

Carboplatin Hypersensitivity and Desensitization in an Infant

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Abstract: Although the reported incidence of carboplatin hypersensitivity is low, it is important to describe it because of its potentially fatal consequences. A 1-year-old Mexican girl weighing 10 kg who had optic nerve glioma was initially scheduled to receive 12 cycles of 600 mg/m² carboplatin (CBP) as two 300-mg/m² intravenous infusions administered over 1 hour on 2 different days and a 1-hour intravenous infusion of 1.5 mg/m² vincristine every 4 weeks. The patient had no history of drug allergies or any type of adverse drug reaction, but she developed itchiness, maculopapular rash, sweating, respiratory distress, and anxiety during the seventh cycle of CBP. According to the algorithm developed by Naranjo et al, the adverse drug reaction was classified as definite secondary to CBP and confirmed by positive skin tests indicating hypersensitivity to the drug. After evaluating the clinical course of the adverse drug reaction and considering the need to continue cancer treatment, a decision was made to desensitize the patient to CBP. The desensitization procedure took 8 hours and was performed during each new chemotherapy cycle until the 12 cycles of chemotherapy were successfully completed. In summary, a case of CBP hypersensitivity in a 1-year-old girl who was successfully desensitized to CBP is reported.

Key Words: anaphylaxis, carboplatin, child, desensitization, optic nerve glioma

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My patient is a 1-year-old Mexican girl weighing 10 kg who has optic nerve glioma. Every 4 weeks for 1 year, the patient was scheduled to receive a cycle of 600 mg/m² carboplatin (CBP) administered as two 300-mg/m² intravenous (IV) infusions over 1 hour on 2 different days and 1.5 mg/m² vincristine administered over 1 hour as an IV infusion. She had no history of drug allergies or any other type of adverse drug reaction. During the seventh cycle of CBP, approximately 5 minutes after initiating the

infusion, she developed an anaphylactic reaction with itchiness, maculopapular rash, sweating, respiratory distress, and anxiety. Her respiratory rate reached 60 beats/min, and her heart rate increased to 180 beats/min with systolic and diastolic blood pressures of 80 mmHg and 60 mmHg, respectively.

She was admitted to the Pediatric Intensive Care Unit and immediately administered 0.1 mg adrenalin (1:1000), 100 mg hydrocortisone, and 5 mg diphenhydramine IV that promptly relieved her symptoms.¹ She had complete recovery from the anaphylactic reaction 2 hours later. How can we confirm whether or not this is a hypersensitivity reaction to CBP?

THERAPEUTIC DRUG MONITORING CONSULTANT

Since its introduction, CBP has proved to be efficacious as a cancer treatment.² However, hypersensitivity reactions soon became a major concern with its use. Although the mechanism of these reactions remains unknown, an immediate type of hypersensitivity reaction mediated by IgE may be involved.³

The clinical manifestations of platinum-associated hypersensitivity reactions are typical of a type I hypersensitivity reaction that includes urticaria, bronchospasm, rash, and hypotension.⁴ The hypersensitivity reaction does not usually develop during the initial exposure; on the contrary, although some cases are reported after the first cycle, the highest incidence occurs during the seventh cycle. The reactions can range from nonserious (facial flushing and/or urticaria) to serious (dyspnea and anaphylaxis).^{3,4}

An allergy diagnosis can be established through the patient's clinical history, skin tests, laboratory tests, and provocation tests. However, a reliable diagnosis for drug hypersensitivity is particularly difficult. In this case, however, the diagnosis may be easier despite the two-drug treatment that the patient received, because the hypersensitivity reaction secondary to CBP was immediately noticeable after the drug was administered.^{5,6}

Drug allergy is generally caused by IgE-mediated immediate-type reactions or T-cell-mediated delayed-type reactions. Was a skin test performed as part of the diagnostic procedure?

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After obtaining verbal informed consent from the patient's parents, skin tests were performed with CBP for IV administration diluted in sterile isotonic solution (10 mg/mL for the skin prick test and 1 mg/mL for the intradermal test). A histamine (1 mg/mL for the skin prick test and 0.1 mg/mL

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for the intradermal test) and glycerin challenge were included as positive and negative controls, respectively.^{7,8} Readings were taken 15 to 20 minutes after the skin tests. The mean diameter of the wheal and erythema of the test preparations and the positive (5 mm wheal) and negative controls were measured. The patient was positive for the CBP skin allergy test.

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According to the algorithm of Naranjo et al⁹ (Table 1), the adverse drug reaction would be classified as definitely associated to CBP with a score of 11. Did you rechallenge the patient with CBP?

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The patient needs to continue treatment with CBP because of her cancer, despite the hypersensitivity reaction.^{10,11} Based on the positive skin tests results and because rechallenge with CBP could be life-threatening, we rechallenged this patient under premedication and strict clinical and cardiovascular monitoring (at the pediatric intensive care unit) 1 week after the first hypersensitivity reaction.¹²

She experienced a second episode of itchiness, maculopapular rash, sweating, respiratory distress, and anxiety. A new course of adrenalin, hydrocortisone, and diphenhydramine was administered to reverse the anaphylactic reaction. However, the cumulative dose of CBP administered was only 10 mg (specific threshold dose). The girl's optic nerve glioma, diagnosed by magnetic resonance imaging because it was not possible to biopsy the tumor, was responding to the CBP treatment. How can we continue to effectively treat her cancer with CBP?

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The patient who develops a reaction to carboplatin but requires further treatment is a concern, especially in the pediatric population. The physician must weigh the potential benefits of continuing therapy with the risk of a life-threatening reaction. Options available to the patient with a positive skin test to CBP are desensitization, changing to a different platinum drug, or discontinuing platinum therapy altogether. Lafay et al¹² reported the Canadian Pediatric Brain Tumor Consortium's experience with carboplatin hypersensitivity in pediatric patients with low-grade glioma. Of 105 patients from 10 Canadian centers, only two centers attempted desensitization. Of these two, neither observed a significant benefit with a desensitization approach. Notably, 32% of patients experienced a more severe reaction on re-exposure to CBP. As a result, this necessitated the procedure to be undertaken in a pediatric intensive care unit.

Various desensitization protocols include prolonged infusion and premedication. Successful desensitization to CBP has been reported primarily in small studies or in case reports. Castells et al¹³ reported a study of 413 cases of rapid desensitization to various chemotherapy agents, including CBP (212 of the cases), using a 12-step protocol. This protocol was safe and effective with mild or no reaction in 94% of cases.

After thorough analysis of the patient's apparent allergy to CBP with skin tests, the clinical course of the adverse drug reaction, and the need to continue with CBP treatments, we recommend desensitizing the patient to the drug.¹⁴⁻¹⁶ Did you attempt a multiple-step, stepwise, gradual dose increase of CBP?

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One week after the second anaphylactic reaction, we attempted an 8-hour desensitization procedure in which the

TABLE 1. Naranjo's Scale

Question	Answer	Score
1. Are there previous conclusive reports on this reaction?	Yes (+1) No (0) Do not know or not done (0)	0
2. Did the adverse event appear after the suspected drug was given?	Yes (+2) No (-1) Do not know or not done (0)	2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes (+1) No (0) Do not know or not done (0)	1
4. Did the adverse reaction appear when the drug was readministered?	Yes (+2) No (-2) Do not know or not done (0)	2
5. Are there alternative causes that could have caused the reaction?	Yes (-1) No (+2) Do not know or not done (0)	2
6. Did the reaction reappear when a placebo was given?	Yes (-1) No (+1) Do not know or not done (0)	1
7. Was the drug detected in any body fluid in toxic concentrations?	Yes (+1) No (0) Do not know or not done (0)	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	Yes (+1) No (0) Do not know or not done (0)	1
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	Yes (+1) No (0) Do not know or not done (0)	1
10. Was the adverse event confirmed by any objective evidence?	Yes (+1) No (0) Do not know or not done (0)	1
Scoring		
> 9 = definite ADR		11
5-8 = probable ADR		
1-4 = possible ADR		

ADR, adverse drug reaction.

TABLE 2. Proposed Desensitization Protocol to Carboplatin

Step No.	Solution No.	Rate (mL/hr)	Time	Observation	Volume Infused per Step	Administered Dose	Cumulative Dose
1	1	8	15 minutes	15 minutes	2 mL	0.03	0.03
2	1	20	15 minutes	15 minutes	5 mL	0.075	0.105
3	1	40	15 minutes	15 minutes	10 mL	0.15	0.255
4	1	80	15 minutes	15 minutes	20 mL	0.3	0.555
5	2	20	15 minutes	15 minutes	5 mL	0.75	1.305
6	2	40	15 minutes	15 minutes	10 mL	1.5	2.805
7	2	80	15 minutes	15 minutes	20 mL	3	5.805
8	2	100	30 minutes	15 minutes	50 mL	7.5	13.305
9	3	40	15 minutes	15 minutes	10 mL	15	28.305
10	3	80	15 minutes	15 minutes	20 mL	30	58.305
11	3	30	120 minutes		60 mL	90	148.305
			Total time	7 hours 45 minutes			

dose was slowly increased while the patient was constantly monitored by noninvasive methods.^{17–20}

An initial dose of 0.03 mg CBP was diluted 1:1000 followed by dose increases every 15 minutes, as shown in Table 2, with an additional 15-minute surveillance period between each of these steps. Her gastrointestinal and cardiovascular tolerance was monitored until a dose of 150 mg CBP (cumulative dose 300 mg/m²) was reached. The documented threshold dose (patients minimal dose with the risk of developing hypersensitivity reaction) was 10 mg and 100 mL/hour diluted 1:10; when reached, the infusion rate was slowed down (30 minutes). At all times, especially during the threshold dose, the patient's vital signs and clinical condition were stable.

At the completion of this procedure, the patient had already received 300 mg/m² of the 600 mg/m² CBP required for her treatment. The patient had developed the necessary tolerance to receive the 300 mg/m² missing to further complete the treatment. It is of utmost importance to keep in mind that the acquired tolerance will not last more than 48 hours.

THERAPEUTIC DRUG MONITORING CONSULTANT

There is no standard protocol to prevent a carboplatin hypersensitivity reaction, but there are precautions that can be taken.²¹ The risk of this reaction increased significantly at Cycle 6 and continues to increase to Cycle 8 to a cumulative risk of 19.5%.²² To identify patients who may be at risk of a reaction, skin testing is recommended after the sixth course. This diagnostic procedure may not be useful beforehand because sensitization to CBP is usually slow and patients tend to need more courses to develop a hypersensitivity reaction.

Zanotti et al²² was the first to demonstrate that CBP skin testing could identify patients who could safely be administered carboplatin with a 99% negative predictive value in a study involving 47 patients. The skin test protocol consisted of an intradermal injection of 0.02 mL of an undiluted aliquot of the carboplatin preparation planned for infusion (100–240 µg of carboplatin). Subsequently, this expanded to 126 patients receiving more than six courses of platinum-based therapy and found a 98.5% negative predictive value, thus

validating skin testing as a method to predict hypersensitivity reactions.²³

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Desensitization to CBP has not been reported in a 1-year-old child. The optic nerve glioma was now in complete remission and she underwent vigilance. Because of the risk of adverse reactions, only experienced physicians should perform desensitization. Once desensitization is achieved, the drug must be continued or tolerance will be lost after 48 hours; the patient would then require repeated desensitization before readministration at the intensive care unit. Pretreatment with antihistamines and corticosteroids is not reliable for preventing IgE-mediated anaphylaxis. Patients with a history of allergy are more likely than the general population to have a drug reaction, which can be severe. In summary, a 1-year-old patient had an anaphylactic reaction to CBP, mediated by IgE, with a positive skin test to the compound and was successfully desensitized.

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ERRATUM

Specificity of a Circulating Antibody that Interferes with a Widely Used Tacrolimus Immunoassay: Erratum

In this article appearing in the April 2010 issue, references 2 and 3 were incorrect. The following are the correct references.

2. United Network for Organ Sharing 2007 Annual report, Table 5.6e. Available at: <http://www.optn.org/AR2007/AR2007.exe>. Accessed December 8, 2008.
3. Participant Summary CSM-A. Northfield, IL: College of American Pathologists. 2008:3.

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