

Asthma due to inhaled chemical agents—complex salts of platinum

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Summary

Sixteen workers, from a platinum refinery, with respiratory disease were tested with solutions of complex salts of platinum and ten gave immediate prick test reactions to concentrations of 10^{-4} – 10^{-6} and immediate nasal reactions in seven out of eleven tested to concentrations of 10^{-3} – 10^{-5} . Occupational-type exposure inhalation tests to the dust from mixtures of 40 mg of the platinum salt with 1 kg of lactose gave immediate asthmatic reactions in eight and in one of these a late reaction, all also giving immediate prick test reactions. The asthmatic reactions were inhibited by disodium cromoglycate. In two with negative prick tests, late asthmatic reactions were elicited. The occupational-type exposure test provides a safe, acceptable procedure for etiological diagnosis.

Introduction

The complex salts of platinum are potent sensitizers and highly allergenic. Investigation of allergic sensitivity to them may be hazardous. Skin, mainly scratch, tests have been used and severe reactions elicited by them and by intracutaneous tests in sensitized workers (Vallery-Radot & Blamoutier, 1929; Hunter, Milton & Perry, 1945; Roberts, 1951; Freedman & Krupey, 1968; Levene & Calnan, 1971). Nasal and bronchial tests have also elicited severe reactions (Vallery-Radot & Blamoutier, 1929; Bijl, 1963).

The occupational type exposure inhalation test, described by Pepys, Pickering & Loudon (1973a) for demonstrating respiratory allergy to inhaled piperazine dihydrochloride, has provided a safe acceptable method for investigation of asthma due to the platinum salts. The bronchial reactions elicited follow the patterns of immediate, late and dual reactions observed in allergy to common allergens, such as fungi, e.g. *Aspergillus fumigatus* (McCarthy & Pepys, 1972), avian antigens (Pepys & Hargreave, 1970), house dust and *Dermatophagoides* spp. (Booij-Noord *et al.*, 1972), and also to a number of inhaled chemical agents, such as piperazine dihydrochloride (Pepys *et al.*,

1972a), wood dusts (Pickering, Batten & Pepys, 1972), flux-fumes (Pepys & Pickering, 1972) and tolylene di-isocyanate (Pepys, Pickering & Terry, 1972b).

Materials and methods

Test materials

Complex salts of platinum: prick and nasal tests. Ammonium hexachlorplatinate, ammonium tetrachlorplatinate and sodium hexachlorplatinate were dissolved in carbol-saline plus 5% glycerol for prick and nasal tests in concentrations of 10^{-3} – 10^{-11} g/ml, and the tests were started with the lowest concentration and were continued with each succeeding higher concentration if negative.

Inhalation tests. The complex salts of platinum were prepared in powder form as separate mixtures containing 40 mg of each salt and 1 kg lactose powder. The control lactose powder and the mixtures were dried for 20 hr at 105°C and then kept in a desiccator or airtight, because the lactose is hygroscopic and loses its powdery, dusty consistency.

The test was made by the patient shaking 250 g of the mixture repeatedly from one tray to another 0.3 m below as described by Pepys *et al.* (1972a) and inhaling the dust so created. Initially, daily tests were made with increasing amounts, in microgram quantities, of the platinum salts mixed with the lactose until it was found that 40 mg in a kilo of lactose sufficed to elicit reactions in sensitive subjects.

The maximum exposure was 30 min, divided into 5, 10 and 15 min periods with intervals of 10 min between them. Exposure was terminated at any time if there was evidence of a clinical reaction or a decrease in ventilatory function. Tests of ventilatory function were made before the test and at each interval during the exposure, then at 10 min intervals up to 1 hr after its completion, followed by hourly tests for 8 hr or until any reaction had resolved. No further exposure was made if the FEV₁ fell by at least 10%, and only one test was made per day. The following exposures were made: (1) control lactose exposure, (2) exposure to a mixture of platinum salt plus lactose, (3) pretreatment with 20 mg disodium cromoglycate, by means of a Spinhaler 10 min before the exposure, (4) pretreatment with 20 mg lactose placebo in a Spinhaler before the exposure.

Prick tests with common allergens

Prick tests were made with twenty-two common allergens and only one of the sixteen subjects gave positive reactions to two of these, showing that almost all of the affected subjects were non-atopic.

Subjects tested

The sixteen subjects investigated had worked in a platinum refinery, in nine cases for less than 6 months, five less than 1 year and two for many years, before showing signs of sensitivity. The majority were either quite well or much improved on leaving the refinery. Detailed measurements of pulmonary function on admission for investigation showed ten to be normal in all respects, five had slight airways obstruction and one who was not found to be sensitive to platinum and was a heavy smoker had evidence of early restrictive ventilatory defect with decrease in CO gas transfer factor. They were investigated many months or more than 1 year after ceasing exposure.

Results

Tests were made with the three different platinum salts in most subjects (Pickering, 1972; Pickering & Pepys, 1972a, b). Of the sixteen workers investigated positive reactions were obtained to one or more of these as follows: prick tests—ten gave positive, immediate wealing reactions to concentrations between 10^{-4} and 10^{-6} ; nasal tests—seven out of eleven tested gave positive immediate reactions consisting of itching, sneezing and rhinorrhoea to concentrations between 10^{-3} and 10^{-5} .

Inhalation tests gave positive immediate reactions (Fig. 1), starting in 10 min and resolving in 1 hr in eight patients, all of whom gave immediate prick test reactions. In one of these there was also a late reaction. In two other subjects only late reactions were elicited, one starting after 30 min, maximal at 1½ hr and resolving in 4 hr in the other. In the other, the reaction started after 4 hr, being maximal at 7 hr when it was reversed by an injection of adrenaline. Neither of these patients gave immediate prick test reactions, and in one so tested the nasal test was also negative. Thus ten of the sixteen subjects gave positive bronchial reactions. Rhinitis was also provoked in six cases, conjunctivitis in three, dermatitis in two and urticaria in one case, some of these occurring together. The overall pattern of reactions is seen in Fig. 1.

Effect of disodium cromoglycate (Table 1, Fig. 2) and reproducibility of bronchial reactions

In five subjects pretreatment with disodium cromoglycate inhibited the reactions. Repetition of the tests following pretreatment with lactose placebo gave bronchial reactions very comparable to the initial tests. This reproducibility was evident in all cases where identical tests were repeated.

Comparison of different platinum salts

Table 2 shows that the salts differed in their capacity to elicit reactions, with ammonium tetrachloroplatinate as the most potent and sodium hexachloroplatinate the least potent.

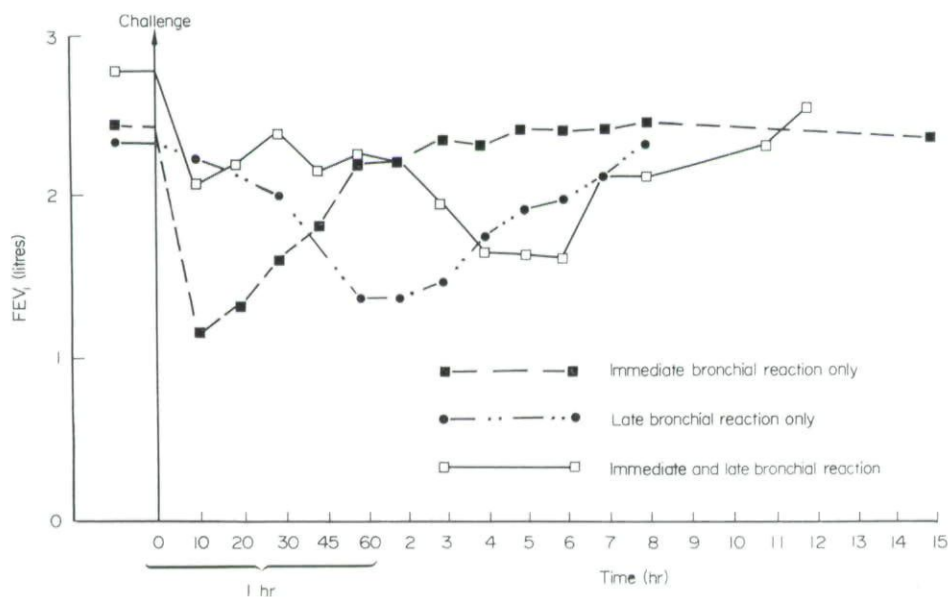


Fig. 1. Bronchial reactions on 'inhalation' testing with the complex salts of platinum.

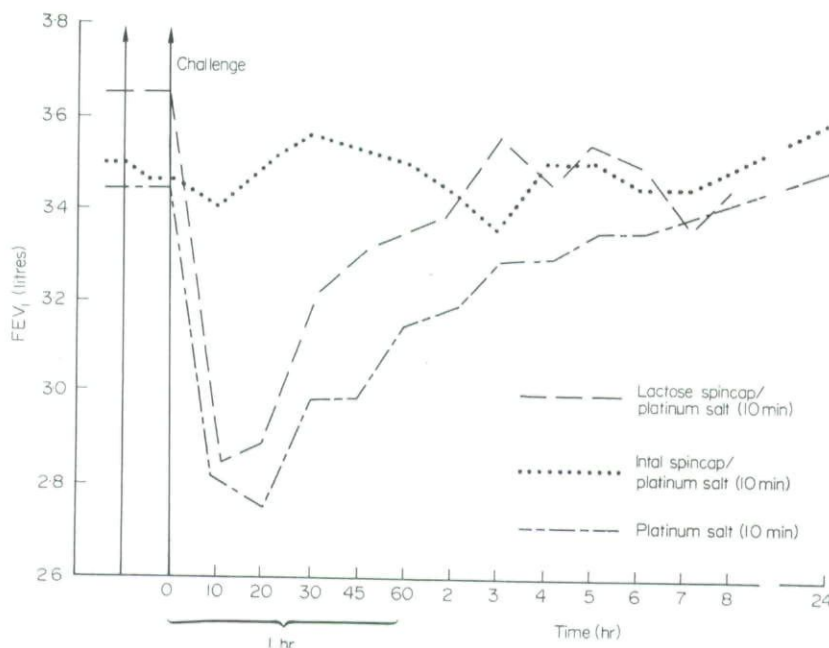


Fig. 2. 'Inhalation' tests with ammonium hexachlorplatinate with and without pretreatment with Intal and Intal placebo (lactose).

Table 1. Effect of disodium cromoglycate on and reproducibility of 'inhalation' tests—ammonium hexachlorplatinate

Patient	Percentage decrease in FEV ₁			Length of exposure (min)
	Initial test	Pre-treatment with Intal	Pre-treatment with lactose	
D.L.	38	7.5	41	15
C.W.	28	19	38	4
R.B.	31	7	28.5	6
F.S.	32	0	20.3	10
S.H.	17	0	36	30

Discussion

The occupational type exposure to the complex salts of platinum as inhaled dusts provides an acceptable, safe procedure for the investigation of allergy to these agents as it has done for chemical and other dusts (Pepys *et al.*, 1972a; Pickering *et al.*, 1972). This permits not only confirmation of the suspected exposure but precise etiological identification of the responsible chemical agent. In the present studies ammonium hexachlorplatinate was shown to be the most potent of the three salts tested. The method of inhalation testing gives very satisfactorily reproducible reactions. Careful prick and nasal tests also have a place showing good correlation with the inhalation test. All of the positive prick test reactors gave immediate asthmatic reactions. One

Table 2. Comparison of inhalation tests with complex platinum salts

Patient No.	Platinum salt	Duration of exposure (min)	Percentage decrease in FEV ₁
(1)	(NH ₄) ₂ Pt Cl ₆	15	38
	(NH ₄) ₂ Pt Cl ₄	10	49
	Na ₂ Pt Cl ₆	10	35
(2)	(NH ₄) ₂ Pt Cl ₆	4	28
	(NH ₄) ₂ Pt Cl ₄	5	45
	Na ₂ Pt Cl ₆	30	16
(3)	(NH ₄) ₂ Pt Cl ₆	6	31
	(NH ₄) ₂ Pt Cl ₄	10	38
	Na ₂ Pt Cl ₆	15	23
(4)	(NH ₄) ₂ Pt Cl ₆	10	32
	(NH ₄) ₂ Pt Cl ₄	10	34
	Na ₂ Pt Cl ₆	30	0
(5)	(NH ₄) ₂ Pt Cl ₆	30	0
	(NH ₄) ₂ Pt Cl ₄	30	18 (L ₁)
	Na ₂ Pt Cl ₆	30	0
(6)	(NH ₄) ₂ Pt Cl ₆	30	0
	(NH ₄) ₂ Pt Cl ₄	30	15.5 (L ₁)
	Na ₂ Pt Cl ₆	30	0
(7)	(NH ₄) ₂ Pt Cl ₆	30	26
	(NH ₄) ₂ Pt Cl ₄	15	30
	Na ₂ Pt Cl ₆	30	0
(8)	(NH ₄) ₂ Pt Cl ₆	15	29
	(NH ₄) ₂ Pt Cl ₄	20	29
	N ₂ Pt Cl ₆	20	19
(9)	(NH ₄) ₂ Pt Cl ₆	30	17
	(NH ₄) ₂ Pt Cl ₄	30	17
	Na ₂ Pt Cl ₆	30	0

of the positive nasal reactors gave a negative bronchial reaction and one of the negative nasal reactors gave a positive immediate bronchial reaction.

The possible mechanism for the isolated late bronchial reactions in two negative skin and nasal reactors is not known. The patterns of bronchial reaction elicited are like those already familiar in relation to allergy to *A. fumigatus*, avian and other allergens and similarly the asthmatic reactions to the platinum salts are effectively inhibited by disodium cromoglycate. The overall similarity of these patterns of bronchial reaction suggests that similar immunological mechanisms are operative. In practical terms the occupational-type exposure gives the necessary clinical and etiological diagnostic information. The wider use of these safe and acceptable methods is indicated, though they entail a prolonged stay of 1-2 weeks or more in hospital under controlled conditions, for the careful testing and assessment which is needed.

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