

Successful Desensitization in a Child with Carboplatin Allergy: A Case Report

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ABSTRACT

Hypersensitivity to platinum is described, although its mechanism is unknown. Carboplatin and cisplatin are cytotoxic agents containing platinum. Carboplatin is used to treat childhood tumors. Desensitization to carboplatin has been reported with some protocols requiring more than 3 days duration. We present a 30-month-old Mexican boy with hypothalamic astrocytoma, ventriculoperitoneal (VP) shunt, and hypersensitivity to carboplatin that developed after six courses of treatment. His symptoms included wheezing and mild urticaria. He failed two attempts before successfully completing three desensitizations with the following regimen: hydroxyzine 2 mg/kg/d and prednisolone 4 mg/kg/d begun at 48 hours prior to the carboplatin infusion, ranitidine 2 mg/kg/d at 24 hours. Carboplatin (1 mg/mL) was given at an initial rate of 1 mg/h with increments every 15 minutes (2, 4, 8, 16, 32, 40 mg/h). He experienced mild wheezing at 40 mg/h and responded well to steroids, diphenhydramine, and nebulized albuterol. The infusion was resumed at a rate of 32 mg/h to complete 308 mg. The total time of desensitization was 12 hours. Immediate hypersensitivity intradermal testing to carboplatin was positive at 0.01 mg/mL after initial prick testing. This patient responded clinically to premedication according to published anaphylaxis on anaphylactoid desensitization regimens for radiocontrast dyes, which included corticosteroids, a combination of H1 and H2 antagonists, and ephedrine, but he continued to have dose-dependent reactions. Dose-dependent reactions may reflect both anaphylactoid and IgE-mediated reactivity in our patient. Desensitization to carboplatin requires monitoring in a controlled environment and careful attention at each infusion because tolerance to previous regimens may not predict response to subsequent infusions. (*Pediatr Asthma Allergy Immunol* 1998;12[4]:281-284.)

INTRODUCTION

HYPERSENSITIVITY TO CANCER CHEMOTHERAPEUTIC AGENTS is well described and primarily represents type I immediate generalized reactions. Cisplatin and carboplatin are cytotoxic agents containing platinum, which are often used in the treatment of childhood brain tumor and other tumors.⁽¹⁾ Platinum becomes antigenic when it forms a complex with protein. The incidence of cisplatin allergic reaction is reported in the

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literature as 5% to 20%.⁽²⁾ The mechanism for cisplatin or carboplatin hypersensitivity is unknown. Desensitization to carboplatin of varying lengths has been described.^(1,3)

METHODS

Immediate hypersensitivity skin testing was performed using a previously described method.⁽⁴⁾ Preservative free saline and histamine were used as negative and positive control, respectively. Carboplatin, manufactured by Bristol-Myers Squibb (Princeton, NJ), was diluted in sterile water to concentrations of 0.001 mg/mL, 0.01 mg/mL, 0.1 mg/mL, and 1 mg/mL. Carboplatin prick testing was performed with dilutions 0.01 mg/mL and 1 mg/mL. Intradermal testing was performed with carboplatin dilutions of 0.001 mg/mL, 0.01 mg/mL, and 0.1 mg/mL.

CASE REPORT

We report a 30-month-old Mexican boy with hypothalamic astrocytoma, VP shunt, and hypersensitivity to carboplatin that developed after his sixth course of treatment and a total dose of 1800 mg. His symptoms included significant wheezing and mild urticaria; no angioedema or hypotension was seen. Our patient underwent nine desensitizations receiving approximately 308 mg of carboplatin at each procedure. His premedication carboplatin concentration intervals between acceleration and infusion rate were altered because of his persistent reactions as illustrated on Table 1.

Infusions 1, 2, and 3 were performed using methylprednisolone alone as premedication (Protocol 1, Table 1). Because of wheezing and urticaria, carboplatin concentration and infusion rates were altered (Protocol 1b, Table 1); however, the child persisted with wheezing, although he did tolerate an infusion rate of 50 mg/h.

The premedication regimen was then altered to include hydroxyzine 2 mg/kg/d, prednisolone 4 mg/kg/d at 48 hours prior to procedure and ranitidine 2 mg/kg/d at 24 hours prior to procedure (Protocol 2, Table 1). Hydroxyzine was continued for 72 hours after desensitization because of the previous persistent post-infusion urticaria. The fourth and fifth desensitizations were performed using Protocol 2a. The patient experienced wheezing and mild urticaria at an infusion rate of 40 mg/h and 32 mg/h, respectively, which responded to a nebulized beta agonist and parenteral diphenhydramine and methylprednisolone. With protocol 2b longer intervals occurred between acceleration and lower maximal infusion rate decreased from 40 mg/h

TABLE 1. DESENSITIZATION PROTOCOLS

	<i>Protocol 1*</i>		<i>Protocol 2†</i>	
Premedication	Methylprednisolone 4 mg/kg/day × 24 hrs		Hydroxyzine 2 mg/kg/d × 48 hrs Prednisolone 4 mg/kg/d × 48 hrs Ranitidine 2 mg/kg/d × 24 hrs	
Protocol Version	Protocol 1a	Protocol 1b	Protocol 2a	Protocol 2b
Carboplatin	2 mg/mL	1 mg/mL	1 mg/mL	1 mg/mL
Intervals for acceleration (mins)	20 min	15 min	15 min	30 min
Infusion rate (mg/hr)	1.5	1	1	1
	3	2	2	2
	7	4	4	4
	15	8	8	8
	30	16	16	16
		32	32	25
		50	40	

*Protocol 1 was used on two successive days with changes only in infusion rate and concentration.

†Protocol 2 was delivered six times with changes only in infusion rate.

SUCCESSFUL CARBOPLATIN DESENSITIZATION

TABLE 2. COMPLICATIONS OF CARBOPLATIN DESENSITIZATION

Infusion #	1*	2	3*	4	5	6	7	8	9
Protocol #	1a	1b	1b	2a	2a	2b	2b	2b	2b
Infusion rate (mg/hr) at onset of symptoms	3	50	8	40	32	25	16	1	16
Total infusion time (hr)	N/A	10	N/A	12	12	16	16	16	16

*Failed attempt.

N/A, not applicable.

to 25 mg/h (Table 1). As shown on Table 2, our patient continued to experience wheezing, although it decreased in severity with his sixth to ninth desensitizations. The duration of infusion with Protocol 2b was extended to approximately 16 hours.

Immediate hypersensitivity skin testing to carboplatin was performed at 4 weeks after his desensitization. He had no cutaneous response to phosphate-buffered saline negative control for both prick and intradermal testing; histamine was positive at 3 mm wheal and 10 mm flare and 10 mm wheal/20 mm flare for prick and intradermal testing, respectively. The patient had a negative carboplatin response by prick testing through the highest concentration (1 mg/mL). Intradermal carboplatin testing revealed a positive response (6 mm wheal, 8 mm flare) at 0.01 mg/mL.

DISCUSSION

From 1985 to 1993, the National Cancer Data Base reported 21,912 cases of childhood cancer; brain tumors were the second most common reported tumors with a total of 5157 cases.⁽⁵⁾ Carboplatin is used to treat primary brain tumors and other tumors in children and ovarian carcinoma in adults.^(2,6) Carboplatin is a cytotoxic agent with fewer adverse effects than its parent compound, cisplatin. Cisplatin is known to cause hypersensitivity reactions in 5% to 20% of patients. The incidence of carboplatin hypersensitivity is unknown and the mechanism for this hypersensitivity is unclear.

Reported symptoms of urticaria, angioedema, bronchospasm, and hypotension suggest an IgE mediated reaction (Table 3). Most reactions occurred early in the carboplatin infusion, again supporting IgE mediated hypersensitivity. Although reactions occur early, they typically follow cumulative dosing and are more consistent with a non IgE mediated response.^(6,7)

Radioallergosorbent test (RAST) and immediate hypersensitivity skin testing have been performed in an attempt to document a type I hypersensitivity to carboplatin. Windom et al. did not find specific IgE to carboplatin by RAST assay for a patient with carboplatin hypersensitivity.⁽⁸⁾ Interestingly, this same patient had a positive response to cisplatin and carboplatin by immediate hypersensitivity skin testing, whereas control individuals were negative to both compounds. Goldberg et al. described a patient with decreasing skin test reactivity following a systemic reaction.⁽³⁾ This observation is suggestive of a mast cell degranulation effect described in other IgE mediated drug reactions.

Our patient's hypersensitivity reaction to carboplatin has characteristics of both IgE and non IgE mediated reactions as outlined in Table 3. Our patient represents an important example of a child with a brain tumor who developed a mixed type hypersensitivity response to carboplatin. Multiple alterations of the de-

TABLE 3. FINDINGS SUGGESTIVE OF IGE AND NON IGE MEDIATED REACTIONS TO CARBOPLATIN

<i>IgE mediated reaction</i>	<i>Non IgE mediated reaction</i>
1. Symptom of urticaria/bronchospasm	1. Symptoms develop following cumulative dosing
2. Immediate response to nebulized beta agonist and antihistamine	2. Dose and/or infusion rate dependent reaction
3. Positive immediate hypersensitivity skin testing	

sensitization protocol were required in his management. With increased usage of carboplatin, clinicians need to be aware of the nature and the management of carboplatin hypersensitivity. Our patient's final premedication and desensitization protocol can be used as a template in pediatric patients with carboplatin hypersensitivity who fail conventional desensitization. Desensitization to carboplatin requires monitoring in a controlled environment and careful attention to each infusion because tolerance to previous regimens may not predict response to subsequent infusions.

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