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Delayed hypersensitivity to palladium dichloride: 15-year retrospective study in a skin allergy unit

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Abstract

Background: Metal allergies are the most frequent causes of allergic contact dermatitis. Although the use of palladium is increasing, it is not included in any baseline series.

Objective: To assess the prevalence of hypersensitivity to palladium and to describe the clinical and demographic characteristics of patients who are sensitized to palladium dichloride (PdCl₂).

Methods: A single-centre, retrospective study of 15 years of patch testing with the Spanish baseline series supplemented with PdCl₂ 2% pet. was performed. We collected clinical and demographic data and data on co-sensitization among the metals studied, and we compared patients who were sensitized to palladium, with or without co-sensitization to nickel, with the rest of the study population.

Results: Among the 3678 included patients, 730 (19.9%) were sensitized to nickel sulfate. The prevalence of sensitization to PdCl₂ (*n* = 316, 8.6%) was higher than the prevalence of sensitization to potassium dichromate (*n* = 240, 6.5%) and similar to the prevalence of sensitization to cobalt chloride (*n* = 353, 9.6%). Only 26 (8.2%) of the patients sensitized to palladium were not co-sensitized to nickel. The percentage of men and patients aged ≥40 years was higher in this subgroup than in the patients with nickel co-sensitization.

Conclusions: Given the high prevalence of hypersensitivity to PdCl₂, this metal salt should be included in the Spanish baseline series, notwithstanding the frequency of co-sensitization to nickel.

KEYWORDS

co-sensitization, metal allergies, nickel sulfate, palladium dichloride

1 | INTRODUCTION

Metal allergies are the most frequent causes of allergic contact dermatitis in our setting.^{1–3} The metal salts included in most baseline series are nickel sulfate, potassium dichromate, and cobalt chloride.^{3–5} The reported prevalence of hypersensitivity to nickel sulfate in the

European population ranges from 8% to 20%, despite regulations implemented in the EU with regard to this metal.^{4–7} Palladium is a ubiquitous metal belonging to the platinum group. It is ductile and malleable,⁸ and its use is increasing in both jewellery and dentistry.

In dentistry, palladium has replaced amalgam and gold, owing to its characteristic hardness, durability, and resistance to corrosion.^{8–10}

In jewellery,⁸ palladium has even been called the metal of the 21st century, as it resembles white gold or platinum but is lighter and cheaper. However, as its use is increasing, so is the number of reports on sensitization. Among patch tested patients in Europe, the estimated prevalence of sensitization to palladium is reported to range between 3% and 9%.^{1,8-13} However, it is not included in any baseline series in Europe, including in Spain. Some authors attribute the high prevalence of palladium hypersensitivity to the frequent co-sensitization between metals.^{13,14} Indeed, sensitization to palladium is usually accompanied by nickel sensitization. This fact, together with the difficulty in delineating the relevance of palladium sensitization, could justify not including palladium in the baseline series.

The primary aims of this study were to assess the prevalence of hypersensitivity to palladium in the study population, and to describe the clinical and demographic characteristics of patients who are sensitized to palladium dichloride (PdCl₂), with or without co-sensitization to nickel. The secondary aims were to estimate, in our population, the prevalence of hypersensitivity to the metals present in the Spanish baseline series, and to describe co-sensitization among the metals studied (palladium, chromium, nickel, and cobalt).

2 | MATERIALS AND METHODS

This retrospective observational study was performed from January 2004 to December 2018. We included all patients who were patch tested with the Spanish baseline series in our Skin Allergy Unit of a tertiary referral hospital. Information about the patients was obtained from the clinic's database, including clinical data and the results of the patch tests that were applied. Clinical data included: age, sex, history of atopic dermatitis, location of the skin lesions prompting the visit to the clinic, and occupational causation of dermatitis.

Patients were classified into four subgroups according to their sensitization to PdCl₂, nickel sulfate, potassium dichromate, and cobalt chloride. Each of these groups, in turn, was subdivided into two subgroups: those sensitized to a single metal, and those with co-sensitization to another metal.

For patients sensitized to palladium, clinical data were compared between those with and those without co-sensitization to nickel and with the remainder of the patch tested study population. To compare the clinical and demographic data in the different groups, we analysed the following variables, most of which included in the MOAHLFA index: sex, occupational dermatitis, personal history of atopic dermatitis, involvement of oral mucosa, and age >40 years.

2.1 | Patch test methods

All patients were patch tested with PdCl₂ 2% pet. and with the Spanish baseline series, which includes the following metal salts: nickel sulfate 5% pet., potassium dichromate 0.5% pet., and cobalt chloride 1% pet., supplied by Chemotechnique Diagnostics (Vellinge, Sweden). The patches were prepared with Finn Chambers (Epitest, Tuusula, Finland) affixed with Scanpor adhesive tape (Norgeplaster, Kristiansand,

Norway), and removed at 48 hours. Readings were performed on day (D) 2 and D4, according to the criteria recommended by the International Contact Dermatitis Research Group. A later reading on D7 was also performed for cases with doubtful results on earlier readings. We defined a positive patch test reaction as one showing at least oedema or infiltration that occupied the whole patch test area on the D4 reading.

2.2 | Statistical analysis

Data were processed with SPSS 20 (SPSS, Chicago, Illinois). Qualitative variables were analysed with the χ^2 test and Fisher's exact tests, as appropriate. In our interpretation of the results, we considered *P* values of ≤ 0.05 to be statistically significant.

3 | RESULTS

3.1 | Prevalence of hypersensitivity to the metals studied

Patch tests were performed in 3678 patients. Table 1 shows the prevalences of positive reactions obtained for the metal salts in these patients. Hypersensitivity to nickel sulfate was most prevalent (*n* = 730, 19.9%). The prevalence of hypersensitivity to PdCl₂ was higher (*n* = 316, 8.6%) than that of hypersensitivity to potassium dichromate (*n* = 240, 6.5%), and was similar to that of hypersensitivity to cobalt chloride (*n* = 353, 9.6%).

3.2 | Co-sensitization between the metals studied

Co-sensitization between PdCl₂, potassium dichromate, nickel sulfate and cobalt chloride is shown in Table 2. The most notable findings were as follows.

- Nickel sulfate was the most common metal provoking a hypersensitivity reaction without co-sensitization to other metals.
- Hypersensitivity to PdCl₂ almost always presented with co-sensitization to another metal, especially nickel.
- Isolated hypersensitivity to cobalt chloride was rare; it usually presented with co-sensitization to chromium or nickel.

TABLE 1 Prevalence of positive patch test reactions to different metal salts in the study population (*N* = 3678)

Allergen	Total, <i>n</i> (%)	Monosensitization, <i>n</i> (%)
Nickel sulfate	730 (19.9)	399 (10.9)
Cobalt chloride	353 (9.6)	40 (1.1)
Palladium dichloride	316 (8.6)	13 (0.4)
Potassium dichromate	240 (6.5)	64 (1.7)

TABLE 2 Co-sensitization among the metal salts studied

Co-sensitization between two metals	No co-sensitization, n (%)	Palladium dichloride, n (%)	Cobalt chloride, n (%)	Potassium dichromate, n (%)	Nickel sulfate, n (%)
Nickel sulfate (N = 730)	399 (54.6)	290 (39.7)	165 (22.6)	58 (7.9)	-
Potassium dichromate (N = 240)	64 (26.7)	28 (11.7)	114 (47.5)	-	58 (24.2)
Cobalt chloride (N = 353)	40 (11.3)	56 (15.9)	-	114 (32.3)	165 (46.7)
Palladium dichloride (N = 316)	13 (4.1)	-	56 (17.7)	28 (8.9)	290 (91.8)

3.3 | Characteristics of patients sensitized to palladium

Of the 316 patients sensitized to PdCl₂, 290 (91.8%) were co-sensitized to nickel sulfate. Of the 26 patients without nickel co-sensitization, 13 had no co-sensitization at all. Tables 3 and 4 show the clinical and demographic characteristics of patients in the different subgroups. Of note,

- The percentage of men in the group with exclusive hypersensitivity to palladium was similar to that in the total study population, but it was much higher than in the group showing co-sensitization to nickel. This difference was statistically significant.
- The percentage of people aged >40 years was greater in the group with exclusive hypersensitivity to palladium, although the differences to the other groups studied were not statistically significant.
- The percentage of cases with mucosal involvement was higher in the group of patients with allergy to palladium alone than the group showing co-sensitization to both metals. However, this result was not statistically significant.

4 | DISCUSSION

In recent years, there has been an increasing number of reports on the prevalence of late hypersensitivity to palladium. Estimates vary among published series; for instance, in patients patch tested in Europe, the

reported prevalences of palladium hypersensitivity range from 3% to 9%.^{1,8-13} Thus, our data (8.6%) are consistent with the published literature. Some authors argue that palladium sensitization could be underdiagnosed.^{9,10,14} One of the reasons for this would be the absence of the metal in all European and US baseline series.^{1,8} Moreover, Muris et al have proposed using disodium tetrachloropalladate (Na₂PdCl₄) 3% pet. instead of PdCl₂ 2% pet.^{9,10} These authors found that approximately half of all patients with hypersensitivity to Na₂PdCl₄ were not identified by patch testing with PdCl₂, and they argued that the prevalence of sensitization to Na₂PdCl₄ 3% pet. in patch tested patients could be comparable to that of nickel sulfate—that is, much higher than the prevalence recognized to date.^{9,10} This group observed sensitization to 3% Na₂PdCl₄ in 18.2% of their study population, a figure that greatly exceeds estimates in all other published reports, and is practically equivalent to that seen for nickel sulfate.

An allergen showing levels of sensitization in patch tested populations as high as those seen with palladium should be included in the baseline series. However, so far, this has not been seriously contemplated in Europe or the United States, in part because hypersensitivity to palladium is frequently associated with hypersensitivity to nickel.^{8-10,13} In our study, >90% of the patients with palladium allergy were co-sensitized to nickel; this finding is similar to the 94% reported by Durosaurio et al.¹³ Some authors do not see the relevance of a positive patch test reaction to palladium.^{3,7,9,10,13} Co-sensitization to several metals would complicate the identification of sources of

TABLE 3 Clinical and demographic characteristics of patients with palladium allergy and the remainder of the study population

N	Patients sensitized to palladium, n (%)	Remaining patients, n (%)	P value
	316	3362	
Men	41 (13.0)	1309 (38.9)	<0.001
Occupational dermatitis	53 (16.8)	344 (10.2)	<0.001
Atopic dermatitis	29 (6.3)	285 (8.5)	0.76
Involvement of oral mucosa	6 (1.9)	55 (1.6)	0.90
Age > 40 y	190 (60.1)	2109 (62.7)	0.40

TABLE 4 Clinical and demographic characteristics of patients allergic only to palladium vs those of patients sensitized to palladium and nickel

	Allergy		P value
	Palladium only, n (%)	Palladium + nickel, n (%)	
N	26	290	
Men	8 (30.8)	33 (11.4)	0.012
Occupational dermatitis	4 (15.4)	49 (16.9)	1.0
Atopic dermatitis	2 (7.7)	19 (6.6)	0.69
Involvement of oral mucosa	2 (7.7)	4 (1.4)	0.08
Age > 40 y	19 (73.1)	167 (57.6)	0.15

exposure, and therefore the assessment of the relevance of a positive reaction.⁷ According to Faurscho et al, hypersensitivity to palladium could almost be considered to be an indicator of nickel allergy.⁸ However, these authors also acknowledge two circumstances in which hypersensitivity to palladium must be considered: lesions in the oral mucosa, and granulomatous lesions (especially in the ears and in piercings). Our data support the notion that palladium can act as a sensitizing agent through the oral mucosa, as we observed a greater number of cases with involvement of the oral mucosa in patients who were allergic to palladium but not sensitized to nickel. Moreover, we did not see the same difference between sexes that was present in patients co-sensitized to both metals. This may be because the corrosive properties of saliva interact with palladium, favouring hypersensitivity more than when only the skin is exposed to this metal.^{9,10,12} Such a relationship would increase the clinical relevance of palladium sensitization, resulting in more frequent hypersensitivity reactions in patients receiving dental interventions such as crowns, bridges, and fillings.

The prevalence of exclusive sensitization to palladium (ie, without nickel allergy) is quite low, ranging from 0.2% to 0.5%.⁸ If it were only possible to establish relevance in these cases, the inclusion of palladium in the baseline series would probably not be warranted. However, cobalt chloride, which is included in the baseline series, shows a similar prevalence of sensitization to that of palladium (9.6% and 8.6%, respectively), and most of the patients in our series also showed co-sensitization to another metal included in the Spanish baseline series (88.7% and 95.9%, respectively). Furthermore, dentists and traumatologists are referring more patients for patch testing prior to fitting a metallic prosthesis. It is debatable whether this should be a routine procedure in all patients receiving these interventions, but it is clearly sensible to do so in patients who report intolerance to metals or who have known hypersensitivity to one or more metals, given the high frequency of co-sensitization between them. Better knowledge of pre-existing metal allergies in these patients can inform decisions on which metallic prosthesis is likely to cause the least allergic complications.^{15,16}

These considerations could justify the inclusion of palladium in the Spanish baseline series.¹⁰ To avoid underdiagnosis, it should probably be included in the form of Na₂PdCl₄. However, further studies are required in order to increase the amount of scientific evidence in support of the inclusion of PdCl₂ in the baseline series.

4.1 | Limitations

This study has several limitations. First, it is a single-centre study, and its results cannot be extrapolated to the rest of Spain. Second, there were few patients with palladium hypersensitivity who were not co-sensitized to nickel; a larger sample size could influence the statistical significance of our results. Finally, our patients were patch tested with PdCl₂ rather than Na₂PdCl₄, so the prevalence of palladium allergy in the studied population could have been underestimated.

4.2 | Conclusion

The use of palladium in jewellery and oral prostheses has increased in recent years, and with this the number of reported cases of associated contact dermatitis. Hypersensitivity to palladium is very prevalent in the patch tested study population, but it may even be underestimated as compared with the prevalences found when Na₂PdCl₄ 3% pet. is used instead of PdCl₂ 2%. Despite the high proportion of co-sensitization with nickel, sensitization to palladium could be relevant on its own, particularly in cases with involvement of the oral mucosa. In cases of oral complaints, dermatologist should test 3% Na₂PdCl₄ in order to diagnose a case of hypersensitivity to this metal, which could otherwise be misdiagnosed if only the current baseline series were used.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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