

patients referred by the ID and SCI clinics. This subgroup had a higher burden of β -lactam utilization than all other referral groups combined, likely due to their increased risk of infections, complicated infections, and recurrent antibiotic use. Thus, our findings suggest that PST may be more successful at maximizing clinical outcomes and cost-effectiveness through developing outpatient programs that proactively target high-risk patient populations. Limitations of our study include the low number of patients and the relatively short follow-up period. In addition, our PST-negative rate of 93% was slightly higher than the reported 90% negative rate in the general population, which may be in part due to a male-predominant population within the VA healthcare system. Collaboration between allergists and local antimicrobial stewardship programs in the outpatient setting is needed to further our understanding of how to address this public health concern and accomplish our shared goals.

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Anaphylaxis and severe immune hemolytic anemia during the course of desensitization with carboplatin



Platinum salts are one of the most frequent cytostatic agents involved in drug hypersensitivity.¹ Drug desensitization may enable continuation of therapy for disease control.² The approach consists of giving incremental doses of the drug by the intravenous route until the therapeutic dose is reached. A transitory desensitization is induced, although release of mast-cell mediators may still occur and require the administration of antihistamines and other drugs.³

We present the case of a patient who had a reaction during the course of desensitization with carboplatin. In addition to developing anaphylactic episodes (type I), the patient also had a severe episode of acute hemolytic anemia (HA) and thrombocytopenia (type II) during the desensitization.

A 66-year-old woman with ovarian cancer with peritoneal dissemination was treated with cisplatin and paclitaxel. She received several courses of paclitaxel, gemcitabine, and topotecan due to relapses. Because of cisplatin neurotoxicity, carboplatin was given. During the third treatment course, she developed facial erythema, pruritus, and malaise. An intradermal skin test with carboplatin was negative. One month later, during a new infusion, she developed pruritus, generalized erythema, and difficulty breathing, with desaturation of 85%. Treatment was interrupted and dexchlorpheniramine and prednisone were administered. Intradermal testing at 0.1 mg/mL was positive (wheal area of 6 mm plus erythema of 12 mm). She was diagnosed with grade III anaphylaxis.

Carboplatin desensitization was indicated,² with incremental doses starting at 0.01 mg up to a final cumulative dose of 149 mg. A total of 13 steps were required. Between January 2011 and November 2015,

she received 6 sessions premedicated with aspirin 350 mg, prednisolone 120 mg, cetirizine 20 mg, montelukast 10 mg, and ranitidine 150 mg.² During the third cycle, she developed an anaphylactic episode with palm and sole pruritus, generalized erythema, difficulty breathing, and tachycardia (140 beats/min), requiring adrenaline administration. Because of tumor relapse she continued to receive desensitization from 2011 to 2014, with good tolerance. During the last cycle, after completing the total dose, she had an episode of generalized malaise; intense pain in the back, lumbar area, and epigastrium; faintness; and cold in the extremities, but with no signs of anaphylaxis. She was transferred to the intensive care unit. Electrocardiographic and x-ray results were normal and acute coronary syndrome, acute aortic syndrome, and pulmonary thromboembolism were all ruled out. Sequential peripheral blood samples were obtained (Table 1). At 2 hours after the episode, the patient's hemoglobin level had decreased from 9.7 to 5.9 g/dL, total leukocytes were $1.7 \times 10^3/\mu\text{L}$, platelet count decreased to $4 \times 10^4/\mu\text{L}$, and there were increases in lactate dehydrogenase (LDH) total bilirubin, with a normal conjugated fraction. Tryptase values were within normal limits and a direct Coombs test was positive. Further analysis 6 hours after the acute episode showed the appearance of reticulocytes and increases in LDH and total bilirubin; the direct Coombs test was strongly positive for anti-immunoglobulin G (anti-IgG) and anti-C3d. Tryptase values remained normal. Blood staining for schistocytes was negative, thereby ruling out thrombotic microangiopathy.

A diagnosis of HA and thrombocytopenia was made and corticosteroids (1.5 mg/kg/day) were administered for 3 weeks. On the third day of treatment the direct Coombs tests became negative. A concentrate of red blood cells was administered with improvement in hematocrit to 35% and hemoglobin to 11.3 g/dL (48 hours post-episode; Table 1). During follow up, LDH, total bilirubin, and leukocyte values became normal, with a decrease in reticulocytes. Platelet count continued to decrease until starting a recovery at 48 hours (Table 1); 1 month later platelet count was $>10^5/\mu\text{L}$. The final diagnosis was HA and thrombocytopenia with an IgG-antibody

Table 1

Sequential Hematologic and Biochemistry Parameters Taken Before and 2, 6, 24, and 48 Hours After Acute Hemolytic Episode

	Pre-episode	2 hours post-episode	6 hours post-episode	24 hours post-episode	48 hours post-episode
Hemoglobin	9.7 g/dL	5.9 g/dL	5.4 g/dL	5.7 g/dL	11.3 g/dL
Hematocrit	28.9%	16.4%	15%	15.5%	35.5%
Leukocytes	$3.9 \times 10^3/\mu\text{L}$	$17 \times 10^3/\mu\text{L}$	$17 \times 10^3/\mu\text{L}$	$9 \times 10^3/\mu\text{L}$	$12 \times 10^3/\mu\text{L}$
Platelets	$114 \times 10^4/\mu\text{L}$	$4 \times 10^4/\mu\text{L}$	$4.1 \times 10^4/\mu\text{L}$	$2.8 \times 10^4/\mu\text{L}$	$4.2 \times 10^4/\mu\text{L}$
Reticulocytes	0%	0%	7.86%	5.9%	3.7%
Schistocytes	ND	No	No	No	No
CPK	ND	144 U/L	125 U/L	120 U/L	110 U/L
Creatinine	0.91 mg/dL	0.81 mg/dL	1.2 mg/dL	1 mg/dL	1.2 mg/dL
Urea	23 mg/dL	38 mg/dL	64 mg/dL	60 mg/dL	35 mg/dL
LDH	ND	1,800 U/L	1,980 U/L	900 U/L	158 U/L
Total bilirubin		3.6 mg/dL	4.1 mg/dL	1.2 mg/dL	0.7 mg/dL
Conj bilirubin	0.4 mg/dL	0.40 mg/dL	0.35 mg/dL	0.30 mg/dL	0.30 mg/dL
Direct Coombs	Negative	Positive	Positive	Positive	Positive
Troponin T		17×10^{-3} ng/mL	30×10^{-3} ng/mL		
Tryptase	8 $\mu\text{g/mL}$	9 $\mu\text{g/mL}$	11 $\mu\text{g/mL}$	8 $\mu\text{g/mL}$	10 $\mu\text{g/mL}$

Abbreviations: CPK, creatinine phosphokinase; LDH, lactate dehydrogenase; Conj bilirubin, conjugated bilirubin; ND, not done.

isotype (type II) in a patient with a history of anaphylaxis to carboplatin (type I), all induced by the same drug.

Although drugs can produce hypersensitivity reactions by any of the 4 mechanisms described by Gell and Coombs, most subjects develop reactions to a single drug with 1 specific mechanism that is usually IgE- or T-cell-dependent.⁴ Cases of an immediate response to various drugs have been reported with amoxicillin and clavulanic acid,⁴ and also in up to 3 different nonsteroidal anti-inflammatory drugs.⁵ More rarely, cases of a combined IgE and T-cell response to dipyrone and penicillin G have been reported.⁶ However, to our knowledge the combination of a type I IgE-mediated reaction and a type II IgG-mediated reaction to the same drug occurring during the course of desensitization has not been reported.

Regarding type II reactions such as HA, although the drugs most commonly implicated are antibiotics, such as second- and third-generation cephalosporins, reports exist of the involvement of chemotherapeutic agents such as platinum salts, which can even be fatal in some cases.⁷

The occurrence of dual immunologic responses to allergens is well known in patients with extrinsic asthma who, after challenge, develop an IgE immediate response followed by a late response several hours afterward, with the latter being more prolonged and severe. The existence of an IgE plus IgG or IgM response, a combination of type I plus type III, has been proposed.⁸ A similar mechanism occurs in occupational asthma to low-molecular-weight compounds. Experimental evidence using methylene diphenyl diisocyanate has shown the production of IgE and IgG antibodies.⁹ In the case described herein, we suggest that the patient developed IgE antibodies to carboplatin, which was responsible for the anaphylactic episodes, and in the course of further exposure she developed an IgG response to a platinum bound to a membrane protein of erythrocytes and platelets. Although no indirect Coombs tests or platelet assays were done to attempt to demonstrate the presence of IgG or other isotypes, the positive direct Coombs test that became negative and the rapid recovery of the erythrocyte and platelet counts after drug withdrawal support the diagnosis of drug-induced HA and thrombocytopenia.

Caution must be exercised in those patients with similar episodes in the course of desensitization to carboplatin. Although no clear signs of anaphylaxis appear, if there are severe symptoms and blood values indicative of hemolysis, HA and thrombocytopenia should be suspected. To our knowledge, this is the first case of this type to be reported in the literature.

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