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# Cremophor EL-containing paclitaxel-induced anaphylaxis: a call to action

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Hypersensitivity reactions to Cremophor EL-containing paclitaxel range from mild pruritus to systemic anaphylaxis and can result in potentially severe clinical outcomes, including respiratory arrest, cardiac collapse, and death.1 In Cremophor EL-containing paclitaxel clinical trials, up to 41% of patients experienced a hypersensitivity reaction. From 2%–4% of patients experienced anaphylaxis or a severe hypersensitivity reaction, characterized by dyspnea, hypotension, angioedema, and generalized urticaria.5 Hypersensitivity reactions occurred even in patients who received prophylaxis.6

**Fast Facts**

ANAPHYLAXIS and severe hypersensitivity reactions are known to occur in patients during paclitaxel infusion. In early phase I studies of paclitaxel, there were a number of anaphylactic reactions and deaths, which raised great concern about the potential development of this drug.2 Although the exact mechanism of these reactions to Cremophor-containing paclitaxel is not known, these responses are clinically consistent with a type I hypersensitivity reaction, an immediate, immunoglobulin E-mediated reaction. The hypersensitivity reactions may result from direct mast cell degranulation induced by either the chemotherapeutic agent itself or by Cremophor EL.1,3

It is generally believed that such reactions are due to the surfactant Cremophor EL, because these effects have also been observed in other drugs utilizing it. The amount of Cremophor EL used in paclitaxel is considerably larger than the amount used in other marketed products and anaphylaxis can occur despite the use of premedication.2,4

Up to 95% of hypersensitivity reactions to taxanes occurred during administration of the first or second dose, and almost 80% of symptoms developed during the first 10 minutes of infusion, with many reactions occurring after only 1 mg was infused.1 A black-box warning on the drug's package insert alerts patients and healthcare professionals to the potential occurrence of fatal hypersensitivity reactions. Although hypersensitivity reaction prophylaxis is recommended, neither the frequency of use nor the efficacy of premedication prophylactic measures is known.

## Pharmacovigilance

As with all serious and potentially fatal adverse drug reactions, the US Food and Drug Administration (FDA) MedWatch database represents an important source of safety information. This is particularly relevant for Cremophor EL-containing paclitaxel-associated hypersensitivity, where the potential for severe anaphylaxis or death exists. No prior study has investigated FDA MedWatch reports for Cremophor EL-containing paclitaxel-associated hypersensitivity.

Investigators affiliated with the Research on Adverse Drug Events and Reports (RADAR), an established pharmacovigilance program, reviewed case reports of paclitaxel-induced hypersensitivity reactions from the FDA's Adverse Event Report System.7 Our objectives were to 1) assess the quality and timing of individual case reports of serious or fatal paclitaxel hypersensitivity reactions submitted to regulatory agencies in the United States, Europe, and Japan; and 2) evaluate whether any of these events occurred despite the use of premedication prophylaxis (Table 1).

## What we reported

In a review of adverse event reports submitted to regulatory agencies between 1997 and 2007 in the United States, Europe, and Japan, 171 unique cases of Cremophor EL-containing paclitaxel-associated hypersensitivity were identified, of which 58 (34%) represented fatalities. For adverse event reports submitted to regulatory agencies in the United States, Europe, and Japan, the median age was 59, 58, and 64 years; the proportion of female patients was 51%, 67%, and 78%; and the most common diagnoses were lung, breast, and ovarian cancers for each region, respectively. Overall, the most common cancer diagnosis was lung cancer. The median duration of time between the date of the event to regulatory notification to the FDA varied between regions, with Japan being the fastest, followed by the United States, and then Europe (18, 27, and 55 days, respectively). In some cases, reports were not filed until after the FDA required the additional black-box warning.

In all three regions, completeness of reporting of anaphylactic reactions to Cremophor EL-containing paclitaxel was poor. Reporting was fairly complete (> 65%) for the date of the anaphylactic event, demographic information on age and gender, type of cancer, and vital status following the adverse event. However, reporting of important clinical information describing the anaphylactic event—including anaphylaxis, duration of symptoms, dosage information, patient history of Cremophor EL-containing paclitaxel allergy, prophylaxis, other concomitant chemotherapy regimens, and hospitalization status—was lacking (≤ 65%

completeness in the reports). Most important and surprising, only 96 reports included information on prophylaxis, of which 21 (22%) cases were fatalities that occurred despite the use of premedication prophylaxis with corticosteroids, antihistamines, and/or histamine-2 (H2)-blockers.

## Conclusion

The published literature indicates that hypersensitivity reactions to Cremophor EL-containing paclitaxel occur quite often and are of varied severity. The use of H1- and H2-receptor antagonists and corticosteroids has significantly decreased the risk of developing a hypersensitivity reaction in this treatment setting.8 However, RADAR investigators found that fatalities occurred in 22% of reported cases despite the use of premedication prophylaxis. Another important finding from this work is that poor-quality adverse event reporting is not unique to the United States: Equally poor adverse event reports were submitted to regulatory agencies in Europe and Japan.

Our findings also have policy implications. As Cremophor EL-containing paclitaxel-associated anaphylaxis is an acknowledged reaction, healthcare professionals may not feel a compelling need to report new cases to regulatory authorities. However, poor reporting and underreporting of this drug are indicative of a wider flaw in global pharmacovigilance efforts and are not the exception. The voluntary nature of the reporting system, coupled with the FDA's passive approach, makes analysis for drug safety signals extremely haphazard, especially when relying solely on these volunteered reports. In fact, half of serious adverse drug reactions are identified 7 years after drug approval by the FDA.9 As recently as 2006, the Institute of Medicine has raised concerns that drug safety signals go largely unnoticed for large periods.10

### Recommendations

- All patients receiving Cremophor EL-containing paclitaxel therapy should be pretreated with corticosteroids, diphenhydramine, and H2-receptor antagonists.
- Because prophylaxis is not always effective, additional precautions should be taken when administering Cremophor EL-containing paclitaxel, such as immediate availability of resuscitative drugs and equipment.1
- Physicians should be informed of the potential alternative of a recently FDA-approved Cremophor EL-free nanoparticle paclitaxel formulation (Abraxane).11
- With respect to pharmacovigilance, as with other serious adverse events, the FDA should consider mandating the development of a risk management program to address this serious toxicity.12 Such an awareness program would alert all physicians and patients of these potentially fatal reactions despite the use of premedication.

  Oncologists are strongly urged to report all cases of potentially serious adverse drug reactions, such as paclitaxel-induced hypersensitivity reactions,

to the FDA's MedWatch Program (www.fda.gov/medwatch/). We can and should do better to protect the safety of our patients.

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## Biography

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**Table 1**

Comparison of quality of case reports of Cremophor EL-containing paclitaxel-associated anaphylaxis from the United States, Europe, and Japan (n = 171)

| | United States | | Europe | | Japan | |
|---|---|---|---|---|---|---|
| | **Dead (n = 36)** | **Survived (n = 59)** | **Dead (n = 17)** | **Survived (n = 21)** | **Dead (n = 5)** | **Survived (n = 31)** |
| Percent of patients who received prophylaxis | 31% | 75% | 41% | 67% | 60% | 86% |
| Median duration between date of event and regulatory notification (days) | 22 | 33 | 43 | 61 | 9 | 20 |
| **Percentage of reports containing information regarding individual data elements** | | | | | | |
| Date of anaphylactic event | 86% | 75% | 82% | 86% | 100% | 90% |
| Anaphylaxis | 25%[a] | 93% | 29%[a] | 76% | 40%[a] | 77% |
| Dyspnea, shortness of breath, bronchospasms | 19%[a] | 49%[a] | 59%[a] | 43%[a] | 20%[a] | 26%[a] |
| Hypotension | 6%[a] | 32%[a] | 12%[a] | 29%[a] | 20%[a] | 23%[a] |
| Duration of symptoms | 3%[a] | 15%[a] | 12%[a] | 24%[a] | 0%[a] | 42%[a] |
| Prophylaxis information | 31%[a] | 73% | 41%[a] | 52%[a] | 60%[a] | 58%[a] |

[a]Percentages are less than or equal to 60% for the individual data element.

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