
- Bruynzeel D P, Maibach H I. Excited skin syndrome (angry back). *Arch Derm* 1986; 122: 323–328.
- Nordlind K, Lidén S. Patch test reactions to metal salts in patients with oral mucosal lesions associated with amalgam restorations. *Contact Dermatitis* 1992; 27: 157–160.
- Imura M, Ota M, Toda K. Three cases of mercurial allergy. *Japanese Journal of Clinical Dermatology* 1981; 35: 45–51 (in Japanese).
- Yamada K, Wakabayashi S. Mercury exanthem. *Acta Dermatol-Kyoto* 1986; 81: 59–64 (in Japanese).
- Yasuno Y, Yamada K, Wakabayashi T. Mercury allergy. *Rinsho derma (Tokyo)* 1988; 30 (suppl 7): 923–929 (in Japanese).
- Faria A, Freitas C. Systemic contact dermatitis due to mercury. *Contact Dermatitis* 1992; 27: 110–111.
- Fernandez L, Maquiera E, Garcia-Abujeta J L, Yañez, Rodríguez F, Martín-Gil D, Jerez J. Baboon syndrome due to mercury sensitivity. *Contact Dermatitis* 1995; 33: 56–57.
- Vena G A, Foti C, Grandolfo M, Angelini G. Mercury exanthem. *Contact Dermatitis* 1994; 31: 214–216.
- Handley J, Todd D, Burrows D. Mercury allergy in a contact dermatitis clinic in Northern Ireland. *Contact Dermatitis* 1993; 29: 258–261.
- Inoue M, Nakayama H. Dentistry and metal allergy. Tokyo: Dental Diamond Co., 1993: 62–69 (in Japanese).
- Osawa J, Kitamura K, Ikezawa Z, Hariya T, Nakajima H. Gold dermatitis due to ear piercing: correlations between gold and mercury hypersensitization. *Contact Dermatitis* 1994; 31: 89–91.

Address:

Tokio Nakada
Department of Dermatology
University of California, School of Medicine
Box 0989, Surge 110
San Francisco
California 94143-0989
USA

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.