

Percutaneous absorption of gold sodium thiosulfate used for patch testing

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Contact allergy to gold has been shown to be correlated to wearing of golden jewellery as well as to the presence of dental gold. The prerequisite for sensitization and elicitation of an allergic contact dermatitis to gold is ionization and percutaneous absorption of the allergen. The present study was undertaken with the aim to demonstrate gold in blood after an occlusive patch testing with gold sodium thiosulfate (GSTS). Patients were patch tested with GSTS 0.5, 2.0 and 5.0% in petrolatum. Venous blood was sampled before testing as well as on day 3 (D3) or day 7 (D7). Blood gold levels were analysed by inductively coupled plasma mass spectrometry. In all 66 patients, the blood level of gold was significantly higher in the 2nd blood sample than in the 1st (median 0.34 versus 0.03 µg/l). The increase was similar in patients allergic and not allergic to gold. There was no difference between gold levels on D3 and on D7 after epicutaneous application. Presumably, other allergens may also be taken up in blood during patch testing.

Key words: gold assay in blood; gold sodium thiosulfate; patch test; percutaneous absorption.

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A high frequency of contact allergy to gold in patients with eczematous disease has now been found in test laboratories worldwide (1). The reason for this is not fully understood, but recently, a positive correlation was demonstrated between gold allergy and the presence of dental gold in the patients. The correlation was not only qualitative but also quantitative: the more the gold surfaces in the oral cavity, the higher the risk of developing contact allergy to gold (2). Furthermore, the presence of dental gold was found to be accompanied by an increased blood level of gold, even in a quantitative relationship (3).

Gold from metal alloys has been shown to be dissolved and released into the saliva (4), and its presence in blood should be explained by an absorption of ionized gold through mucous membranes. Metallic gold is not released into 'artificial sweat' and other salt solutions (5,6), but it seems to be soluble in a wide range of aqueous amino acid solutions (7,8) with a stronger similarity to real human sweat. Also, there is clinical as well as experimental evidence of elicitation of an allergic

contact dermatitis by metallic gold exposure to the skin (9). As a consequence, we found it warranted to study whether a gold salt could penetrate and be absorbed through intact or inflamed skin, situations which are present during patch testing with gold.

Materials and Methods

Patients

In a previous study (3), 80 patients were investigated for a contact allergy because of eczematous disease. Interest was focused on contact allergy to gold, and, at the same time, on the level of gold in blood. In 67 of these patients, it was possible to obtain a venous blood sample not only before patch testing but also on day 3 (D3) ($n=50$) or day 7 (D7) ($n=17$). There were 31 males and 36 females; the mean age was 47.7 (range 23–73) years.

Patch testing

The patients were patch tested on the back with the European standard series, with the dental screening series including various titanium compounds (Chemotechnique Diagnostics, Tygelsjö,

*Dr Schütz died before this article was completed.

Sweden) and, when indicated, with additional test series as well as patient-supplied materials. Test substances included in the standard series were excluded from the dental test series. In addition, GSTS 0.5, 2.0 and 5.0% (wt/wt in petrolatum), all applied at the same time, was included. It was calculated that, by these epicutaneous applications, the patients were exposed to a total amount of approximately 0.9 mg of Au. Finn chambersTM with an inner diameter of 8 mm (Epitest, Tuusula, Finland) were attached on Scanpor tapeTM (Norgesplaster, Vennesla, Norway). The patches were removed by the patients (without touching the patch test material) after 48 h (D2) and the reactions read after a further day (D3) and on D7.

Assay of gold in blood

Sampling and storage of venous blood as well as method for gold determination has been described in detail (3). Gold in whole blood (B-Au) was assayed by inductively coupled plasma mass spectrometry. The detection limit was 0.04 µg/l and the method reproducibility 7%.

Statistical analyses

Calculations were carried out with the Wilcoxon signed-rank test (mean concentration of B-Au before and after gold exposure) and the Mann-Whitney *U*-test (B-Au on D3 versus D7 and in allergic versus non-allergic patients). All data from blood analyses were used for calculations. Thus, results below the detection limit were not rejected or changed, so that distribution or median values would not be distorted.

Results

The assay of gold produced fairly homogenous results in blood sampled before patch testing. The same held true for the 2nd sample, however, with one exception in which a patient with an extremely high value was found; the results from this 'outlier' were excluded from the calculations. In the remaining 66 patients, the median gold concentration before patch testing was 0.03 µg/l to compare with the level at D3/D7 which was 0.34 µg/l (Fig. 1). The difference was highly significant ($P < 0.0001$). The same degree of significance was reached when comparing the 2 blood levels within the group of males (median 0.02 versus 0.34 µg/l) and those of females (median 0.04 versus 0.33 µg/l).

In 50 patients, the 2nd blood sample was taken on D3 and in 16 patients on D7. There was a tendency towards a decrease of median blood values from D3 to D7 (Fig. 2), but the statistical

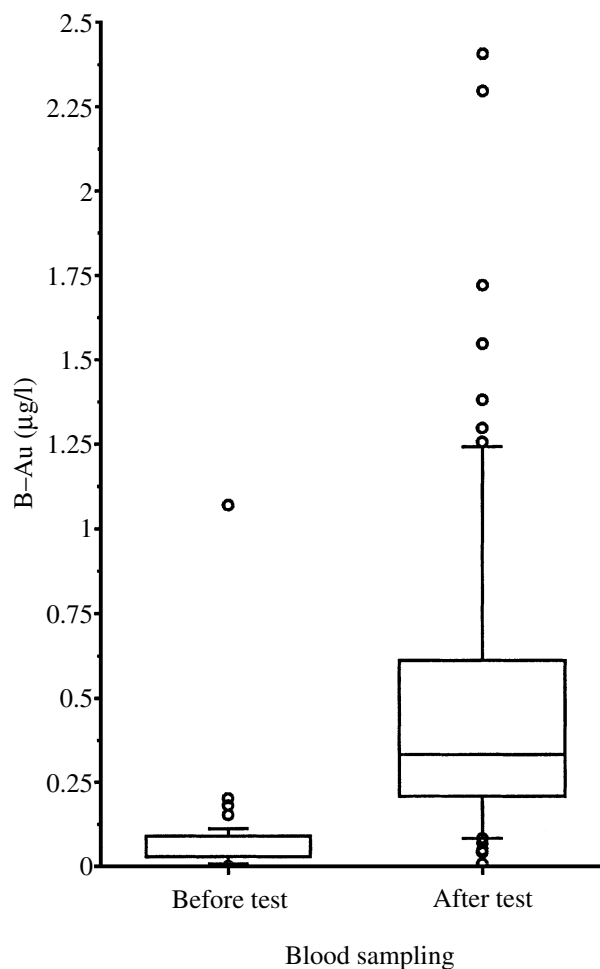


Fig. 1. Gold in whole blood (B-Au) in 66 patients before and after patch testing with gold sodium thiosulfate. The box is defined by the upper and lower quartiles and with the median marked by a subdivision of the box. The whiskers are the lines that extend from the top and bottom of the boxes to the lowest and highest observations, excluding outliers (circles).

difference was not significant. A similar tendency could be seen when comparing median blood values of patients being allergic ($n = 20$) and not allergic ($n = 46$) to gold, the level being somewhat higher in the allergic patients (Fig. 3); however, the difference was not statistically significant.

Discussion

Absorption of contact allergens through human skin has been studied by methods based on different principles. Thus, percutaneous absorption can be studied by disappearance measurements, by appearance of the chemical in living epidermis; by its uptake in peripheral blood or other organs or by following its excretion. None of these methods have been used to demonstrate percutaneous absorption of ionized gold.

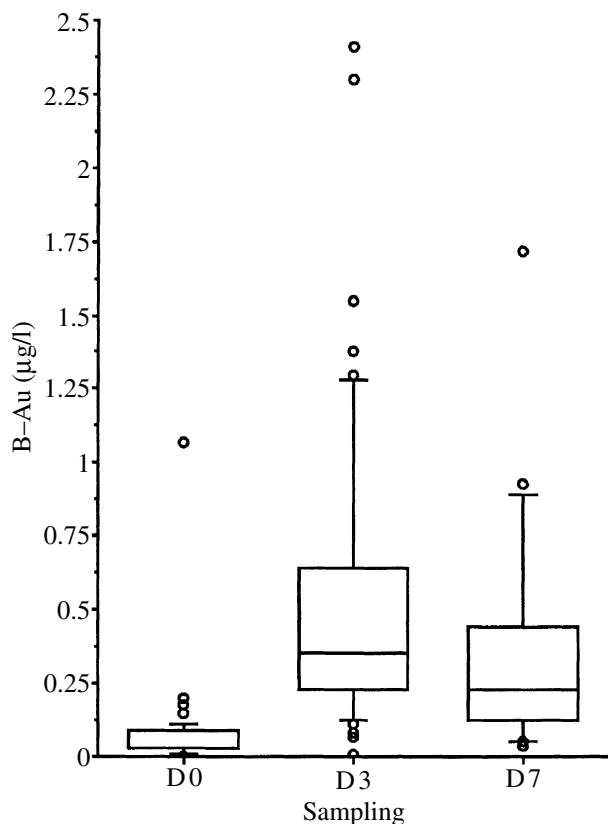


Fig. 2. Gold in whole blood (B-Au) in all the 66 patients sampled before patch testing [day 0 (D0)] ($n=66$) as well as in those sampled a 2nd time on day 3 (D3) ($n=50$) and those on day 7 (D7) ($n=16$). The box is defined by the upper and lower quartiles and with the median marked by a subdivision of the box. The whiskers are the lines that extend from the top and bottom of the boxes to the lowest and highest observations, excluding outliers (circles).

For the present purpose, we chose to study the gold level of whole blood during occluded patch testing with GSTS. Each patient was exposed to 3 test patches with a total amount of 0.9 mg of Au, and this led to a 10-fold increase of B-Au (Fig. 1). It might be expected that the allergen should more easily penetrate the inflamed skin of a positive patch test and, consequently, a damaged skin barrier, but a comparison between findings in patients with a positive patch test to gold and those negative did not confirm this (Fig. 3).

Brown et al. (7) were able to demonstrate that 2 gold(I) salts, gold sodium thiomalate and auranofin, are readily absorbed through rat skin. In our present study in humans, it could be calculated that, based on the quantity of gold under the test patches, the estimated blood volume and the blood concentrations found, approximately 0.2% of the amount applied was taken up in the circulation. Such a minute amount seems, however, sufficient to evoke distant flare-up reactions after local clinical or experimental provocation

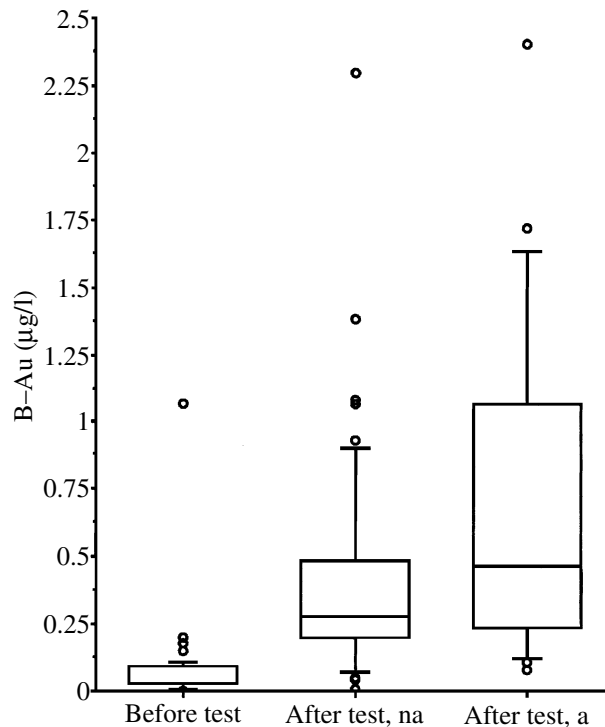


Fig. 3. Gold in whole blood (B-Au) in all the 66 patients sampled before patch testing ($n=66$) as well as in those not allergic (na, $n=46$) and those allergic (a, $n=20$) to gold at the 2nd sampling. The box is defined by the upper and lower quartiles and with the median marked by a subdivision of the box. The whiskers are the lines that extend from the top and bottom of the boxes to the lowest and highest observations, excluding outliers (circles).

(9). Also, a chemical analysis of skin samples taken from the area that comes in direct contact with the ring showed measurable amounts of gold (7). Actually, continuous wearing of a gold ring on the left ring finger seems to imply percutaneous absorption of gold in a quantity sufficient to protect from an articular erosion in rheumatoid arthritis (10).

The peak of the eczematous reaction in a positive patch test to GSTS is often delayed and may therefore be missed if the reading takes place on D3 only or even earlier (11). This fact, together with a presumably slow pace of percutaneous absorption of the allergen, might result in a higher B-Au on D7 than on D3. However, no difference in gold level between the 2 blood samplings could be ascertained (Fig. 2).

An eczematous flare-up at distant body areas after the local application of a contact allergen may be taken as indirect evidence of percutaneous absorption. This phenomenon was demonstrated experimentally in the mouse with picryl chloride and nickel sulfate (12), and recently, in human during the repeated open application test with budesonide (13). It is sometimes casuistically

reported as a side effect of patch testing (14), not the least with sesquiterpene lactones (15). As a matter of fact, flare-up was a remarkable finding in the very 1st case report on allergic contact dermatitis to gold (16) and also part of the clinical-experimental reactions in patients exposed to gold jewellery (9).

Conclusions

Gold sodium thiosulfate, applied in small amounts by patch testing on normal skin, is systemically absorbed and can be demonstrated in circulating blood. Probably, this finding must be of principal nature and hold true for other contact allergens as well. A percutaneous absorption might explain reactivation and other side effects observed during patch testing.

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