

Successful parenteral desensitization to paclitaxel

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Background: Paclitaxel, a member of a new class of antineoplastic agents called the taxanes, has been associated with anaphylactoid reactions.

Objective: We report a case of successful parental desensitization to paclitaxel.

Methods: Desensitization was performed with serial 10-fold dilutions (up to 1:100,000) of paclitaxel in sufficient volume to administer successive doses of 1, 2, 4, and 8 ml. Basophil histamine release tests were performed with paclitaxel alone, vehicle alone, and paclitaxel and vehicle combined to determine which agent was responsible for the anaphylactoid reactions.

Results: After parental desensitization was performed, the patient was able to tolerate infusion of paclitaxel without complications or need for antihistamines or steroids. Basophil histamine release occurred only with paclitaxel and not with the vehicle.

Conclusions: Successful parenteral desensitization to paclitaxel can be achieved; it is paclitaxel, and not its vehicle, that is most likely responsible for anaphylactoid reactions in patients undergoing treatment. (*J ALLERGY CLIN IMMUNOL* 1996;97:42-6.)

Key words: Paclitaxel, desensitization, histamine release

Paclitaxel is the first member of a new class of plant-derived, antineoplastic agents called the *taxanes*. An isolate from the bark of *Taxus brevifolia* (the Pacific yew tree), paclitaxel has demonstrated antineoplastic activity in patients with advanced, platinum-resistant ovarian carcinoma, as well as breast cancer and non-small-cell lung cancer.¹

Hypersensitivity reactions, characterized by bronchospasm, hypotension, and dermatologic involvement, have been reported with the use of paclitaxel since the initial phase I trials.¹ Although

current estimates of severe reaction rates are 2%, an earlier series reported that 32 of 301 patients treated with paclitaxel had experienced hypersensitivity reactions; 41% of these occurred despite prophylactic premedication with steroids and antihistamines.² Notwithstanding a recent report of successful retreatments with paclitaxel after severe hypersensitivity reactions, such events may be grounds for termination of treatment with this agent.^{3,4} Interestingly, the precise mechanism for these anaphylactoid reactions remains unclear. Various reports have implicated the vehicle, Cremophor EL, as the causative agent.⁵⁻⁷ However, in a study of nine children with teniposide-induced hypersensitivity reactions, basophil histamine release occurred only with the active drug and not with its vehicle, Cremophor EL.⁸ To our knowledge, no direct studies have been performed to either document or refute the involvement of paclitaxel in anaphylactoid reactions.

We report the results of retreatment of a patient with severe and documented anaphylactoid reactions to paclitaxel in whom retreatment had previously failed. A modification of the standard regimen for parenteral desensitization to β lactam antibiotics in patients with β lactam allergy was

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used.⁹ The results of in vitro studies from our patient are detailed; basophil histamine release was measured with paclitaxel alone, the Cremophor EL vehicle alone, and the combination of these agents.

CASE REPORT

A 35-year-old woman with stage IIIC ovarian carcinoma was admitted to the hospital for paclitaxel infusion, despite a published history of recurrent hypersensitivity reactions to this agent.⁴ The patient had been diagnosed with ovarian carcinoma in March of 1991; she was first seen 2 weeks post partum with fever, abdominal discomfort, and bloating. Pathologic findings demonstrated serous cystadenocarcinoma with metastatic carcinoma in 13 of 15 para-aortic and pelvic lymph nodes. Eight cycles of carboplatin (360 to 440 mg/m²) and cyclophosphamide (500 mg/m²) were administered from March 1991 to October 1991. A second-look laparotomy on November 8, 1991 demonstrated a complete remission of disease. Six cycles of altretamine (260 mg/m², orally, on days 1 to 14 of each month) were administered adjuvantly until June 1992. However, the patient had recurrent disease in August of 1992, with a rise in the CA-125 level (a serum marker for ovarian carcinoma) to 64 and an enlarged left external iliac lymph node as determined by physical examination. She achieved a clinical partial remission after six cycles of single agent carboplatin (440 to 500 mg/m²) were administered, but progressive disease developed in March of 1993, with a rise in the CA-125 level to 2280. Abdominal pelvic computed tomographic scan demonstrated a left pelvic wall mass with soft tissue invasion adjacent to the left internal iliac vessels.

The patient was started on a regimen of paclitaxel (135 mg/m² over 24 hours). The first cycle resulted in a marked response with a fall in the CA-125 level to 147; however, the patient complained of flushing during the infusion. One month later, the patient was readmitted for a second cycle of paclitaxel. Despite intravenous premedication with 20 mg of dexamethasone, 300 mg of cimetidine, and 50 mg of diphenhydramine, the patient had acute respiratory distress with hypotension on initiation of the infusion. Paclitaxel was discontinued, and 300 µg of subcutaneous epinephrine was administered along with nebulized albuterol sulfate, 60 mg of methylprednisolone, and oxygen. Three days later, paclitaxel was readministered according to published recommendations: premedication with dexamethasone, H₁ blockers, and H₂ blockers; reduction of the infusion rate of paclitaxel by 75% to 90% for the initial 1 to 2 hours of therapy.³ Within minutes of starting paclitaxel administration, the patient experienced acute shortness of breath, tachycardia, and flushing. Paclitaxel was again discontinued; epinephrine, methylprednisolone, and oxygen were administered. The patient recovered completely over the ensuing 24 hours.⁴

Because of grade IV toxicity from the paclitaxel, the

patient was switched to altretamine (260 mg/m², orally on days 1 to 14 of each month), but the disease progressed after four cycles. The patient began receiving ifosfamide (5 g/m²) with mesna support and cisplatin (75 mg/m²), but once again, progression of disease was noted after four cycles. At this point, the patient was referred to our institution. The patient had a history of an intravenous contrast dye reaction, consisting of flushing and a sensation of warmth; her history of allergy, including allergies to medications, was otherwise negative. Her medical history was otherwise unremarkable.

METHODS

Materials

The following items were purchased: piperazine-N,N'-bis[2-ethanesulfonic acid] buffer, paclitaxel [5β, 20-Epoxy-1, 2α, 4, 7β, 10β, 13α-hexahydroxytax-11-en-9-one 4, 10-diacetate 2-benzoate 13-ester with (2R, 3S)-N-benzoyl-3-phenylisoserine; molecular weight = 853.9], calcium chloride, magnesium chloride, and Cremophor EL (Sigma Chemical Co., St. Louis, Mo.); crystalline human serum albumin (Calbiochem Co., La Jolla, Calif.); ethylenediaminetetraacetic acid, 60% perchloric acid, and dextrose (Fisher Scientific Co., Fair Lawn, N.J.). Goat anti-human IgE was prepared as previously described.¹⁰

Preparation of peripheral blood basophils and assay for histamine release

All blood donors gave informed consent. Venous blood was obtained from atopic and nonatopic volunteers and from the patient; blood was processed as previously described.¹¹ Aliquots of approximately 20,000 basophils in buffer were incubated for 45 minutes at 37° C with several doses of either paclitaxel alone (10⁻² to 10⁻⁵ mol/L), Cremophor EL alone (1:100 to 1:100,000 vol/vol), or the combination of paclitaxel (10⁻² to 10⁻⁵ mol/L) with 1:1000 (vol/vol) Cremophor EL (approximately the same dilution of vehicle present in the actual infusions administered to patients). Control cell aliquots were challenged with anti-IgE. The histamine released was measured by using the automated fluorometric technique of Siraganian.¹² Spontaneous histamine release was assessed with cells in buffer alone; total histamine content was obtained by lysis with 2% perchloric acid. All assay conditions were performed in duplicate, with replicates consistently showing less than 10% difference. Data are expressed as the percentage of histamine release after subtracting spontaneous release of unstimulated samples from the total histamine content.

Statistical analysis

Results are expressed as the mean ± SEM of three experiments at each condition of drug and vehicle concentration for the patient and for three control subjects.

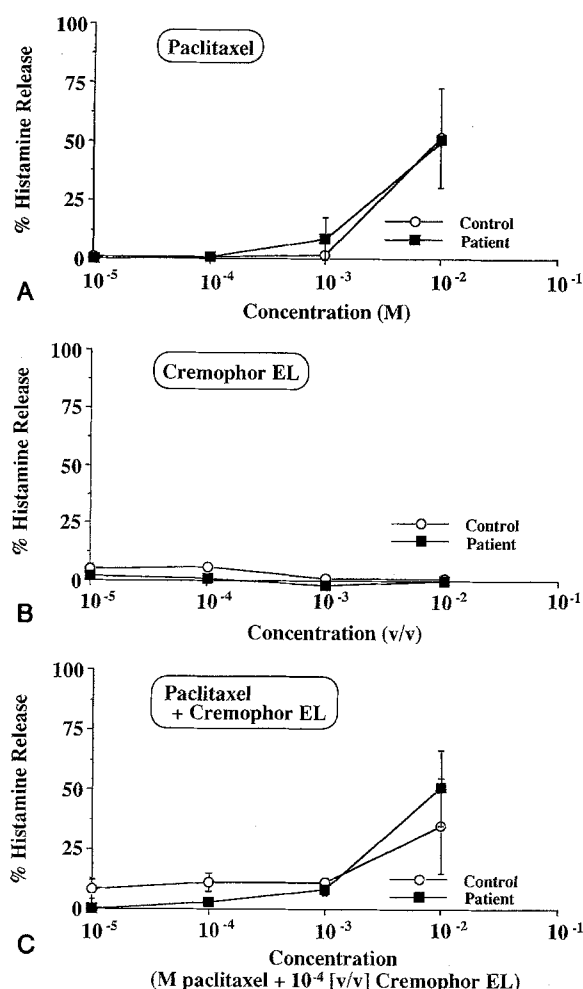


FIG. 1. Basophil histamine release in response to paclitaxel and Cremophor EL. Dose-response curves of basophil histamine release for paclitaxel (A), Cremophor EL (B), and the combination of paclitaxel with Cremophor EL (C). Each curve represents the mean $\pm$ SEM for three separate experiments, either three prechallenge studies of the patient or single studies of three control subjects.

Parenteral desensitization

Desensitization was performed in the intensive care unit of the Fox Chase Cancer Center, Philadelphia, Pa. Serial 10-fold dilutions up to 1:100,000 of the actual infusate were made in sufficient volume to administer successive doses of 1, 2, 4, and 8 ml. These escalating doses of paclitaxel in Cremophor EL were administered intravenously at 15-minute intervals for each dilution until the patient tolerated a 1 ml dose of the undiluted solution, at which point the patient began receiving a continuous infusion to a total dose of 160 mg/m². All desensitizations were preceded by a placebo challenge with diluent alone. General symptoms, blood pressure, heart rate, respiratory rate, and any changes in physical signs were monitored throughout the course of the desensitization.

RESULTS

Parenteral desensitization

Parenteral desensitization was performed before each of three consecutive administrations of paclitaxel. On the first rechallenge, the patient's heart rate, blood pressure, and general status remained stable until the 2 ml dose of the 1:1000 dilution was given, when the patient had an erythematous macular eruption on her chin. Over the subsequent two doses, this area enlarged to include the patient's neck and upper torso and was associated with tachycardia and persistent throat clearing. The patient repeatedly denied shortness of breath, dizziness, nausea, and headache. She remained supine. There was no change in blood pressure. The signs and symptoms slowly resolved without treatment. A similar reaction, commencing at the same dose of paclitaxel and persisting for the same time interval, occurred during the patient's second desensitization. For the third desensitization, the time interval between doses at the 1:100,000 and 1:10,000 dilutions was shortened to 10 minutes. The patient received the entire dose escalation without any adverse effect until the 1:1 challenge dose. Within seconds of administration of this dose, the patient experienced bradycardia associated with flushing, which resolved spontaneously. After each of these three desensitizations, the patient was able to tolerate the full-dose infusion of paclitaxel, 160 mg/m², without complications or further need for steroids and antihistamines. Skin testing was not performed because of the risk of local toxicity.

Basophil histamine release

Basophil histamine release results from the patient and three control subjects are shown in Fig. 1. Experiments with the patient's cells were performed before each of the three desensitizations; because these results are essentially identical, they are shown as a single curve. The anti-IgE response of the patient was $54\% \pm 2\%$ in the three experiments. Data from one atopic and two nonatopic control subjects were also averaged, and the resultant curve is also shown in Fig. 1. Both paclitaxel alone and paclitaxel with Cremophor EL caused significant histamine release from the patient's basophils at 10^{-2} mol/L paclitaxel. Release at this dose also occurred with the cells of the three control subjects. At doses lower than 10^{-2} mol/L, no significant histamine release was detected in any of the subjects tested. With Cremophor EL alone, no histamine release was detected at any of the dilutions with any of the donors' cells.

DISCUSSION

We undertook treatment of a patient with documented paclitaxel retreatment failures, using a modified parenteral desensitization protocol. Basophil histamine release tests were performed with both the drug and its vehicle in an attempt to determine the true etiologic agent for these anaphylactoid reactions. The primary conclusion to be drawn from this study is that successful parenteral desensitization to paclitaxel is achievable. We base this conclusion on a number of observations. First, the patient had experienced previous severe anaphylactoid reactions to paclitaxel, despite retreatment with a published prophylaxis scheme. Second, all parameters for her treatment with paclitaxel, including premedication, dose, and infusion rate, were left unchanged when our desensitization protocol was used. It is well documented, in models of systemic hypersensitivity, that a patient challenged with antigen may not experience anaphylaxis after every challenge; the actual incidence is believed to be approximately 60%.¹³ One could argue that the success of our protocol was circumstantial. However, this protocol has been completed successfully on three consecutive occasions, making the odds of coincidence roughly 6%. Furthermore, the patient reproducibly and predictably had mild symptoms of a systemic response during the desensitizations, analogous to the experience with β lactam and salicylate desensitizations.⁹ To conclusively confirm our findings, we would have to challenge the patient with paclitaxel without desensitization and precipitate a systemic reaction; we do not believe this is advisable.

The second conclusion to be drawn from this study is that paclitaxel, and not the Cremophor EL vehicle, is the likely etiologic agent for these anaphylactoid reactions. Although Cremophor EL has been implicated as the inciting agent, scant data in human beings exist for this assertion.^{5,6} The most detailed studies of Cremophor EL-induced histamine release have been performed by Lorenz et al.⁷ These authors observed a high incidence of systemic responses in conjunction with histamine release in mongrel dogs administered various preparations of Cremophor EL; they concluded that a minor component of this mixture, oleic acid, was the most effective trigger for these responses. However, these authors have also reported that the administration of Cremophor EL is not an effective stimulus for hypersensitivity responses in human beings.¹⁴ Nolte et al.⁸ studied 16 subjects with teniposide-induced hypersensitivity responses. These authors concluded that tenipo-

side, and not the Cremophor EL vehicle, was responsible for basophil degranulation and consequent histamine release. Our data also show a uniform lack of histamine release in response to Cremophor EL. This unresponsiveness occurred with the patient's cells, as well as with those of atopic and nonatopic control subjects. Moreover, this unresponsiveness was maintained in vitro despite the use of vehicle concentrations 10-fold greater than the maximal concentration given to the patient. Although paclitaxel caused basophil histamine release in the patient at a concentration of 10^{-2} mol/L, this concentration, 10 to 100-fold greater than the maximal concentration given to patients, also induced histamine release from the cells of the control subjects. Therefore this result most likely represents direct, non-IgE-mediated release, similar to that seen with mannitol.¹⁵ Histamine release of less than 100% in all cases militates against a direct cytotoxic effect on the basophils. Interestingly, these same doses of paclitaxel and Cremophor EL were unable to cause histamine release from purified human skin mast cells (data not shown). This suggests a selective effect on the circulating basophil and again argues against cytotoxicity. The uniform response of the patient and the control subjects to these agents precluded the utility of IgE passive transfer studies for further elucidating a mechanism for this phenomenon. Although our data cannot rule out an IgE-mediated mechanism caused by either a metabolite of or a haptentation product from either component, the paucity of reactive groups on both components make this hypothesis unlikely. We believe that a challenge of vehicle alone in the patient was unwarranted.

It is noteworthy that docetaxel, a structural analog of paclitaxel currently in phase II trials, has also been associated with hypersensitivity reactions, which have been ascribed to its formulation with the polysorbate-80 vehicle.¹⁶ Though polysorbate-80 is known to induce anaphylactoid responses in dogs, we are unaware of any data showing a similar effect in human beings. Because data exist suggesting that the efficacy of paclitaxel, particularly as related to overcoming the multidrug resistance phenotype, may be augmented directly by its formulation in Cremophor EL, our data, showing a uniform lack of histamine release in response to this vehicle, are particularly significant.¹⁷

In summary, this study demonstrates the feasibility of a protocol for parenteral desensitization to paclitaxel. This protocol produced minimal re-

sponses to the challenge drug, making broader and safer use of this agent possible. Our data implicate paclitaxel, and possibly the taxane class of compounds, as non-IgE-mediated activators of circulating basophils and shed doubt on the role of Cremophor EL in these responses.

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