

The unusual suspects: A surprise regarding reactions to omalizumab

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Omalizumab is a humanized monoclonal antibody approximately 5% of which is composed of mouse polypeptide. This mouse polypeptide is appended to the complementary-determining region of the human IgG1 kappa molecule. Considering that this molecule contains 10 amino acid domains (two in each light chain and four in each heavy chain) of 100–110 amino acids each, there is an approximate total of 1,000–1,100 amino acids in the entire structure. Noting again that 5% of this structure is mouse derived, one could assume therefore that there are perhaps 50–55 amino acids in murine sequences. Also noting that the sequences, being located in the complementary-determining region (the idiotype), which is normally exposed, it would not be unreasonable to assume that the administration of omalizumab to humans would invoke an immune response. Also given the fact that it is administered to atopic individuals, one might further suspect that this response could result in IgE-mediated hypersensitivity reactions. Thus it has been somewhat remarkable to date that, in spite of the new FDA “black box warning,” immediate hypersensitivity reactions have been relatively rare. Still, one would suspect that these reactions would be directed against the murine epitope regardless of the fact that early studies demonstrated no IgE response to infusion of the molecule.¹ Nonetheless, these 55 amino acids located in what is normally an exposed area of the molecule are at least theoretically sufficient to invoke the synthesis of and react with antibodies. The HLA System presents amino acid peptides 8–19 residues long to the T-cell receptor, and epitopes as small as a few amino acids can nestle into small (10–15 Å) crevices in the complementary-determining region. Thus the amount of mouse amino acid residue is clearly sufficient not only to sensitize but also to bind to antibody.

Thus the fact that anaphylactic reactions have occurred to omalizumab is not in itself surprising. The surprise is the culprit, at least as described by Price and Hamilton² in this issue of the *Proceedings*. They present two cases of what they describe as anaphylactoid reactions (which, by the new World Allergy Organization parlance, would be classified as nonimmunologic anaphylactic reactions) that they attribute to an excipient, polysorbate (Tween 80) contained in the omalizumab preparation. These findings are consistent with a previously reported case by Chipps in which there was no demonstrable IgE antibody to omalizumab.³ They are also consistent with observations by Varghese,⁴ who demonstrated that omalizumab could be given without adverse event to individuals with evidence of sensitivity to murine antigen as demonstrated by positive skin tests to a commercially available mouse extract. Indeed with the administration of omalizumab these tests converted to negative.

Making this observation more important is the recent “black box warning” regarding omalizumab issued by the FDA which suggests a two-hour waiting period. Such a lengthy wait could result in a significant reduction in the administration of omalizumab, thus perhaps preventing its use in those who might benefit from it the most. If an excipient was responsible for a significant percent of reported instances of anaphylaxis, at least theoretically, a preparation free of this excipient could be given with greater safety. Such instances have already been demonstrated with both cancer chemotherapeutic agents and erythropoietin. In an instance of anaphylaxis to polysorbate contained in erythropoietin preparation, an identical preparation (except for the substitution of albumin for polysorbate) was administered without ill effect. It is interesting to note that, in this case as in the two cases reported in the *Proceedings*, skin tests to the preparations containing the excipient in question were positive.⁵

The observations detailed above indicate that it would behoove us to be familiar with polysorbate and related emulsifiers such as Cremophor EL. The most detailed review of polysorbate-induced reactions that the author could find was a fairly recent publication by

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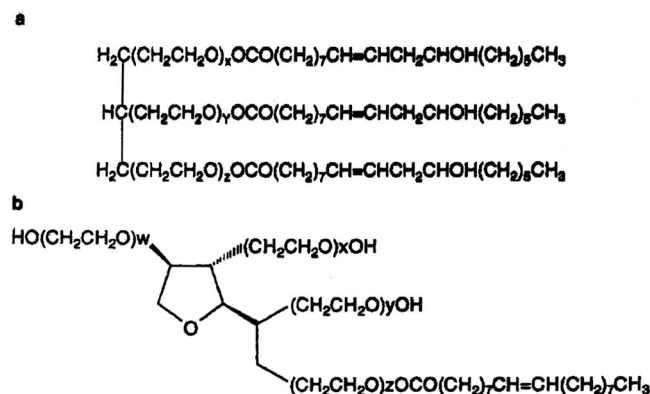


Figure 1. Structures of (a) Cremophor EL (polyoxyethylene glycerol triricinoleate 35) and (b) Tween 80 polyoxyethylen-20 monoleate.

Coors, et al.⁶ These authors reported a case of anaphylaxis due to intravenous administration of a multivitamin product containing polysorbate and investigated the potential mechanisms underlying this reaction. They failed to demonstrate an immunologic response to polysorbate but did, *via* both measurement of basophil CD63 and skin tests, demonstrate that this substance was capable of inducing basophil and probably mast cell degranulation. Other studies have demonstrated similar findings, and in at least one instance noted that this degranulation could be enhanced by activation of complement.⁷

Polysorbates (referred to as Tweens) are composed of a mixture of oleic acids of sorbitol and sorbitans containing chains of polyethylene glycol. They are present in numerous preparations and used as stabilizing, emulsifying, and dissolving excipients. Other such agents with different structures such as Cremophor EL (polyoxyethylated castor oil) serve similar purposes and have also been responsible for hypersensitivity reactions, which in at least one case has been fatal.⁸ Cremophor EL and polysorbate have both been used in numerous cancer chemotherapy agents as solubilizers, stabilizers, and emulsifiers. Their structures are seen in Figure 1. As was cited by Price and Hamilton,² the incidence of reactions to such agents has been reported to be as high as 40%. Thus the observation that these agents can cause anaphylactic reactions is not new, and the literature is actually fairly replete with examples of such reactions.

Reactions to Cremophor EL probably date back to the early 1980s, and as early as 1986 it was found that this agent could release histamine from rat peritoneal mast cells.⁹ Allergic-like reactions to Tween 80 were reported as early as 1974 in intrinsic asthmatic patients¹⁰ and anaphylactic reactions in cows were noted in the early 1990s.¹¹ Thus these excipients have long been known to produce allergic-like reactions that have been reported to exacerbate asthma and rhinitis and cause anaphylactic events.

The mechanism of production of reactions to these agents has not been clearly elucidated. As noted, the drugs are capable of producing complement activation and mast cell degranulation. The latter may be enhanced by the simultaneous activation of complement. The effect on complement activation is concentration dependent and can occur at fairly low concentrations (approximately 2 $\mu\text{L/mL}$) in regards to Cremophor EL. This concentration is easily achieved during the i.v. administration of cancer chemotherapeutic agents containing this excipient, consistent with the observation that slowing the infusion rate of these agents can reduce the severity of anaphylactic symptoms upon administration. Also of note, in a dog *in vivo* model, the administration of Cremophor EL can induce histamine release, perhaps through its free fatty acid constituents such as oleic acid.¹¹ Oleic acid is also present in Tween 80 and thus it may be the actual substance common to both that is responsible for at least this biological effect. However, there are a number of other possibilities as to the nature of these agents responsible for hypersensitivity-like reactions. They are both highly amphiphilic and they both appear to affect cellular enzyme activity. For example, both modulate the activity of the P-glycoprotein system.¹²

Regardless of the molecular mechanism of action of these agents, it has become quite clear that they can cause anaphylactic events, and that these events are probably due to mast cell or basophil degranulation and are possibly enhanced by the activation complement. It is of course not known how frequently these excipients have played a role in allergic events reportedly due to the administration of Xolair. Nonetheless further investigation into the possibility that they could be one of the major causes of such reactions is indicated.

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