

Usage test with palladium-coated earrings in patients with contact allergy to palladium and nickel

Cecilia Tillman^{1,2}, Malin Engfeldt¹, Monica Hindsén¹ and Magnus Bruze¹

¹Department of Occupational and Environmental Dermatology, Skåne University Hospital, Lund University, Malmö S-205 02, Sweden, and ²Department of Dermatology, Skåne University Hospital, Lund University, Malmö S-205 02, Sweden

doi:10.1111/cod.12118

Summary

Background. Since the EU Nickel Directive came into force, concern has been raised that palladium may increasingly replace nickel in alloys used in jewellery and dentistry, and that it may cause as many allergy problems as nickel.

Objectives. (i) To investigate the clinical relevance of contact allergy to palladium resulting from the wearing of palladium-coated earrings, and (ii) to evaluate the concordance in test results between palladium chloride (PdCl₂), sodium tetrachloropalladate (Na₂PdCl₄), and nickel(II) sulfate hexahydrate (NiSO₄·6H₂O), as well as variability in patch test reactivity.

Materials/methods. Forty female patients with pierced earlobes and previously known contact allergy to palladium and nickel were patch tested with dilution series of nickel and palladium salts. They wore earrings covered with palladium and titanium for 9 weeks to monitor the appearance of any clinical manifestations.

Result/conclusion. There is a low risk of eczema in palladium-allergic and nickel-allergic individuals when they wear jewellery coated with pure palladium, but further studies are needed to determine whether palladium, when present in alloys, could cause allergic reactions. PdCl₂, like NiSO₄·6H₂O, shows variability in patch test reactivity over time. Furthermore, Na₂PdCl₄ seems to be a more sensitive test substance than PdCl₂ for the detection of palladium allergy.

Key words: contact allergy; jewellery; nickel; palladium; patch test reactivity; sodium tetrachloropalladate; variability.

Introduction

Nickel is one of the most common allergens known to cause allergic contact dermatitis (1). Allergic contact dermatitis caused by nickel is more frequent among women, owing to more exposure from the wearing of jewellery (2, 3). Palladium is also a known contact

sensitizer in humans and guinea-pigs (4). However, the clinical relevance is less well known. Both palladium and nickel are silvery-white metals, and are often used in alloys with other metals. They belong to the same group in the periodic table, group X, suggesting similar chemical properties. Sensitization to palladium is almost always seen together with sensitization to nickel. In the literature, this has mostly been explained by cross-reactivity, but both contamination and multiple sensitization have also been mentioned as possible explanations for the association between nickel and palladium allergy. Contamination as the cause of simultaneous allergies was later excluded in several studies (5). There are both *in vitro* and *in vivo* studies supporting the idea that sensitization to both nickel and palladium results from cross-reactivity

Correspondence: Cecilia Tillman, Department of Occupational and Environmental Dermatology, Jan Waldenströmsgata 16, plan 5, S-205 02 Malmö, Sweden. Tel: +46 40 33 17 08; Fax: +46 40 33 70 13. E-mail: cecilia.tillman@skane.se

Conflicts of interest: The authors have declared no conflicts.

Accepted for publication 21 May 2013

(4–8). However, in a previously published article, it was concluded that the reactivity pattern of 1 of the patients included in this study supported the idea that sensitization to nickel and palladium might also be caused by multiple sensitization (9).

Since the EU Nickel Directive, which regulates the amount of nickel released from consumer products, came into force in July 2001, there has been a decrease in nickel allergy in many European countries (10). At the same time, concern has been raised that nickel may be replaced by palladium in alloys used in jewellery and dentistry (11), and it has been suggested that the prevalence of palladium allergy has increased in recent years (12, 13). Furthermore, in 2008, Muris et al. (14) showed that the palladium allergy prevalence might even be underestimated, as the most commonly used patch test salt for diagnosing palladium allergy, palladium chloride (PdCl_2), failed to show as many positive reactions as another palladium salt, sodium tetrachloropalladate (Na_2PdCl_4). Regarding the clinical manifestations of palladium allergy, there are reports describing oral symptoms in palladium-allergic individuals exposed to palladium-containing materials (15, 16), as well as allergic granuloma related to the use of palladium-containing earrings by individuals with palladium allergy (17, 18). However, it is generally difficult to find any clinical relevance for palladium allergy (19).

The aims of this prospective study were:

- (1) To investigate the clinical relevance of contact allergy to palladium resulting from the wearing of palladium-coated earrings.
- (2) To evaluate the concordance in test results between PdCl_2 , Na_2PdCl_4 , and nickel(II) sulfate hexahydrate ($\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$), and the degree of intensity of test reactions at a given time.

Patients/Materials

Subjects

Forty female patients with pierced earlobes were enrolled in the study after approval by the Ethics Committee of Lund University, Sweden. They were all over the age of 18 years. Informed consent was obtained from each patient. All patients had previously been tested with a baseline series or a dental series on at least one occasion because of dermatitis or stomatitis (Table 1), and had had at least a + reaction to both nickel sulfate 5.0% (wt/wt) in petrolatum (pet.) and PdCl_2 2.0% (wt/wt) in pet. according to the International Contact Dermatitis Research Group (ICDRG) scoring system (20). Contact allergy to other substances was not an exclusion criterion.

Some patients had also been tested with Na_2PdCl_4 3.0% (wt/wt) in pet., which has been a part of our baseline series since February 2009. The mean age was 49 years (median 51 years; range 20–83 years). Because 1 patient dropped out after the first reading, we included an additional patient, resulting in 39 participants completing the usage period, and a total of 40 patch tested individuals.

Patch testing

Patch testing was performed with serial dilutions of the metal salts PdCl_2 , Na_2PdCl_4 , $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$, calcium titanate (CaTiO_3), titanium, titanium nitride (TiN), and titanium isopropoxide (Table 1). The titanium preparations were patch tested because titanium earrings were used as controls in the provocation tests. Three of the titanium preparations have been used for many years for testing dental patients at the Department of Occupational and Environmental Dermatology, and one preparation, titanium isopropoxide, was included after personal communication with T. Rustemeyer (Amsterdam, The Netherlands). Before the study had started, titanium isopropoxide was tested in 18 individuals at 20%, 10% and 2% pet. (wt/wt). No positive reactions were seen. One patient had a doubtful reaction to titanium isopropoxide 10%.

Patch test preparations were applied on Finn Chambers[®] (Ø 8 mm; Allerderm, Phoenix, AZ, USA) on Scanpor[®] tape (Norgesplaster A/S, Vennesla, Norway). A 15-µl volume of each of the test preparations in aqueous solution was applied with a micropipette to the filter paper discs in the test chambers (21). For the test preparations in pet., 20 mg was applied as recommended by the European Society of Contact Dermatitis (22). All subjects were tested on the upper back. The patches were removed from the back after 2 days, and readings were carried out on D3 or D4 and D7.

Patch test scoring

The patch test reactions were scored according to the ICDRG scoring system, with two classifications added to the usual positive test score gradings: strong + and ++ reactions were graded as ++(+) and ++(+). The scorings were graded as: –, negative reaction; (+), erythema without infiltration or erythematous infiltration not covering the whole test area, +, erythema and infiltration covering the whole test area; ++(+), erythema, infiltration, and a few papules; ++, erythema infiltration and papules; ++(+), erythema, infiltration, papules, and a few vesicles; and +++, intense erythema, infiltration, and vesicles (23).

Table 1. Patch test concentrations, origin of test material, and corresponding concentrations of palladium and nickel ions

Substance	Concentration of metal salts* (%)	Concentration of Pd ²⁺ (%)	Concentration of Ni ²⁺ (%)	Vehicle [†]	Purchased from:
Nickel sulfate hexahydrate	5.0; 0.5; 0.05; 0.005; 0.0005	–	0.22; 0.02; 0.002; 0.0002; 0.00002	aqua	Acros Organics, Geel, Belgium
Palladium chloride	5.0; 1.6; 0.5; 0.16; 0.05	3.0; 0.96; 0.3; 0.096; 0.03	–	pet.	ICN Biomedicals, Eschwege, Germany
Sodium tetrachloropalladate [‡]	3.5; 1.0; 0.35; 0.1; 0.035	1.25; 0.39; 0.13; 0.039; 0.013	–	pet.	Acros Organics, Geel, Belgium
Titanium	50.0; 5.0	–	–	pet.	Alfa Aesar, Karlsruhe, Germany
Calcium titanate	10.0; 1.0	–	–	pet.	Johnson Matthey, Royston, UK
Titanium nitride	5.0; 0.5	–	–	pet.	Chempur, Karlsruhe, Germany
Titanium isopropoxide	20.0; 2.0	–	–	pet.	Alfa Aesar Karlsruhe, Germany

* Highest concentration of nickel sulfate hexahydrate in wt/vol and the dilutions in vol/vol. All other preparations in wt/wt.

[†] Petrolatum was purchased from APL, Stockholm, Sweden.

[‡] The highest concentration of sodium tetrachloropalladate was meant to be equimolar to 1.6% palladium chloride. However, owing to calculation errors, the concentration was 30% higher than intended.

Provocation

In connection with the patch testing on D0, all patients received one earring with a surface layer of palladium and one earring with a surface layer of titanium. The latter served as a control. The earrings were indistinguishable from each other in appearance, and were randomized to be used daily in either the left or the right pierced earlobe. The participants were instructed, verbally and in writing, to use the same earring in the same ear for the whole test period. Using the earrings while sleeping was optional, and the females received colour-coded boxes on where to place the earrings during the night, blue indicating the right earlobe and red indicating the left earlobe. The women used the earrings for 9 weeks, and were observed at the department on D7 and then approximately every second week for local skin reactions. They were instructed to state at each visit if and for how long they had removed their earrings. A positive reaction was defined as an eczematous reaction, and thus including morphological features such as erythema, infiltration, vesiculation, and possibly scaling. Erythema without infiltration was not considered to be an eczematous reaction.

Earrings. The palladium-coated earrings (Fig. 1) were manufactured especially for this study by Blomdahl Medical AB, Halmstad, Sweden, and are not normally produced by the company. There were two types: type 1 consisted of pure medical-grade titanium, and type 2 had a core of pure medical-grade titanium that was then covered with 0.5–1.0 µm of palladium. The clasps used to attach the earrings on the back side of the earlobe were all made of pure medical-grade titanium. The two types were indistinguishable from each other (Fig. 1).

Statistical calculations. The reactivity was measured as the minimal elicitation concentration (MEC), defined as the lowest concentration eliciting at least a + reaction. The positive reactions were not always continuous. When the number of negative and/or doubtful reactions were followed by the same number or more of positive reactions, the lowest positive reaction was registered as the MEC (24). When positive test results are referred to otherwise in the article, this signifies that there was at least a + reaction.

To compare the intensity of reactivity between PdCl₂ and Na₂PdCl₄, McNemar's test was used, comparing MECs for these two test preparations. The readings were performed on D3 and D7, and the lowest MEC from either of these days was chosen as the MEC for this test occasion.

Results

We found no clinically relevant local skin reaction to the earrings. In 6 patients, some minor scaling or discrete erythema was noted at one or more of the follow-up visits (nos. 7, 21, 25, 26, 32, and 38; Table 2). Five of the 6 women in whom minor skin reactions were noted also complained of itching of the skin that had been in contact with the earrings. However, no eczema was seen. Of the 6 individuals with minor scaling or erythema, 3 had reactions on the ear with the palladium-coated earring, and 3 had reactions on the ear with the titanium earring.

One woman did not come for a test reading on D7 (no. 7; Table 2) or follow-up later. Another patient could not come for a test reading on D7, but was followed regarding skin reactions (no. 35; Table 2), and continued to wear the earrings. Another patient who did not want to continue (no. 32; Table 2) after the test reading at D7 experienced



Fig. 1. Size and shape of the earrings used in the study. The palladium-coated earrings were indistinguishable from the titanium earrings. All clasps were made of titanium.

itching both on the back, owing to patch test reactions, and on the ears.

One woman had a ++ reaction to TiN 5% on D3 (no. 13; Table 2). She was later retested, and gave a negative result. Another woman (no. 39, Table 2) had no positive test reactions except for nickel 5% at readings on D3 and D7, but reported reactions after D7. She was retested 4 months later, and she tested positive on D3 and D7 for both PdCl_2 and Na_2PdCl_4 , but this time not for nickel sulfate (9). There was 1 patient (no. 33; Table 2) who did not react to any of the palladium salts. However, this patient was never retested. Two patients (nos. 22 and 25; Table 2) failed to show any positive reactions to nickel sulfate.

The lowest MECs for nickel sulfate, PdCl_2 and Na_2PdCl_4 were 0.0002% (wt/vol), 0.03% (w/w), and 0.013% (wt/wt), respectively (Table 2). The inter-individual ratio for MECs for nickel sulfate and PdCl_2 , and for nickel sulfate and Na_2PdCl_4 , varied between 0.001 and 73.3 and between 0.002 and 169.2, respectively (Table 2; Fig. 2).

There were statistically significantly ($p = 0.0066$, McNemar's test for statistical calculations) stronger reactions to Na_2PdCl_4 than to PdCl_2 . Nineteen individuals

showed a lower MEC for Na_2PdCl_4 than for PdCl_2 , whereas 5 individuals showed lower MECs for PdCl_2 than for Na_2PdCl_4 . Two individuals (nos. 23 and 25; Table 2) reacted to Na_2PdCl_4 only, and would have been missed if they had been tested just with PdCl_2 .

Discussion

Investigation of the clinical relevance of contact allergy to palladium resulting from the wearing of palladium-coated earrings

The median prevalence of palladium sensitization was 7.8% in dermatitis patients in a review by Faurschou et al. (19), but little is known about the clinical relevance or time between exposure to palladium and the possible development of dermatitis. The use of ordinary earrings daily for a longer period mimics reality, as exposure to palladium most commonly comes from jewellery and dental restorations. This approach has previously been used when exposure to metallic gold has been studied (25). An alternative would have been, for example, to use larger metal discs to obtain exposure to a larger skin area, as in the study by Lidén et al., when the patients used

Table 2. Reported and/or found symptoms on the ears of each patient and patch test results for nickel and palladium metal salts reported as the lowest minimal elicitation concentration (MEC) seen on either D3 or D7

Patient	Palladium	Titanium	MEC	MEC	MEC	MEC	MEC Ni ²⁺ / MEC Pd ²⁺ ratio		Years since last patch tested with a positive palladium reaction
			NiSO ₄ ·6H ₂ O (%)	PdCl ₂ (%)	Na ₂ PdCl ₄ (%)	Na ₂ PdCl ₄ > MEC PdCl ₂ *	PdCl ₂	Na ₂ PdCl ₄	
1	ND	ND	0.22	0.30	0.39	No	0.73	0.56	3 [†]
2	ND	ND	0.22	0.96	0.13	Yes	0.23	1.69	2 [†]
3	ND	ND	0.02	0.96	0.13	Yes	0.021	0.15	1 [†]
4	ND	ND	0.02	0.30	0.13	=	0.067	0.15	1 [†]
5	ND	ND	0.02	0.30	0.039	Yes	0.067	0.51	6 [†]
6	ND	ND	0.002	0.96	0.39	=	0.002	0.005	3 [†]
7	ND	Discrete erythema	0.02	0.30	0.39	No	0.067	0.051	1 [†]
8	ND	ND	0.002	0.096	0.13	No	0.021	0.015	1 [†]
9	ND	ND	0.22	0.30	0.013	Yes	0.73	16.9	1 [†]
10	ND	ND	0.02	0.96	0.13	Yes	0.021	0.15	1 [†]
11	ND	ND	0.22	0.96	0.013	Yes	0.23	16.9	4 [†]
12	ND	ND	0.22	0.96	0.39	=	0.23	0.56	2 [†]
13	ND	ND	0.22	0.96	0.13	Yes	0.23	1.69	11 [†]
14	ND	ND	0.002	0.30	0.13	=	0.007	0.015	7 [†]
15	ND	ND	0.002	0.96	1.25	No	0.002	0.002	5 [†]
16	ND	ND	0.02	0.96	0.039	Yes	0.021	0.51	1 [†]
17	ND	ND	0.0002	0.30	0.13	=	0.001	0.002	3 [†]
18	ND	ND	0.0002	0.096	0.039	=	0.002	0.005	1 [†]
19	ND	ND	0.002	0.096	0.039	=	0.021	0.051	2 [†]
20	ND	ND	0.22	3.0	0.39	Yes	0.073	0.56	2 [†]
21	Scaling on the back of the ear	ND	0.02	0.96	0.13	Yes	0.021	0.15	2 [†]
22	ND	ND	–	0.03	0.013	=	73.3 [‡]	169.2 [‡]	4 [†]
23	ND	ND	0.02	–	1.25	Yes	0.007 [‡]	0.016	2 [†]
24	ND	ND	0.002	0.96	0.39	=	0.002	0.005	3 [†]
25	ND	Itching sensation. Slight erythema	–	–	1.25	Yes	1.67	40	3 [§]
26	Itching sensation. Slight erythema	ND	0.02	0.96	0.13	Yes	0.021	0.15	2 [†]
27	ND	ND	0.02	0.30	0.039	Yes	0.021	0.51	4 [†]
28	ND	ND	0.02	3.0	0.39	Yes	0.007	0.051	4 [†]
29	ND	ND	0.02	0.96	0.13	Yes	0.021	0.15	4 [†]
30	ND	ND	0.22	0.96	0.39	=	0.23	0.56	3 [§]
31	ND	ND	0.02	0.96	0.39	=	0.021	0.051	4 [†]
32	Some itching. Slight erythema	Some itching	0.02	0.96	0.39	=	0.021	0.051	5 [†]
33	ND	ND	0.22	–	–	=	0.007 [‡]	0.017 [‡]	1 [†]
34	ND	ND	0.02	0.03	0.039	No	0.67	5.64	6 [§]
35	ND	ND	0.22	0.96	0.39	=	0.23	0.56	5 [†]
36	ND	ND	0.22	0.96	0.39	=	0.23	0.56	5 [†]
37	ND	ND	0.22	0.96	0.13	Yes	0.23	1.69	5 [†]
38	Some itching (Pd)	ND	0.002	0.30	0.039	Yes	0.007	0.051	2 [†]
39	ND	ND	–	–	–	=	0.007 [‡]	0.017 [‡]	2 [§]
40	ND	ND	0.02	0.96	0.13	Yes	0.021	0.15	3 [†]

ND, no dermatitis; Palladium, palladium ear ring was worn; Titanium, titanium earring was worn. MEC is reported as the concentration of Ni²⁺ and Pd²⁺, as calculated in Table 1.

* To enable statistical calculations to be performed, the strongest reaction (i.e. the lowest MEC) between PdCl₂ and Na₂PdCl₄ was calculated.

[†] Dermatitis patient tested with baseline series.

[‡] If there was no reaction, it was assumed that the patients, who were all allergic to nickel and palladium, would have reacted to a 10-fold higher concentration, corresponding to MECs of 2.2% for NiSO₄, 30% for PdCl₂, and 12.5% for Na₂PdCl₄.

[§] Stomatitis patient tested with dental series.

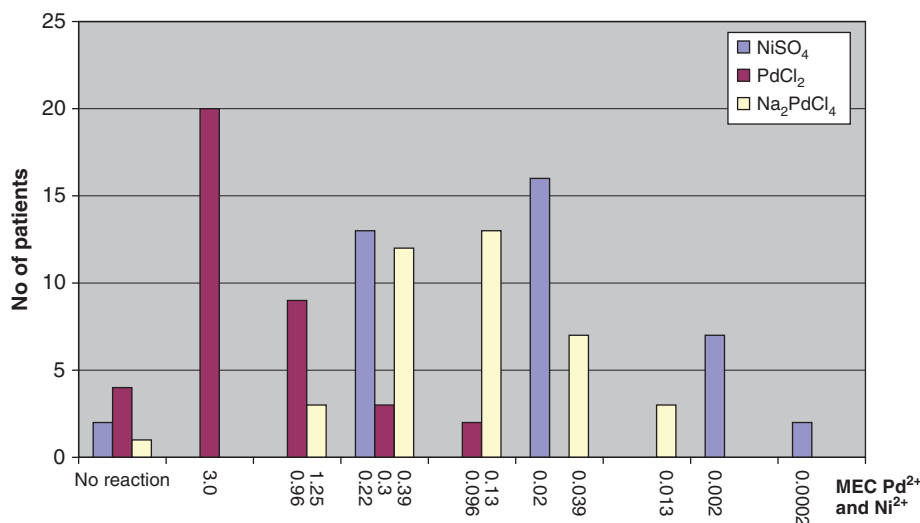


Fig. 2. Distribution of minimal elicitation concentrations (MECs) (grouped to represent similar concentrations).

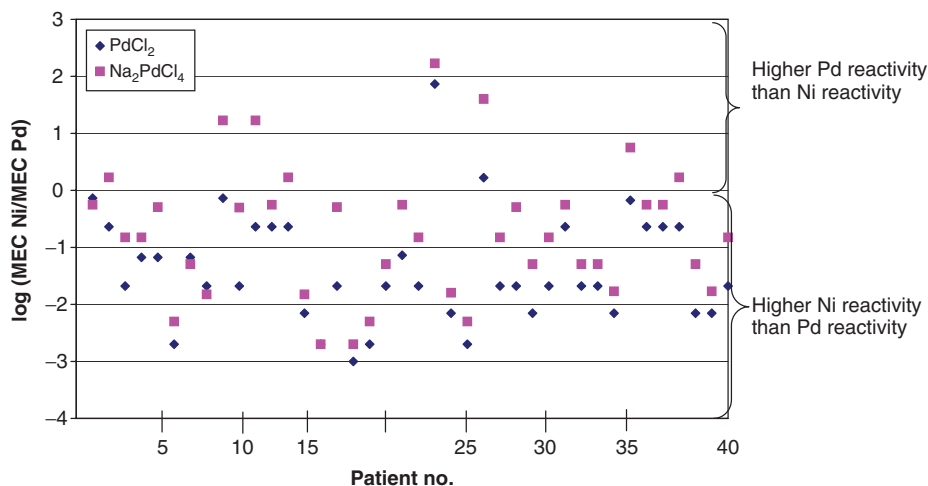


Fig. 3. The distribution of individual ratios of minimal elicitation concentrations (MECs) for nickel ions versus palladium ions for palladium chloride and sodium tetrachloropalladate, respectively.

12-mm discs on the ears for 1 week (26). However, in this study, in which the patients used the earrings for 9 weeks, it was believed that it was better to use earrings resembling actual jewellery.

None of the participants in the study developed any dermatitis resulting from wearing palladium-coated earrings. Most women, at least 35 of 40, also wore the earrings when sleeping. Five of the women were not asked whether they also wore the earrings at night. All women had previously been patch tested and had had at least a + reaction to both nickel and palladium. This suggests that palladium is safe to use in jewellery for people with hypersensitivity to palladium and nickel. However, in

this study, we used earrings with a surface of metallic palladium, but, when palladium is used in jewellery, it is often present as an alloy with gold. It is possible that palladium ions are more readily released from such alloys than from pure palladium. In order to draw any definite conclusions, provocation with palladium alloys and/or chemical studies on the release of palladium ions from different alloys need to be performed.

Furthermore, it should be noted that the earrings used in the study were rather small, and it was only the actual earring pin that contained palladium, the larger earring clasp used to attach the earring to the ear being made of titanium, so it was only the small area at the front of the

earlobe and the actual hole in the earlobe that were in contact with the palladium surface. The possibility cannot be excluded that wearing larger palladium jewellery might cause dermatitis.

Evaluation of concordance in test results between PdCl_2 , Na_2PdCl_4 and $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$, and the degree of intensity of test reactions at the given time

In order to be able to truly compare the concordance in test results and the degree of the intensity in test reactions between metal salts, they should be tested in equimolar concentrations with regard to the concentration of the metal ions. In the present study, the plan was to test Na_2PdCl_4 equimolar to 1.6% PdCl_2 . Equimolar testing with the highest PdCl_2 concentration of 5% was not possible, because the highest non-irritative test concentration for Na_2PdCl_4 is 3% (14). However, because of false information retrieved from a database, Na_2PdCl_4 was tested at a concentration 30% higher than intended (27). Nevertheless, conclusions can be drawn from the patch test results. In order to facilitate the interpretation of the patch test results, the concentrations of PdCl_2 and Na_2PdCl_4 were recalculated as the concentration of palladium ions (Tables 1 and 2). There were statistically significantly stronger reactions to Na_2PdCl_4 than to PdCl_2 when MECs were compared. As the palladium salts were not tested in equimolar amounts, the MEC values were compared, so that the concentration of palladium ions in PdCl_2 was compared, not with the immediately lowest concentration of palladium ions in Na_2PdCl_4 , but with the concentration after one further dilution step (Table 2). Therefore, in the statistical calculations, 19 individuals were considered to have a stronger reaction to Na_2PdCl_4 , and 5 were considered to have a stronger reaction to PdCl_2 . The corresponding numbers when the immediately closest concentrations were compared were 32 with stronger reactions to Na_2PdCl_4 and 5 with stronger reactions to PdCl_2 .

Our observations are consistent with those described by Muris et al. (14), who showed more positive reactions to Na_2PdCl_4 in pet. than to PdCl_2 in aqua. However, in this study, we used another vehicle when testing PdCl_2 (pet.), and it was also stated that a standardized amount

of test preparation was used per unit skin area (22) to minimize technical variations.

On the whole, more subjects tested positively to lower nickel ion concentrations than to palladium ions (Table 2; Figs 2 and 3), which, in a way, may be in favour of nickel as the prime sensitizer, with cross-reactions to palladium. However, the distribution and the wide range of ratios between MECs for nickel ions and palladium ions indicate other explanations for the simultaneous reactions to nickel and palladium.

All women included in the study had previously been patch tested and shown positive test reactions to nickel sulfate 5% pet. and PdCl_2 2% pet. However, on the present test occasion, 4 individuals failed to show positive reactions to PdCl_2 5% pet and 2 failed to show positive reactions to nickel sulfate when tested in 5% aqua. It has previously been shown that patch test reactivity to nickel sulfate in nickel-allergic women can vary by up to 250-fold from one time to another (23), but, to our knowledge, this is the first time such individual variation in patch test reactivity has also been shown for PdCl_2 . Therefore, if there is a clinical suspicion of palladium or nickel allergy but patch testing is negative, one should consider retesting the patient.

Conclusion

This prospective study indicates no risk of dermatitis in individuals with delayed hypersensitivity to palladium and nickel when they wear jewellery coated with pure palladium, but further studies are needed to determine whether palladium, when present in alloys, might give rise to allergic reactions. It was also seen that PdCl_2 , just like nickel sulfate, shows variability in patch test reactivity over time. Furthermore, the study shows that Na_2PdCl_4 seems to be a more sensitive test substance than PdCl_2 for the detection of palladium allergy.

Acknowledgements

The work was supported by grants from the Swedish Asthma and Allergy Association's Research Foundation. The authors would also like to thank Blomdahl Medical AB in Halmstad, Malmö for providing the earrings.

References

- Garner L A. Contact dermatitis to metals. *Dermatol Ther* 2004; **17**: 321–327.
- Jensen C S, Lisby S, Baadsgaard O, Volund A, Menné T. Decrease in nickel sensitization in a Danish schoolgirl population with ears pierced after implementation of a nickel-exposure regulation. *Br J Dermatol* 2002; **146**: 636–642.
- Uter W. The European Surveillance System of Contact Allergies (ESSCA): results of patch testing the standard series, 2004. *J Eur Acad Dermatol Venereol* 2008; **22**: 174–181.
- Wahlberg J E, Boman A S. Cross-reactivity to palladium and nickel studied in the guinea pig. *Acta Derm Venereol* 1992; **72**: 95–97.

- 5 Hindsén M, Spiren A, Bruze M. Cross-reactivity between nickel and palladium demonstrated by systemic administration of nickel. *Contact Dermatitis* 2005; **53**: 2–8.
- 6 Bordignon V, Palamara F, Cordiali-Fei P, Vento A, Aiello A, Picardo M, Ensoli F, Cristaudo A. Nickel, palladium and rhodium induced IFN-gamma and IL-10 production as assessed by in vitro ELISpot-analysis in contact dermatitis patients. *BMC Immunol* 2008; **9**: 19. Available at: <http://www.biomedcentral.com/1471-2172/9/19> (last accessed 01 December 2012)
- 7 Minang J T, Arestrom I, Troye-Blomberg M, Lundeborg L, Ahlborg N. Nickel, cobalt, chromium, palladium and gold induce a mixed Th1- and Th2-type cytokine response in vitro in subjects with contact allergy to the respective metals. *Clin Exp Immunol* 2006; **146**: 417–426.
- 8 Moulon C, Vollmer J, Weltzien H U. Characterization of processing requirements and metal cross-reactivities in T cell clones from patients with allergic contact dermatitis to nickel. *Eur J Immunol* 1995; **25**: 3308–3315.
- 9 Engfeldt M, Tillman C, Hindsén M, Bruze M. Variability in patch test reactivity over time, falsely indicating patch test sensitization, in a patient tested with palladium salts. *Contact Dermatitis* 2012; **67**: 109–111.
- 10 Thyssen J P, Uter W, McFadden J, Menné T, Spiewak R, Vigan M, Gimenez-Arnau A, Lidén C. The EU Nickel Directive revisited – future steps towards better protection against nickel allergy. *Contact Dermatitis* 2011; **64**: 121–125.
- 11 Kielhorn J, Melber C, Keller D, Mangelsdorf I. Palladium – a review of exposure and effects to human health. *Int J Hyg Environ Health* 2002; **205**: 417–432.
- 12 Larese Filon F, Uderzo D, Bagnato E. Sensitization to palladium chloride: a 10-year evaluation. *Am J Contact Dermat* 2003; **14**: 78–81.
- 13 Cristaudo A, Bordignon V, Petrucci F, Caimi S, De Rocco M, Picardo M, Cordiali Fei P, Ensoli F. Release of palladium from biomechanical prostheses in body fluids can induce or support PD-specific IFN-gamma T cell responses and the clinical setting of a palladium hypersensitivity. *Int J Immunopathol Pharmacol* 2009; **22**: 605–614.
- 14 Muris J, Kleverlaan C J, Feilzer A J, Rustemeyer T. Sodium tetrachloropalladate ($\text{Na}_2[\text{PdCl}_4]$) as an improved test salt for palladium allergy patch testing. *Contact Dermatitis* 2008; **58**: 42–46.
- 15 Kanerva L, Rantanen T, Aalto-Korte K et al. A multicenter study of patch test reactions with dental screening series. *Am J Contact Dermat* 2001; **12**: 83–87.
- 16 Marcusson J A. Contact allergies to nickel sulfate, gold sodium thiosulfate and palladium chloride in patients claiming side-effects from dental alloy components. *Contact Dermatitis* 1996; **34**: 320–323.
- 17 Goossens A, De Swert A, De Coninck K, Snauwaert J E, Dedeurwaerder M, De Bonte M. Allergic contact granuloma due to palladium following ear piercing. *Contact Dermatitis* 2006; **55**: 338–341.
- 18 Jappe U, Bonnekoh B, Gollnick H. Persistent granulomatous contact dermatitis due to palladium body-piercing ornaments. *Contact Dermatitis* 1999; **40**: 111–112.
- 19 Faurschou A, Menné T, Johansen J D, Thyssen J P. Metal allergen of the 21st century – a review on exposure, epidemiology and clinical manifestations of palladium allergy. *Contact Dermatitis* 2011; **64**: 185–195.
- 20 Wilkinson D S, Fregert S, Magnusson B et al. Terminology of contact dermatitis. *Acta Derm Venereol* 1970; **50**: 287–292.
- 21 Fischer T, Maibach H. Finn chamber patch test technique. *Contact Dermatitis* 1984; **11**: 137–140.
- 22 Bruze M, Isaksson M, Gruvberger B, Frick-Engfeldt M. Recommendation of appropriate amounts of petrolatum preparation to be applied at patch testing. *Contact Dermatitis* 2007; **56**: 281–285.
- 23 Hindsén M, Bruze M, Christensen O B. Individual variation in nickel patch test reactivity. *Am J Contact Dermat* 1999; **10**: 62–67.
- 24 Hindsén M, Bruze M, Christensen O B. The significance of previous allergic contact dermatitis for elicitation of delayed hypersensitivity to nickel. *Contact Dermatitis* 1997; **37**: 101–106.
- 25 Ahnlide I, Björkner B, Bruze M, Möller H. Exposure to metallic gold in patients with contact allergy to gold sodium thiosulfate. *Contact Dermatitis* 2000; **43**: 344–350.
- 26 Lidén C, Menné T, Burrows D. Nickel-containing alloys and platings and their ability to cause dermatitis. *Br J Dermatol* 1996; **134**: 193–198.
- 27 Engfeldt M, Mowitz M, Tillman C, Hindsén M, Bruze M. Can reliable information sources be trusted? *Contact Dermatitis* 2012; **65**: 364–367.