

IgE-mediated anaphylaxis after first intravenous infusion of cyclosporine

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Background: Intravenous administration of cyclosporine, which contains Cremophor EL (a polyethoxylated castor oil; BASF, Berlin, Germany), has occasionally resulted in an anaphylactic reaction. An apparent hypersensitivity reaction (bronchospasm and decrease in blood pressure) had occurred during heart transplantation in a 59-year-old woman after intravenous infusion of cyclosporine. Subsequent oral administration of cyclosporine precipitated no reaction.

Objective: The purpose of this study was to attempt to ascertain the mechanism responsible for the anaphylactic reaction.

Methods: Hypersensitivity investigations, including total serum IgE and allergen-specific IgE quantifications, skin testing, and basophil activation tests by flow cytometric determination of CD63 upregulation were undertaken in the study patient and in two healthy control subjects who were free of medication.

Results: The results of intradermal testing with Cremophor EL were positive after 15 minutes in the study patient only. Both cyclosporine and Cremophor EL induced considerable activation of the basophils from our study patient, with an upregulation of CD63 expression from 1% to 39% and 55%, respectively. In contrast, the expression of CD63 on basophils from the two control subjects remained essentially unchanged.

Conclusions: The negative investigative findings in the control subjects, the patient's clinical manifestations in temporal relationship to the infusion, her positive results on intradermal testing with Cremophor, the basophil activation test results, and her uneventful course after oral administration of cyclosporine strongly support the presence of IgE antibodies to Cremophor EL in our patient.

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INTRODUCTION

Anaphylactic reaction to a first infusion of cyclosporine is considered anecdotal; such a reaction is more likely to occur at a second exposure or during prolonged administration of the drug. The responsible agent is thought to be the polyethoxylated castor oil (Cremophor EL; BASF, Berlin, Germany) and not cyclosporine itself. Several mechanisms have been proposed for the induction of anaphylactic reactions after

intravenous administration of Cremophor EL.¹ We present a case of an anaphylactic reaction to a first intravenous administration of cyclosporine. Results of skin testing and basophil activation tests (by flow cytometric measurement of CD63 upregulation)² suggest that the reaction could be attributable to IgE antibody to Cremophor EL.

CASE REPORT

Pertinent History

Six months after undergoing heart transplantation, a 59-year-old woman was referred for evaluation because of an apparent hypersensitivity reaction that had occurred during the transplant procedure. Review of her history revealed no previous allergies. Careful perusal of the anesthesia report showed that prevention of graft rejection had been attempted, with almost

simultaneous intravenous administration of prednisolone, azathioprine, antithymocyte globulin (muromonab-CD3, Orthoclone OKT3; Johnson and Johnson, New Brunswick, NJ), and cyclosporine (Sandimmune; Novartis Pharmaceuticals, East Hanover, NJ). Immediately after initiation of the infusion of cyclosporine, her systolic blood pressure declined from 120 mm Hg to 70 mm Hg. In addition, she experienced bronchospasm, and while she was breathing 100% O₂ (12 L/minute), the partial pressure of oxygen (Pao₂) and partial pressure of carbon dioxide (Paco₂) were 54 mm Hg and 40 mm Hg, respectively. Administration of cyclosporine was discontinued, and the patient was treated with epinephrine and dopamine. All other drug therapy was continued without subsequent reactions. Two days later, oral administration of cyclosporine was begun. The patient had an uneventful course and was dismissed with a satisfactorily functioning graft.

Hypersensitivity Investigations

Total serum IgE and allergen-specific IgE quantifications for natural rubber latex, ethylene oxide, and *Ricinus* seed were determined by the Immuno-CAP method (Upjohn-Pharmacia, Brussels, Belgium). Skin testing was done with serial dilutions of cyclosporine and Cremophor EL in suspension. Buffer was used as a negative control, and 10 mg/mL histamine phosphate was used as a positive control. The results were evaluated after 15 minutes; reactions were considered positive if the largest diameter of the wheal exceeded that with the buffer control by 3 mm or more. Flow cytometric analysis (FACScan, Becton Dickinson Immunocytometry Systems, San Jose, CA) of activated basophils was performed by using fluorescein isothiocyanate-conjugated anti-CD63 and phy-

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coerythrin-conjugated anti-IgE double labeling (Basotest, Orpegen Pharma, Heidelberg, Germany); the test included a negative control (stimulation without any drug), a positive control (with *N*-formyl-methionyl-leucyl-phenylalanine), and activation with cyclosporine and Cremophor EL. To exclude nonspecific cyclosporine-induced or Cremophor EL-induced basophil activation, investigations were performed in the study patient as well as in two healthy control subjects who were free of any medication (Table 1).

DISCUSSION

Hypersensitivity reactions after intravenous administration of cyclosporine have been reported since 1984.³ All described patients have shown a reaction to the intravenous formulation of cyclosporine, but only two of them also reacted to the oral suspension. Reactions occurred at various doses and were generally characterized by pruritus, erythematous rashes, facial flushing, urticaria, angioedema, nausea, vomiting, dyspnea, and bronchospasm. Recovery was rapid after cessation of drug infusion. Severe life-threatening re-

Table 2. Galenic Formulations of Cyclosporine

Formulation	Solvent
Intravenous (Sandimmune) (250 mg/5 mL)	Cremophor EL (polyethoxylated castor oil)
Oral solution* (Sandimmune Neoral) (10 mg/mL)	Corn oil + polyethoxylated hydrogenated castor oil
Oral capsules* (Sandimmune Neoral) (25, 50, and 100 mg)	Corn oil + polyethoxylated hydrogenated castor oil

* Although the oral formulations do not contain Cremophor EL, they do contain Cremophor RH.

actions, however, have also been reported.¹ Although these reactions may be attributable to cyclosporine, the occurrence in patients previously treated with orally administered cyclosporine without experiencing such reactions and, as in our patient, the absence of recurrence with reexposure to the oral formulation suggest an alternative mechanism.

Cyclosporine is almost insoluble in water and is generally soluble in lipids and organic solvents. Therefore, unlike the oral preparations of cyclosporine, the intravenous formulation contains the emulsifier and solubilizer Cremophor EL (Table 2). Cremophor EL, or polyoxyl 35 castor oil, is a nonionic surfactant obtained by polyethoxylation of castor oil, which is expressed

from the seeds of *R. communis* (Euphorbiaceae). Cremophor EL consists of a complex mixture of unmodified castor oil and a variety of polyethylene glycols, polyethoxylated glycerols, polyethoxylated fatty acids, and monoesters, diesters, and triesters of glycerol that are polyethoxylated to different degrees.

In 1974, Kessell and Assem⁴ were the first to report Cremophor EL-mediated hypersensitivity reactions. Subsequently, cumulative evidence has suggested that Cremophor EL may be responsible for the hypersensitivity reactions to the parenteral formulations of some anesthetic agents, diazepam (Stesolid MR; Dumex, Copenhagen Denmark), vitamin K, multivitamins, and several antineoplastic drugs. The presence of Cremophor EL in several drugs probably explains why anaphylaxis could occur after a first intravenous administration of cyclosporine. In fact, in some cases, previous sensitization by other drugs containing Cremophor EL could be demonstrated or was suspected. In our patient, sensitization could have resulted from previous exposure to Cremophor EL present in the anesthetic drug used in 1970 for a hysterectomy.

Several mechanisms have been proposed for the induction of a hypersensitivity reaction after intravenous administration of Cremophor EL: 1) IgE-mediated hypersensitivity; 2) activation of the classic pathway of complement; 3) nonspecific in vivo Cremophor-induced histamine release by mast cells or basophils (or both); and 4) involvement of IgG short-sensitizing antibodies.¹ Apart from skin testing, however, no evidence has indicated that these reactions could be attributable to IgE antibodies to Cremo-

Table 1. Results of Investigations for Hypersensitivity in Study Patient and Control Subjects*

Variable	Patient	Control 1	Control 2	Normal
Total serum IgE	63	8	92	<120 kU/L
IgE latex	<0.35	<0.35	<0.35	<0.35 kU/L
IgE ethylene oxide	<0.35	<0.35	<0.35	<0.35 kU/L
IgE <i>Ricinus</i> seed	<0.35	ND	ND	<0.35 kU/L
Skin prick test†				
Cyclosporine	0/0	0/0	0/0	<3 mm
Cremophor EL	0/0	0/0	0/0	<3 mm
Intradermal test‡				
Cyclosporine	0/0	0/0	0/0	<3 mm
Cremophor EL	4/8§	0/0	0/0	<3 mm
Basophil activation test¶				
Without any drug (neg control)	1	1	3	<10
fMLP (pos control)	49	31	65	
Cyclosporine (10 µg/mL)	39	2	1	<10
Cremophor EL (10 µg/mL)	55	7	2	<10

* fMLP = *N*-formyl-methionyl-leucyl-phenylalanine; ND = not done; neg = negative; pos = positive.

† Serial dilution in suspension starting at 10⁻³ up to neat solution. Results are shown as wheal/flare size in millimeters after 15 minutes.

‡ Done at 10⁻³ and 10⁻². Results are shown as wheal/flare size in millimeters after 15 minutes.

§ Concentration = 10⁻³.

|| Concentration = 10⁻².

¶ Results are shown as % CD63-positive basophils after activation.

phor EL. Because of the physical incompatibilities among the drug, its solvent, and nitrocellulose, we were unable to determine specific IgE reactions against cyclosporine and Cremophor EL. IgE-sensitized basophils, on encounter with a specific allergen that is recognized by surface receptor (FcεRI)-bound IgE, not only secrete and generate bioactive mediators that facilitate the development of allergic inflammation, but also upregulate the expression of certain membrane markers (eg, CD63). CD63 is anchored in the basophilic granule membrane (which contains histamine) and is only weakly expressed on the surface of resting basophils. In contrast, as a result of fusion between the granule and plasma membrane, CD63 is expressed with a high density on activated basophils, where it reflects cell degranulation. This upregulated expression of CD63 on the plasma membrane can be detected by flow cytometry, and calculating the percentage of anti-IgE-positive cells that co-express CD63 allows evaluation of basophil activation.⁵

As is clearly shown in Table 1, both cyclosporine and Cremophor EL induced substantial activation of the basophils from the study patient, with an upregulation of CD63 expression from 1% to 39% and 55%, respectively. In contrast, after stimulation with cyclosporine and Cremophor EL, expression of CD63 on the basophils obtained from the two control subjects remained essentially unchanged. Collectively, the negative investigative results in the healthy control subjects, the temporal relationship of the hypersensitivity reaction and the infusion, the patient's clinical manifestations, the positive results of intradermal testing with Cremophor EL, and the basophil activation test results strongly support the presence of IgE antibodies to Cremophor EL in our patient.

Although the chemical nature of Cremophor EL and of polyoxyl 40 hydrogenated castor oil is comparable (the major difference is that the castor oil is hydrogenated), similar reactions have thus far been reported only twice after administration of an oral solution of cyclosporine. The newer microemulsion forms of cyclosporine use corn oil and a polyoxyl 40 hydrogenated castor oil as a base; however, to our knowledge, no hypersensitivity reactions to these microemulsion formulations have been reported. Nevertheless, BASF (the supplier of Cremophor) urges prudence in the use of formulations containing Cremophor RH 40, inasmuch as hypersensitivity reactions may not be excluded.

CONCLUSION

Use of oral preparations of cyclosporine whenever possible and avoidance of intravenous administration in patients with a history of reactions to Cremophor vehicles, as well as in patients who react even mildly (other than flushing) to intravenous administration of the solvent, seem advisable. Although certain precautions, such as slow rate of infusion, proper mixing, and premedication with antihistamines and corticosteroids, have been reported to reduce the risk for anaphylactic reactions to Cremophor EL,⁶ they do not eliminate the risk. Further, in the setting of an IgE-mediated reaction, premedication and drug rechallenge are contraindicated.

Development of new formulations for these drugs would be of interest. This approach was already undertaken for the injectable (intravenous) form of miconazole (Daktarin; Janssen-cilag Pty Ltd, Beerse, Belgium), which contained Cremophor EL as solubilizer. This form of the drug was withdrawn in 1997, probably because of anaphylactic reactions as-

sociated with its administration. A new injectable form was proposed with hydroxypropyl-β-cyclodextrin, a safe solubilizer.⁷ This type of reformulation could be envisaged for cyclosporine and other drugs as well.

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