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An allergic reaction to erythropoietin secondary to polysorbate hypersensitivity

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To the editor:

An allergic reaction to an oral or injected medication might be due to any component of the preparation, including excipients used to preserve and stabilize the active components. We report the first case of an allergic reaction to erythropoietin due to polysorbate hypersensitivity, and we describe subsequent management with polysorbate-free erythropoietin.

A 41-year-old female laboratory worker with no history of atopy was prescribed erythropoietin for symptomatic anemia secondary to chronic renal failure. Two years previously she had experienced a large local reaction after influenza vaccination. Forty minutes after the administration of erythropoietin (Eprex, Janssen-Cilag, Beersa, Belgium), she developed generalized pruritis, erythema, and orofacial angioedema. An allergic reaction to Eprex was suspected, and therapy was suspended.

The Eprex formulation contained recombinant human erythropoietin and polysorbate 80 as excipient (0.15 mg/mL).

Skin prick and sequential intradermal testing with increasing concentrations of Eprex and Neupogen (Amgen, Thousand Oaks, Calif; polysorbate-containing 0.04 mg/mL) gave positive reactions (Table I ■).

Table I. Controlled skin prick and intradermal tests demonstrating patient reactivity to polysorbate-containing preparations

Substance tested	Patient reaction (mm)	Control reaction (mm)
Skin prick tests		
Histamine	7 × 7	9 × 9
Normal saline solution	0	0
Neupogen (polysorbate 80, 0.04 mg/mL)	0	0
Eprex (polysorbate 80, 0.15 mg/mL)	0	0
Polysorbate 100%	0	0
Intradermal tests		
Eprex (polysorbate 80, 0.15 mg/mL) 1/100	6 × 6	0
Neupogen (polysorbate 80, 0.04 mg/mL) 1/10	10 × 10	0
Polysorbate 100% 1/10	1 × 1	0
Polysorbate 100% undiluted	5 × 50	

Intradermal testing with pharmaceutical-grade polysorbate resulted in a positive local reaction followed by mild orofacial angioedema 1 hour later. No reaction was observed in a control subject. A polysorbate-free erythropoietin preparation was obtained. Skin and intradermal testing results were negative, and no reaction occurred during supervised clinical challenge. Therapy was commenced at 4000 units weekly with no adverse effect.

Constituents of the initial Eprex preparation were sodium chloride, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate, sodium citrate, glycine, recombinant erythropoietin, and polysorbate 80. Comparison with the polysorbate-free Eprex preparation revealed that it differed only in the substitution of albumin for polysorbate 80 and the absence of glycine. Polysorbate 80 was considered the agent most likely responsible for the patient's hypersensitivity given her reaction to Neupogen, which contains polysorbate 80 but not glycine, and, more convincingly, in view of her reaction to pure polysorbate. Inasmuch as Fluarix (GlaxoSmithKline, Melbourne, Australia), an influenza virus vaccine, also contains polysorbate 80, the history of significant local reaction following influenza vaccination might also represent a polysorbate reaction.

Recombinant human erythropoietin has an amino acid sequence identical to that of natural human erythropoietin and represents a major therapeutic development in the management of uremic patients. Previous formulations contained human serum albumin as a protein stabilizer; however, reformulation was approved in 1998 because of concerns regarding

biological hazards associated with human-derived material. A randomized, double-blind trial comparing the 2 formulations demonstrated equivalence in safety, tolerability, and pharmacokinetics.¹

Allergic reactions to erythropoietin have been reported rarely in the literature. Garcia et al² reported a case of anaphylaxis after erythropoietin infusion. Although skin and intradermal test results proved negative, IgE antibodies to recombinant human erythropoietin were present. A generalized eczematous reaction to erythropoietin has been documented in the presence of negative skin test results and undetectable anti-erythropoietin antibodies.³ Excipient testing was not performed in either case.

Polysorbate 80 is a nonionic surfactant widely used in pharmaceutical preparations because of its emulsifying, dispersant, and stabilizing properties. Although hypersensitivity to polysorbate has been reported,⁴ this is the first reported case of erythropoietin allergy due to polysorbate contained as excipient.

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