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Case Report

Hypersensitivity reaction to parenteral nutrition after severe hypersensitivity reaction to paclitaxel: a case report

Janiel M Cragun[1], Jennifer H Baggs[2], Carol Rollins[3], Setsuko K Chambers[1]

[1]Department of Obstetrics and Gynecology, University of Arizona, University of Arizona Cancer Center, Tucson, AZ, USA; [2]Department of Pharmacy, University of Arizona Medical Center, Tucson, AZ, USA; [3]Department of Pharmacy Practice and Science, University of Arizona, Tucson, AZ, USA

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Abstract: Paclitaxel, an anti-microtubule chemotherapeutic agent, is known for hypersensitivity reactions. Hypersensitivity reactions associated with paclitaxel may be secondary to its vehicle, Cremophor EL rather than the paclitaxel itself. In contrast, hypersensitivity reactions to parenteral nutrition are uncommon. Both the lipid component and multivitamin have been implicated in hypersensitivity reactions to parenteral nutrition. Similar to paclitaxel, the vehicle for IV vitamins, polysorbate 80, may be the source of reaction rather than the vitamin, itself. We present a case report of a patient who had a severe hypersensitivity reaction to paclitaxel and also a hypersensitivity reaction to the multivitamin component of parenteral nutrition, as well as to vitamin K administered separate from parenteral nutrition. To our knowledge this is the first case report describing a potential cross-hypersensitivity to these agents.

Keywords: Hypersensitivity, parenteral nutrition, paclitaxel

Introduction

Paclitaxel is an anti-microtubule agent derived from the *Taxus baccata* tree [1]. The use of paclitaxel has improved survival in many solid tumors to include ovarian and breast cancer. Early clinical studies showed major toxicity of hypersensitivity to paclitaxel occurring in 41% of infusions leading to routine premedication with steroids, diphenhydramine and a histamine2 antagonist [1]. The most common described reactions to paclitaxel are dyspnea, urticaria or rash [2]. Less common, are serious hypersensitivity reactions (HSR) occurring in 2-4% of infusions [1, 3]. These consist of hypotension, hypertension, and angioedema including epiglottis swelling and stridor [2]. In extreme reactions, fatalities have been reported [4].

Reactions to paclitaxel are traditionally believed to be from the drug, itself, through a classic IgE mediated pathway. IgE mediated, or Type 1 allergies, arise from repeated exposure to an antigen. They become stronger with repeat exposure and they are rare, with a reaction rate below 2% [5]. Recent investigation supports that Cremophor EL, the vehicle for paclitaxel which contains polyoxyethylated castor oil, may actually be the cause of hypersensitivity through a complement activated, non-IgE mediated pathway [5-8]. Both pathways present with similar characteristics to include, but not limited to, flushing, erythema, rash, skin eruptions, urticaria, wheezing, dyspnea, angioedema, bronchospasm, hypotension, and death [5]. As presentation can mimic a true IgE mediated allergy, complement mediated reactions have adopted the term C activation-related pseudoallergy (CARPA) [5]. CARPAs are thought to trigger mast cells through anaphylatoxins, C3a and C5a [5, 7]. In contrast to true type 1 allergies, CARPAs can arise without prior exposure and repeated exposure can result in decreased symptoms including resolution of symptoms. In addition, CARPAs can present with a high reaction rate (45%) occurring within minutes after starting infusion [5, 6].

In contrast to paclitaxel, HSRs to parenteral nutrition (PN) are rare [9]. Case reports have

identified the multi-vitamin component, thiamine, vitamin B complex, vitamin K and magnesium sulfate as likely causes of reaction [9-15]. Polyoxyethylated fatty acid derivatives, similar to Cremophor EL, can also be found as a vehicle for fat soluble vitamins leading to CARPA. In addition, the inactive component, polysorbate, is believed to be a primary cause of hypersensitivity [10]. Other case reports have identified the lipid component as the causative agent. Lipid emulsion (LE) contains egg phospholipids, plant-derived oils, and glycerol [10]. Cross-reactivity with egg allergies have been reported [12].

We present a unique case in which a patient had both a severe HSR to paclitaxel and also to PN.

Case report

The patient is a 65 year-old gravida 2, para 2, white female with stage IIA, grade 3, endometrial serous carcinoma diagnosed approximately 5 weeks prior to presentation. At the time of presentation she was post robotic hysterectomy, bilateral salpingo-oophorectomy, and full staging with lymphadenectomy and omental biopsy, complicated by a lymphatic leak, which resolved with conservative management. The tumor involved 40% of her myometrium and the cervix. There was no involvement of lymph nodes, omentum, washings, tubes or ovaries. She was presented at the institutional tumor board and was recommended vaginal brachytherapy and adjuvant chemotherapy with carboplatin and paclitaxel. Her baseline CA125 was 67 U/mL (reference range 0-35 U/mL) and the baseline CT of chest, abdomen, and pelvis did not show any suspicious findings.

Upon initial presentation, she reported allergies only to codeine (rash) and an acetaminophen - oxycodone combination product (dizziness, nausea). Her past medical history was significant for left breast DCIS in 1991 treated with lumpectomy and radiation therapy and left invasive ER positive ductal cancer in 2000 treated with mastectomy and tamoxifen for 5 years, then letrozole which she was still taking. She had a history of viral cardiomyopathy resulting in ventricular tachycardia for which she had an initial defibrillator placed in 1998, subsequently complicated by perforation resulting in pericardiac effusion requiring a pericardiac window in 2000. The defibrillator was replaced in 2004. In 2009, her nuclear stress test was normal with an ejection fraction of 60%. Her family history was significant for one daughter with chronic urticaria and another daughter with lupus. Her BMI was 23.2.

The patient's first infusion of carboplatin and paclitaxel went uneventfully. Five days later, around the same time as she was started on clonazepam for adjustment disorder and anxiety by her psychiatrist, she noticed some pruritus and 4 days after the start of pruritus (9 days after chemotherapy), diphenhydramine was initiated. Eleven days after the chemotherapy she developed hives. She was seen in the emergency room and was treated with diphenhydramine, prednisone at 20 mg daily, and hydrocortisone cream for urticaria. She followed up with the dermatologist the next day (day 12 after chemotherapy) where the diagnosis of allergic vasculitis was made. The examination showed non-branching purpuric non palpable plaques on the lower extremities. Her prednisone dose was increased to 60mg daily and doxepin was added at night. In follow-up with the dermatologist, 2 days later (day 14 post chemotherapy), the prednisone was replaced by cetirizine as the patient could not tolerate the insomnia and anxiety associated with prednisone. At that time, the rash had responded well, and upper extremity urticaria was controlled when she took diphenhydramine.

The etiology of the drug reaction was not known; however, paclitaxel and clonazepam were felt to be unlikely candidates at this time. She was felt to have chronic recurrent urticaria and possibly an autoimmune process, with a lupus work-up ordered during her initial radiation oncology consultation on that same day. Her anti-nuclear antigen titer was low (<1:40), generally considered negative. The next day (day 15 after chemotherapy) she saw a rheumatologist. At that time, urticaria was noted on both upper and lower extremities. After discussion, further vasculitis and autoimmune work-up was postponed for the time being.

At the time of presentation for consideration of her second cycle of chemotherapy, she was asymptomatic with pruritus and urticaria resolved. She was off many medications at that time. Several of her usual home medications had been stopped, including alendronate, ranit-

idine, aspirin, vitamins, and glutamine. She was also off prednisone and doxepin. Her CA125 was down to 22 U/mL and her examination did not reveal any rashes or hives. In light of the timing of the urticaria being atypical for a reaction to paclitaxel, the decision was made to proceed with her second cycle. The patient was premedicated with dexamethasone (20 mg), diphenhydramine (50 mg), palonosetron (250 ug) and famotidine (20 mg), but only 1.6 mL into her infusion with paclitaxel she experienced sudden onset shortness of breath and chest pain, with subsequent vomiting and cardiopulmonary arrest. The rapid response team was called. The patient was resuscitated and transferred via ambulance from the outpatient infusion facility to the hospital emergency department. After further stabilization in the emergency department, she was transferred intubated to the ICU on vasopressors, methylprednisolone, and epinephrine. On hospital day 2, she complained of mid-abdominal pain. Work-up with CT scan suggested ischemic bowel and she was taken for laparotomy with subtotal colectomy for ischemia of the right, transverse, and left colon. Her abdomen was left open at this time with follow-up wound closure and creation of ileostomy. She was advanced to a diet without requiring PN during this hospital admission. She was discharged on hospital day 13 with home health, physical therapy, psychiatry, and gynecologic oncology follow-up.

Following full recovery, and subsequent considerable discussion, the patient opted for therapy with single agent carboplatin for 3 cycles preceded each time with carboplatin skin testing, along with adjuvant vaginal radiation therapy, all of which she received and tolerated well. Her course was complicated by a brief admission for ileostomy stricture requiring manual dilatation.

After her last cycle of carboplatin, despite manual ileostomy dilatation, she was admitted to the hospital with partial small bowel obstruction with severe nausea and vomiting, profuse watery diarrhea, and hyponatremia. There was a potential transition point in the terminal ileum on CT scan. A nasogastric (NG) tube was placed for initial decompression and conservative management. The patient developed neutropenia from the chemotherapy delaying any potential surgical intervention, so the decision was made to start the patient on PN. Almost immediately after starting the lipid containing PN infusion, the patient developed hypotension, tachycardia, and hypoxemia. She also had an urticarial skin rash on bilateral upper extremities and abdomen. The PN was stopped immediately and the rapid response team was called. Her symptoms improved with oxygen via nonrebreather, fluid bolus, hydrocortisone and diphenhydramine. The clinical pharmacist/director of PN was consulted.

Secondary to the patient's continued need for nutrition, and in close consultation with the clinical pharmacist/director of PN, separate 30 mL test doses of the elements of PN were given following premedication with diphenhydramine and hydrocortisone. The LE was held from all doses secondary to the statistical likelihood that this was the element responsible for her reaction. The first test dose had dextrose and amino acids; this was followed by the addition of electrolytes, and then the addition of an adult vitamin formulation. The final combination of electrolytes, amino acids, dextrose, and vitamins was tolerated well during the test dose. This formulation was subsequently given to the patient, but she developed a rash, which resolved with stopping the PN and administration of diphenhydramine. The patient tolerated PN with no rash or urticaria noted with the removal of multivitamins from succeeding PN solutions. A second allergy trial was performed, again in close conjunction with the clinical pharmacist, with the patient tolerating the addition of ascorbic acid, thiamine, and folate individually and then in combination to the base non-lipid containing PN solution. After receiving PN with dextrose, amino acids, electrolytes and the three vitamin combination for several days without a reaction, the patient received an intramuscular injection of vitamin K secondary to an elevated prothrombin time. She developed a severe rash, and mild hypotension, which responded to a fluid bolus, diphenhydramine and steroids.

The patient proceeded to receive a PN formulation with only dextrose, amino acids, folate, ascorbic acid, thiamine, and electrolytes. She was supported during this entire time for neutropenia, anemia, and thrombocytopenia with daily filgrastim, and with red blood cells and platelet transfusions as required. Her liver function tests (LFTs) started to rise with gamma-

glutayml transferase in the 400's IU/L (reference range 10-47 IU/L), bilirubin to 13.9 mg/dL (reference range (0.2-1.3 mg/dL), and alkaline phosphatase in the 200's IU/L (reference range 37-107 IU/L). Gastroenterology consultation with liver imaging revealed biliary sludge only. She also was treated for aspiration pneumonia. After resolution of her bone marrow suppression, and with improvement in her LFTs, the patient underwent revision of her ileostomy, with resection of her terminal ileum, lysis of adhesions, and cholecystectomy. It should be noted that the LFTs improved post-operatively despite continuation of this formulation of PN. The NG tube was subsequently discontinued, the PN weaned, and she was discharged home tolerating a soft diet.

Discussion

In this report, we describe a HSR to PN in a patient with a history of serious paclitaxel-related HSR. The majority of paclitaxel reactions occur with the first or second exposure to the medication [2]. In a study from the Cleveland Clinic, 77% of hypersensitivity reactions occurred with the first episode, 18% with the second course, and 5% after the second course of paclitaxel [16]. Reactions usually occurred within the first 5 minutes, with the majority in the first 1-2 minutes [16]. This pattern of quick onset in first exposure is more common in CARPA [5] than in IgE-mediated reactions. In the patient presented, the agent responsible for her allergic reaction was unclear as the timing was remote from the infusion of paclitaxel (5 days post initial infusion). However, CARPA can be delayed in premedicated patients, as this patient was, and may have caused her initial rash and urticaria [6]. Although early studies suggested that reactions to paclitaxel were delayed no longer than 12 hours after infusion, patients can have delayed reactions presenting as erythematous rashes up to 10 days post infusion [2, 7, 17]. This type of delayed reaction can lead to IgE sensitization and severe hypersensitivity upon re-exposure even with premedication [7].

The ability to predict a patient's hypersensitivity to paclitaxel has yet to be established. Genetic associations have been proposed [11, 18]. Sendo et al. evaluated possible risk factors of hypersensitivity reactions [19]. They found hypersensitivity increased as the numbers of identified risk factors increased: 1) history of mild dermal reactions such as facial flushing and urticaria in previous courses; 2) presence of respiratory dysfunction; 3) obesity with BMI >25 and 4) postmenopausal status at time of oophorectomy [19]. Interestingly, they found that reactions appeared to be higher in ovarian cancer patients. Further, patients with oophorectomy after menopause had 5.8 fold higher risk of paclitaxel associated hypersensitivity reaction [19]. The reasons for this are unclear. The patient presented here had only one risk factor, being postmenopausal at the time of oophorectomy. In absence of a screening tool to predict hypersensitivity reactions, once treated, patients suspicious of having a HSR can be evaluated for rapid desensitization at time of infusion. Successful desensitization protocols have provided a mechanism for patients to continue valuable standard therapy following a hypersensitivity reaction [7, 17].

This patient's reaction to paclitaxel was known when the PN formulation was compounded; however, there was no suspicion for potential cross-reactivity to any of the PN components. Initially, the LE component of the PN formulation was thought to be the cause of the reaction. LEs are a complex mixture of plant-based oils, egg yolk phospholipids, and glycerin. Only two LE products are currently FDA-approved, one containing soybean and safflower oil and the second containing only soybean oil, which was used in this case. Several reports of PN-induced HSRs have implicated LEs as a cause of the reaction with multiple etiologies. Allergy testing in affected patients has revealed soybean oil and egg yolk phospholipid as potential causes of HSRs [12, 20]. Manufacturers of LE indicate that egg, soy, or peanut protein allergies are contraindications to the use of LE. The patient presented in this case did not have any known food allergies, in fact denied allergy specifically to soy or eggs. In this case, the concern was that the reaction was related to a cross-reactivity between the castor oil-based Cremophor EL and soybean oil in the LE as both are natural oil polyols and part of the legume family. Therefore LE were removed from all further PN formulations. Although the LE likely contributed to the reaction given the severity of the reaction with lipid containing PN, the patient also developed a rash to the PN formulation without lipids, suggesting an additional cause for the reaction.

Multivitamin for injection (MVI) was considered the second most likely PN component to cause the HSR in this patient. Case reports of hypersensitivity with PN formulations without LEs have concluded that the polysorbate excipient in the MVI preparation may be the agent responsible for the reaction [10]. The MVI preparations used in PN are complex mixtures containing both water-soluble and fat-soluble vitamins. Polysorbates, also called Tweens, are used to solubilize fat-soluble vitamins A, D, E, and K. Polysorbate 80, the excipient used exclusively in the MVI formulation for the patient presented, has been reported to cause severe anaphylactic reactions, including shortness of breath, bronchospasm, tachycardia, and hypotension [21]. In addition, polysorbate 80 been associated with complement activation and can result in release of anaphylatoxins C3a and C5a [22]. The patient had no further PN associated HSR after the MVI preparation was removed from the PN formulation.

Guidelines for safe PN state that all PN formulations are to include vitamins [23]. Nationwide shortages of parenteral MVI preparations occurring in the 1980s led to the death of a patient receiving PN without MVIs. The cause of death was reported to be refractory lactic acidosis and autopsy findings of brain lesions were diagnostic of acute thiamine deficiency [23]. Therefore, in this patient, thiamine was considered essential and was added to all subsequent PN formulations after she tolerated her trial PN with thiamine. Addition of the monovitamin water-soluble products folic acid and ascorbic acid was also considered essential given the patients history of poor oral intake prior to hospitalization. Ideally, all water soluble vitamins would have been included in the PN; however, most vitamins are not available as individual injectable products.

This patient had hypersensitivities to both paclitaxel and PN. Although the exact cause of her reactions is not known definitively, both reactions were consistent with CARPA through their vehicles, Cremophor EL containing castor oil and polysorbate 80. Historically, there is little to predict that the two vehicles would have cross-reactivity as their chemical structure is different. Further, in practice, patients who react to paclitaxel are often changed to docetaxel, which uses polysorbate 80 for its vehicle. Hypersensitivities to docetaxel range 5-40% [21]. As the incidence of hypersensitivity in docetaxel approximates that of paclitaxel, the cross-reactivity is believed more likely to the taxanes rather than the vehicles. In challenge to this, some studies suggest that hypersensitivity of both drugs is related to their vehicles rather than the drug [22]. There has been one case report presenting a possible cross-reactivity between paclitaxel and etoposide. As the vehicle for paclitaxel is Cremophor EL and the vehicle for etoposide is polysorbate 80, the case report also presents a possible cross-reactivity between the two vehicles, both of which can result in release of anaphylatoxins C3a and C5a [3, 22, 24].

The case presented here exemplifies the importance of investigating components other than the active drug when evaluating HSRs. In addition to the paclitaxel, itself, Cremophor EL has been implicated as a possible cause of the HSRs that occur with paclitaxel infusions. Cremophor EL, of which the principal component is a polyoxyethylated derivative of castor oil, can be found in several other intravenous pharmaceutical products including anesthetics, sedatives, and immunosuppressant agents [8]. Examples include lipophilic vitamins A, D, E and K; miconazole, hexedetine, clotrimazole, benzocaine, cyclosporine A, ixabepilone, loxitane, VePesid, and diphtheria, pertussis, tetanus vaccines [3, 25-27]. Vitamin K in this case was found to have a common vehicle of a polyoxyethylated fatty acid derivative identified as castor oil. While the MVI product did not contain a castor oil derivative, it did contain polysorbate 80 as a solubilizing agent. Polysorbate 80 has been implicated in severe reactions to a variety of products, including MVI [21]. In addition, other solvents that could contribute to HSRs are often present in pharmaceutical products. Cremophor EL contains polyethylene glycol and MVI contains propylene glycol. These solvents are widely used in pharmaceutical products and both have been associated with HSRs [28, 29]. Either or both solvents could have played a secondary role in the case presented. The three monovitamins administered in this case, which did not cause a HSR, were water-soluble and did not require solubilizing agents; they contained no castor oil, polysorbate 80, polyethylene glycol or propylene glycol. Heightened vigilance should be applied to patients believed to have hypersensitivity to any non-active component of a medication and

avoid other medications prepared with the same or potentially cross-reactive components.

Conclusion

Primary HSRs to paclitaxel are well described. In some cases, however, the reaction may be due to complement mediated response to Cremophor EL rather than a classic IgE mediated response to the paclitaxel, itself. In contrast, reactions to PN are rare and may represent a response to the lipid component, or may be due to a complement mediated response to polysorbate 80. This represents the second case in the literature that may show a cross-reactivity between Cremophor EL and polysorbate 80 through CARPA. Serious hypersensitivities can be life threatening. Patients who have had a reaction to paclitaxel should not receive other drugs containing Cremophor EL or castor oil, which could potentially include any lipid soluble drug or vitamin requiring a solubilizing agent in the formulation. Patients who have had a reaction to drugs with polysorbate 80 should be vigilant for other drugs containing this vehicle. Desensitization protocols may allow for patients with less severe reactions to continue needed therapy without increased risk of second reaction. Although this potential cross-hypersensitivity appears to be rare, this relationship should be kept in mind, in the case of a very severe HSR to either Cremaphor EL containing agents, such as paclitaxel, or polysorbate 80 containing products, such as MVI.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Janiel M Cragun, Department of Obstetrics and Gynecology, University of Arizona, University of Arizona Cancer Center, 1515 N. Campbell Avenue, PO Box 245024, Tucson, AZ 85724, USA. Fax: 520-694-9287; E-mail: Janiel.Cragun@uahealth.com

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