

Case Report

Occupational Immediate-Type Asthma and Rhinitis Due To Rhodium Salts

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Background Whereas platinum salts are well known occupational allergens, rhodium salts have not been identified as inhalative sensitizing substances.

Methods A 27-year-old atopic operator of an electroplating plant developed work-related shortness of breath and runny nose with sneezing after exposure to rhodium salts. Quantitative skin prick tests (SPT) and bronchial challenge tests with a dosimeter protocol were performed with quadrupling doses of the sodium chloride salts of rhodium (Na_3RhCl_6) and platinum (Na_2PtCl_6).

Results The patient showed positive SPT reactions and positive bronchial immediate-type reactions with rhodium and platinum salts. Sensitivity to rhodium salt was much higher than to platinum salt; the molar concentrations differed by a factor of 256 in SPT and a factor of 16 in bronchial challenges.

Conclusions Rhodium salts should be considered as occupational immediate-type allergens. Am. J. Ind. Med. 2009. © 2009 Wiley-Liss, Inc.

KEY WORDS: occupational; rhodium; asthma; allergy

INTRODUCTION

Precious metals include copper, gold, iridium, mercury, osmium, palladium, platinum, rhenium, rhodium, ruthenium, and silver. Allergic occupational asthma due to precious metals is a rare disease, with the exception of platinum salt asthma, which belongs to the most prominent causes of occupational asthma with high numbers of cases in a small number of plants [Bernstein and Merget, 2006]. Platinum salt allergy occurs in precious metals refineries [Bernstein and

Merget, 2006] and catalyst productions [Merget et al., 2000], both with exposures to various precious metals. In most cases the diagnosis is made by work-related symptoms and a positive skin prick test (SPT) with platinum salt, which is highly specific. Bronchial challenges may be performed by mixing platinum salt powder with lactose [Pepys et al., 1972] or by direct inhalation of the platinum salt solution by a nebulizer [Merget et al., 1991].

Platinum belongs to the third series of transitional metals. Iridium is a further precious metal of this series, but there is only one case report about iridium-induced allergic occupational asthma [Bergman et al., 1995]. The diagnosis of iridium salt allergy was made in a worker exposed to iridium chloride in an electrochemical factory manufacturing titanium anodes. A SPT with iridium chloride showed a positive reaction at a concentration of 5×10^{-4} g iridium (as metal)/ml, and scratch tests with an iridium chloride solution of 5.8×10^{-4} g iridium (as metal)/ml and iridium salt-containing solutions from the workplace produced systemic allergic reactions.

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The second series of transitional metals includes palladium, rhodium, and ruthenium. It is known that refinery and catalyst production workers with platinum salt allergy show positive SPT also with the salts of these metals [Murdoch et al., 1986; Murdoch and Pepys, 1987; Cristaudo et al., 2005]. As these subjects were exposed primarily to platinum salts, SPT reactions to salts of palladium, rhodium, and ruthenium are interpreted as cross-reactivity [Bernstein and Merget, 2006]. There is only one case report about occupational allergic asthma due to palladium salt that was related to fumes of an electrolysis bath containing palladium chloride. This worker exhibited an isolated positive SPT to tetramminepalladium(II)chloride (1 µg/ml) as well as a positive bronchial provocation test to this salt administered as an aerosol (10 µg/ml) for a period of 3.5 min [Daenen et al., 1999]. To our knowledge, direct evidence of allergic asthma due to rhodium and ruthenium salt is not available.

MATERIALS AND METHODS

Case Report

The 27-year-old male patient reported hay fever during adolescence, but was without allergic symptoms during recent years. Otherwise he was without prior illness and he had never smoked cigarettes. He started to work as an operator in an electroplating plant in 1997, but he had rarely contact to metals until 2002 when he had to prepare the electrolysis baths containing rhodium salts (sulphates, phosphates, chlorides, and others), but also gold salts. While exposure to rhodium salts occurred daily, contact to platinum salts was less frequent, about once a month. He developed work-related shortness of breath and runny nose with sneezing about 3 years afterwards. Symptoms developed occasionally, but not always after contact to rhodium salts (which were heated to about 40°C), but never when handling platinum salts (which were used at room temperature). A medical evaluation in January 2007 yielded a positive immediate-type bronchial reaction when he inhaled heated rhodium sulphate which he had taken from his workplace during an occupational-type challenge. The exact concentration of this rhodium sulphate solution was not described in the report, but a fall of forced expiratory volume in 1 s (FEV₁) of 66% from baseline was documented. Chest X-ray and routine laboratory tests including differential blood count were normal. He was transferred to another department for medical reasons by the end of 2007, but he continued to complain of occasional shortness of breath and runny nose after handling rhodium salts about once a week in spite of extractor hood and respiratory protective device. There was no increased susceptibility to airway irritants, which occurred as well at his workplace.

The patient was referred for a medical opinion by the accident insurance in May 2008. He was without medication and without symptoms during the previous days. The patient gave written informed consent for the tests and publication of his case in the medical literature.

Medical Evaluation

After physical examination, bodyplethysmography, and spirometry were performed (Master Screen Body, Cardinal Health). ECSC reference values were used [Quanjer et al., 1993]. Methacholine testing was done with a reservoir method as described earlier on days 1 (baseline) and 4 (after testing with metals) [Baur et al., 1998]. Briefly, five doubling doses of methacholine with a starting dose of 15 µg are inhaled from a reservoir, yielding a total cumulative dose of about 465 µg. A positive reaction with the test is assumed with a PD₂₀FEV₁ < 300 µg. SPT was performed with a battery of environmental allergens (ALK-Abelló, Wedel, Germany). Total IgE and specific IgE antibodies in the patient's serum were measured with ImmunoCAP 250 (Phadia, Freiburg, Germany). To prepare protein-metal conjugates, biotinylated human serum albumin (HSA) was incubated for 4 hr at 40°C with a 50-fold molar excess of Na₃RhCl₆ or Na₂PtCl₆. Free metal salts were discarded by gel filtration on PD-10 columns (GE Healthcare, Munich, Germany), the eluted HSA/metals were bound to Streptavidin ImmunoCAP (Phadia), and subsequently, IgE binding was measured.

Skin Prick Tests (SPT) With Metal Salts

Metal salt solutions were prepared by Degussa (Hanau, Germany). The sodium chloride salts of platinum (Na₂PtCl₆), rhodium (Na₃RhCl₆), palladium (Na₂PdCl₄), iridium (Na₃IrCl₆), and gold (NaAuCl₄) were provided as 22 mmol/L solutions. The stock solutions were stored for about 4 weeks and diluted 10-fold with phosphate-buffered saline (PBS) to 2.2 mmol/L at the day before platinum salt challenge. To exclude impurities, the 2.2 mmol/L rhodium and platinum solutions were analyzed for their precious metal content (Rh, Pt, Pd, Ru, Ir, and Au) by inductively coupled plasma optical emission spectrometry (ICP-OES; analyses were done by Umicore, Hanau, Germany). No impurities were found: 440 mg/L platinum or 220 mg/L rhodium were measured in the respective solution; all other metals were below 0.2 mg/L. All 2.2 mmol/L metal salt solutions were used for SPT on the volar part of both forearms in duplicate, as was histamine 10 mg/ml and PBS (positive and negative control). Wheal reactions were measured after 20 min. For those metals with a wheal diameter >0 mm the dose-response curve was recorded in quadrupling dilutions down to 0.13 µmol/L (seven dilution steps).

Bronchial Challenges With Metal Salts

Bronchial challenges were performed with the same rhodium and platinum salt dilutions as for SPT, but, for security, the lowest concentrations were 0.13 nmol/L (i.e., 1,000-fold lower than for SPT). Inhalations were performed with an APSpro dosimeter (Cardinal Health) and a DeVilbiss 646 nebulizer (DeVilbiss, Malsch, Germany), filled with 2 ml of the solutions, on two consecutive days, starting with the platinum salt. The nebulizer output of about 900 μ l/min was measured by weighing, and the inhalation procedure was closely adapted to recent recommendations [American Thoracic Society, 2000], with two minor modifications: firstly, the nebulizer was actuated 0.5 s after the start of inspiration to ensure a significant airflow upon nebulization; secondly, we omitted breathhold after inhalation. Each solution was given in five consecutive slow inspirations from functional residual to near total lung capacity, while the nebulizer was actuated over 0.6 s. Inspiratory airflow was kept close to 1 L/s by observation of a visual scale. PBS was inhaled as a negative control. The lowest metal salt dose was 0.0000059 nmol.

Bodyplethysmography and spirometry were performed, and specific airway resistance (sRt) and FEV₁ were recorded about 10 min after each inhalation step, yielding time intervals between consecutive steps of about 12 and 13 min. The end-of-test (positivity) criterion was a $\geq 20\%$ fall in FEV₁. Doubling of sRt was the positivity criterion of bodyplethysmography. Follow-up measurements were performed 10 min, 1, 2, 4, and about 24 hr afterwards. The patient's spirometric maneuvers were considered excellent, and all measurements met the American Thoracic Society's acceptability and reproducibility criteria [American Thoracic Society, 1995]. A second methacholine testing was performed about 24 hr after the challenge with rhodium salt.

RESULTS

Physical examination was normal. Cutaneous sensitizations to *Dermatophagoides pteronyssinus* (6 mm wheal diameter) and *Dermatophagoides farinae* (4 mm) and grass pollen mixture (4 mm) were measured. Total IgE was 126 kU/L (slightly elevated). Cutaneous sensitizations were corroborated by CAP results (CAP class 4 to house dust mites [d1 and d2], class 2 to grass pollen mixture [gx1]). The patient's IgE did not bind to platinum or rhodium Streptavidin-HSA-ImmunoCAPs. Lung function was normal (FEV₁ 109% predicted), but bronchial hyperresponsiveness to methacholine was measured (PD₂₀FEV₁ 161 μ g).

Histamine gave a wheal diameter of 4 mm, and PBS was negative, as were SPT with palladium, iridium, and gold salts, but positive reactions were observed with rhodium and platinum salts. The platinum salt yielded mean wheal sizes of 3 and 4 mm with the two highest concentrations, 0.55 mmol/

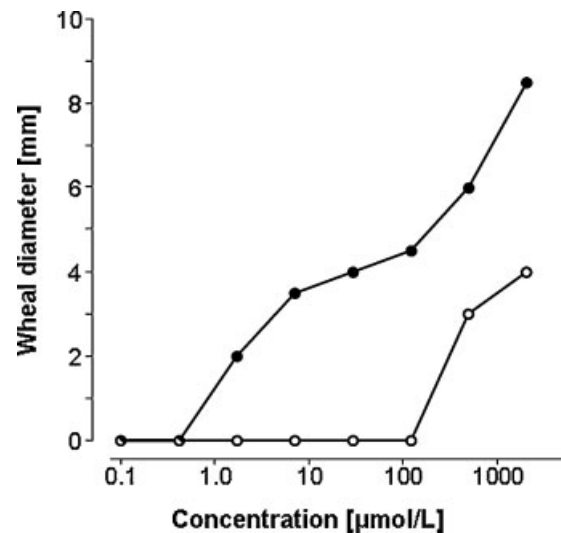


FIGURE 1. Wheal diameters of SPT with Na₂PtCl₆ (open dots) and Na₃RhCl₆ (filled dots). Values represent arithmetic means of the tests performed in duplicate. The concentration range was 0.1 μ mol/L to 2.2 mmol/L.

L (107 mg metal/L) and 2.2 mmol/L (429 mg metal/L). With the rhodium salt a shift of the (almost linear) dose-response curve about 256-fold to lower concentrations (with the lowest concentration causing a wheal >0 of 2.1 μ mol/L (216 μ g metal/L) and a mean wheal size of 8.5 mm with the highest concentration of 2.2 mmol/L (226 mg metal/L) was obtained (Fig. 1).

Immediate-type asthmatic reactions were documented with Na₂PtCl₆ and Na₃RhCl₆ (Fig. 2). Both effect parameters (sRt and FEV₁) fulfilled the positivity criteria. In the case of platinum salt, the concentration causing a positive reaction was 34.4 μ mol/L (6.7 mg metal/L, that is, a dose of 1.55 nmol or 293 ng metal), for rhodium salt the reactive concentration was 2.1 μ mol/L (216 μ g metal/L, i.e., a dose of 0.097 nmol or 10 ng metal). Thus, bronchial sensitivity to rhodium salt was about 16-fold higher than to the platinum salt. Methacholine testing 24 hr after the challenge with rhodium salt (i.e., after both specific tests) gave a PD₂₀FEV₁ of 73 μ g (i.e., a decrease of one step).

DISCUSSION

The diagnosis of rhodium salt allergy was based on typical work-related symptoms of asthma and rhinitis, and both positive SPT and bronchial challenge with rhodium chloride. Specificity of SPT with rhodium salts has been demonstrated by others [Murdoch et al., 1986; Murdoch and Pepys, 1987; Santucci et al., 2000; Cristaudo et al., 2005]. Thus, we did not test non-exposed subjects for control. Also we did not perform challenge tests with rhodium salts in controls for ethical reasons and in view of the very low dose of rhodium salt for a positive bronchial reaction in the patient,

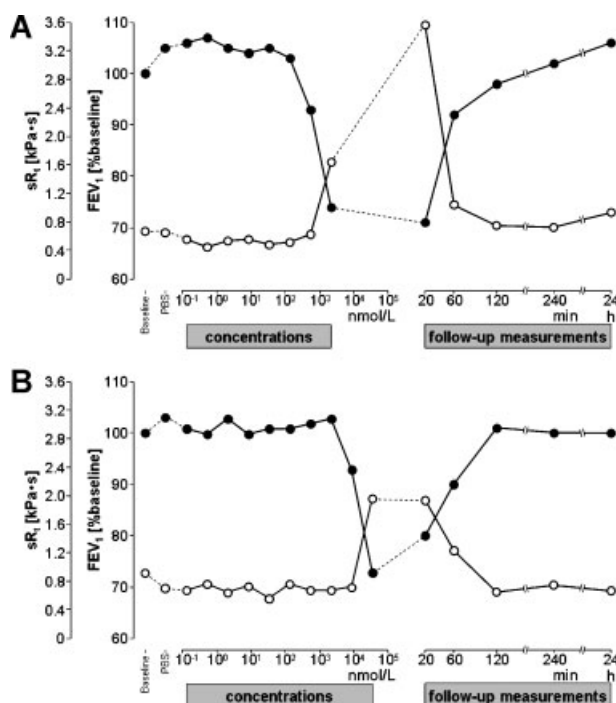


FIGURE 2. Time course of bronchial challenges with Na₃RhCl₆ (A) and Na₂PtCl₆ (B). Inhalations started with a concentration of 0.13 nmol/L (a dose of 0.0000059 nmol) with both metal salts. For platinum salt the highest concentration was 34.4 μ mol/L or 6.7 mg metal/L (a dose of 1.55 nmol or 293 ng metal), for rhodium salt the highest concentration was 2.1 μ mol/L or 216 μ g metal/L (a dose of 0.097 nmol or 10 ng metal). Open dots: specific airway resistance (sR_i); filled dots: forced expiratory volume in 1 s (FEV₁). Measurements were done 10 min after each inhalation. PBS, phosphate-buffered saline.

which makes an irritant reaction highly unlikely. The increase in bronchial hyperresponsiveness after testing with metals argues for an immunologic mechanism. We have shown earlier that bronchial challenges with platinum salts in subjects without occupational exposure to metal salts are highly specific even at much higher doses [Merget et al., 1991]. The patient's reactivity to rhodium salt in SPT as well as in the challenge was in the same range as reactivity to platinum salts in refinery workers [Merget et al., 1991].

Interestingly, SPT and bronchial challenge became positive with the same rhodium salt concentrations. Retrospectively, the starting dose for the bronchial challenge was chosen too low, but quadrupling doses were appropriate, as no severe bronchial reactions were observed.

As rhodium salts are known to produce positive SPT in platinum salt allergic workers of precious metals refineries [Murdoch et al., 1986; Murdoch and Pepys, 1987; Nakayama and Ichikawa, 1997] and catalyst productions [Cristaudo et al., 2005], rhodium salt sensitization might be interpreted as cross-reactivity in a primarily platinum salt-sensitized subject. This is not likely in the present case. Firstly, the patient was an electroplater, and rhodium salt exposure

occurred with much higher frequency than platinum salt exposure. The opposite is true for refinery and catalyst production workers, where platinum salt exposure is dominant. Secondly, symptoms were not related to platinum salts, but to rhodium salts. Thirdly, the patient was much more sensitive both in SPT and challenge to rhodium salt than to platinum salt. Relevant contamination of the test solutions can be excluded by the analytic determination of metals in the test solutions. Reactions to platinum salt may be interpreted as cross-reactivity or cosensitization; a further distinction is not possible as the patient was exposed to both metals. We were unable to detect specific IgE antibodies to rhodium salt. This does not exclude IgE-mediated disease as it is well known for platinum salts that specific IgE antibody testing is less sensitive than SPT and is not useful in the clinical diagnosis of platinum hypersensitivity [Bernstein and Merget, 2006].

The patient developed symptoms after contact to different rhodium salts. We performed tests only with rhodium chloride, but probably other salts would have given similar results, as known for platinum salts [Cleare et al., 1976]. This assumption is supported by the patient's self-reported susceptibility to different rhodium salts and the previous positive challenge test with rhodium sulphate. Quantitative exposure assessment at the workplace was not available in the present case. In view of the low frequency of work-related symptoms, we did not insist to have air measurements done. According to the patient's statements protective measures had been implemented to a high degree at his last workplace. As occasional symptoms persisted and bronchial hyperresponsiveness was documented, we recommended complete exposure cessation to rhodium and platinum salts.

Occupational allergic contact dermatitis has been described in subjects working in the jewelry trade [Bedello et al., 1987; De la Cuadra and Grau-Massanés, 1991; De la Fuente et al., 2003], but there are no cases with immediate-type allergic asthma due to rhodium salts in the literature. The impact of rhodium salt sensitization in workers of precious metals refineries remains unknown, but it is likely that platinum salts are the primary allergen in these settings. We performed a database research in Germany (BK-Dok; M. Butz), Finland (Register on Occupational Diseases; H. Nordman), and UK (SWORD and OPRA; THOR research team), which provided two cases of rhodium salt asthma in SWORD from 1989 to 2008, both from precious metals refineries. It is not known whether these cases were also sensitized to platinum salts. Thus, the present case is the first case of rhodium salt asthma in the literature with demonstration that it is not caused by cross-reactive platinum salts.

To our knowledge, asthma due to precious metals has been described only as a work-related disease. Platinum, palladium, and rhodium are the most important metals that are emitted from catalytic converters, but there are no cases

of environmental asthma due to these metal salts. This may be explained by qualitative and quantitative differences between workplaces and environment [Merget and Rosner, 2001].

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