

Original article

Occupational hypersensitivity to metal salts, including platinum, in the secondary industry

Background: Exposure to platinum group elements (PGEs) – platinum (Pt), palladium (Pd), rhodium (Rh) and iridium (Ir) – may cause acute toxicity or hypersensitivity with respiratory symptoms, urticaria and (less frequently) contact dermatitis. Our aim was to determine the prevalence and the clinical characteristics of hypersensitivity to platinum salts and to other elements of the platinum group.

Methods: A total of 153 subjects working in a catalyst manufacturing and recycling factory were examined. The examination consisted of a work exposure and medical questionnaire, physical examination, skin prick test for PGEs and other common aeroallergens, and patch tests for PGEs. Skin prick tests and patch tests were performed with $\text{H}_2[\text{PtCl}_6]$, $\text{K}_2[\text{PtCl}_4]$, $\text{Na}_2[\text{PtCl}_6]$, IrCl_3 , RhCl_3 , PdCl_2 , aqueous solutions at different concentrations.

Results: Positive prick test reactions to Pt-salts at various concentrations were found in 22 (14.4%) of 153 workers; eight had simultaneous reactions to all Pt-salts tested; seven had positive responses to $\text{H}_2[\text{PtCl}_6]$ only; four had simultaneous positive reactions to both $\text{H}_2[\text{PtCl}_6]$ and $\text{K}_2[\text{PtCl}_4]$; three had positive reactions to $\text{H}_2[\text{PtCl}_6]$ and $\text{Na}_2[\text{PtCl}_6]$. Three of 22 had positive reactions to $\text{H}_2[\text{PtCl}_6]$ and IrCl_3 solutions, two of these had positive reactions to $\text{H}_2[\text{PtCl}_6]$, IrCl_3 and RhCl_3 solutions. Positive patch test reactions to platinum salts at day 2 were seen in two of 153 subjects.

Conclusions: The results of this study demonstrate that Pt-salts are important allergens in the catalyst industry and that the clinical manifestations involve both the respiratory system and the skin. Hexachloroplatinic acid should be considered the most important salt to use for skin prick tests.

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The platinum group elements (PGEs) – platinum (Pt), palladium (Pd), rhodium (Rh) and iridium (Ir) – are rare in the earth's crust in comparison with other elements (1). In contrast, their specific physical and chemical properties have led to the development of some highly sophisticated technical applications, especially in the field of catalysis (2).

Occupational exposure occurs during the mining and processing of platinum. However, the most common current occupational exposure to soluble platinum compounds is through platinum refining and catalyst manufacturing. World mine production of platinum-group metals (40–50% is platinum), has steadily increased over the last two decades since the introduction of the automobile exhaust gas catalyst. In fact, the excellent catalytic properties of platinum have led to its progressively increased use (sometimes in association with rhodium, iridium and palladium). It is also used in making jewellery and in dentistry, but most widely used as an automotive catalyst. In recent years, there has been an increased demand for platinum that has consequently

led to an increase in both the worldwide mine production and the environmental emission of the element (3).

Platinum salts have been reported to induce toxicity or hypersensitivity reactions with respiratory symptoms (rhinitis, conjunctivitis, asthma), contact urticaria and (less frequently) contact dermatitis (4–5). Pt is a transitional metal, belonging to VIII of the periodic system, with partly filled d-shells (6), which is unable to act as an antigen. It has a marked tendency to form complexes and react with donor groups in amino acids to form a complete antigen (7). Chlorinate soluble compounds such as hexachloroplatinic acid, its ammonium and potassium salts, potassium and sodium tetrachloroplatinate represent the most dangerous chemical forms. Some of these salts have displayed strong sensitizing power in animal models. Using popliteal lymph node assay in mice, Schupple et al. drew the conclusion that the highest sensitizing power might be in hexa and tetrachloroplatinates (8). Currently, most of the information about the effects of PGEs in humans comes from the field of occupational exposure in the refinery process (9–11).

However, only limited data are currently available about the prevalence of hypersensitivity to PGEs in catalyst production (12). Furthermore, the studies performed only took hypersensitivity to platinum salts into consideration. No attention was given to possible effects of exposure to other Pt-group elements in occupational environments. The risk factor for developing sensitization has not been clearly delineated. A preliminary study showed an increased prevalence of occupational allergy in atopic workers (13), but other studies did not show any significant link between atopy and allergy to Pt-salts (9, 10). Moreover, other studies showed that allergy to Pt-salts was strongly associated with cigarette smoking (5, 12).

Current research documents the findings of a cross-sectional study in PGEs exposed workers.

Our purpose was to determine the prevalence and the clinical characteristics of hypersensitivity to Pt-salts and other Pt-group elements (Pd, Rh, Ir) among exposed workers in a catalyst production plant. This was due to the fact that these elements are all present in the workplace environment, all belonged to the transitional metals group, and all were highly reactive elements capable of causing inflammatory and mediating immunological effects.

Material and methods

The study was carried out in a large industrial complex on the outskirts of Rome where several types of catalysts are produced. Here the workplace is divided into departments, where different types of production activities are carried out. Platinum metals are solubilized in closed reactors. The solutions obtained are used both in the production of intermediate products (dust, granules, pellets, beads, etc.) and in the production of finished products (catalysts for transport and domestic electrical appliances). The different substrates are impregnated in different production areas, automatically with robots or manually, complete with aspirator systems. Finally, the pieces are calcinated in kilns. In addition, precious metal contained in exhaust catalysts is refined after a combustion cycle. The analysis of products and quality control of raw materials, intermediate and finished products is carried out in their own laboratories.

Subjects

The subjects were examined at 2-month intervals. A total of 153 workers were in the factory and no one entered or left the factory during the time of the study. The subjects were duly informed about the purpose of this study and their consent was obtained. The examination consisted of a work exposure and medical questionnaire, physical examination, skin prick test to Pt-salts and other common aeroallergens, and patch tests to platinum salts. Physical examination was carried out by the author and by the company doctor in the medical department of the plant. Data pertaining to health history, previous work exposure to Pt-salts and other potentially hazardous materials, number of cigarettes smoked per day, length of service in the company, job title and job location were collected. The presence of asthma, rhinitis, eye and skin symptoms was assessed by the severity, duration and if the symptoms appeared when the subjects were at the workplace or/and away from it.

As no data were available on the environmental exposure to the Pt-group elements, the workers were assigned to one of three categories according to job title and job location:

1. High exposure (consisting of those workers, who while under observation, worked in the production side of salts, solution and in refining).
2. Low exposure (all the other workers in the production area).
3. No exposure (office personnel, whose workplaces were outside the production area).

Skin prick test

Skin prick tests were performed with a series of 16 common diagnostic inhalants (Stallergenes, Antony, France) including pollens, dusts, moulds and animals and controls. Atopy was defined as a positive reaction to one or more environmental allergens. Skin prick tests with Pt-salts were performed with the following freshly prepared aqueous (aq.) solutions at different concentrations: hexachloroplatinic acid ($\text{H}_2[\text{PtCl}_6]$) 10^{-2} – 10^{-8} M, potassium tetrachloroplatinate ($\text{K}_2[\text{PtCl}_4]$) 10^{-2} – 10^{-8} M, sodium hexachloroplatinate ($\text{Na}_2[\text{PtCl}_6]$) 10^{-2} – 10^{-8} M, iridium chloride (IrCl_3) 10^{-3} – 10^{-6} M, rhodium chloride (RhCl_3) 10^{-3} – 10^{-6} M, palladium chloride (PdCl_2) 10^{-3} – 10^{-6} M. Prick tests were performed by placing a small drop of each compound tested on the volar surface of the forearm. A disposable hypodermic needle was passed through the drop and inserted into the epidermal surface. Readings are scored after 25 min according to international guidelines. The salts of all the Pt-group elements were generously supplied by the manufacturer. The purity checked was >99.2%.

Patch test

The subjects were all patch tested with 15 μl of the following aqueous solutions $\text{H}_2[\text{PtCl}_6]$ 10^{-2} M, $\text{K}_2[\text{PtCl}_4]$ 10^{-2} M, $\text{Na}_2[\text{PtCl}_6]$ 10^{-2} M, IrCl_3 10^{-3} M, RhCl_3 10^{-3} M, PdCl_2 10^{-2} M. Patch tests were carried out with Al-test on Leukotest. Readings are scored, following international guidelines at day 2. A first reading was carried out after 25 min in subjects with urticaria.

A subject was considered allergic to platinum if a positive reaction to the skin prick test and/or to patch test was present.

Statistical analysis

The analysis of data began with univariate analysis of each variable of interest (age when hired, gender, exposure category, atopy, smoking, history on the job). We categorized the quantitative variables (age when hired, months of work) using the percentile of noncases distribution. Then we produced a contingency table of outcome (allergy to platinum salts) vs the k levels of the independent variable. In addition to the chi-square test, we estimated the prevalence odds ratio (with 95% confidence intervals, 95% CI) using the level with lower prevalence as the reference group. We then produced multivariate logistic regression models to evaluate the independent role of the variables of interest. All statistical analyses were performed using the SPSS statistical package (14).

Results

The 153 subjects had the following characteristics: 137 men; 16 women; age range between 21 and 60, average

age 34. Length of employment ranged from 1 to 360 months; mean 103.9 STD (98.5) and median time 84 months. In all, a total of 23 subjects were found to be positive to different types of Pt-salts with the prick or patch tests. Positive prick test reactions to PGEs salts at various concentrations were found in 22 (14.4%) of 153 workers. Eight had simultaneous reactions to all Pt-salts tested; seven had positive responses to $H_2[PtCl_6]$ only, four had simultaneous positive reactions to both $H_2[PtCl_6]$ and $K_2[PtCl_4]$ and three had positive reaction to $H_2[PtCl_6]$ and $Na_2[PtCl_6]$. Three of 22 had positive reactions to $H_2[PtCl_6]$ and $IrCl_3$; two of these had positive reactions to $H_2[PtCl_6]$, $IrCl_3$ and $RhCl_3$.

Positive patch test reactions to platinum salts at day 2 were seen in two of 153 subjects. The first subject with rhinitis, asthma and hand dermatitis had positive reactions to patch and prick test with $H_2[PtCl_6]$. The second, with contact dermatitis of the hands, had positive patch

test reactions to $H_2[PtCl_6]$ and $PdCl_2$ only. Another two subjects with urticaria and asthma had an urticarial reaction to $H_2[PtCl_6]$ at 25 min. The wheals faded in 3 h (Table 1).

Forty subjects (26.1%) had positive prick tests to common inhalants (21 to pollens, 10 to household dust mites and nine to both).

Table 2 shows the prevalence of clinical symptoms (conjunctivitis, rhinitis, asthma, urticaria and eczema) in different groups defined according to the results of the skin tests. Rhinitis and eczema had a similar prevalence in subjects with allergies to common inhalants (91% for rhinitis and 9% for eczema), in subjects with allergies to Pt-salts (73% for rhinitis and 7% for eczema), and in subjects who were allergic to both (88% for rhinitis and 12% for eczema). Asthma and urticaria were more prevalent in subjects allergic to Pt-salts (47% for asthma and 27% for urticaria) compared with those allergic to

Table 1. Clinical characteristics in 23 subjects with positive skin tests

Subject	Prick tests					Patch test		Clinical characteristics			
	$H_2[PtCl_6]$	$K_2[PtCl_4]$	$Na_2[PtCl_6]$	$IrCl_3$	$RhCl_3$	$H_2[PtCl_6]$	$PdCl_2$	Rhinitis	Asthma	Urticaria	Eczema
1	—	—	—	—	—	+	—	No	No	No	Yes*
2	+	—	—	—	—	—	—	No	No	No	No
3	+	+	—	—	—	—	—	Yes	No	No	No
4	+	+	+	—	—	—	—	Yes	Yes*	No	No
5	+	+	+	—	—	—	—	Yes*	Yes*	Yes*	No
6	+	—	—	—	—	—	—	No	No	No	No
7	+	+	+	+	+	—	—	Yes	Yes*	Yes*	No
8	+	+	+	+	—	—	—	Yes	Yes*	Yes*	No
9	+	—	+	—	—	—	—	Yes	Yes*	No	No
10	+	—	+	—	—	—	—	Yes	No	No	No
11	+	—	—	—	—	—	—	No	No	No	No
12	+	+	—	—	—	—	—	Yes	No	No	No
13	+	+	+	—	—	—	—	Yes	No	No	No
14	+	+	—	—	—	—	—	Yes	Yes*	Yes	No
15	+	+	+	—	—	—	—	Yes	Yes*	No	No
16	+	—	—	—	—	—	—	Yes	No	No	No
17	+	—	—	—	—	—	—	Yes	No	No	No
18	+	—	+	—	—	—	—	Yes	No	No	No
19	+	+	+	+	+	—	—	Yes	Yes*	Yes*	No
20	+	+	+	—	—	—	—	Yes	Yes*	Yes*	No
21	+	—	—	—	—	—	—	No	No	No	No
22	+	+	—	—	—	—	—	Yes	No	No	No
23	+	—	—	—	—	+	+	Yes	Yes*	No	Yes*

* Work-related symptom.

Table 2. Prevalence of clinical symptoms (conjunctivitis, rhinitis, asthma, urticaria) in four groups categorized on the basis of their reaction to skin tests

Response to allergological tests	n	Rhinitis		Asthma		Urticaria		Eczema	
		n	%	n	%	n	%	n	%
Negative	98	5	5.1	2	2.0	1	1.0	6	6.1
Positive to common inhalants	32	29	90.6	3	9.4	0	0.0	3	9.4
Positive to platinum salts	15	11	73.3	7	46.7	4	26.7	1	6.7
Positive to common inhalants and platinum salts	8	7	87.5	3	37.5	2	25.0	1	12.5

Table 3. Univariate and multivariate analysis to assess predicting factors of positive response to skin tests for platinum salts

	<i>n</i>	Cases	Prevalence rate	Prevalence odds ratio	95% CI	Adjusted prevalence odds ratio	95% CI
Exposure category							
No exposure: white collar, employees	11	0	0.0				
Low exposure	105	14	13.3	1.0		1.0	
High exposure	37	9	24.3	2.1	0.8–5.3	2.4	0.8–6.9
Age at work (years)							
20–25	50	9	18.0	1.0		1.0	
26–29	48	6	12.5	0.7	0.2–2.0	1.0	0.3–3.3
30–46	44	8	18.2	1.0	0.4–2.9	1.0	0.3–3.1
Atopy							
No	107	15	14.0	1.0		1.0	
Yes	35	8	22.9	1.8	0.7–4.7	2.2	0.8–6.0
Smoking							
Nonsmoker	69	10	14.5	1.0		1.0	
Smoker	73	13	17.8	1.3	0.5–3.1	1.1	0.4–3.0
Years of work							
0–5	72	7	7.2	1.0		1.0	
6–30	70	16	22.9	2.8	1.1–7.2	3.2	1.2–8.9

common inhalants (9% asthma, 0% urticaria). All the subjects with asthma and five of six with urticaria, positive to prick tests for platinum salts, noted the symptoms in the workplace exclusively. Whereas, the subjects with rhinitis referred an exacerbation of the symptoms during working hours.

Of the 98 subjects negative for the patch and prick test, five had rhinitis, two asthma, one urticaria and six dermatitis. Table 3 shows the prevalence of allergic reaction to platinum compared with factors such as: when hired, job title, duration of employment, atopy and smoking habits.

A total of 105 subjects were classified according to job title as having a high exposure, 37 subjects low exposure and 11 subjects no exposure. Univariate analysis showed a prevalence of allergies to Pt-salts. None was reported among the office personnel. There was an increase in the prevalence in the category with high exposure compared with those with a low exposure with prevalence odds ratios equal to 2.1 (95% CI: 0.8–5.3). The rate of prevalence in two classes of length of employment 1–5 years and 6+ years was 9.7 and 22.9%, respectively, with prevalence odds ratios for the class 6+ years equal to 2.8 (95% CI: 1.1–7.2). These results are compatible with a constant incidence model. Univariate analysis shows a slight increase in the prevalence of sensitivity to Pt-salts in atopic subjects (prevalence odds ratios were 1.8 (95% CI: 0.7–4.7)); while in smokers the prevalence of allergic reactions to Pt-salts was slightly higher, with prevalence odds ratios of 1.3 (95% CI: 0.5–3.1). Multivariate analysis confirms the results of the univariate analysis with prevalence odds ratios of 2.4 (95% CI: 0.8–6.9) for the high exposure category and prevalence odds ratios of 2.2 (95% CI: 0.8–6.0) for atopic subjects. In addition, we evaluated the presence of multiple interactions between atopy, smoking, and job title, but were unable to find any mechanism of interaction between them.

Discussion

The results of this study clearly indicate that among PGEs, Pt-salts and especially $H_2[PtCl_6]$, are relevant allergens in catalyst production plants and that both hypersensitivity and clinical manifestation are associated with high levels of exposure. In fact, in all nonexposed subjects and all those employees whose job location was outside the production area, the allergic tests were negative. This was in agreement with our previous study (15), which showed that in 800 consecutive nonexposed working patients with dermatitis and urticaria, the prick as well as patch tests with Pt element groups were negative. This was also in line with the studies of other authors (16) that show that, although there has been an increase in platinum pollution in the past few years (mostly due to emissions of automobile exhaust gas catalysts), the present environmental concentrations are not enough to cause a general outbreak of allergic reactions in the population. This is also due to the fact that platinum emitted by catalyst exhausts is mostly metallic platinum (state of oxidation: 0). The allergic reactivity of this has not yet been demonstrated, while ionic complexes, which contain associated allergens do produce an allergic reaction (3). Therefore, although the classification of the subjects with high, low and no exposure might have methodological problems, the study demonstrates a zero prevalence amongst the office staff and an increased prevalence in the category of high compared with low exposure with a prevalence odds ratio equal to 2.4 (95% CI: 0.8–6.9).

Some reports (13) in the literature indicate that atopic status may be a risk factor for platinum salts allergy. Other authors (9–10) have pointed out the fact that there is no risk of sensitivity in atopic subjects. Our study shows a slight increase in the prevalence of platinum salts sensitivity in atopic subjects [prevalence odds ratios of 2.2 (95% CI: 0.8–6.0)], although the nature of the experi-

mental design does not allow us to establish the causal nature of the relationship. Although smoking does not seem to be a high risk factor (also confirmed by multivariate analysis), it would seem to be a modifier of effects compared with length of time on the job. In fact, the prevalence odds ratio of current smokers is 0.3 (95% CI: 0.01–2.1) in subjects on the job less than 5 years and it is 2.8 (95% CI: 0.7–10.7) in subjects working there more than 5 years. The increase in prevalence observed compared with the classification of time on the job can be explained by the type of study undertaken. The results are compatible with a model of constant incidence.

Descriptive analysis demonstrates that asthma and urticaria are more frequent in subjects allergic to Pt-salts, while rhinitis and dermatitis commonly belong to allergies of common inhalants as well as allergies to Pt-salts. Moreover, as all subjects with asthma and five of six with urticaria reported symptoms in the workplace, asthma and urticaria may be considered work-related symptoms (17, 18). Only two subjects with contact dermatitis of the hands were found positive to the platinum salts patch test. True allergic contact dermatitis from chlorinate Pt compounds is rarely reported in the literature (19), and

this fact is partly in contrast with the sensitizing potency of Pt-salts observed by Schupple et al. in animal models. Although we have not patch tested the two positive subjects at lower concentrations, the allergic nature of the reactions cannot be excluded. In both cases, the symptoms worsened only at the workplace and negative reactions were found in many controls. Skin prick tests, with freshly prepared solutions of soluble platinum salts, are considered highly specific biological monitors of Pt-group allergenicity. At concentrations varying from 10^{-2} to 10^{-8} M, the tested compounds are capable of producing immediate wheal and flare reactions in sensitized subjects (20).

In conclusion, the results of this study show that Pt-salts are important allergens in the catalyst industry and that the clinical manifestations involve both the respiratory system (particularly asthma) and the skin (urticaria). The sensitivity is associated with the degree of exposure; $H_2[PtCl_6]$ may be considered the most important salt to use for skin test. The prevalence of positive reactions to prick tests for other Pt-group elements (Pd, Ir, Rh) is very low and these are only positive in individuals sensitive to Pt-salts.

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