

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

JORIS MURIS¹, CORNELIS J. KLEVERLAAN¹, ALBERT J. FEILZER¹ AND THOMAS RUSTEMEYER²

¹Department of Dental Materials Science, Academic Centre for Dentistry Amsterdam (ACTA), Louwesweg 1, 1066 EA Amsterdam, The Netherlands, and ²Department of Dermatology, VU University Medical Centre, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

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 ($\text{Na}_2[\text{PdCl}_4]$) in petrolatum is a better test salt for diagnosing palladium allergy. Positive reactions to the investigated test salt are compared not only with $\text{PdCl}_2(\text{aq.})$, but also to $\text{NiSO}_4(\text{aq.})$ and $\text{NiSO}_4(\text{pet.})$.

Patients/Methods: Concentration series of $\text{Na}_2[\text{PdCl}_4]$ were carried out. 164 consecutive patients were patch tested.

Results: 3% of $\text{Na}_2[\text{PdCl}_4](\text{pet.})$ was found to be the highest non-irritative concentration. The results show ($n = 164$) that $\text{Na}_2[\text{PdCl}_4]$ covers all reactions to PdCl_2 (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 $\text{Na}_2[\text{PdCl}_4]$ is increased compared with the PdCl_2 salt. Therefore, it can be concluded that $\text{Na}_2[\text{PdCl}_4]$ is to be a better test salt for diagnosing palladium allergy with patch testing.

Key words: cross-reactions; dental exposure; palladium allergy; palladium dichloride; patch test; sodium tetrachloropalladate. © Blackwell Munksgaard, 2007.

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Everyday exposure to nickel via nickel 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 nickel or 1 of its alloys, a metal salt, nickel sulfate, is generally used to diagnose nickel 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% nickel sulfate in pet. and 5% nickel chloride in water show a concordance of 71%. 21% of these patients reacted to nickel sulfate alone, and 8% reacted only to nickel chloride (1). Besides the concentra-

tion 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 nickel 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 nickel, a comparative study of nickel chloride, bromide, iodide, and dioctanoate showed that not the polarity but the molecular

volume was the decisive factor for membrane diffusion (5).

Nickel is a group VII transition metal of the periodic table together with palladium and platinum. Palladium and its alloys are used as catalysts in the chemical- and automotive industry, jewelry, and dentistry (7). Palladium allergy emerged in the literature after the introduction of palladium-containing dental alloys in 1973 (8). Nowadays, palladium is an important constituent of dental precious alloys varying from 2 wt% to approximately 90 wt%. The common allergen used to diagnose palladium allergy is 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 nickel sulfate (9). The relevance of a positive patch test reaction to palladium is likely compromised by potential cross-reactions to nickel, although also few exclusive positive reactions to palladium are reported (10). The simultaneous positive reactions of nickel and palladium are explained by (i) sensitization to both metals, (ii) contamination of the palladium patch test material with little traces of nickel, however, several studies have disproved this theory (11), and (iii) by the fact that nickel and palladium have similar chemistry and electron arrangement, which might be responsible for true cross-reactivity at the T-cell level (12, 13). Hindsén et al. (14) gave strong evidence for cross-reactivity to nickel and palladium *in vivo* by systemic administration. They yielded flare-up reactions on sites previously patch tested with nickel and palladium after oral nickel provocation. Also, in this study, contamination was excluded by chemical analysis.

The choice for PdCl_2 as test salt is remarkable. Compared with the nickel salts, PdCl_2 is nearly insoluble in water, and if it dissolves, it forms oligo- or polynucleotide molecules (15, 16). As the molecular volume is the decisive factor for membrane diffusion, as shown for nickel (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 palladium salt, sodium tetrachloropalladate ($\text{Na}_2[\text{PdCl}_4]$), was added to our test series. It was hypothesized that the well-soluble $\text{Na}_2[\text{PdCl}_4]$ would be more suitable to diagnose palladium allergy than the currently used PdCl_2 salt.

The aim of this study was, 1st to determine the optimal non-toxic test concentration for $\text{Na}_2[\text{PdCl}_4]_{(\text{pet.})}$, and 2nd, to evaluate its usefulness for diagnosing palladium allergy as patch test metal salt by evaluating the concordance with $\text{PdCl}_{2(\text{aq.})}$, $\text{NiSO}_{4(\text{aq.})}$, and $\text{NiSO}_{4(\text{pet.})}$.

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, nickel sulfate 2.5% in water, nickel sulfate 5.0% in pet., palladium dichloride 1.0% in water (Hermal, Hamburg, Germany), and sodium tetrachloropalladate 3% in pet. (Sigma-Aldrich Chemie BV, Zwijndrecht, The Netherlands) were included. 1st, sodium tetrachloropalladate ($\text{Na}_2[\text{PdCl}_4] \cdot 3\text{H}_2\text{O}$; 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 (17). 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.

Results

1st, the highest non-toxic concentration for $\text{Na}_2[\text{PdCl}_4]_{(\text{pet.})}$ 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 nickel positive reactions. Therefore, $\text{Na}_2[\text{PdCl}_4]$, 3.0% in pet., was used as the patch test concentration in subsequent patients for this study.

Of the 164 patients, 3 patients (1.8%) showed a sensitization to PdCl_2 , 23 patients (14.0%) to $\text{Na}_2[\text{PdCl}_4]$, and 30 patients (18.3%) to at least

1 of the nickel salts. The nickel salts had concomitant reactions in 19 cases. 2 patients reacted positively only to nickel sulfate in water, and 9 patients showed positive reactions only to nickel sulfate in pet. All patients with positive reactions to PdCl₂ were also positive to Na₂[PdCl₄]. Prevalence in percentages is summarized in Table 1. A considerable amount of doubtful reactions were observed (Table 2), but these were analysed as non-allergic. From 5 patients with doubtful reactions to Na₂[PdCl₄], 2 had follicular reactions to nickel and 3 had positive reactions to 1 of the nickel salts. From 2 patients with a follicular reaction to Na₂[PdCl₄], 1 had a positive and the other had a doubtful reaction to nickel. Finally, 7 patients with doubtful reactions to Na₂[PdCl₄] had negative reactions to 1 of the nickel salts. Of all patients with a positive reaction to nickel, 56.6% reacted positively to Na₂[PdCl₄]. 74% of the palladium reactors showed sensitization to nickel as well. From the tested group, 6 patients (3.7%) reacted exclusively to Na₂[PdCl₄], and 13 patients (7.9%) reacted only to 1 of the nickel salts. The results are graphically depicted in Fig. 1.

Table 1. Patch test results from 164 consecutive patients

	PdCl ₂ ^a (%)	Na ₂ [PdCl ₄] ^b (%)	NiSO ₄ ^c (%)
Positive	1.8	14.0	18.3
Negative	98.2	86.0	81.7

^a1% in water.

^b1% in pet.

^c2.5% in water or 5.0% in pet.

Table 2. Follicular and doubtful reactions from 164 consecutive patients

	PdCl ₂ ^a (%)	Na ₂ [PdCl ₄] ^b (%)	NiSO ₄ ^c (%)
Follicular	1.2	1.2	1.8
Doubtful	2.4	7.9	5.5

^a1% in water.

^b1% in pet.

^c2.5% in water or 5.0% in pet.

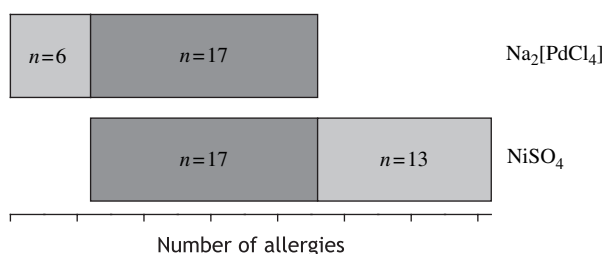


Fig. 1. Positive reactions to the tested allergens of 164 consecutive patients. Nickel sulfate may be 2.5% in water or 5.0% in pet. Dark area's reflect concordant reactions and light area's reflect exclusive reactions.

Spearman Rank Order correlation between positive reactions to Na₂[PdCl₄] and 1 of the nickel salts is 0.581 ($P < 0.0001$), which is a moderate positive correlation.

Discussion

The most remarkable outcome of this study is the large amount (14.0%) of positive patch test results to Na₂[PdCl₄] compared with the commonly used PdCl₂ (1.8%). Apparently, the skin permeation of Na₂[PdCl₄] is indeed better than the skin permeation of PdCl₂, with as a result that a larger amount of palladium ions will reach the antigen presenting cells in the epidermis. To our knowledge, only 1 attempt with a different palladium salt than PdCl₂ has been reported. Santucci et al. (13) showed negative results from [PdCl₄]²⁻ in water. The [PdCl₄]²⁻ was synthesized *in situ* by adding hydrochloric acid to a PdCl₂ in distilled water thereby giving most probably H₂[PdCl₄] (18). 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, I have to consider that 3% sodium tetrachloropalladate contains 1.67 times more palladium when compared with the 1% palladium dichloride. Using higher concentrations will probably not resolve the problem of forming large oligo- or polynucleotide molecules and is still hardly soluble in water.

I may conclude that sodium tetrachloropalladate (Na₂[PdCl₄] 3% in pet.) is more sensitive than the standard PdCl₂ 1% in water and H₂[PdCl₄] as described above. As the specificity of patch testing in general is considered to be high [e.g. 95% for nickel sulfate (19)], Na₂[PdCl₄] is because of these results considered to be better patch test salt to diagnose palladium allergy. With this knowledge, the prevalence of palladium allergy might be underestimated considerably.

The moderate Spearman Rank Order correlation coefficient (0.581) between positive reactions to Na₂[PdCl₄] and to the nickel salts is no strong evidence to confirm cross-reactivity between palladium and nickel. Next to cross-reactivity, solely Pd-sensitization may occur. In this study, 6 exclusive palladium allergic patients, with respect to nickel allergy, have been identified. Of these 6 patients, 4 had a positive metal allergic anamnesis. The other 17 palladium allergic patients had concordant reactions to 1 of the nickel salts, which means that approximately 75% of the palladium reactors is allergic to nickel as well. The other way round concordance is less significant. Only 56% of the nickel reactors show a positive reaction to

palladium. On the other hand, the moderate Spearman Rank Order correlation coefficient does not exclude cross-reactivity, because of the low sensitivity of nickel sulfate patch testing and most probably also of $\text{Na}_2[\text{PdCl}_4]$ patch testing. Therefore, a substantial portion of the nickel and palladium allergic patients might be missed.

A considerable amount of doubtful reactions were observed with $\text{Na}_2[\text{PdCl}_4]$ 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 palladium and nickel does exist, has been carried out. In this analysis, doubtful or follicular reactions to palladium are calculated as positive in nickel reactors and vice versa. These results are graphically depicted in Fig. 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 palladium and nickel, especially considering the negative effect of false-negative results on the correlation.

As palladium is mainly used in dentistry, automotive industries, and jewellery, I should consider the possible palladium exposure because of dental restorations, especially in Europe where dental palladium has been used extensively. Some alloys may contain up to 90 wt% of palladium. 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 palladium allergies in specific are not well-known; clinical relevance is still an challenging issue (8, 20). In our dental referral clinic often negative patch test results with PdCl_2 were observed, where palladium allergy was expected from a clinical view point. Furthermore, most patients with adverse reactions to dental restorations have palladium in their restorations, which is determined

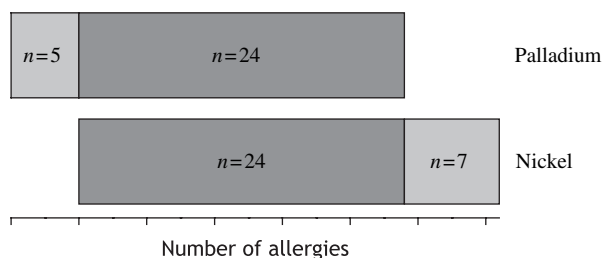


Fig. 2. Positive reactions to the tested allergens of 164 consecutive patients, when doubtful reactions to palladium with concordant positive reactions to nickel, are considered to be positive and vice versa. Palladium may be PdCl_2 or $\text{Na}_2[\text{PdCl}_4]$. Nickel may be NiSO_4 5% (aq.) or NiSO_4 5% (pet.).

by microanalysis (21). Microanalysis may be used to determine the components of jewellery as well.

In conclusion, it can be stated that sodium tetrachloropalladate ($\text{Na}_2[\text{PdCl}_4]$) 3% in pet. is an improved patch test salt for diagnosing palladium allergy, and it is, therefore, recommended to use as a standard test allergen, next to palladium dichloride (PdCl_2). It may be expected that using the new salt results in significant increase of positive reactions to palladium. Therefore, it is suggested to include the palladium salts and especially $\text{Na}_2[\text{PdCl}_4]$ in the recommended European standard patch test series.

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Address:

Joris Muris, DDS
Department of Dental Materials Science
Academic Centre of Dentistry Amsterdam (ACTA)
Louwesweg 1
1066 EA Amsterdam
The Netherlands
Tel: +31 20 518 82 35
Fax: +31 20 669 27 26
e-mail: dental.materials@acta.nl