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Cross-reactivity to Palladium and Nickel Studied in the Guinea Pig

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In recent years there have been several reports on concomitant patch test reactions to palladium and nickel, which belong to the same group in the periodic table. Exposure to palladium mainly takes place via dental alloys and jewellery. However, the clinical relevance of simultaneous reactivity to these metals is unknown. To elucidate the question of cross-reactivity, guinea pigs were induced with palladium *or* nickel and simultaneously challenged with palladium *and* nickel. Animals sensitized to palladium according to the guinea pig maximization test method (GPMT) or to a new method by van Hoogstraten & Scheper (H&S) reacted to palladium as well as to nickel. On the other hand, animals sensitized to nickel according to H&S reacted to nickel but not to palladium. The GPMT shows that palladium is a more potent sensitizer than nickel: could palladium be the primary sensitizer in humans? *Key words: Contact allergens; Sensitization methods; Simultaneous challenge.*

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Concomitant patch test reactions to the metal compounds in the standard series are usually explained by previous exposure (1). Often quoted examples are nickel and cobalt from metal objects and chrome and cobalt from cement. By analyzing a huge material of patients, Pirilä & Förström (2) rejected the suggestion/assumption that the simultaneous reactivity to nickel and cobalt was due to true cross-sensitivity and instead named it "pseudo-cross-sensitivity".

However, in some cases the reactivity to these standard allergens is combined with reactivity to other and probably unrelated metals in the periodic table such as arsenic (3) or tin (4). The clinical significance of these reactions is usually hard to tell. In recent years there have been several reports on concomitant test reactions to palladium and nickel compounds (5–12). Exposure to palladium mainly takes place via dental alloys and jewellery. Palladium is used in the chemical industry as a catalyst and in the electronics industry for contacts and in electroplating (13). The relationship between palladium and nickel is interesting because they are in the same group in the periodic table. Only one case of a reaction to palladium alone seems to have been reported (14). Concomitant reactions to palladium and tin (12), to palladium, nickel and copper (12), and to palladium, nickel, cobalt and mercury (7, 11) have been reported.

That the simultaneous reactivity to palladium and nickel does not depend on nickel contamination of the palladium salt has been checked and ruled out by chemical analysis (4, 7, 9–11, 15). In a previous study we demonstrated that palladium chloride ($PdCl_2$) was a potent sensitizer in the guinea pig (15).

To further elucidate possible cross-reactivity to palladium and nickel, guinea pigs were induced with palladium *or* nickel and challenged simultaneously with palladium *and* nickel. Since the guinea pig maximization test (GPMT) fails to sensitize a sufficient number of animals with nickel we used another method for induction, developed by van Hoogstraten & Scheper.

MATERIALS AND METHODS

Chemicals

Palladium chloride ($PdCl_2$), waterfree for synthesis (Merck-Schuchardt, Germany), Nickel sulfate ($NiSO_4 \cdot 6H_2O$) p.a. (Merck, Germany). When purity was checked, $PdCl_2$ contained < 20 µg/g Ni according to energy dispersion X-ray fluorescence and $NiSO_4$ contained < 1 µg/g Pd according to inductive coupled plasma detection. Freund's complete adjuvant (FCA) (Difco laboratories, Detroit, Michigan, USA).

Animals

The animals used were female Dunkin-Hartley guinea pigs from AB Sahlin försöksfarm, Malmö, Sweden. Their average weight was 350 g at induction. Sham-treated controls were used in each series.

Sensitization methods

To $PdCl_2$: a) Guinea pig maximization test (GPMT) as described in our previous paper (15). Concentrations for induction and challenge were determined in guinea pigs pretreated with FCA. For intradermal induction, the slightly irritant concentration 0.03% $PdCl_2$ in water was chosen. $PdCl_2$ 2.5% in water was used for epidermal induction, preceded by treatment with 10% sodium dodecylsulfate.

b) A new method developed by van Hoogstraten & Scheper (16) was also used. On day 0 the animals received intradermal injections of FCA/NaCl (50:50) at 4 sites – two in the neck and two in the hind leg region. On day 1, 0.05 ml of 0.03% $PdCl_2$ (in saline) was injected into the four adjuvant sites.

To $NiSO_4$: The method developed by van Hoogstraten & Scheper (see above) was used. The concentration of $NiSO_4$ solution (in saline) injected on day 1 was 0.3%.

Challenge

Closed challenge with Finn chambers was used, with concentrations 2.5, 1.25, 0.625, and 0.313% $PdCl_2$ in saline (15). For $NiSO_4$, the concentrations were 1.0, 0.5, and 0.125% (in saline). Vehicle controls, rotations of test sites and blind reading were used in each series (17). For positive reaction, a confluent erythema was required.

Statistical analyses

X^2 analysis or Fisher's exact test.

RESULTS

The results are presented in Tables I-IV.

Sensitization to $PdCl_2$

Of the animals induced with $PdCl_2$ according to the GPMT method, all (10/10) became sensitized to $PdCl_2$ and 6–8/10 also

Table I. *Induction with $PdCl_2$ according to the GPMT method. Challenge with $PdCl_2$ and $NiSO_4$. The number of positive animals for each concentration is given*

		$PdCl_2$			$NiSO_4$			
conc (%)		2.5	1.25	0.625	1	0.5	0.125	Control[a] (Saline)
Controls	24 h	0	0	0	1	1	0	1/10
n=5	48 h	0	0	0	0	1	0	0/10
Exposed	24 h	9**	10***	10***	2	6*	0	2/20
n=10	48 h	9**	10***	10***	6*	8*	0	0/20

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared to the controls.
[a] Two sites per animal.

reacted to $NiSO_4$, and compared to the control animals the difference was statistically significant at the 48 h reading (Table I).

Of the animals induced with $PdCl_2$ according to van Hoogstraten & Scheper, 5–6/15 became sensitized to $PdCl_2$. Compared to the control animals, the difference was statistically significant at the 48 h reading (Table II). A maximum of three animals also reacted to nickel (0.125%), but compared to the controls the difference was not statistically significant. The reactivity in four selected animals from this series is shown in Table III. Guinea pigs nos. 23 and 30 reacted to both compounds, while no. 10 reacted to $PdCl_2$ only and no. 17 to $NiSO_4$ only.

Sensitization to $NiSO_4$

Of animals induced with $NiSO_4$ according to van Hoogstraten & Scheper, 13/15 became sensitized. Compared to the control animals the difference was statistically significant at both readings (Table IV). However, no animal reacted to $PdCl_2$.

DISCUSSION

The results from these experimental studies seem clear-cut: animals induced with $PdCl_2$ also react to $NiSO_4$ (Tables I, II). Since it is difficult to sensitize guinea pigs with nickel (for a review, see (18), it is unlikely that the minute amounts of nickel in the $PdCl_2$ salt (< 20 µg/g according to the analytical method used) can be responsible for the test reactions to $NiSO_4$ at challenge.

We have long experience with the GPMT method (17), while this was our first attempt with the new sensitization method developed by van Hoogstraten & Scheper. We succeeded in inducing sensitivity to both salts (Tables II and IV, respectively), but as a dose-response relationship can be anticipated on sensitization, the conditions were probably not optimal. Some animals reacted to the lower concentrations while remaining negative to the highest challenge concentration (Table III). This may be explained by the fact that each guinea pig was exposed to 8 challenge patches – 4 on each flank, randomly distributed on the animals in the sensitized group – why some regional variation in skin reactivity in that group of animals was observed. The result in guinea pig no. 17 (Table III) is puzzling, since it was negative to $PdCl_2$ but positive to $NiSO_4$. Various concentrations for induction should be tried to further elucidate these somewhat contradictory results. A high proportion of the animals became sensitized to nickel, but the frequency of reactions in the control animals was undesirably high (Table IV). In spite of this none of these nickel-sensitive animals reacted when challenged with $PdCl_2$.

At present it is difficult to tell what clinical relevance these findings in the guinea pig have. Our experience with the GPMT method indicates that $PdCl_2$ has a stronger allergenic potential than $NiSO_4$. Could it be that $PdCl_2$ is the primary sensitizer in humans? To further elucidate these questions we have started experimental studies where guinea pigs are induced with one metal compound and challenged with this but also with compounds from the same and from other groups in the periodic table. Patients reacting to metal compounds in the standard series will also be tested with other metals to study the pattern of concomitant reactivity.

Table II. *Induction with $PdCl_2$ according to van Hoogstraten & Scheper. Challenge with $PdCl_2$ and $NiSO_4$. The number of positive animals for each concentration is given*

		$PdCl_2$				$NiSO_4$			
conc (%)		2.5	1.25	0.625	0.313	1	0.5	0.125	Control (Saline)
Controls	24 h	0	0	0	0	0	0	0	0
n=15	48 h	0	0	0	0	0	0	0	0
Exposed	24 h	1	2	3	3	1	2	2	0
n=15	48 h	5*	5*	6**	3	1	2	3	0

* $p<0.05$, ** $p<0.01$ compared to the controls.

Table III. *Reactivity to $PdCl_2$ and $NiSO_4$ in four selected guinea pigs induced with $PdCl_2$ according to the method of van Hoogstraten & Scheper, 48 h reading*

	$PdCl_2$				$NiSO_4$		
conc (%)	2.5	1.25	0.625	0.313	1	0.5	0.125
Guinea pig no.							
10	pos	pos	pos	neg	neg	neg	neg
23	pos	pos	pos	neg	pos	neg	neg
30	neg	pos	pos	pos	neg	pos	pos
17	neg	neg	neg	neg	neg	pos	pos

Table IV. *Induction with $NiSO_4$ according to van Hoogstraten & Scheper. Challenge with $NiSO_4$ and $PdCl_2$. The number of positive animals for each concentration is given*

		$NiSO_4$				$PdCl_2$			
conc (%)		1	0.5	0.25	0.125	2.5	1.25	0.625	Control (Saline)
Controls	24 h	2	5	0	2	0	0	0	0
n=15	48 h	2	5	0	0	0	0	0	0
Exposed	24 h	13***	11*	8**	6	0	0	0	0
n=15	48 h	13***	12**	7**	7**	0	0	0	0

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared to the controls.

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