
Anaphylaxis to intravenous cyclosporine and tolerance to oral cyclosporine: case report and review

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Background: Hypersensitivity reactions to cyclosporine are rare. The mechanism of the reaction and guidelines for subsequent use of cyclosporine are not well defined.

Objective: To investigate the mechanisms involved in hypersensitivity reactions to cyclosporine and determine the feasibility of future cyclosporine use.

Methods: We report a patient who had an anaphylactic reaction during the intravenous infusion of cyclosporine. Skin-prick tests were performed for the antibiotics he received earlier in the day and the cyclosporine. A MEDLINE search identified all the reported cases of hypersensitivity reactions to cyclosporine. Each was analyzed to determine a mechanism of the hypersensitivity reaction and subsequent management outcomes.

Results: Intradermal tests to intravenous cyclosporine formulation (1 mg/mL) were positive in the patient and negative in two controls. There was no reaction to the antibiotics. The literature search revealed 22 cases of hypersensitivity reaction to cyclosporine. The clinical setting and diagnostic evaluation suggest multiple mechanisms for the hypersensitivity response. All seven patients who were given an oral formulation of cyclosporine tolerated it well after a reaction to the intravenous infusion. Two patients who initially reacted to an oral solution formulation subsequently tolerated the corn oil-based soft gelatin capsule.

Conclusions: Hypersensitivity reactions to cyclosporine are due to Cremophor EL. There is direct and indirect evidence for various immunologic and nonimmunologic pathways precipitating the reaction. This case suggests a role for IgE in the hypersensitivity reaction. Fortunately, a hypersensitivity reaction to one formulation of cyclosporine does not preclude use of a different formulation. The corn oil-based soft gelatin capsule appears to be the safest formulation.

Ann Allergy Asthma Immunol 1998;80:159–63.

INTRODUCTION

Cyclosporine is a potent immunosuppressant agent used to prevent rejection of transplanted organs. Cyclosporine blocks the activation of resting T cells by inhibiting calcineurin phosphatase activity, thereby preventing the transcription of genes encoding interleukin-2 and the high-affinity interleukin-2 receptor, which are essential for activation.¹ Cyclosporine has been

shown to be effective in reducing rejection episodes after transplantation of bone marrow, heart, kidney, and liver.² Adverse effects of cyclosporine include nephrotoxicity, hepatotoxicity, hypertension, hirsutism, gum hyperplasia, tremors, and seizures.³ Anaphylactic reactions to cyclosporine are rare. We report on a patient with an anaphylactic reaction to intravenous (IV) infusion of cyclosporine and subsequent tolerance of oral administration of cyclosporine. We reviewed the literature to discern the possible pathogenic mechanisms involved and further management of these patients in regard to the continued use of cyclosporine.

METHODS

Case Report

A 26-year-old man with acute myelogenous leukemia presented with marked urticaria, periorbital edema, nausea, vomiting, and throat tightness approximately 15 minutes after the start of an IV infusion of cyclosporine on the 16th day after bone marrow transplantation. Medications at the time of the bone marrow transplantation and continued to the time of the reaction included fluconazole, acyclovir, cyclosporine, methylprednisolone (added day 7 post-transplantation), ceftazidime (added day 11 for neutropenic fever), and vancomycin (added day 12 for neutropenic fever). The medications received the morning of reaction included vancomycin 500 mg IV 6:30 to 8:30 AM, ceftazidime 2 g IV 6:10 to 6:30 AM, methylprednisolone 37 mg IV 8:30 AM (push), and cyclosporine 180 mg IV 8:30 AM and stopped during reaction at 8:45 AM. During the reaction, his blood pressure was 125/70 mm Hg, pulse 120 beats/min, and respiratory rate 28 breaths/min. He was treated with epinephrine, diphenhydramine, and methylprednisolone. Three hours later, his vital signs were steady: blood pressure 110/70 mm Hg, pulse 100 beats/min, and respiratory rate 20 breaths/min. The urticaria, nausea, vomiting, and throat tightness had cleared, although there was still marked periorbital edema.

He had a history of seasonal allergic rhinitis and childhood asthma for which he no longer was taking medications. Serial skin prick and intradermal testing were negative to vancomycin at concentrations of 0.01 µg/mL to 1 µg/mL and ceftazidime (4 mg/mL) from 1:1,000 to neat. Serial testing of IV cyclosporine (1

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Received for publication August 1, 1997.

Accepted for publication in revised form October 21, 1997.

mg/mL) that contains cyclosporine and the diluent Cremophor EL revealed a positive reaction to the neat preparation intradermally and was negative in serial dilutions to 1:1,000. Intradermal testing on two volunteers was negative. The diagnosis was an anaphylactic reaction to IV cyclosporine.

After a review of the literature, the patient was given a test dose of 25 mg of the corn oil-based soft gelatin formulation (Sandimmune) of cyclosporine. This was tolerated without difficulty. He then received a 100-mg dose 30 minutes later that was also well tolerated. He was started on a maintenance dose of 300 mg twice daily without any complications and continued on this regimen without any reactions.

Further skin testing was planned with the diluent Cremophor EL. Our hospital receives the IV cyclosporine already mixed, and Cremophor EL was not available. When the Cremophor EL was obtained approximately 1 week later, the patient had been dismissed. He died months later secondary to a relapse of the leukemia, and further testing was not performed.

DISCUSSION

A MEDLINE search was performed to find all the reported cases of hypersensitivity reactions to cyclosporine. After an extensive review, 22 cases of a hypersensitivity reaction to cyclosporine were found.⁴⁻¹⁵ Seventeen of these reactions were in patients requiring cyclosporine for immunosuppression and five were in normal volunteers as part of a drug trial. Of the seventeen patients with a reaction, 12 had previous exposure to cyclosporine or Cremophor EL.^{4,5,7,9-12,14,15} Of these 12, 11 had a reaction to an IV infusion and 1 to the oral solution. Seven of the 11 patients were subsequently given an oral formulation of the cyclosporine, and all of them tolerated it well. The one patient who never received an IV infusion but had a reaction to the oral solution subsequently tolerated the corn oil-based soft gelatin capsule.⁹

Skin testing was performed in only two patients with a reaction to the IV infusion.^{12,15} The skin testing was re-

ported to be positive to the IV solution and negative to the oral solution in one patient, but the concentration used and the criteria for a positive reaction were not specified. The other patient had a negative intradermal test to the oral solution and IV preparation (50 mg/mL, 1:1,000 dilution, where 1:100 gave an irritant reaction). The patient who reacted to the oral solution formulation of cyclosporine had positive symptom reproduction with oral challenge of the oral solution and oral challenge of the IV formulation.⁹ Skin testing was not performed. In these patients who were previously exposed, the positive skin test in one patient (number 8 in Table 1) and symptom reproduction with oral challenge in another patient (number 12 in Table 1) suggest an IgE-mediated reaction. Another mechanism, perhaps complement activation or direct histamine release, is suggested by the negative skin test in one patient (number 11 in Table 1). None of the patients with a reaction to the IV formulation had a reaction with the oral formulation when it was given. These reactions, previous exposure, timing of symptoms, skin testing, and subsequent use of cyclosporine are summarized in Table 1.

Of the five patients with a reaction to their first exposure to cyclosporine, four had reactions to the IV formulation and one to the oral solution.^{8,13,14} The IV formulation was retried in two of the four patients; one tolerated it, and the other again developed anaphylactic symptoms despite extra care in the mixing of the cyclosporine-Cremophor and a slower rate of delivery. Skin testing, complement testing, or use of oral cyclosporine was not done in these patients with a reaction to the IV infusion. The patient who reacted to the oral solution had a positive skin test to the solvent of the oral solution, polyoxyl-5-oleate, and an equivocal response to the solvent of the IV solution, Cremophor EL.⁸ This patient subsequently tolerated the corn oil-based soft gelatin formulation of cyclosporine. These results are summarized in Table 2.

Of the five volunteers who had a reaction to the cyclosporine, one reaction occurred with the first dose and the other four on the second dose (2 weeks later).⁶ Skin testing or a trial of oral cyclosporine was not undertaken on these volunteers. The high incidence of reactions in this group was thought to be secondary to lack of steroid use in these volunteers. The patients who receive the cyclosporine are typically on high-dose steroids as part of their immunosuppression program, and the steroid use may temper the hypersensitivity reaction.

This review confirms that the reported hypersensitivity reactions to cyclosporine are not due to the cyclosporine itself but rather to the solubilizing agent for the parenteral administration of cyclosporine: Cremophor EL, a polyoxyethylated castor oil, or the diluent for the oral solution, Ph. Helv./Labrafil M 1944 CS (polyoxyethylated oleic glycerides), a chemically similar compound. Although the chemical nature of the Cremophor EL and the polyoxyl-5-oleate is comparable, most patients have a hypersensitivity reaction to the Cremophor EL only. The oral soft gelatin capsule (Sandimmune) uses corn oil and polyoxyethylated glycolysed glycerides as a base. There have been no reported hypersensitivity reactions with this compound. Both of the microemulsion forms of cyclosporine (Neoral), the oral solution and the soft gelatin capsule, use corn oil and a polyoxyl 40 hydrogenated castor oil as a base. This is similar to the Cremophor EL used in the IV formulation. Table 3 summarizes the various formulations.

Several possible immunologic mechanisms for Cremophor EL hypersensitivity reactions have been studied. It was the association between anaphylactoid reactions and Cremophor EL in various IV anesthetics that led to the implication of this compound. Evidence for classic type I hypersensitivity reactions includes positive skin tests to the Cremophor EL compound alone and to the anesthetic agents such as Althesin that use Cremophor EL as a diluent in patients having an anaphylactoid reaction.^{16,17} Other an-

Table 1. Patients with Reaction to Cyclosporine After Previous Exposure

Pt/ref*	Age, yr/sex	Previous Exposure	Time/Symptoms	Oral Formulation	Skin Testing
1/4	39/M	Day 10 IV* cyclosporine	Within 5 min of start of infusion: hypotension, bandlike chest pain, tachycardia	Oral solution tolerated	Not performed
2/5	20/M	3 months prior received 7-day course IV cyclosporine	Start of infusion: dyspnea, laryngeal spasm, bandlike chest pain, dizziness, erythematous skin rash	Not given	Not performed
3/7	39/F	7 months prior received Althesin (Cremophor EL containing)	Within 5 min of start of infusion: maculopapular rash trunk and extremities, pruritus, dyspnea, palpitations	Oral solution tolerated	Not performed
4/10	44/M	On oral cyclosporine	Start of first infusion: dyspnea, tachypnea, facial flushing	Oral solution continued and tolerated	Not performed
5/10	44/M	On oral cyclosporine	Start of first infusion: burning at injection site, chest pain, headache, dyspnea	Oral solution continued and tolerated	Not performed
6/10	22/F	Day 8 of IV cyclosporine	Start of infusion: pruritus, palpitations, headache	Oral solution tolerated	Not performed
7/11	38/F	Possibly Cremophor EL from vitamin K in past	Start of first infusion: choking sensation, apnea, pulseless	Not given	Not performed
8/12	29/M	Day 17 of IV cyclosporine	Two minutes after the start of IV infusion: bronchospasm, hypotension, maculopapular rash	Oral solution tolerated	IV solution: positive Oral solution: negative
9/14	2/—	Second dose of IV cyclosporine	Ten minutes after start of infusion: emesis, breath-holding, facial erythema	Not given; IV retried with slight breath-holding, dusky skin, tolerated 10 further cycles of IV cyclosporine	Not performed
10/14	2/—	Second dose of IV cyclosporine	Ten minutes after start of infusion: choking, gasping, coughing, face and neck edema, cyanosis, tachypnea, hypotension	Not given; IV retried and tolerated 5 further cycles of IV cyclosporine	Not performed
11/15	2/—	Ninth dose of IV cyclosporine	Twelve minutes after start of infusion: urticaria, facial edema, pallor, cough, nausea, diarrhea, tachycardia	Soft gelatin capsule tolerated	Negative (50 mg/mL) 1:1,000 (1:100 irritant)
12/9	37/F	Day 20 of oral cyclosporine	Within 1 hour of ingestion: pruritus, facial swelling, erythematous rash	Soft gelatin capsule later tolerated	Positive symptom reproduction with oral challenge of oral and IV formulations

IV, intravenous; pt, patient; and ref, reference.

tibody reagins have been implicated. Moneret-Vautrin et al¹⁸ reported on a 16-year-old girl who developed a reaction to Althesin after undergoing multiple operations. Complement levels (C3 and C4) were normal during the reaction. Later, studies including a Prausnitz-Küstner test and human basophil degran-

ulation test suggested an IgG antibody, most likely IgG4 to Cremophor EL. Complement activation via the alternative pathway, evidenced by decreased C3 with normal C1, C1q, and C4, has been shown with Althesin and Stesolid MR in patients experiencing a hypersensitivity reaction to the drug.¹⁹ The sol-

vent Cremophor EL, common to both, was implicated as the causative agent.

Nonimmunologic mechanisms of direct histamine release by Cremophor EL also have been studied. Elevated plasma histamine concentrations have been demonstrated after Cremophor EL injection in pigs and dogs.^{20,21} Clin-

Table 2. Patients with Reaction to First Dose of Cyclosporine

Pt/ref	Age, yr/sex	Time/Symptoms	Oral Formulation	Skin Testing
13/13	5/F	Within 5 min of start of IV infusion: hypotension, tachypnea, generalized macular rash	Not given	Not performed
14/14	5/—	Five minutes after start of IV infusion: nausea, stridor, cyanosis, urticaria and edema of face and neck	Not given; IV retried with subsequent swelling of face, clutching of throat, itchiness of legs	Not performed
15/14	13/—	Two minutes after start of IV infusion: nausea, tachycardia, periorbital edema, dyspnea	Not given	Not performed
16/14	2/—	Three minutes after start of IV infusion: choking and coughing, facial erythema, emesis, bronchospasm, tachycardia	Not given; IV retried with small amount of gagging; tolerated 11 further cycles of IV cyclosporine	Not performed
17/8	24/M	Eight hours after oral solution: headache, erythema, periorbital edema, tachycardia	Soft gelatin capsule later tolerated	Patch test: negative for oral solution and IV solution Intracutaneous: positive for solvent of oral solution and equivocal for solvent of IV solution Oral challenge with IV formulation resulted in generalized erythema of the skin

IV, intravenous; pt, patient; ref, reference.

Table 3. Formulations of Cyclosporine

Delivery route	Concentration	Diluent
Intravenous (Sandimmune)	50 mg/mL cyclosporine; 650 mg/mL Cremophor EL	Cremophor EL (polyoxyethylated castor oil)
Oral solution (Sandimmune)	100 mg/mL cyclosporine	Olive oil: Ph. Helv./Labrafil M 1944 (polyoxyethylated oleic glycerides) Corn oil: Labrafil M 2125 (polyoxyethylated glycolysed glycerides)
Oral soft gelatin capsule (Sandimmune)	25, 50, 100 mg capsules	Corn oil: Polyoxyl 40 hydrogenated castor oil
Oral solution microemulsion (Neoral)	100 mg/mL cyclosporine	Corn oil: Polyoxyl 40 hydrogenated castor oil
Oral soft gelatin capsule-microemulsion (Neoral)	25, 100 mg capsules	

ically, this may be manifest by a reaction to the drug on the first exposure, and the mechanism may be similar to that seen with radiocontrast agents and vancomycin. Theis et al¹⁴ studied the techniques of preparing the IV infusion of cyclosporine and found a significant correlation between suboptimal mixing of the cyclosporine-Cremophor EL and the occurrence of anaphylactoid reactions. They believed the initial bolus of the poorly mixed, highly concentrated Cremophor EL produced the anaphylactoid response, because further treatment was tolerated with proper mixing

in the majority of patients. There was one patient in the series who continued to have a reaction despite proper mixing of the IV cyclosporine.

In this review, the majority of reactions occurred in patients who had previous exposure to cyclosporine. All the reactions to the IV formulation occurred within 30 minutes of the start of the infusion, and the majority were within the first 5 minutes. Unfortunately, skin testing of cyclosporine is not standardized and was not performed in the majority of patients who had a reaction to cyclosporine. Based

on the previous studies with Cremophor EL and clinical settings in this review, there appear to be multiple mechanisms involved in sensitivity to cyclosporine. There is evidence for IgE-mediated reactions based on the positive skin tests in patients who received the drug previously. Indirect evidence for complement activation or direct histamine-releasing activity occurred in those who had a reaction to the first dose of the drug and those who subsequently tolerated the drug when the infusion was well mixed and the speed of infusion was lowered. With-

out a full evaluation, however, it is difficult to identify the exact mechanism. Complement levels have not been reported in patients with a hypersensitivity reaction to cyclosporine—only in those receiving Cremophor EL as a vehicle for Stesolid and Althesin.

Many of these patients were not started on another formulation of cyclosporine because of concern about anaphylaxis. Given the serious nature of the underlying illness in those taking cyclosporine, it is important to know what options are available. It appears that the oral formulations without Cremophor EL are a safe alternative in those who had a reaction to the IV formulation. Interestingly, the two patients with reported sensitivities to IV and oral solution (numbers 12 and 17) were patients who ingested the IV formulation during a challenge and never actually received an IV infusion.^{8,9} Both of these patients subsequently tolerated the corn oil-based capsule.

Hypersensitivity reactions to IV cyclosporine are rare, and those reported are secondary to the diluent Cremophor EL—a castor oil-based solubilizing agent. Besides cyclosporine, Cremophor EL has been used in paclitaxel (Taxol), alphaxalone (Althesin), diazepam (Stesolid MR), propanidid (Eponol), and vitamin K₁ (phytonadione), and these should be avoided in patients who have had a hypersensitivity reaction to cyclosporine.^{19,22,23} Various immunologic pathways such as complement activation and IgG antibodies and nonimmunologic pathways such as direct histamine release have been implicated as the cause of the hypersensitivity reaction with Cremophor EL. Our case and the data from the literature also support mediation by IgE. An anaphylactic reaction to the IV formulation of cyclosporine does not preclude oral cyclosporine use. The corn oil-based soft gelatin capsule (Sandimmune) appears to be the safest formulation of cyclosporine. Although reactions have not been reported to the microemulsion forms of cyclosporine (Neoral), the base is a castor oil prod-

uct and could theoretically be allergenic in a patient with a reaction to the IV formulation. In evaluation of a patient with a reaction to cyclosporine, complement levels, skin tests, and review of the mixing and administration of the cyclosporine may help in determining the mechanism.

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