Palladium allergy in relation to dentistry
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Chapter 2

Sodium tetrachloropalladate \( \text{Na}_2\text{PdCl}_4 \) as an improved test salt for palladium allergy patch testing

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2.1 Abstract

Background: In the last decades, palladium is widely used in dentistry. Allergic reactions to palladium are rarely diagnosed with patch testing, even when positive results would be expected. Palladium tends to cross-react with nickel, which should give rise to more positive reactions to palladium dichloride (standard test salt).

Objective: The aim of the study was to test whether or not mono-nuclear sodium tetrachloropalladate (Na₂PdCl₄) in petrolatum is a better test salt for diagnosing palladium allergy. Positive reactions to the investigated test salt are compared not only with PdCl₂ aqua, but also to NiSO₄ aqua and NiSO₄ pet..

Patients/Methods: Concentration series of Na₂PdCl₄ were carried out. 164 consecutive patients were patch tested.

Results: 3% of Na₂PdCl₄ pet. was found to be the highest non-irritative concentration. The results show (n = 164) that Na₂PdCl₄ covers all reactions to PdCl₂ (1.8%) and provokes more positive reactions (14%). From the 164 patients, 18.3% reacted positively to at least 1 of the nickel salts.

Conclusion: The sensitivity of patch testing with Na₂PdCl₄ is increased compared with the PdCl₂ salt. Therefore, it can be concluded that Na₂PdCl₄ is to be a better test salt for diagnosing palladium allergy with patch testing.
2.2 Introduction

Everyday exposure to nickel (Ni) via Ni containing alloys is common, because it is used in jewellery (1), money (2), and dentistry (3), and approximately 20% of the industrialized female population is allergic to this metal. Instead of pure Ni or 1 of its alloys, a metal salt, nickel sulphate (NiSO$_4$), is generally used to diagnose Ni allergy by epicutaneous patch testing. It is known that reactivity to the allergen depends on the concentration and on the vehicle (4) in which it is presented, for example in water or pet. For example, 5% NiSO$_4$ in pet. and 5% nickel chloride (NiCl$_2$) in water show a concordance of 71%. Twenty-one percent of these patients reacted to NiCl$_2$ alone, and 8% reacted only to NiCl$_2$ (1). Besides the concentration and the vehicle of the allergen, the permeability kinetics of the allergen through the skin or oral mucosa can play an important role in eliciting allergic reactions. Metal permeation into the skin depends on many factors such as molecular volume, counter ions, valence, polarity, nature of the chemical bond, and reactivity (5). The depth-concentration profiles of a number of different Ni salts in the human stratum corneum demonstrated a pronounced hierarchy between the different salts with respect to their penetration depth: acetate > nitrate > sulfate > chloride (6). With respect to Ni, a comparative study of Ni chloride, bromide, iodide, and dioctanoate showed that not the polarity but the molecular volume was the decisive factor for membrane diffusion (6).

Nickel is a group VII transition metal of the periodic table together with palladium (Pd) and platinum. Palladium and its alloys are used as catalysts in the chemical- and automotive industry, jewellery, and dentistry (7). Palladium allergy emerged in the literature after the introduction of Pd containing dental alloys in 1973 (8). Nowadays, Pd is an important constituent of dental precious alloys varying from 2 wt% to approximately 90 wt%. The common allergen used to diagnose Pd allergy is palladium chloride (PdCl$_2$), 1–2% in pet. or in water. The elicitation rate to PdCl$_2$ was 4.2% in a population, where 14.6% was allergic to NiSO$_4$ (9). The relevance of a positive patch test reaction to Pd is likely compromised by potential cross-reactions to Ni, although also few exclusive positive reactions to Pd are reported (10). The simultaneous positive reactions of Ni and Pd are explained by (i) sensitization to both metals, (ii) contamination of the Pd patch test material with little traces of Ni, however, several studies have disproved this theory (11), and (iii) by the fact that Ni and Pd have similar chemistry and electron arrangement, which might be responsible for true cross-reactivity at the T-cell level (12-14). Hindsén et al. (15) gave strong evidence for cross-reactivity to Ni and Pd in vivo by systemic administration. They
yielded flare-up reactions on sites previously patch tested with Ni and Pd after oral Ni provocation. Also, in this study, contamination was excluded by chemical analysis. The choice for PdCl$_2$ as test salt is remarkable. Compared with the Ni salts, PdCl$_2$ is nearly insoluble in water, and if it dissolves, it forms oligo- or polynucleotide molecules (16, 17). As the molecular volume is the decisive factor for membrane diffusion, as shown for Ni (5), the oligo- or polynucleotide molecules of PdCl$_2$ might be not the optimal choice as test salt. Skin penetration of these larger molecules is less reliable or should react 1st to give smaller PdCl$_2$ fragments. Therefore, a commercially available mononuclear Pd salt, sodium tetrachloropalladate (Na$_2$PdCl$_4$), was added to our test series. It was hypothesized that the well-soluble Na$_2$PdCl$_4$ would be more suitable to diagnose Pd allergy than the currently used PdCl$_2$ salt. The aim of this study was, 1st to determine the optimal non-toxic test concentration for Na$_2$PdCl$_4$ pet., and 2nd, to evaluate its usefulness for diagnosing Pd allergy as patch test metal salt by evaluating the concordance with PdCl$_2$ aqua, NiSO$_4$ aqua, and NiSO$_4$ pet.

### 2.3 Patients and Methods

164 consecutive patients with suspected allergic contact dermatitis were patch tested at the Department of Dermatology at the VU Medical Centre in Amsterdam. The patients were included in the study if (i) the patient is over 18 years old and not pregnant, (ii) contact dermatitis suspected from history, (iii) no systemic corticosteroid or immunosuppressive treatment was prescribed during the previous 30 days, and (iv) no topical treatment with corticosteroids or exposure to ultraviolet radiation during the previous 15 days on or around the test area.

Van der Bend patch test chambers (Van der Bend BV, Brielle, The Netherlands) on Fixomull tape were used. To routine series, NiSO$_4$ 2.5% in water, NiSO$_4$ 5.0% in pet., PdCl$_2$ 1.0% in water (Hermal, Hamburg, Germany), and Na$_2$PdCl$_4$ 3% in pet. (Sigma-Aldrich Chemie BV, Zwijndrecht, The Netherlands) were included. 1st, sodium tetrachloropalladate (Na$_2$PdCl$_4$; purity: 99.998%) highest non-toxic patch test concentrations were determined in 20 patients using a concentration range from 0.3%, 1.0%, and 3.0% in pet. Patches were removed after D2 and were evaluated on D2 and D3. Additional reading was performed on D7 (18). Patch tests were regarded to be positive, if at least at 1 reading a positive reaction (+, ++, or +++ reaction) to the test salt occurred. Doubtful reactions and follicular reactions were also noted.

For statistical analysis, Spearman rank order correlations (SigmaStat 3.0; SPSS, Inc., Chicago, IL, USA) was used, and $p<0.05$ was considered significantly different. For
the statistical analysis, doubtful and follicular reactions are considered to be negative.

2.4 Results

1st, the highest non-toxic concentration for Na$_2$PdCl$_4$ pet. for patch testing was determined by the following results. Concentration of 0.3% and 1.0% gave no irritative reactions but resulted in 1 positive reaction to both concentrations on the D2 and D3. The 3.0% concentration resulted in 4 allergic and no irritative reactions. All reactions were positive on D3, but not on D2, which is in favour of the development of an allergic reaction. Furthermore, all positive reactions were found in patients showing Ni positive reactions. Therefore, Na$_2$PdCl$_4$, 3.0% in pet., was used as the patch test concentration in subsequent patients for this study.

Table 2.1  Patch test results from 164 consecutive patients.

<table>
<thead>
<tr>
<th></th>
<th>PdCl$_2$ $^a$</th>
<th>Na$_2$PdCl$_4$ $^b$</th>
<th>NiSO$_4$ $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>1.8 %</td>
<td>14.0 %</td>
<td>18.3 %</td>
</tr>
<tr>
<td>Negative</td>
<td>98.2 %</td>
<td>86.0 %</td>
<td>81.7 %</td>
</tr>
</tbody>
</table>

$^a$ 1% in water, $^b$ 1% in pet., $^c$ 2.5% in water or 5.0% in pet.

Table 2.2  Follicular and doubtful reactions from 164 consecutive patients.

<table>
<thead>
<tr>
<th></th>
<th>PdCl$_2$ $^a$</th>
<th>Na$_2$PdCl$_4$ $^b$</th>
<th>NiSO$_4$ $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>1.2 %</td>
<td>1.2 %</td>
<td>2.4 %</td>
</tr>
<tr>
<td>Doubtful</td>
<td>2.4 %</td>
<td>7.9 %</td>
<td>8.5 %</td>
</tr>
</tbody>
</table>

$^a$ 1% in water, $^b$ 1% in pet., $^c$ 2.5% in water or 5.0% in pet.

Of the 164 patients, 3 patients (1.8%) showed a sensitization to PdCl$_2$, 23 patients (14.0%) to Na$_2$PdCl$_4$, and 30 patients (18.3%) to at least 1 of the Ni salts. The Ni salts had concomitant reactions in 19 cases. 2 patients reacted positively only to NiSO$_4$ in water, and 9 patients showed positive reactions only to NiSO$_4$ in pet. All patients with positive reactions to PdCl$_2$ were also positive to Na$_2$PdCl$_4$. Prevalence in percentages is summarized in Table 2.1. A considerable amount of doubtful reactions were observed (Table 2.2), but these were analysed as non-allergic. From 5 patients with doubtful reactions to Na$_2$PdCl$_4$, 2 had follicular reactions to Ni and 3 had positive reactions to 1 of the Ni salts. From 2 patients with a follicular reaction to Na$_2$PdCl$_4$, 1 had a positive and the other had a doubtful reaction to Ni. Finally, 7 patients with
doubtful reactions to Na$_2$PdCl$_4$ had negative reactions to 1 of the Ni salts. Of all patients with a positive reaction to Ni, 56.6% reacted positively to Na$_2$PdCl$_4$. 74% of the Pd reactors showed sensitization to Ni as well. From the tested group, 6 patients (3.7%) reacted exclusively to Na$_2$PdCl$_4$, and 13 patients (7.9%) reacted only to 1 of the Ni salts. The results are graphically depicted in Figure 2.1.

Spearman Rank Order correlation between positive reactions to Na$_2$PdCl$_4$ and 1 of the Ni salts is 0.581 ($p<0.0001$), which is a moderate positive correlation.

**Figure 2.1** Positive reactions to the tested allergens of 164 consecutive patients. Nickel sulfate may be 2.5% in water or 5.0% in petrolatum. Dark area's reflect concordant reactions and light areas reflect exclusive reactions.

**Figure 2.2** Positive reactions to the tested allergens of 164 consecutive patients, when doubtful reactions to palladium with concordant positive reactions to nickel, are considered to be positive and *vice versa*. Palladium may be PdCl$_2$ or Na$_2$PdCl$_4$. Nickel may be NiSO$_4$ 5% aqua or NiSO$_4$ 5% pet..
2.5 Discussion

The most remarkable outcome of this study is the large amount (14.0%) of positive patch test results to Na$_2$PdCl$_4$ compared with the commonly used PdCl$_2$ (1.8%). Apparently, the skin permeation of Na$_2$PdCl$_4$ is indeed better than the skin permeation of PdCl$_2$, with as a result that a larger amount of Pd ions will reach the antigen presenting cells in the epidermis. To our knowledge, only 1 attempt with a different Pd salt than PdCl$_2$ has been reported. Santucci et al. (14) showed negative results from [PdCl$_4$]$^{2-}$ in water. The [PdCl$_4$]$^{2-}$ was synthesized in situ by adding hydrochloric acid to a PdCl$_2$ in distilled water thereby giving most probably H$_2$PdCl$_4$ (19). The different results, with respect to solubility and penetration rate, may be because of (i) difference in counter ion (H$^+$ versus Na$^+$), and (ii) difference in acidity because of the use of hydrochloric acid. However, 1 has to consider that 3% Na$_2$PdCl$_4$ contains 1.67 times more Pd when compared with the 1% PdCl$_2$. Using higher concentrations will probably not resolve the problem of forming large oligo- or polynucleotide molecules and is still hardly soluble in later.

1 may conclude that Na$_2$PdCl$_4$ 3% in pet. is more sensitive than the standard PdCl$_2$ 1% in water and H$_2$PdCl$_4$ as described above. As the specificity of patch testing in general is considered to be high [e.g. 95% for NiSO$_4$ (20)], Na$_2$PdCl$_4$ is because of these results considered to be better patch test salt to diagnose Pd allergy. With this knowledge, the prevalence of Pd allergy might be underestimated considerably. The moderate Spearman Rank Order correlation coefficient (0.581) between positive reactions to Na$_2$PdCl$_4$ and to the Ni salts is no strong evidence to confirm cross-reactivity between Pd and Ni. Next to cross-reactivity, solely Pd-sensitization may occur. In this study, 6 exclusive Pd allergic patients, with respect to Ni allergy, have been identified. Of these patients, 4 had a positive metal allergic anamnesis. The other 17 Pd allergic patients had concordant reactions to 1 of the Ni salts, which means that approximately 75% of the Pd reactors is allergic to Ni as well. The other way round concordance is less significant. Only 56% of the Ni reactors show a positive reaction to Pd. On the other hand, the moderate Spearman Rank Order correlation coefficient does not exclude cross-reactivity, because of the low sensitivity of NiSO$_4$ patch testing and most probably also of Na$_2$PdCl$_4$ patch testing. Therefore, a substantial portion of the Ni and Pd allergic patients might be missed.

A considerable amount of doubtful reactions were observed with Na$_2$PdCl$_4$ 3.0% in pet. As all the tested concentrations did not result in irritative reactions, a higher non-toxic concentration may be found. Extra concentration series will be carried out in the future. Further analysis of the data, with the assumption that cross-reactivity of Pd and Ni does exist, has been carried out. In this analysis, doubtful or follicular
reactions to Pd are calculated as positive in Ni reactors and vice versa. These results are graphically depicted in Figure 2.2. By reanalyzing the data, the Spearman Rank Order correlation increased from 0.581 to 0.756 ($P< 0.001$). This correlation favours the theory of cross-reactivity of Pd and Ni, especially considering the negative effect of false-negative results on the correlation.

As Pd is mainly used in dentistry, automotive industries, and jewellery, 1 should consider the possible Pd exposure because of dental restorations, especially in Europe were dental Pd has been used extensively. Some alloys may contain up to 90 wt% of Pd. Exposure from dental restorations is mainly because of corrosion, which is a continuous process that will affect all metals, precious and non-precious. As the complaints associated with metal allergy in general and Pd allergies in specific are not well-known; clinical relevance is still an challenging issue (8, 21). In our dental referral clinic often negative patch test results with PdCl$_2$ were observed, where Pd allergy was expected from a clinical view point. Furthermore, most patients with adverse reactions to dental restorations have Pd in their restorations, which is determined by microanalysis (22). Microanalysis may be used to determine the components of jewellery as well.

In conclusion, it can be stated that sodium tetrachloropalladate (Na$_2$PdCl$_4$) 3% in pet. is an improved patch test salt for diagnosing Pd allergy, and it is, therefore, recommended to use as a standard test allergen, next to Pd dichloride (PdCl$_2$). It may be expected that using the new salt results in significant increase of positive reactions to Pd. Therefore, it is suggested to include the Pd salts and especially Na$_2$PdCl$_4$ in the recommended European standard patch test series.
2.6 References