

Brief communications

Anaphylaxis to carboplatin—A new platinum chemotherapeutic agent

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Hypersensitivity to platinum is well established among refinery workers inhaling complex salts of platinum. Platinum-specific IgE by RAST has been demonstrated, and challenging the skin, nose, and lung with platinum salts produces typical type I reactions in sensitized individuals.^{1,2} Immunologic sensitization to platinum has been reported with the cytotoxic agent, cisplatin.³ A new drug containing platinum, carboplatin, was approved by the Food and Drug Administration (FDA) in 1989 for salvage treatment of ovarian cancer (Fig. 1). We present a patient who tolerated eight courses of cisplatin but experienced an anaphylactic reaction shortly after beginning her second course of carboplatin.

CASE HISTORY

A 68-year-old nonatopic white woman with rheumatoid arthritis and bulky adenocarcinoma presumably of ovarian origin tolerated eight courses of cisplatin in early 1990, with surgically confirmed complete response. Seven months later the tumor recurred, and monthly intravenous carboplatin was begun. Pruritus of the hands responsive to a parenteral antihistamine was noted during her first infusion. A CT scan before her second course revealed a major tumor response. Thirty minutes before the next dose, she was pretreated with 20 mg dexamethasone intravenously and 50 mg diphenhydramine intravenously. Minutes after beginning the infusion of carboplatin she complained of perioral tingling, palmar pruritus, and dyspnea. She became ashen and cyanotic, incontinent of urine, hypotensive, and hypoxemic. She responded to aggressive fluid replacement, oxygen, and epinephrine.

Two days after the event she received a standard dose of carboplatin (350 mg/m² in 100 ml 5% aqueous dextrose solution [D₅W]) as follows: 0.1 ml, 1 ml, and 10 ml diluted

further in 100 ml D₅W given over 1 hour each, followed by the remainder of her standard dose over 1 hour. She tolerated this session and completed her four monthly carboplatin courses with only mild pruritus.

INVESTIGATION

The need to continue chemotherapy and concern about a postanaphylactic refractory period precluded allergy testing during her initial hospital stay. When she returned to the hospital 1 month later skin testing to carboplatin and cisplatin was performed (Table I). Repeat skin testing before her remaining carboplatin courses produced similar results. To avoid exposing normal subjects to intradermal injections of mutagenic chemotherapeutic agents, four controls were selected from patients in the oncology clinic who had previously tolerated platinum chemotherapy. After obtaining informed consent, skin testing with both platinum compounds up to 1 mg/ml was performed and was negative in the control subjects. Complete serial dilution testing was not performed in all controls because of intense transient skin burning, which was not related to the dose.

Serum collected 1 month after the anaphylactic event revealed a total IgE of 646 ng/ml and a negative multiallergen RAST. A repeat serum IgE drawn 4 months after the event had fallen to 88 ng/ml. An inadequate number of basophils were obtained to perform basophil release studies, presumably because of chemotherapy-induced granulocytopenia. Passive transfer of the patient's serum to donor basophils for histamine release with carboplatin challenge was negative. A RAST assay was attempted by adding 5 ml of 6.5 mg/ml carboplatin to epoxy-activated agarose (Pharmacia Fine Chemicals, Piscataway, N.J.); 33% of drug bound on the basis of absorption at 229 nm. Only serum from 4 months after the event remained for RAST analysis; no evidence of specific IgE was demonstrated, but a positive control was not available to validate the assay.

DISCUSSION

This patient demonstrated skin test sensitivity to both the drug provoking anaphylaxis, carboplatin, and the prior immunologically cross-reactive drug, cisplatin. Although a previous study of cisplatin-induced anaphylaxis documented drug hypersensitivity by

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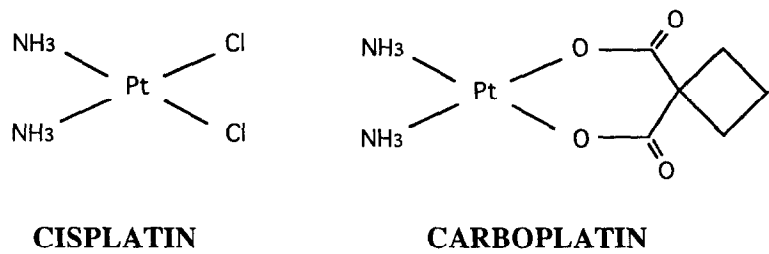


FIG. 1. Chemical structures of platinum cytotoxic agents.

TABLE I. Wheal/flare (mm) response to prick and intradermal skin testing with increasing log concentrations of carboplatin and cisplatin

		Controls									
		Case									
				1		2		3		4	
		P	ID	P	ID	P	ID	P	ID	P	ID
Carboplatin (µg/ml)	1	0	nt	0	0	0	0	0	0	0	0
	10	0	nt	0	0	0	nt	0	nt	0	0
	100	0	8/15	0	0	0	nt	0	0	0	0
	1000	0	10/12	0	0	0	nt	0	nt	0	0
Cisplatin (µg/ml)	1	0	11/26	0	0	0	0	0	0	0	0
	10	5/21	nt	0	0	0	nt	0	nt	0	0
	100	3/12	nt	0	0	0	nt	0	0	0	0
	1000	5/21	nt	0	0	0	nt	0	nt	0	0
Diluent		0	0	0	0	0	0	0	0	0	0
Histamine		2/4	6/16	6/18	16/38	5/12	10/38	4/15	10/33	4/4	14/17

P, Prick; ID, intradermal; nt, not tested.
Positive (histamine) and negative (diluent) control results included.

properly controlled skin testing,³ this case is the first such investigation with the new platinum agent carboplatin.

Platinum is a tetravalent inorganic molecule that readily complexes with proteins to form a neoantigen. While specific IgE has been demonstrated in individuals occupationally exposed to inhaled platinum salts, our efforts to identify specific IgE were hampered by the lack of a positive control and our use of serum obtained 4 months after the anaphylactic event. There is precedent for falls in total IgE over this time period, presumably attributable to drug-specific IgE.⁴

Although a postanaphylactic refractory period likely existed during the first carboplatin retreatment after the acute event, monthly courses of carboplatin were tolerated with a modified desensitization protocol. Documentation of desensitization by posttreatment skin tests is lacking because of the patient's need

for antihistamines during chemotherapy infusion. Although pretreatment corticosteroids and antihistamines are recommended for prophylaxis of anaphylactoid reactions of various types,^{5,6} this patient's reaction highlights the difficulty of preventing true anaphylaxis.

Cisplatin is second only to L-asparaginase in frequency of allergic reactions among chemotherapeutic agents. One may anticipate a similar high reaction rate with carboplatin, especially since it may follow treatment with potentially cross-reactive cisplatin. The investigation of appropriate control subjects has shown that intradermal skin testing with carboplatin up to concentrations of 1 mg/ml can be performed without nonspecific skin reactivity. Furthermore, we have demonstrated successful retreatment with a desensitization protocol that enabled the patient to continue a medically necessary drug.

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The incidence of severe adverse reactions to food in Colorado

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The incidence of fatal or severe life-threatening adverse reactions to foods is unknown. Unfortunately, these data cannot be gathered from national health statistics because there is no International Classification of Diseases code for "food anaphylaxis." These data are frequently sought by the scientific community, by the media, and by government agencies. The objective of this pilot project was to gather data on severe food reactions in the population of Colorado to estimate the magnitude of the problem so that a more comprehensive and accurate national study could be designed. The concept of this project was supported by the Adverse Reactions to Foods Committee of the American Academy of Allergy and Immunology.

METHODS

This was a prospective survey of 73 Colorado emergency departments carried out over a 2-year period. In each emergency department an individual volunteered to identify any subjects admitted to that emergency facility with a severe allergic reaction that could probably be attributed to food.

The responsible individual was asked to complete a reporting form and send it to National Jewish Center. Each emergency department was contacted every 3 months during the first 6 months and then every 3 to 6 months during the subsequent 18 months. Subjects were considered appropriate for inclusion only if their reaction included respiratory or cardiovascular symptoms requiring emergency intervention (or symptoms that would have required emergency treatment if they had not subsided by the time the patient reached the emergency department).

RESULTS

Table I presents the results in 25 individuals ages 2 to 71 years who were identified over the 2-year period of the study and who fulfilled the study criteria. Eleven of the subjects were male. It is of particular note that one third of the patients were suspected of reacting to peanut. Twenty patients received epinephrine. Two patients required cardiopulmonary resuscitation. One subject died. She was known to have systemic mastocytosis and had had previous anaphylactic reactions to foods that were under investigation when she had the fatal reaction. One subject had two reactions a few months apart.

On the basis of the findings in this study and taking into account the United States population, a minimum of 950 severe reactions to food may occur each year.

DISCUSSION

Fatal or nearly fatal reactions to food are important preventable causes of death in a small number of per-

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