

Review Article

Gold – a controversial sensitizer

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Until recently, gold allergy was considered to be extremely rare. Gold has been used and worshipped for thousands of years without any obvious complaints of skin problems, either in those participating in mining and other ways of prospecting, or in those wearing jewellery. When studies on contact allergy to gold sodium thiosulfate were published at the beginning of the 1990s, the allergic nature of the reported positive patch test reactions to gold was questioned. The major argument for such questioning was the lack of demonstrable clinical relevance in most positive reactors. A major reason for the questioning may have been confusion in differentiating between contact allergy and allergic contact dermatitis. To arrive at a diagnosis of allergic contact dermatitis, 3 steps have, in principle, to be fulfilled: (i) establishment of contact allergy; (ii) demonstration of present exposure; (iii) assessment of clinical relevance, i.e., causing or aggravating a contact dermatitis. In this paper, these steps are discussed with regard to gold. With our present knowledge of contact allergy – allergic contact dermatitis, we do not recommend including gold sodium thiosulfate in the standard series. It should be applied for scientific purposes and when allergic contact dermatitis from gold is suspected.

Key words: allergic contact dermatitis; allergic contact stomatitis; clinical relevance; contact allergy; gold sodium thiosulfate, dental patients; jewellery, late-appearing patch test reactions; biological availability. © Munksgaard, 1999.

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Within the field of contact dermatitis, gold has been, and partly still is, one of the most controversial subjects. The reason for this is understandable. Until recently, gold allergy was considered to be extremely rare, so it was remarkable when a contact allergy rate to gold of around 10% was reported in consecutively patch tested dermatitis patients (1). Gold, maybe the most beloved and precious metal, has been used and worshipped for thousands of years without any obvious complaints of skin problems, either in those participating in mining and other ways of prospecting, or in those wearing jewellery. Furthermore, gold as a metal is a non-reactive metal and to be a hapten it has to be ionized. Expectedly, ionic gold, monovalent and trivalent, is very reactive chemically. Gold salts and compounds have therefore been tried, and are still used, for treatment of many dis-

eases including skin diseases (2–6). Currently, gold-containing drugs are used particularly for treatment of rheumatoid arthritis and occasionally for pemphigus. Gold preparations may cause adverse reactions and, when correlating the frequency of these to the degree of use, gold is at the top of the list of drugs causing side-effects (7). Interestingly, symptoms and lesions from the skin and mucous membranes predominate (2–8). The background for the majority of these adverse reactions has not been completely clarified. Allergic mechanisms, including contact allergy, have been proposed but never proven (3, 9), not even after the acquisition of knowledge of how to test gold sodium thiomalate, the active ingredient of Myocrisin®, to trace contact allergy to gold (10,11).

Allergic contact dermatitis and stomatitis from gold have occasionally been reported (12–21). The

allergy has been demonstrated by patch testing with various gold salts (12–21) and even with the metal itself (12). In the 1960s, Kligman found gold chloride to be a strong sensitizer in a human maximization test (22).

In the late 1980s, Fowler (23) reported that gold sodium thiosulfate at 0.5% in petrolatum was a good screening preparation for tracing contact allergy to gold. After insertion of this gold salt into the dental screening series at the department of occupational and environmental dermatology in Malmö, positive test reactions were registered within a short period of time (1). When gold sodium thiosulfate was introduced in our standard series, a contact allergy rate of 9% was noted (1). The patients testing positively participated in additional testing to elucidate the nature of the positive patch test reactions. Thereafter, contact allergy rates to gold in the range 1–23% were reported from various countries (24–32).

The Controversy

When studies on contact allergy to gold were published at the beginning of the 1990s, the allergic nature of the reported positive patch test reactions to gold was questioned. The major argument for the questioning was the lack of demonstrable clinical relevance in most positive reactors. A major reason for the questioning may have been confusion in differentiating between contact allergy and allergic contact dermatitis. To arrive at a diagnosis of allergic contact dermatitis, 3 steps have in principle to be fulfilled: (i) establishing of contact allergy, (ii) demonstration of present exposure, (iii), assessment of clinical relevance; i.e., causing or aggravating a contact dermatitis (33).

Establishment of Contact Allergy

The establishment of contact allergy is never equivalent to diagnosis of allergic contact dermatitis. Contact allergy itself is not a disease but the sensitized person has contracted a property which is a prerequisite for the acquisition of allergic contact dermatitis, but again, only if the 2 other requirements are met (33). Thus, when is a person sensitized? As long as the decisive biomolecular step determining sensitization is unknown, we are obliged to define contact allergy by other means. There is no single method or test that can ascertain the presence of contact allergy, but we have to rely on various indirect methods, with results and reactions which are considered able to establish or support the presence of contact allergy. Examples of such methods are listed in Table 1.

The positive result of a patch test can never

stand alone as the proof of contact allergy. Principally, there are 2 types of reactions. Some reactions have morphological features consistent with irritant reactions, so they will never be subjected to further discussions on allergenicity. Other reactions may show features of erythema, infiltration, papules, and vesicles in various combinations. For substances which have been accepted as sensitizers, e.g., nickel and colophony, the presence of at least a homogenous erythema with infiltration is considered to be equivalent to the establishment of contact allergy (34). However, when substances not recognized as well-established sensitizers give patch test reactions morphologically indistinguishable from allergic reactions, supplementary investigations have to be performed (35, 36). Patch testing with serial dilutions, different vehicles, different salts when applicable, and testing of controls will determine, or rather guide, whether the reactions should be considered to be expressions of irritant or allergic processes. With regard to gold, all these requirements have been fulfilled except for the testing in controls. Gold was considered to be a rare sensitizer when gold sodium thiosulfate at 0.5% pet. was suggested as a screening preparation for tracing contact allergy to gold. The insertion of this petrolatum preparation into the standard series, therefore, in a way represented a test of controls and the yield of positive reactions at a frequency exceeding 5% consequently suggested an irritant nature of the patch test reactions. At least, this is true for a substance to which few persons are exposed. Positive patch-test reactions to such a substance in controls, who have not been exposed to the substance, strongly suggest an irritant nature, unless the substance is cross-reacting or metabolized to a common sensitizer. On the other hand, for a ubiquitous substance such as gold, testing in controls may not be as conclusive, as the positive patch test reactions may also suggest, or at least not exclude, an allergic nature. Furthermore, by lowering the test concentration, the number of positive reactors will decrease below 5%, but the reactions will share the same morphology. When patch tests are followed over an extended period of time, late-appearing reactions and long-lasting reactions are considered to indicate allergic reactions. Positive patch test reactions to gold appear late and they are extremely long-lasting (1, 14, 18, 23, 37–39).

Other tests and investigations listed in Table 1, except for active sensitization and predictive testing in animals, have supported the interpretation of an allergic nature of the positive test reactions to gold (1, 10, 24, 37, 40–46).

Predictive testing in animals or man can, under certain conditions, demonstrate whether a sub-

Table 1. Tests and investigations which can help establish a substance, e.g., gold, as a contact sensitizer

patch testing
morphology of positive reactions
controls
serial dilutions
different gold compounds
different vehicles
crescendo – type of reactions
duration of positive reactions
patch test sensitization
intracutaneous testing
systemic challenge
histopathology
immunohistochemical investigations
lymphocyte transformation test
cytokine release
predictive testing in animals

stance is a sensitizer. As already mentioned, Kligman (22) sensitized humans with gold chloride in the 1960s, but so far, there are no reports on successful sensitization to gold in animals. In Malmö we have not succeeded in sensitizing guinea pigs with gold sodium thiosulfate (in manuscript form).

Keeping in mind all requirements to be fulfilled by a substance before it is accepted as a sensitizer, it must currently be accepted that ionic gold is a sensitizer and that a positive patch test reaction to gold sodium thiosulphate represents an allergic reaction. However, when the exact biomolecular nature of sensitization is disclosed in the future, it may be shown that not all presently known and accepted sensitizers will meet the requirement to be recognized as contact allergens. This may be true for gold but also for other sensitizers, in particular metal salts. Allergic and irritant contact dermatitis show a remarkable similarity regarding clinical appearance, histology and immunohistology. Antigen recognition by specific memory T cells and irritants can induce the same pattern of inflammation, including activation of T cells obviously independent of exogenous antigen (47). Gold seems to be able to bind directly to the MHC class II molecule and thus induce an inflammatory response indistinguishable from traditional hapten-peptide conjugate-induced contact hypersensitivity (48, 49).

Demonstration of Present Exposure

Many persons are or may be exposed to metallic gold as it is present in jewellery and dental materials (24–32, 50). To act as a sensitizer, gold, like other metals, has to be ionized. Occupationally, there might be exposure to gold salts besides exposure to metallic gold (16–18, 51). Even if there are reports on release of gold from gold items ex-

posed to human sweat, particularly when sulfur-containing amino acids are present, we need more knowledge on the exposure to gold with regard to factors such as bioavailability, ionization, release from various gold items and alloys in contact with the skin and the mucous membranes in the oral cavity (52–55).

Clinical Relevance

So far, we have only sparse knowledge of the general clinical relevance of contact allergy to gold (1, 24–32, 39, 50). There are reports on allergic contact dermatitis and stomatitis (12–31, 30, 39). Actually, to conclude unambiguously that a gold exposure in an allergic individual is clinically relevant, it has to be known or shown that contact with dental or jewellery gold releases the minimum number of gold molecules required to elicit an allergic contact dermatitis/stomatitis. The possible influence of anatomical region, presence of occlusion, damaged skin/mucous membrane and degree of reactivity must also be taken into account (33). Another factor to consider is the fate of gold when entering the skin/mucous membranes. Most likely, only minute amounts of gold will be released from gold objects in contact with the skin/mucous membrane and this argues against any clinical relevance of the exposure, unless gold is accumulated locally and eventually reaches the threshold level where a dermatitis/stomatitis will be elicited.

Recommendations

With our present knowledge of contact allergy – allergic contact dermatitis, many patients seem to have clinically non-relevant gold allergies (1, 24–32, 39, 50). For most of those with a relevant gold allergy, the patient has suspected the allergy and by avoiding exposure to gold objects, the patients are free of dermatitis or can continue to use the objects as the symptoms are very mild. Therefore, we do not recommend including gold sodium thiosulfate in the standard series. It should be applied for scientific purposes and when allergic contact dermatitis from gold is suspected.

The gold salt potassium dicyanoaurate at a low concentration was included in the dental screening series recommended in the early 1980s (56). When patch testing patients with suspected adverse reactions to dental materials with higher concentrations of either gold trichloride or gold sodium thiosulfate, a higher number of patients with a clinically relevant contact allergy to gold was found (26, 57–60). Whenever patch testing with gold, keep in mind that a test reading should also be performed after 1 week (38, 39). Actually, read-

ing even on D 14–21 may be indicated (38, 39). However, we emphasize that an established contact allergy to gold does not mean that all oral symptoms and lesions can be attributed to the gold allergy. Again, a present exposure to gold that explains the symptoms and lesions has to be demonstrated. Most dermatologists do not have the training and experience to do this with regard to dental materials, so the assessment of exposure and clinical relevance has to be done in cooperation with experts within dentistry. For many gold-allergic patients with dental gold, the allergy seems to be without any significance for the oral symptoms and lesions, and it is therefore important to inform the patient and referring dentist that the dental gold need not be removed, unless it is highly likely that the gold exposure is clinically relevant.

Need for Scientific Investigations

To understand gold allergy and allergic contact dermatitis/stomatitis from gold better, certain areas should be subjected to further explorations scientifically. What is the cause of sensitization? Can jewellery sensitize (27, 61–63)? The question of whether dental gold is significant for sensitization should be addressed further (25, 26, 28, 29, 32, 50). Late-appearing positive patch test reactions to gold do not need to be examples of active sensitization (38) but, actually, the possibility of active sensitization as the explanation for a part of the late-appearing reactions has not been investigated and is thus not excluded. Various gold objects and alloys should be investigated with regard to gold release when exposed to human sweat and saliva. There is a need for prospective studies on the significance of gold exposure for the development of dermatitis and stomatitis. Can a continuous and low release of gold from dental materials cause systemic allergic contact dermatitis?

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