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The Hidden Culprit: A Case of Repeated Anaphylaxis to Cremophor

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Drug-induced anaphylaxis is a big pitfall in patients receiving antineoplastic chemotherapy. We report a case of lung cancer patient who experienced two near-fatal anaphylactic reactions that resulted from paclitaxel and multivitamin, seperately. Recurrent severe reactions to different agents led to further investigation to which material the patient was hypersensitive. The skin prick test revealed sensitization to cremophor, which is a commonly used emulsifying agent. This case emphasizes the importance of correctly identifying the culprit drug of anaphylaxis to avoid potentially fatal reaction.

Key Words: Anaphylaxis; paclitaxel; multivitamin; cremophor; hypersensitivity

INTRODUCTION

Anaphylaxis is a potentially fatal adverse reaction to various drugs. The most important aspect in diagnosing anaphylaxis is to precisely identify the offending agent to prevent future events. Although clinicians usually find the culprit drug by thoroughly reviewing the list of medications the patient was given, it is often overlooked that besides the therapeutic agents, additives can cause hypersensitivity reactions.

Cremophor is a nonionic solubilizer and emulsifier that is widely used in oil-in-water emulsion preparations.[1] Despite its wide use in various pharmaceutical products, the role of cremophor and other emulsifiers in drug hypersensitivity reactions has not been completely recognized. We present a case of a 47-year-old man who experienced 2 incidents of severe anaphylactic reaction, one following intravenous injection of paclitaxel and the other following multivitamin.

CASE REPORT

A 46-year-old man was diagnosed with stage I a non-small cell lung cancer and underwent a left upper lobectomy in January, 2014. Five months later, multiple metastases to lymph nodes were detected. Palliative chemotherapy was started with paclitaxel and cisplatin. The first dose of chemotherapeutic agents was uneventful. Three weeks later, the second cycle of chemotherapy was given. After dexamethasone (20 mg), chlorpheniramine (4 mg), and ranitidine (50 mg) were injected for premedication, 94 mg of paclitaxel (Taxol®, BMS Pharmaceutical, Seoul, Korea) mixed with 200 mL of 5% dextrose solution was infused at a rate of 200 mL/h. Approximately 8 minutes after initiation of paclitaxel infusion, the patient reported chest tightness and dyspnea. His blood pressure (BP) was 62/20 mm Hg, and the oxygen saturation (SpO_2) dropped to 80%. Paclitaxel infusion was immediately stopped, and intramuscular epinephrine (0.3 mg) injection, fluid resuscitation, and endotracheal intubation were performed simultaneously. He was transferred to the intensive care unit, and his vital signs stabilized in 30 minutes. He was immediately extubated and monitored in the intensive care unit. He remained stable afterward. With the suspicion of anaphylaxis due to paclitaxel, the regimen was changed to etoposide (E.P.S®, Boryung Pharmaceutical, Seoul, Korea) and cisplatin (CISPLAN®, DONG-A ST, Seoul, Korea). Six days later, 192 mg of etoposide mixed with 500 mL of normal saline was administered at a rate of 200 mL/h following two hours after completion of cisplatin (134 mg) infusion. Thirty minutes after initiation of the etoposide infusion, he complained of cough, chest discomfort, dyspnea, and sweating, but his vital signs were stable. After the infusion was stopped, chlorpheniramine (4 mg), hydrocortisone (100 mg), and ranitidine (50 mg) were injected intravenously. One hour later, the symptoms were relieved, and the infusion was completed at a rate of 80 mL/h without further reactions. Three

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Table. The ingredients of paclitaxel, etoposide, and multivitamin

Drug	Ingredient
Paclitaxel 30 mg/5 mL (Taxol®, BMS Pharmaceutical)	Paclitaxel 30 mg, Cremophor EL 2,635 mg, Ethanol absolute 1,950 mg
Etoposide (E.P.S®, Boryung Pharmaceutical)	Etoposide 150 mg, Citric acid 15 mg, Polyethylene glycol 4,500 mg, Polysorbate 600 mg, Ethanol absolute 7.6 mg, Nitrogen
Multivitamin 5 mL (M.V.I.®, Samung Pharmaceutical)	Vitamin A 11.5 mg, Vitamin B1 65 mg, Vitamin B2 15 mg, Vitamin B3 115 mg Vitamin B5 32.5 mg, Vitamin B6 18 mg, Vitamin C 600 mg, Vitamin D2 0.03 mg Vitamin E 6 mg, Sodium hydroxide 70 mg, Butylated hydroxyl toluene 0.285 mg Butylated hydroxyl anisole 0.076 mg, Cremophor 400 mg

Figure. Skin prick test results of ingredients of multivitamin and polysorbate (A: patient, B: healthy control). 1, cremophor; 2, polysorbate; 3, vitamin B_3; 4, vitamin C; 5, vitamin E; 6, vitamin A; 7, vitamin B_5; 8, vitamin B_1; 9, vitamin B_6; 10, sodium hydroxide; 11, vitamin B_2; 12, propyleneglycol.

weeks later, cisplatin infusion was completed without any events. However, 20 minutes after initiation of etoposide at a rate of 120 mL/h, the patient experienced similar symptoms: cough, dyspnea, and chest tightness. His vital signs were stable except tachycardia (pulse rate 133 beats/min). Etoposide infusion was stopped during the day. Additional chlorpheniramine (4 mg) and hydrocortisone (100 mg) were injected. His symptoms relieved after 30 minutes. On the next day, following dexamethasone premedication, etoposide infusion was completed at a rate of 80 mL/h without any events.

Two weeks later, multivitamin supplement (M.V.I.® 5 mL; Samsung Pharmaceuticals, Seoul, Korea) was prescribed. One liter of dextrose fluid mixed with the vitamin supplement was infused at a rate of 250 mL/h. Nine minutes after infusion, he complained of dyspnea and cold sweating. Blood pressure dropped to 52/22 mmHg, SpO_2 to 85%. Normal saline (1 L) was rapidly administered, and the patient was intubated. Epinephrine (0.3 mg) was injected intramuscularly twice at 3-minute intervals. It took about 30 minutes to return to stable vital signs. He was extubated 8 hours later, and no further reactions were observed.

Upon our request, the manufacturers provided the list of components of paclitaxel and multivitamin solution. As shown in Table, cremophor was the only ingredient used in both chemicals. The etoposide contains polysorbate instead of cremophor as an emulsifier.

Skin prick tests were performed with vitamins A (100%), B_1 (1 mg/mL), B_2 (0.25 mg/mL), B_3 (1 mg/mL), B_5 (100%), B_6 (1 mg/mL), C (1 mg/mL), and E (100%), sodium hydroxide (1 mg/mL), cremophor (100%), and polysorbate (100%) (Figure). All the agents were kindly supplied by Samsung Pharmaceuticals. Butylated hydroxyl toluene, butylated hydroxyl anisole, and vitamin D_2 were excluded because they needed to be mixed with an emulsifier to be prepared for skin prick tests. Positive reaction to cremophor, and borderline reaction to polysorbate and sodium hydroxide were observed (cremophor 5×4 mm, polysorbate 4×3 mm, sodium hydroxide 4×3 mm, and histamine 4×4 mm). In a healthy control, nothing except a histamine control resulted in a positive reaction (histamine 2×2 mm). Sodium hydroxide did not induce a wheal but a 3-mm circular pit in the healthy control probably due to its strong alkalinity. In another healthy control, skin prick tests were performed with cremophor and polysorbate, which resulted in negative reactions.

We concluded that cremophor contained in paclitaxel and

multivitamin preparations caused both incidents of anaphylaxis. Also, polysorbate contained in etoposide compound may have caused hypersensitivity reactions. Based on this conclusion, we warned him and his oncologist not to administer cremophor-containing products and to check the entire chemical compound included before injecting any medications. Polysorbate was also advised to be avoided if possible.

DISCUSSION

Intravenous administration is an important method to deliver drugs and nutrients in the medical field. Water solubility is required to prepare injectable products. Therefore, water-insoluble chemicals adopt emulsifiers to produce oil-in-water emulsion preparations. Cremophor is a synthetic, nonionic surfactant made by reacting castor oil with ethylene oxide. It is widely used for water-insoluble drugs, including paclitaxel, cyclosporine, propofol, althesin, propanidid, and vitamin supplements.

Hypersensitivity reactions to paclitaxel have been reported since the phase I trial.[2] Whether cremophor or paclitaxel itself causes hypersensitivity reactions is still inconclusive. However, it is widely recognized that hypersensitivity reactions are caused by cremophor rather than paclitaxel itself.[3] Hypersensitivity reactions have been reported consistently with other drugs containing cremophor as a vehicle.[4-7] Cremophor alone induced hypersensitivity reactions in an *in vitro* or animal study.[2] Furthermore, severe hypersensitivity was not observed with nanoparticle albumin-bound paclitaxel (nab-paclitaxel) which adopted albumin instead of cremophor in phase III trial.[8,9] However, fatal hypersensitivity reactions were reported with nab-paclitaxel in postmarketing surveillance.[10] In a study, paclitaxel alone induced histamine release in 3 healthy controls but cremophor alone did not.[11] These reports imply that paclitaxel itself may cause hypersensitivity reactions.

Symptoms caused by hypersensitivity reactions to cremophor include dyspnea, flushing, rash, chest pain, tachycardia, hypotension, angioedema, and generalized urticaria.[12] Mechanism underlying cremophor-induced hypersensitivity reaction have not yet been fully understood. Several hypotheses were suggested in earlier studies. Positive skin test results and symptoms like type I hypersensitivity reaction suggest IgE-mediated reactions in cremophor hypersensitivity.[7] Allergic reactions following the first dose of cremophor-containing drugs can be explained by the wide use of cremophor contained in various products, which can result in prior sensitization to cremophor.[13] In addition, symptoms induced by cremophor are more likely to be type I hypersensitivity reaction.[14] *In vitro* studies have demonstrated that cremophor stimulates complement activation, causing hypersensitivity reactions.[15] In addition to complement activation, oleic acid, a component of cremophor, directly causes histamine release.[1] Involvement of IgG short-sensitizing antibodies is also suggested.[7]

Between 1997 and 2007 in the United States, Europe, and Japan, 171 cases of anaphylaxis caused by cremophor-containing paclitaxel have been reported.[12] In those reports, 58 (34%) of the patients could not survive anaphylactic shock. The fatality of patients who received premedication before injection of paclitaxel was 22%. Medical Research on Adverse Drug Events and Reports (Med-RADAR), a pharmacovigilance team,[16] also reviewed 6 cases of cremophor-containing paclitaxel induced anaphylaxis. Two patients died, even though the entire patients were given prophylactic drugs before paclitaxel administration. Approximately 45% of patients treated with paclitaxel experience minor hypersensitivity reactions, and 2% of the patients have fatal reactions mostly within the first 2 courses of drug administration despite the use of premedication.

Frequent hypersensitivity reactions to paclitaxel aroused the need for the second generation taxanes. Docetaxel adopts polysorbate 80 instead of cremophor. Nevertheless, hypersensitivity reactions occur with polysorbate 80-containing docetaxel as well. A report also documented about hypersensitivity reactions to polysorbate-containing docetaxel in patients who switched chemotherapeutic agents because of hypersensitivity reactions to cremophor-containing paclitaxel.[14] During a period of 5 years, 16 patients experienced hypersensitivity reactions to paclitaxel and 10 patients changed regimen to docetaxel. Nine out of the 10 patients complained of hypersensitivity reactions with docetaxel. Despite controversy, hypersensitivity both to cremophor-containing and polysorbate-containing agents in many patients including the present case suggest cross reactivity between cremophor and polysorbate.[3,17]

Anaphylactic reactions have also been reported with other cremophor-containing drugs, including althesin,[18] propanidid,[5] propofol,[6] cyclosporine,[7,13] and vitamin K supplements.[4] Althesin and propanidid were withdrawn from the market due to serious adverse reactions. In a report, patients who were allergic to intravenous administration of cremophor-containing cyclosporine well tolerated cremophor-free oral cyclosporine.[7]

To our knowledge, this is the first case of 2 separate anaphylactic reactions that occurred in the same patient after administration of different drugs containing the same emulsifier, cremophor. Despite the potential to cause fatal anaphylactic reactions, additives, including emulsifiers, are rarely marked on drug labels and clinicians are often unaware of their existence in the drugs they use. Awareness of the possibility of additives to cause severe hypersensitivity reactions should be heightened to avoid repeated reactions.

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