Atopic Hypersensitivity to cis-Dichlorodiammineplatinum(II) and Other Platinum Complexes

Amanullah Khan, Joseph M. Hill, William Grater, Ellen Loeb, Ayten MacLellan, and Norwood Hill

SUMMARY

Allergic reaction to an antitumor agent, cis-dichlorodiammineplatinum(II) (DDP) was investigated. A 15-year-old white male with pulmonary metastases from embryonal carcinoma of testis was treated with a combination of DDP, bleomycin, and vinblastine. The dose of DDP varied from 2 to 2.25 mg/kg given i.v. He received 7 doses of DDP in 9 months. An anaphylactic reaction was seen within 3 min of the initiation of i.v. infusion of the 8th dose of DDP. The reaction was due to atopic hypersensitivity, as confirmed by an immediate wheal and flare reaction and increased histamine release from leukocytes with DDP. His serum IgE level was elevated. Neither the presence of chloride nor the amine grouping in DDP was essential for reactivity. The replacement of platinum with palladium abrogated the reactivity. There was no cross-reactivity with 3 other platinum complexes of known antitumor activity (platinum blue, platinum(II) 1,2-diaminocyclohexane malonate, and platinum(II) ethylenediamine malonate). This was also confirmed by the lack of reaction to subsequent i.v. administration of platinum(II) 1,2-diaminocyclohexane malonate (10 mg/kg) in this patient.

INTRODUCTION

Platinum coordination complexes were reported by Rosenberg et al. (29, 30) to have antitumor effects. These reports were confirmed in a variety of tumors (4, 22, 26, 33, 34). Other platinum complexes with antitumor activity have also been prepared (3, 29, 32). Phase I and II clinical trials with DDP have shown the effectiveness of this compound in various human tumors (7, 9–14, 23, 28, 31). Side effects have included nausea, vomiting, deafness, renal impairment, and bone marrow toxicity. The present report describes an allergic reaction due to DDP in a patient who received multiple doses of this drug.

MATERIALS AND METHODS

A 15-year-old white male (R. C.) weighing 62 kg was referred to the Wadley Institutes of Molecular Medicine with pulmonary metastases from embryonal carcinoma of testis. The only significant finding in his past history was the repeated attacks of rhinorrhea since childhood, occurring with high frequency during the winter months. He was never seen by a physician for this complaint. His brother had allergic reaction to penicillin, and his mother had a history of unexplained urticaria.

He was treated with DDP, bleomycin, and vinblastine. The dose of DDP varied from 2 to 2.25 mg/kg given as an i.v. infusion in 0.9% NaCl solution over a 2-hr period. He received 7 doses of DDP in 9 months. The interval between different doses varied from 4 to 10 weeks.

Vinblastine, 0.1 mg/kg i.v., and bleomycin, 15 units i.m., were given on the day following DDP administration. These 2 drugs were given once a week initially, and gradually the interval between treatments was increased to 4 weeks. Therefore, some courses of vinblastine and bleomycin were not preceded by DDP due to the difference in the frequency of administration of these drugs and DDP. The good clinical response of the tumor to chemotherapy will be part of another report. The present report dwells mainly on the allergic reaction.

During the administration of the 8th dose of DDP (8 weeks after the 7th dose), the patient complained of a burning sensation all over his body. He became flushed, started vomiting, and developed respiratory difficulty within 3 minutes of the initiation of i.v. infusion of DDP. His heart rate increased to 120 cpm and blood pressure dropped to 100 systolic and 50 diastolic. DDP was discontinued. The patient recovered quickly following 50 mg prednisolone and 50 mg diphenhydramine hydrochloride, given i.v. However, epiinephrine is recommended as the drug of choice in anaphylaxis. Investigations regarding the nature of this reaction were carried out 3 weeks later.

Skin Tests. Each compound listed in Table 1 was dissolved in 0.9% NaCl solution at a concentration of 50 μg/ml for performing skin tests. cis-Diaquadiammineplatinum(II) (Table 2) was prepared according to the method described by Davidson et al. (6). This method involved the removal of chloride from DDP solution with the addition of silver nitrate. The silver chloride precipitate

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2 To whom requests for reprints should be addressed.
3 The abbreviation used is: DDP, cis-dichlorodiammineplatinum(II).

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was removed by passing through a sintered glass filter. The concentration of diaquo compound was adjusted to 50 μg/ml. The skin tests were graded according to the following system: +, erythema up to 20 mm with no wheal or 3 to 4 mm wheal; ++, 4 to 8 mm wheal; ++++, wheal over 8 mm; and +++++, wheal, pseudopods, and erythema.

**Lymphocyte Transformation.** Lymphocyte transformation was tested in the presence and absence of DDP and phytohemagglutinin (35). Serum IgG, IgA, IgM, and IgD levels were determined with an immunodiffusion technique and IgE was determined using radioimmunoassay. The histamine release test was done according to the method described by May et al. (24). DDP was prepared at Wadley Institutes by Speer et al. (32).

**RESULTS**

**Skin Reactions.** The scratch test performed with DDP solution gave only erythema, which was 15 mm in diameter. The scratch test with the diluent was negative. In view of the weak scratch test, it was decided to perform intracutaneous tests with a 0.05-ml volume of each solution, under direct supervision of 1 of the authors (A. K.). The patient gave a +++++ immediate wheal and flair reaction to DDP (Fig. 1). Table 1 shows the skin reactions to DDP and other compounds. Substitution of chloride with iodide in DDP did not change the skin reaction. Similarly, the platinum complexes were reactive in the absence of the amine group (potassium chloroplatinate and potassium chloroplatinate). The reactivity was abrogated when platinum was replaced with palladium (potassium chloropalladite). Negative skin reactions were obtained with platinum(II) ethylenediamine malonate, platinum(II) 1,2-diaminocyclohexane malonate, and platinum blue. Complete removal of chlorides from DDP (diaquo form) did not remove reactivity (Table 2). Skin tests were done on 3 other patients before starting DDP treatment and were found to be negative. A patch test with DDP (0.5 mg) dissolved in water was negative on the patient at 24 and 48 hr. The patient's lymphocytes responded to phytohemagglutinin stimulation with a blastogenic index of 112 (normal). No stimulation of lymphocytes was observed with 25-, 2.5-, 1-, 0.1-, 0.01-, or 0.001-μg/ml concentrations of DDP.

Table 3 shows the histamine release from the patient's leukocytes following incubation with DDP. A significant increase in the histamine release was observed with this compound. Nonspecific release of histamine was not seen with DDP utilizing leukocytes from a normal (nonsensitized) individual. The patient gave a ++++ immediate reaction to intradermal skin test with house dust (1:1000).

The patient's blood count at the time of immunological work-up was as follows: hemoglobin, 11.1 g/100 ml; WBC, 4082/cu mm, with 69% segmented, 22% lymphocytes, and 9% monocytes. His immunoglobulin levels are shown in Table 4. The IgE was elevated.

![Image](http://cancerres.aacrjournals.org)
Table 1

Skin reactions of the patient to various platinum compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>Skin reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluent control</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DDP</td>
<td>![DDP Diagram]</td>
<td>++++*</td>
</tr>
<tr>
<td><em>cis</em>-Diiododiammineplatinum(II)</td>
<td>![cis-Diiododiammineplatinum(II) Formula]</td>
<td>++++</td>
</tr>
<tr>
<td>Potassium chloroplatininate</td>
<td>![Potassium chloroplatininate Diagram]</td>
<td>+++</td>
</tr>
<tr>
<td>Potassium chloroplatininate</td>
<td>![Potassium chloroplatininate Diagram]</td>
<td>+++</td>
</tr>
<tr>
<td>Potassium chloropalladite</td>
<td>![Potassium chloropalladite Diagram]</td>
<td>-</td>
</tr>
<tr>
<td>Platinum(II) ethylenediamine malonate</td>
<td>![Platinum(II) ethylenediamine malonate Diagram]</td>
<td>-</td>
</tr>
<tr>
<td>Platinum(II) 1,2-diaminocyclohexanemalonate</td>
<td>![Platinum(II) 1,2-diaminocyclohexanemalonate Diagram]</td>
<td>-</td>
</tr>
<tr>
<td>Platinum blue</td>
<td>?</td>
<td>-</td>
</tr>
</tbody>
</table>

* ++++, wheal, pseudopods, and erythema; +++, wheal over 8 mm and erythema.
The patient received platinum(II) 1,2-diaminocyclohexane malonate, 10 mg/kg, in a single dose given i.v. over 3 hr. This was done 3.5 months after the allergic reaction to DDP. He developed nausea and vomiting but no allergic reaction was seen.

**DISCUSSION**

DDP has been shown to be effective in various malignant diseases. Further clinical evaluation of this compound alone and in combination is in progress. The reaction to i.v. administration of DDP seen in our patient resembled atopic hypersensitivity. The clinical picture of the reaction, typical wheal and flare response following skin test, and the positive histamine release test support this contention. Passive transfer to test Prausnitz-Küstner reaction was not attempted due to the malignant nature of his disease. Hypersensitivity developed after 7 doses of DDP. Therefore, patients receiving multiple doses of DDP should be watched for allergic reactions. One should especially be careful with patients who have personal or family history of allergy. Skin tests may be used to screen patients for DDP allergy.

It has been shown that individuals exposed to atmosphere containing dusts of complex salts of platinum can develop asthma and show immediate and delayed reactions (25). It is, therefore, suggested that patients with a history of possible exposure to platinum salts should be tested before administration of the platinum coordination complexes. The skin test reaction seen in our patient was a typical wheal and flare reaction appearing in 3 min, reaching a maximum in 20 min, and disappearing in about 50 min. Three other patients were skin tested before being given the lst dose of DDP and none of them showed a positive reaction. Delayed reaction was not seen to the skin test or the patch test. Similarly, there was no blastogenic response to DDP by our patients' lymphocytes. This compound is inhibitory to lymphocyte blastogenesis in concentrations of 0.25 μg/ml or more (18). However, concentrations less than 1 μg/ml failed to stimulate the lymphocytes, which may suggest the absence of delayed hypersensitivity to DDP. Skin tests were done with different compounds to see if the presence of a particular ligand was necessary for allergic reaction. Tables 1 and 2 show that the presence of halogens was not essential. Positive reaction was obtained in the absence of NH₃ was also not needed because positive skin tests were seen with potassium chloroplatinate and potassium chloroplatinate. Substitution of platinum by palladium (potassium chloropalladate) abrogated the reactivity, showing that platinum was essential for the skin reaction to occur. However, some of the square-planar complexes failed to give positive reaction (platinum(II) ethylenediamine malonate and platinum(II) 1,2-diaminocyclohexane malonate). It was evident that some other property of platinum complexes was influencing the skin reactivity. It is suggested that the kinetics of ligand substitution may be the other determining factor. In this regard, the nonlabile as well as the leaving ligand will have an important role (8). A review of Tables 1 and 2 shows that the compounds that reacted readily in aqueous solution gave positive skin reactions. It is therefore, likely, that DDP acted as a hapten and bound with proteins to induce allergy after administration. DDP has been shown to be immunosuppressive (1, 2, 5, 15, 16, 18–21). The ability of atopic reactions to develop in the presence of treatment with immunosuppressive drugs has been shown in the past. Asparaginase, which is an immunosuppressive drug, can induce atopic hypersensitivity (17). The inhibition of lymphocyte blastogenesis after DDP administration in man lasted only up to 72 hr (21). Therefore, the immunosuppression with DDP is likely to last for a short period. The presence of platinum complexes in the individual for a longer period of time (11) could induce hypersensitivity. Bleomycin is a nonimmunosuppressive drug (36) and could have played a role in the induction of allergic reaction.

Platinum blue was shown to have potent antitumor activity (6). The absence of skin reaction to platinum blue suggests that it will be possible to give platinum blue to patients allergic to DDP. Platinum(II) ethylenediamine malonate and platinum(II) 1,2-diaminocyclohexane malonate also did not cross-react with DDP. These compounds have been shown to possess antitumor effects (4, 34; G. Gale and S. Meischen, personal communication; R. J. Speer and H. Ridgway, personal communication). There was no allergic reaction to platinum(II) 1,2-diaminocyclohexane malonate given i.v., while the patient still showed a positive skin reaction to DDP. This confirmed the lack of cross-reactivity between DDP and platinum(II) 1,2-diaminocyclohexane malonate.
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