

Chapter 6

Occupational Immediate-Type Allergic Asthma due to Potassium Tetrachloroplatinate in Production of Cytotoxic Drugs

E. Thanasias, I. Polychronakis, V. van Kampen, T. Brüning, and R. Merget

Abstract Allergic immediate-type reactions by halogenated compounds of platinum (Pt) (platinum salts) have been described in workers in precious metal refineries and catalyst productions. In both industries there are exposures to many different Pt compounds. It is believed that the most important allergens are those compounds with the highest number of halide ligands. It is unknown whether sensitizations to compounds with a lower number of halide ligands represent co-sensitizations or are due to cross-reactivity. We report a worker engaged in the production of cytotoxic drugs with occupational asthma and exposure to only one Pt salt with four halide ligands. The 22-year-old worker developed work-related sneezing, runny nose, and variable dyspnea about a year after he had started to work in the cytotoxic drugs production with exposure to potassium tetrachloroplatinate(II) (K_2PtCl_4). He was immediately removed from his workplace and admitted for a medical opinion about 6 months afterwards. Spirometry was normal, but asthma was corroborated by a positive response to methacholine. The results of skin prick testing could not be interpreted due to urticaria factitia. Challenge with K_2PtCl_4 by a dosimeter method yielded a clear immediate-type reaction with an increase of exhaled nitric oxide from 32 to 156 ppb after 24 h indicating an increased airway inflammation. Pt salts with four halide ligands like K_2PtCl_4 may cause an allergic immediate-type reaction and occupational asthma. Workers in the production of Pt-containing cytotoxic drugs with exposure to these substances should be included in medical surveillance programs for the prevention of occupational asthma caused by Pt salts.

Keywords Bronchial challenge • Immediate reaction • Occupational asthma • Platinum salts • Potassium tetrachloroplatinate(II)

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6.1 Introduction

Due to its outstanding catalytic properties platinum (Pt) and its halogenated compounds have an extensive use in a variety of industries. The first case reports on asthma due to Pt salts in humans were published at 1911 in a small number of photographers (Karasek and Karasek 1911). However, allergic occupational asthma by halogenated compounds of Pt (Pt salts) have been described in recent years only in workers of precious metal refineries and catalyst productions. In both industries there are exposures to many different Pt compounds. Longitudinal cohort studies in a large number of exposed subjects reported high incidences in both industries (Calverley et al. 1995; Merget et al. 2000; Venables et al. 1989) and it has been suggested that the cumulative incidence of sensitization after 5 years may be higher than 50% (Linnett and Hughes 1999). In addition, Pt salts were the third most frequent cause of occupational asthma and represented 12% of all occupational asthma cases in the South Africa (Hnizdo et al. 2001). Cisplatin (cis-stereoisomer of diammonium chloroplatinate or cis-DDP) and carboplatin (cis-diammine (1,1-cyclobutanedicarboxylate) platinum(II)) (Fig. 6.1) are Pt complexes which react *in vivo*, binding to and causing crosslinking of DNA, which ultimately triggers programmed cell death (apoptosis) (Wheate et al. 2010). Halogenated Pt compounds are used in the production of these anti-cancer drugs (Keller and Moeller 1963).

Whereas hypersensitivity reactions to carboplatin and cisplatin are well known in patients after several courses of anticancer treatment (Kawaoka et al. 2010; Syrigou et al. 2010) occupational allergic diseases after exposure due to these cytotoxic drugs are limited to a case of a nurse with contact urticaria (Scheda et al. 1996).

It is believed that the most important allergens are those compounds with the highest number of halide ligands (Cleare et al. 1976). As exposure to halogenated Pt compounds in refineries and catalyst productions is complex and comprises Pt compounds with varying numbers of halide ligands, it is unknown whether positive skin prick test reactions with, e.g., tetrachloroplatinates in workers with allergic symptoms are due to cross or co-sensitizations (Cristaudo et al. 2005).

6.2 Case Report

A 22-year-old subject suffered from asthma and rhinoconjunctivitis due to animal danders (hair of cats, dogs and rabbits) since his childhood and he was a non-smoker. In the family of the patient neither allergic nor respiratory diseases were known. About a year after he had started to work in the

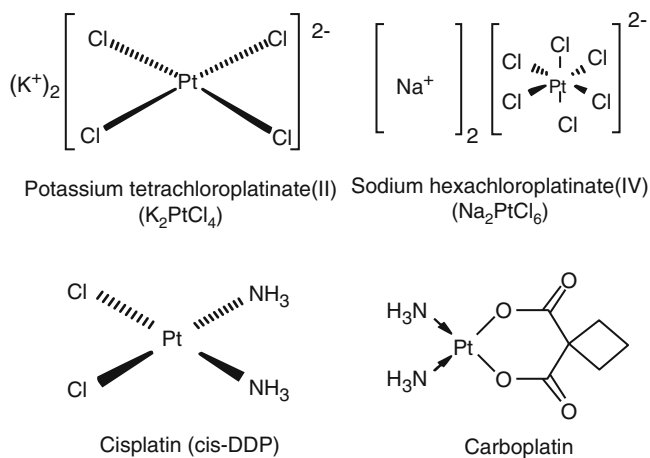


Fig. 6.1 Molecular structures of K_2PtCl_4 (MW=415.09 g/mol), Na_2PtCl_6 (MW=453.77 g/mol), cisplatin (cis-stereoisomer of diammonium chloroplatinate or cis-DDP), carboplatin (cis-diammine (1,1-cyclobutanedicarboxylate) platinum(II))

cytotoxic drugs production in 11/2007 he developed work-related sneezing, runny nose and variable dyspnea and was immediately removed from his workplace. His symptoms occurred only at the workplace and were relieved during weekends and holidays, while they did not change substantially over the different seasons of the year. He was exposed to K_2PtCl_4 which is used in the production of cisplatin, but not to further halogenated Pt salts. The patient was admitted to our institute for a medical opinion about 6 months afterwards. He gave written consent for the investigations and publication of his case.

6.3 Methods

The study was performed in conformity with the Declaration of Helsinki of the World Medical Association and was approved by a local Ethics Committee.

6.3.1 General Diagnostic Tests

After a detailed medical and occupational history was taken, the patient underwent a comprehensive diagnostic examination including basic blood chemistry tests, complete and differential blood count, serum protein electrophoresis, semi-quantitative urine examination, total IgE and antigen-specific antibodies to environmental allergens in serum (ImmunoCAP, Phadia, Freiburg, Germany), electrocardiogram (ECG), chest X-rays, spirometry (reference values according to Quanjer et al. 1993) and body plethysmography. Exercise testing was carried out on a cycle ergometer in a semi-sitting position using a Masterlab system (Jäger, Würzburg, Germany). Capillary blood gases were determined from the hyperemic earlobe. Skin prick testing (SPT) was performed with 13 common environmental allergens. Bronchial hyperresponsiveness was evaluated with a 4-step reservoir method. Briefly, the patient inhaled doubling doses with a starting dose of about 30 μ g methacholine, using a 3.3 mg/100 mL freshly prepared solution aerosolized by Provotest II (Pari, Starnberg) (Baur et al. 1998).

6.3.2 Specific Diagnostic Tests

Specific testing was performed with K_2PtCl_4 (SPT and inhalation challenge) and sodium hexachloroplatinate (IV) (Na_2PtCl_6 , SPT) (Fig. 6.1). Both substances were provided by Heraeus (Hanau, Germany). SPT with both substances were done with concentrations up to 100 mg/mL. Tests were performed on the volar side of the patient's forearm and the skin reaction was evaluated after 15 min. Histamine 10 mg/mL and saline were used as positive and negative controls, respectively.

The inhalation challenge was performed with a 646-DeVilbiss nebulizer and an APSpro dosimeter (Jäger, Würzburg, Germany) with a freshly prepared K_2PtCl_4 solution (diluted in phosphate buffer (PBS) from a 10 g/L stock solution) in quadrupling doses from 2.7 pg to 2.8 μ g (11 steps). A 10 min pause was made between steps. PBS was used as placebo. The response was evaluated by spirometry, body plethysmography, blood gas analysis, serial methacholine testing and exhaled nitric oxide (eNO, NIOXFlex, Aerocrine, Bad Homburg, Germany). As end-of-test criterion we used a 20% fall of the forced expiratory volume in 1 s (FEV_1) and a doubling of specific airway resistance (sRt) to >2 kPa/s. Follow-up measurements were performed on the same day up to 2 h afterwards and again on the next morning.

6.4 Results

The general medical examination showed no pathological findings, but total IgE was 757 kU/L. Increased specific IgE antibodies to dogs and rabbits (CAP class 3) and cats (CAP class 5) were measured. FEV₁ was 107% predicted, but asthma was corroborated by a positive response to methacholine after inhalation of a cumulative dose of 92 µg (PD₂₀FEV₁: 78 µg). The results of SPT to environmental allergens and both Pt salts could not be interpreted due to urticaria factitia.

After inhalation of a cumulative dose of 3.75 µg K₂PtCl₄, the patient reported shortness of breath; there was a significant maximal fall of FEV₁ of 38% from baseline (Fig. 6.2) and a maximal increase of sR_t from 0.58 to 5.1 kPa/s (Fig. 6.3). There was a fall of oxygen partial pressure from 73 to 56 mmHg (after 20 min) and an increase of eNO from 32 to 156 ppb (after 24 h Fig. 6.4). Serial methacholine testing on the day after the specific challenge with K₂PtCl₄ did not show higher bronchial hyperresponsiveness (PD₂₀FEV₁: 49 µg) than before the challenge with K₂PtCl₄.

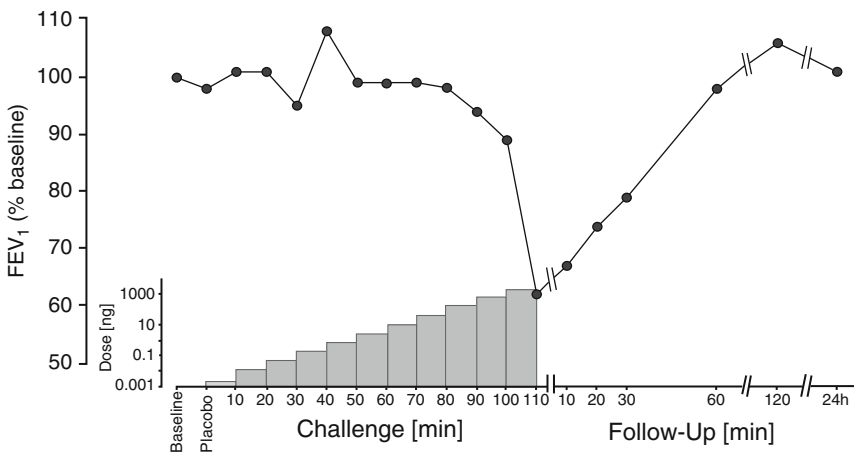


Fig. 6.2 Time-response curve of forced expired volume in 1 s (FEV₁) for specific inhalant challenge with K₂PtCl₄

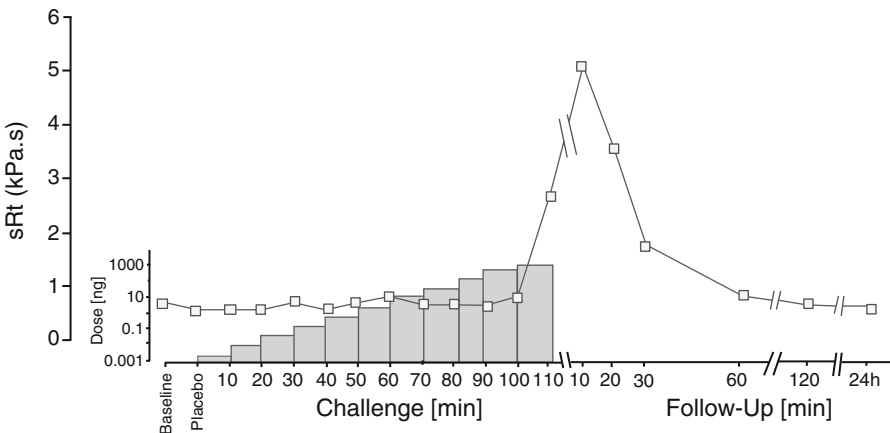
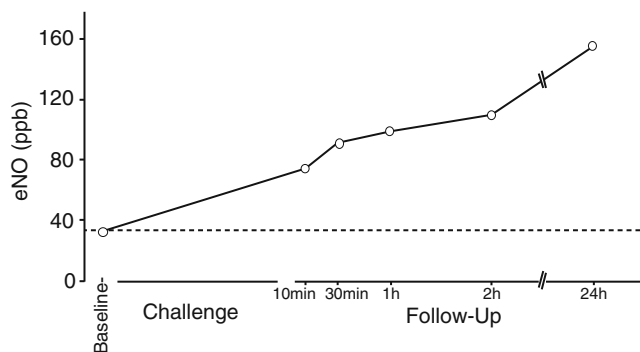


Fig. 6.3 Time-response curve of specific airway resistance (sR_t) for specific inhalation challenge with K₂PtCl₄

Fig. 6.4 Time-response curve of exhaled nitric oxide (eNO) for specific inhalation challenge with K_2PtCl_4



6.5 Discussion

In the present case, a diagnosis of allergic occupational asthma was made by typical work-related symptoms and an immediate-type reaction after inhalation challenge with K_2PtCl_4 . Although no specific challenge testing was performed for rhinitis, the subject's symptoms suggest also occupational allergic rhinitis which is generally associated with asthma in subjects with Pt salt sensitization (Merget et al. 2000). Sensitizations to various animals were documented by *in vitro*-testing, compatible with a history of allergy to animal dander since childhood. SPT to environmental as well as to Pt salts could not be interpreted due to urticaria factitia.

The increase in eNO after challenge testing with K_2PtCl_4 indicates an increased airway inflammation (Lim and Mottram 2008; Quirce et al. 2010), suggesting an immunologic mechanism that could not be substantiated by the demonstration of sensitization in this case. *In vitro* demonstration of sensitization to halogenated Pt compounds is of limited value for an individual diagnosis (WHO 1991) and has not been attempted in the present case. Pt salt allergy seems to be IgE-mediated because there is a clear SPT reactivity and total IgE increased during the sensitization period, as shown in longitudinal studies (Merget et al. 2001). However, atopy seems not to be associated with Pt salt allergy (Calverley et al. 1995; Merget et al. 2000).

This is the first case report of a pharmaceutical plant worker with an exclusive exposure to K_2PtCl_4 . This proves that Pt salts with four halide ligands like K_2PtCl_4 may cause an allergic immediate-type reaction and occupational asthma. In precious metals refineries and catalyst productions workers are exposed to Pt compounds with six halide ligands and it remains unknown whether sensitizations to compounds with a lower number of halide ligands represent co-sensitizations or are due to cross-reactivity. The present case clearly demonstrates that Pt salts with four halide ligands may be hazardous.

There is evidence of hypersensitivity reactions to Pt-containing cytotoxic agents like cisplatin and carboplatin in patients treated with these agents, but occupational allergy to these substances seems extremely rare and has not been described in the production of these substances. In the present case we did not perform skin testing with these substances due to their cytotoxic effects and urticaria factitia in the patient which did not allow interpretation of skin testing results.

The prevalence and incidence of sensitization and allergic reactions resulting from Pt salt exposure remain high in spite of rather low exposure degrees both in precious metals refineries and catalyst productions (Bolm-Audorff et al. 1992; Merget et al. 1988, 2000). In the present case, no exposure data were made available by the company, and no further assessment was possible.

It has been shown that medical surveillance is effective in workers of a catalyst production with exposure to Pt compounds if subjects with symptoms are immediately transferred to areas without contact to Pt salts (Merget et al. 2001). The present case was transferred a few days after

he developed work-related symptoms by his plant physician and became free of symptoms afterwards. Persisting bronchial hyperresponsiveness was attributed to his preexisting allergy to animal dander. Workers in the production of Pt-containing cytotoxic drugs with exposure to these substances should be included in medical surveillance programs for the prevention of occupational asthma caused by Pt salts.

Conflicts of Interest: The authors declare no conflicts of interest in relation to this article.

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