

SHORT REPORT

Absence of platinum salt sensitivity in autocatalyst workers exposed to tetraamine platinum dichloride

D. P. Steinfors, J. Pilmore, S. Brenton and D. H. L. Hart

Background	Platinum salt sensitivity (PSS) is well recognized following occupational exposure to platinum salts, though specific platinum compounds have been suggested to be non-allergenic. We report on a cohort of autocatalyst workers exposed to tetraamine platinum dichloride (TPC) and other platinum-group elements.
Methods	All subjects employed at an autocatalyst production plant undertook medical surveillance with symptoms, examination findings and results of skin prick testing and spirometry prospectively recorded. Environmental testing of the workplace was also performed to determine the level of exposure.
Results	Twenty-six subjects had a mean duration of employment of 46 (± 30) months and undertook a mean 6.8 (± 4.3) examinations. No subjects described the development of new respiratory or dermatological symptoms. No patients developed positive skin reactivity to platinum salts. FEV ₁ remained unchanged for all subjects over the course of the study period.
Conclusions	TPC and platinum-group elements are not associated with the development of PSS or occupational asthma. Identification of chemical compounds is important when advising on occupational health screening. TPC and/or platinum-group elements should be used in preference to chloroplatinic acid in catalyst production to minimize the impact of occupational illness due to PSS.
Key words	Hexachloroplatinate; occupational asthma; platinum salt sensitivity; tetraamine platinum dichloride.

Introduction

Occupational asthma as a result of exposure to inhaled platinum salts is well recognized [1]. Studies have demonstrated a positive association between exposure and sensitization and subsequent development of symptoms involving the eye, skin or respiratory system. Greater intensity of exposure produces a higher rate of sensitization [2].

Incidence of platinum allergy in chemical process workers has been reported at up to 6.8 cases per 100 person-months [3] (cphpm) and the cumulative incidence of sensitization after 5 years has been noted at >50% in some studies [3,4]. Recommendations regarding maximum exposure limits have therefore been made

in an attempt to minimize adverse health outcomes in workers exposed to platinum salts [5].

However, a single observational study has demonstrated the importance of chemical speciation, with the soluble platinum compound tetraamine platinum dichloride (TPC) noted to be non-allergenic in normal industrial conditions [3].

We present findings supporting this concept, with no detected cases of platinum salt sensitivity (PSS) among a cohort of factory workers exposed to TPC for prolonged periods despite exposure to higher levels of TPC than have previously been reported.

Methods

A medical surveillance programme was established at a catalyst manufacture plant in Melbourne, Australia. Participation in the surveillance programme was an occupational health and safety condition of employment. All

Department of Respiratory Medicine, St Vincent's Hospital, Victoria 3065, Australia.

Correspondence to: D. P. Steinfors, Department of Respiratory Medicine, St Vincent's Hospital, Victoria 3065, Australia. Tel: +61 416 275 750; fax: +61 3 9288 3138; e-mail: dsteinfors@yahoo.com

employees at 1 July 1999 were included in the study. Those subsequently employed between 1 July 1999 and 31 December 2005 were prospectively enrolled at the commencement of employment. Subjects were informed at enrollment that deidentified data may be used for audit purposes. All workers were examined in the respiratory department of our hospital.

Catalyst production utilized TPC ($[\text{NH}_3]_4\text{PtCl}_2$) as well as the platinum-group elements palladium and rhodium. At the commencement of the study, air sampling throughout the factory was undertaken. Subsequent exposure surveillance measurements were performed by surface exposure recordings.

Initial examination was performed at the commencement of the trial period or for those employed subsequent to 1 July 1999, within 3 months of commencement of employment. Subsequent reviews were performed at 6 monthly intervals. Personal data, including history of smoking or atopy, and symptomatology were noted. Duration of employment was also noted.

At each review, all subjects underwent clinical review, as well as respiratory function testing and skin prick testing (SPT). The primary aim was to document what proportion of individual subjects experienced a significant decrease in FEV_1 that would indicate a possible development of PSS following exposure to TPC. The study was not designed to identify magnitude of change in FEV_1 and was powered only to detect a change of 10% in FEV_1 ($\beta = 0.8$ and $\alpha = 0.05$).

Respiratory function examination included spirometric studies and gas transfer studies performed using Sennormedics Vmax 22 PFT system (Viasys Healthcare, Conshohocken, PA, USA). Bronchial hyperresponsiveness was determined by methacholine challenge at each visit. Subjects previously demonstrating hyperresponsiveness to methacholine were subsequently examined for bronchodilator responsiveness using nebulized salbutamol 5 mg.

SPT was performed using hexachloroplatinic acid at a concentration of 1.471 g/kg, as well as histamine and a saline control. A wheal of 3 mm or greater was considered positive. Hexachloroplatinic acid has previously been used to demonstrate development of skin reactivity to platinum salts [2–4,6] and the dose chosen was in excess of that used to confirm PSS in previous cohorts [7,8]. To confirm accurate dosing of SPT, chemical analysis of hexachloroplatinic acid solution was performed on a single occasion in 2006.

Results

One hundred and twelve subjects were employed at the plant and underwent health screening as described. Seventy-one subjects were found to be exposed to TPC concentrations <10% of the recommended maximum exposure limit [5]. Air concentration of TPC in high-

exposure areas, performed over three separate days, was recorded to be between 10 and 20 $\mu\text{g}/\text{m}^3$. Subsequent surface testing for platinum demonstrated consistent exposure levels over the period examined. Forty-one subjects in high-exposure areas were identified. Fifteen of these left employment before a second examination was performed. The remaining 26 subjects, with a sum exposure of 1196 person-months, form the basis of our report.

Mean duration of employment was 46 months ($\text{SD} \pm 30$). Mean number of examinations was 6.8 (± 4.3). Eighteen subjects had been employed for >24 months. This group had been exposed for a mean of 59.7 (± 26.2) months (1075 person-months) and underwent examination on 8.4 (± 4.2) occasions. Nine of 26 subjects (35%) left employment during the study period. The reasons for leaving were not recorded.

Chemical analysis of chloroplatinate solution used for SPT confirmed a concentration of 1.471 g/kg. No patients were noted to have positive SPT to platinum salts at their initial examination. During the study period, no patients demonstrated positive skin reactivity to platinum salts. Two patients demonstrated dermographism, with 4 and 6 mm wheal, respectively, to saline. Wheal size in these patients of 4 and 5 mm, respectively, to platinum salts were seen.

Baseline FEV_1 was not significantly different between subjects in high-exposure areas and low-exposure areas or between the 26 subjects who undertook multiple examinations and those 15 ceasing employment prior to follow-up examination. FEV_1 remained unchanged for all 26 subjects over the course of the study period (see Table 1). During the study, no subjects described the development of new respiratory or dermatological symptoms. Two patients reported stable eczematous rashes that pre-dated commencement of employment. Three patients had a prior history of mild episodic asthma.

Table 1. Comparison of baseline FEV_1 between groups and baseline and final FEV_1 for subjects in high-exposure areas

Group	FEV_1 (% predicted $\pm$ SD)
Subjects in low-exposure areas ($n = 71$)	
Baseline FEV_1	99 $\pm$ 16%
Subjects in high-exposure areas leaving employment without follow-up examination ($n = 15$)	
Baseline FEV_1	96 $\pm$ 13%
Subjects in high-exposure areas completing follow-up examinations ($n = 26$)	
Baseline FEV_1	98 $\pm$ 15%
Final FEV_1	98 $\pm$ 16%

Measured differences in FEV_1 were not significant for all comparisons.

No increase in respiratory symptoms was noted, nor did use of asthma medication increase during the study period.

One single non-smoking subject with a past (pre-employment) history of symptomatic seasonal hay fever and episodic wheeze, when initially examined on 17 March 2005, recorded a reduction in FEV₁ of 17% in response to inhaled methacholine at a concentration of 3.1 mg/ml. After 6 months, inhalation of methacholine at 1.0 mg/ml produced a reduction in FEV₁ of 27%. Twelve months after the demonstration of bronchial hyperreactivity, a 0 mm wheal in response to platinum SPT was recorded in this subject. This subject's baseline FEV₁ did not change significantly over the 25 months they were employed (92% predicted at commencement and 84% predicted 25 months later).

Discussion

Our findings confirm the initial report by Linnett and Hughes [3] who demonstrated the non-allergenic nature of TPC. We did not intend to examine the magnitude of FEV₁ change in response to exposure to TPC over time. Rather, in examining individuals we note there has been no subjects whose FEV₁ has changed significantly which we feel supports our hypothesis that TPC does not induce PSS. Pre- and post-exposure FEV₁ (% predicted) values are identical, suggesting that the magnitude of change (if any) is small.

Despite 1196 person-months, none of our subjects demonstrated PSS on SPT and there were no subjects who developed airway reactivity following exposure to TPC. This is despite exposure to significantly higher TPC levels than reported by Linnett and Hughes [3] and to exposure levels 10-fold those previously associated with the development of PSS in subjects exposed to hexachloroplatinate [2,3] and well above the level of 2 µg/m³ advocated as a maximum exposure limit [5].

In their comparative study, Linnett and Hughes [3] reported development of PSS in none of 100 subjects in a production plant using TPC compared to a rate of 0.5 cphpm among 41 subjects exposed to hexachloroplatinate. This occurred despite airborne platinum exposure being significantly higher ($P < 0.001$) in the group exposed to TPC.

The single subject that developed bronchial hyperreactivity, as defined by >20% reduction in FEV₁ to inhaled methacholine at a concentration of <3.9 mg/ml, had demonstrated borderline reactivity at their initial examination, with 17% reduction in FEV₁ in response to inhalation of methacholine at 3.1 mg/ml. While worsening of bronchial hyperreactivity due to TPC exposure cannot definitively be excluded, we feel this is very unlikely. This patient did not demonstrate PSS on SPT over the following 19 months. In most cases of PSS, symptoms

and signs of allergic disease develop subsequent to positive SPT [2], so we consider this finding not to be a result of occupational exposure to TPC.

It was an occupational health and safety requirement of employment that all employees undertake regular surveillance for the development of sensitization to platinum salts. Our cohort is therefore highly representative of the at-risk population. The possibility of a survivor bias cannot be discounted as subjects leaving the high-risk area of the plant were not required to specify reasons, so it is possible that some workers may have left due to undisclosed development of PSS symptoms. However, in our cohort, the attrition rate was notably lower than in previous cohorts [2,9]. There was also no difference in FEV₁ between groups leaving employment and those remaining in current employment and therefore, while a small survivor benefit cannot be discounted, we believe this does not alter the major finding of a zero rate of development of PSS.

The study period is comparable to previously published cohorts in terms of duration, though as subjects were enrolled upon employment, rather than at a specific and common time, the duration each subject studied is variable. Development of sensitization has been noted to be most likely in the first 24 months of exposure [2,6], so we feel the duration of observation is sufficient to allow confidence in our finding of zero cases of PSS.

Numerous other examples of exposure to platinum without development of allergy exist, demonstrating the importance of chemical speciation. Increasing urban dust and soil platinum concentrations from car exhausts have not been associated with an increased rate of platinum sensitivity in the general population [10]. Similarly, significantly increased serum platinum levels among oncology nurses have not been associated with the development of platinum sensitization [11].

Platinum allergy is induced by charged platinum salts binding serum proteins to form an antigen. Hexachloroplatinate ([PtCl₆]²⁻) is among the most potent such compounds [12]. In contrast, TPC is a neutral complex salt. As such, it is inert and no antigen is formed following normal occupational exposure [3]. TPC also does not provoke a reaction on skin prick tests in subjects allergic to chloroplatinates [13].

Our findings support the concept that occupational exposure to high levels of TPC is not associated with the development of PSS or occupational asthma and reiterate the importance of chemical speciation in the development of occupational PSS. The differing properties of alternate metal salt compounds need to be considered when formulating future occupational health policy. Our results confirm that TPC may be preferable to chloroplatinic acid in catalyst production in minimizing the impact of occupational illness due to PSS.

Key points

- TPC is not associated with the development of PSS.
- Chemical speciation is important when advising on the need for and extent of medical surveillance in occupational exposure to metal compounds.
- Where possible, catalyst manufacture should be performed using TPC, in preference to hexachloroplatinate to minimize the development of occupational disease.

Conflicts of interest

Our department received payment for medical services provided to the autocatalyst production company during the period reported in the study. The company had no role in the development of the surveillance programme. No authors received individual payments.

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