Oral Lichen Planus and Allergy to Dental Amalgam Restorations

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Objectives: To determine contact allergies in patients with oral lichen planus and to monitor the effect of partial or complete replacement of amalgam fillings following a positive patch test reaction to ammoniated mercury, metallic mercury, or amalgam.

Design: In group A (20 patients), the oral lesions were confined to areas in close contact with amalgam fillings. In group B (20 patients), the lesions extended 1 cm beyond the area of contact with amalgam fillings. In group C (20 patients), the oral lesions had no topographic relationship with amalgam fillings. Partial or complete replacement of amalgam fillings was recommended if there was a positive patch test reaction to ammoniated mercury, metallic mercury, or amalgam. Control group D (20 patients) had signs of allergic contact dermatitis.

Results: Amalgam fillings were replaced in 13 patients of group A, with significant improvement. Dental amalgam was replaced in 8 patients of group B, with significant improvement. In group C, amalgam replacement in 2 patients resulted in improvement in 1 patient. These results were evaluated after 3 months. No positive patch test reactions to mercury compounds were found in patients with concomitant cutaneous lichen planus and in group D.

Conclusions: Contact allergy to mercury compounds is important in the pathogenesis of oral lichen planus, especially if there is close contact with amalgam fillings and if no concomitant cutaneous lichen planus is present. In cases of positive patch test reactions to mercury compounds, partial or complete replacement of amalgam fillings will lead to a significant improvement in nearly all patients.

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Oral Lichen Planus (OLP) has a prevalence of about 0.5% to 2%. Generally, it is a disease of middle-aged and older persons, and the female-male ratio is about 2:1.1-4 Oral lichen planus can be categorized into several clinical variants. The hyperkeratotic variant is usually asymptomatic. The atrophic or erythematous variant and the erosive or ulcerative variant mostly have persistent symptoms of pain or stinging. The various terms for OLP in the literature are oral lichenoid lesions, lichenoid contact lesions, and lichenoid contact stomatitis and are used interchangeably, which is confusing. In this study, we only use the term oral lichen planus because there is no difference in clinical practice based on the symptoms of disease, clinical examination, and histopathologic findings.5-9 Oral lichen planus is usually a persistent disorder and may last many years, despite several kinds of treatment.10,11 The exact cause of OLP remains unknown, but an immune-mediated (T-cell dependent) pathogenesis is proposed.1,3,12

The concept of contact allergy to dental restorative materials aggravating or inducing OLP is well recognized but somewhat controversial.13-15 However, several authors have reported resolution of signs and symptoms in OLP after replacement of amalgam, particularly if there was a positive patch test result to mercury, which is the most important allergen in amalgam.6,16-18

The aim of this study was to determine contact allergies in patients with OLP and amalgam fillings and to investigate whether there are specific subgroups of patients with OLP, based on differences in the relationship between oral lesions and amalgam fillings. A second objective was to monitor the presence of signs and symptoms in OLP after replacement of amalgam, particularly if there was a positive patch test result to mercury, which is the most important allergen in amalgam.
This prospective nonrandomized control study included 80 white patients who were older than 18 years with 1 or more silver amalgam fillings. Sixty patients had the diagnosis of OLP established on the basis of medical history, physical examination, and histopathologic evaluation. They were categorized into 3 equal groups based on the topographic relationship between oral lesions and the amalgam fillings. In group A (20 patients), the oral lesions were confined to areas in close contact with amalgam fillings. In group B (20 patients), the lesions extended 1 cm beyond the area of contact with amalgam. In group C (20 patients), the oral lesions had no topographic relationship with dental amalgam restorations. A control group (group D; 20 patients) had allergic contact dermatitis without any oral pathologic evidence of OLP. Patient recruitment ended when there were 20 patients in each group.

The study was carried out from 1991 to 1993 at the Department of Dermato-Venereology, University Hospital Rotterdam, and continued from 1994 to 2001 at the Department of Dermatology, Albert Schweitzer Hospital.

Patch tests with a standard series (according to the European standard series) and a dental metal series (Table 1) were included with Finn chambers on the skin and evaluated after 72 hours. The reactions were read 30 minutes after removal of the patches to minimize false-positive readings. Erythematous and indurated test results were regarded as positive. If there was only an erythematous patch test reaction (which was regarded as negative), another evaluation was made after 3 days and, if necessary, several days or weeks later. Patients were instructed to return if there was a possible late positive reaction. Replacement of amalgam fillings was recommended in case of a positive patch test reaction to ammoniated mercury, metallic mercury, or amalgam. Alternative dental restorations consisted of composite resins, glass ionomers, ceramics (porcelain), and gold.

If there was a positive patch test reaction to ammoniated mercury, metallic mercury, or amalgam in groups A, B, and C, the advice was first given to replace the amalgam fillings in close contact with the oral lesions. If there was a significant improvement in the lesions, the patients were advised to replace any remaining part of the amalgam in the dental fillings in the future, but only for dental reasons. In group C, all dental amalgam was replaced if there was a positive patch test reaction to the allergens. In group D, no advice on replacement of amalgam fillings was given. In all groups, participants were advised to desist from new dental amalgam restorations in the future if there was a positive reaction to 1 or more mercury compounds.

One or two 3-mm punch biopsy specimens for histopathologic examination were taken from the hyperkeratotic or erythematous lesions and were fixated in buffered 4% formalin. Histopathologic changes in OLP comprised varying degrees of focal hyperkeratosis or parakeratosis, irregular acanthosis or atrophy, liquefaction degeneration of the basal cell layer, and, characteristically, a dense bandlike lymphocytic infiltrate high in the lamina propria. Hyaline (Civatte) bodies, which represent degenerative basal cells, are occasionally seen in the epithelium. If the histopathologic changes in the mucosa were less pronounced (especially the basal cell layer degeneration and the inflammatory infiltrate), the diagnosis of “compatible with OLP” was made. If there were more aspecific changes, this was diagnosed as “nonspecific.” If there were signs of cutaneous lichen planus (CLP), histopathologic examination of the skin lesions was performed. The clinical effect of treatment in the patients with OLP was graded as worse (+), unchanged (±), improved (+), and healed (++) Statistical analysis of the results was performed by means of the exact χ² test for trend, Fisher exact test, 1-way analysis of variance test, and Kruskal-Wallis test, in which 2-sided P values were calculated (with statistical significance set at P<.05).

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### Table 1. Patch Test Antigens

<table>
<thead>
<tr>
<th>Standard Series</th>
<th>Dental Metal Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium dichromate 0.5% pet</td>
<td>Ammoniated mercury 1% pet</td>
</tr>
<tr>
<td>Neomycin sulfate 20% pet</td>
<td>(mercury ammonium chloride)†</td>
</tr>
<tr>
<td>Thiram mix 1% pet</td>
<td>Copper sulfate 2% pet</td>
</tr>
<tr>
<td>Paraphenylenediamine 1% pet</td>
<td>Potassium dichromate</td>
</tr>
<tr>
<td>Cobalt chloride 1% pet</td>
<td>Sodium thiosulfatoaurate</td>
</tr>
<tr>
<td>Benzocaine 5% pet</td>
<td>0.002% aq</td>
</tr>
<tr>
<td>Formaldehyde 1% aq</td>
<td>0.25% pet</td>
</tr>
<tr>
<td>Colophony 20% pet</td>
<td>Balsam of Peru 25% pet</td>
</tr>
<tr>
<td>Clioquinol 5% pet</td>
<td>Ni-propyl-N-phenylparaphenylenediamine 0.1% pet</td>
</tr>
<tr>
<td>A, B, and C</td>
<td>Ammonium tetrachloroplatinate</td>
</tr>
<tr>
<td></td>
<td>0.5% pet*</td>
</tr>
<tr>
<td></td>
<td>Gold sodium thiosulfate 0.5% pet</td>
</tr>
<tr>
<td></td>
<td>Palladium chloride 1% pet</td>
</tr>
<tr>
<td></td>
<td>Cadmium chloride 1% aq</td>
</tr>
<tr>
<td></td>
<td>Silver nitrate 1% aq</td>
</tr>
<tr>
<td></td>
<td>Gold (trichlor) 0.5% aq</td>
</tr>
<tr>
<td></td>
<td>Zinc chloride 2.5% pet</td>
</tr>
<tr>
<td></td>
<td>Copper oxide 5% pet</td>
</tr>
<tr>
<td></td>
<td>Aluminum chloride hexahydrate</td>
</tr>
<tr>
<td></td>
<td>2% pet</td>
</tr>
<tr>
<td></td>
<td>Tin 50% pet</td>
</tr>
<tr>
<td></td>
<td>Thimerosal 0.1% pet (Methylthiolatet)</td>
</tr>
<tr>
<td></td>
<td>Ferrous sulfate 5% pet</td>
</tr>
<tr>
<td></td>
<td>Gallocatechin 0.2% pet</td>
</tr>
<tr>
<td></td>
<td>Gallic acid 1% pet</td>
</tr>
<tr>
<td></td>
<td>Titanium oxide 1% pet</td>
</tr>
<tr>
<td></td>
<td>Zirconium oxide 0.1% pet</td>
</tr>
<tr>
<td></td>
<td>Amalgam 5% pet (gulderized amalgam powder)*</td>
</tr>
</tbody>
</table>

Abbreviations: aq, aqueous solution; pet, in petrolatum.
*Inorganic mercury compound.
†Organic mercury compound.

The basic characteristics, such as sex, age, duration of the lesions before patch testing, and number of dental amalgam fillings, in groups A, B, C, and D are shown in Table 2 and did not differ significantly (P>.05). The most commonly affected areas in OLP were the buccal mucosa, the lateral part of the tongue, and, less frequently, the gingiva. In groups A, B, and C, histopathologic examination led to a diagnosis of OLP in 30% (18/60) of the patients, a diagnosis compatible with OLP in 35% (21/60) of the patients, and a diagnosis of nonspecific changes in 35% (21/60) of the patients. These results were irrespective of positive or negative patch test reactions to mercury compounds. Direct im-

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This page contains a table of patch test antigens, including standard and dental metal series. The table highlights various allergens such as formaldehyde, mercury compounds, and other metals, along with their concentrations and forms. The text describes the methodology and results of a study comparing the effect of partial or complete replacement of dental amalgam restorations following a positive patch test reaction to ammoniated mercury, metallic mercury, or amalgam. The study involved 80 patients with 1 or more silver amalgam fillings, categorized into groups based on the topographic relationship with lesions. The study's aim was to assess the clinical effect of treatment and the histopathologic changes in oral lichen planus (OLP) with and without amalgam fillings. The results indicated that the presence of amalgam fillings was associated with a diagnosis of OLP, and the study recommended replacing amalgam fillings if a positive patch test reaction was observed. The study used a standard series and a dental metal series for patch testing, with various allergens listed in Table 1. The results were analyzed statistically using χ² test for trend, Fisher exact test, and 1-way analysis of variance, with significance set at P<.05.
munofluorescence was performed in 6 patients, and the results were not compatible with a diagnosis other than OLP. In the 3 groups with oral lesions, the clinical variant of OLP and the histopathologic examinations were not significantly different. Seven patients (12%) among 60 with OLP had concomitant CLP (Table 2). The exact test for trend in groups A, B, and C showed a statistically significant difference (P = .02) in the concomitance of CLP. Moreover, no positive patch test reactions to mercury compounds were found in the patients with concomitant CLP.

The positive patch test reactions to the organic or inorganic mercury compounds are shown in Table 3. No positive patch test reactions to inorganic or organic mercury compounds were found in group D. Partial or complete replacement of amalgam fillings in patients with OLP with positive patch test results to organic or inorganic mercury compounds was successful in nearly all patients (Table 4). All patients with OLP without positive patch test reactions to mercury compounds and without the recommendation of replacement of amalgam fillings had unchanged oral lesions. One patient in group A had an amalgam replaced of his own accord, despite a negative patch test reaction to inorganic mercury compounds. His oral lesions did not change at all.

Statistical analysis was performed in an overall test per mercury compound (exact χ² test) in the 4 groups, with a significant difference for ammoniated mercury and metallic mercury (P < .001). There were no significant differences for amalgam (P = .11) and thimerosal (P = .37) (Table 3). In the Fisher exact test, comparisons in pairs were performed for ammoniated mercury and metallic mercury, with significant differences between groups A and D (P < .001 and P < .003) and groups B and D (P < .008 and P < .047) (Table 3). In the exact χ² test (linear-by-linear association), there was a significant difference (P = .01) in the tendency of healing whether the amalgam fillings were more associated with OLP and whether there was at least a positive patch test reaction to ammoniated mercury (Table 4).

Other positive reactions occurred in group A to nickel sulfate (2 patients), fragrance mix (1 patient), silver nitrate (1 female patient, who also had a positive reaction to ammoniated mercury), and thiuram mix (1 patient). Other positive reactions occurred in group B to nickel sulfate (1 patient), fragrance mix (1 patient), Kathon CG (5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one) (1 patient), potassium dichromate (1 patient), and palladium chloride (1 patient). Other positive reactions oc-
curred in group C to nickel sulfate (1 patient), fragrance mix (1 patient), balsam of Peru (1 patient), and neomycin sulfate (1 patient). There were no significant differences between the occurrence of positive reactions and the specific variant of OLP. In group D, positive reactions occurred to nickel sulfate (4 patients), fragrance mix (3 patients), formaldehyde (2 patients), colophony (2 patients), balsam of Peru (2 patients), paraben mix (1 patient), Quaternium-15 (1 patient), cocamidopropyl betaine (2 patients), benzocaine (1 patient), and cobalt chloride (1 patient).

In 8 (35%) of 23 patients, positive patch test reactions to ammoniated mercury, metallic mercury, or amalgam only occurred after the regular 3-day evaluation, with a variation of 5 to 18 days (mean, 8 days). Moreover, there were persistent patch test reactions in 6 (26%) of 23 patients, with a variation of 4 to 24 days (mean, 10 days). The effects of replacements of amalgam fillings were mostly seen after 1 to 4 months (mean, 3 months).

If there was a positive effect of the replacement of amalgam fillings in patients with OLP, this effect did not change significantly during follow-up of 2 to 7 years (mean, 4 years). In the patients without replacement of dental amalgam restorations, the lesions remained unchanged during follow-up. No malignant transformation of OLP was observed in this study.

**COMMENT**

Amalgam has been used as a dental restorative material since its inception in 1831 for people all over the world, with few adverse effects. It is good for dental use because it is strong, long lasting, well fitting, easy to handle, and cheap. Conventional silver amalgam fillings consist of about 50% mercury and about 50% alloy powder containing silver, tin, copper, and zinc.

Mercury and mercury compounds appear to be the most common allergens in amalgam, with the other metals being rarely responsible for allergic reactions. Contact sensitivity to mercury in amalgam confirmed by patch testing was previously reported by Shovleton. Amalgam in the oral cavity is prone to corrosion and, by releasing metal ions, may be responsible for sensitization and allergic reactions (type IV, T-cell dependent). This process may lead to long-term antigenic stimulation, with mucosal changes, and ultimately to OLP. A less favorable hypothesis is that close contact between dissimilar metals (eg, amalgam and gold) may produce different potentials and lead to electrochemical reactions, corrosion, and increased release of metal ions, also leading to mucosal changes.

Martin et al reported that the presence of amalgam or gold was not associated with increased risk of OLP, but that the corrosion of amalgam and the presence of electrogalvanism from dissimilar dental materials in continuous contact were associated with increased risk of OLP. The incidence of positive patch test reactions to mercury compounds and OLP varied considerably in several studies and depended largely on whether the mucosal lesions were in direct contact with amalgam (34%-89%, 65% [13/20] in our study) or not (0%-33%, 10% [2/20] in our study) and on the specific allergens and the concentrations that were used to detect allergy to mercury. Mercury is able to penetrate the healthy and the compromised mucosa, but the circumstances in which sensitization occurs are not exactly known. It is reasonable to say that possibly involved allergens are dissolved and spread via saliva; therefore, mucosal reactions may extend beyond the contact areas.

From our study, it appeared that there were essential differences in the incidence of contact allergy to mercury compounds between groups A, B, and C based on the topographic relationship of amalgam and OLP (especially if there is an asymmetry). Moreover, no positive patch test reactions to mercury compounds were found in group D. In the case of positive patch test reactions to ammoniated mercury or amalgam, partial or complete replacement of amalgam fillings is beneficial after several months. This suggests that, in these cases, contact allergy is an important etiologic factor in OLP. Moreover, there is frequently more than 1 positive reaction to mercury compounds, which favors true sensitization and underlines the clinical importance. The most reliable allergen for silver dental amalgam allergy in our study was ammoniated mercury. Less reliable allergens are (in diminishing frequency) metallic (elementary) mercury, amalgam, and thiomerosal. Mercury chloride was used in patch tests in some studies if there was a suspicion of allergy to mercury. However, in our opinion, it is not a reliable allergen because the literature also states that it is a strong sensitizer and often produces a nonspecific pustular or an irritant reaction even when diluted to a 0.05% aqueous solution. It is wise to test ionized mercury (ammoniated mercury or mercury chloride [0.1% mercury chloride in petrolatum is perhaps better than a 0.05% mercury chloride aqueous solution]) and nonionized mercury (metallic mercury and amalgam). An important issue is that positive reactions to inorganic mercury compounds may occur after the regular evaluation of 3 days, a finding in 33% (8/23) of the patients in our study. This may be a major cause of the different frequencies of positive reactions in the literature. The same phenomenon may occur with several other allergens such as gold, palladium, potassium dichromate, neomycin sulfate, and paraphenylenediamine. Histopathologic examination of the positive patch test specimens in these cases often shows lichenoid in addition to eczematous changes. In some cases, there is also a different time of occlusion of the allergens. In the study by Koch and Bahmer, there was an occlusion only during 1 day, with histopathologic examination of the oral lesions performed in a small number of patients. The clinical relevance of the remaining positive patch test reactions to other allergens in relation to OLP is not clear. Gold, palladium, copper, silver, and acrylates may also be responsible in the pathogenesis of OLP. We could not confirm the finding by Yiannias et al that allergy to flavorings may also be important in the pathogenesis of OLP. In our experience, this may be relevant in the diagnosis of allergic contact stomatitis. In the study by Yiannias et al, an important aspect may be that macular erythema as a result of the patch test was regarded as positive. Dunsche et al reported that the removal of amalgam fillings should be recommended to all patients with symptomatic OLP associated with amalgam fillings if no concomitant CLP is present, regardless of patch test results to amalgam and other inorganic mercury compounds, because almost all patients (97.1%) benefited from amalgam removal.
However, patients with a positive patch test reaction to amalgam showed complete healing more frequently than those with a negative patch test reaction, and in about 8% of the patients, the lesions recurred after a mean period of 14.6 months. Wong and Freeman reported that, in patients with a negative patch test result who improve after amalgam removal, mercury may act as an irritant factor in the pathogenesis of OLP. In our opinion, several other aspects may play a role in these cases, such as “ill-fitting” amalgam fillings leading to OLP by the isomorphous response or Koebner phenomenon (which is a common feature in lichen plaques), “missed” late (>3 days) positive patch test reactions to inorganic mercury compounds, concomitant improvement in oral hygiene during amalgam removal, possible variations in the specific allergens and concentrations, and the time of occlusion used in the patch tests.

It is reported in the literature that the inorganic mercurials (ammoniated mercury, metallic mercury, and amalgam) may cross-react with the organic mercurials (thimerosal and the phenylmercuric salts). In this study, there was a cross-sensitivity between thimerosal (containing an organic mercury compound and a thiosalicylate), which is used as an antiseptic and as a preservative, and the inorganic mercurials ammoniated mercury and amalgam in 2 patients. The results of this study also indicate that there are several subtypes in the 3 different groups of OLP based on accompanying aspects as CLP, because none of the patients with OLP and CLP had positive reactions to 1 or more organic or inorganic mercury compounds. In these patients, other factors played a major role in the pathogenesis of OLP. Replacement of amalgam fillings should be undertaken for good reasons with a proper diagnosis of OLP. This leads to healing or a significant improvement in the oral lesions in nearly all patients within several months.

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