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Well-tolerated oral cyclosporine in a case of hypersensitivity to parenteral cyclosporine in post allogeneic bone marrow transplantation

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Abstract

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Cyclosporine is one of the main drugs used for the prophylaxis of graft versus host disease in bone marrow transplanted patients. Hypersensitivity reaction to intravenous cyclosporine is rare and might be due to its vehicle polyoxyethylated castor oil, Cremophor EL. The exact mechanism is unknown, but IgE and IgG antibodies, complement, and histamine release have been considered to play a role in the development of this reaction. Here, we describe a case of anaphylaxis to intravenous cyclosporine, which was developed in a 19-year-old Iranian female with acute myeloid leukemia who underwent allogeneic bone marrow transplantation from her sister. The corn oil-based soft gelatin capsule (Sandimmune[®]) was substituted with no reaction. Our observation along with the previous reports confirms the role of Cremophor EL in hypersensitivity reaction to cyclosporine, according to which, modifying the formulation of the intravenous (IV) form could be the solution for this problem.

Keywords: Bone marrow transplantation, cyclosporine, hypersensitivity

Introduction

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Cyclosporine as an immunosuppressive agent inhibits calcineurin phosphatase activity, so transcription of interleukin-2 genes and induction of resting T-lymphocytes would be suppressed subsequently. It is widely used in several disorders such as inflammatory diseases, autoimmune diseases, as well as bone marrow and solid organ transplantation.[1,2] It has a number of side effects such as renal, hepatic, dermatologic, cardiovascular, gastrointestinal, and central nervous system adverse effects. Anaphylactic reaction has been reported only in 1%–3% of patients.[3] Polyoxyethylated castor oil (Cremophor EL), which is present in parenteral form as the solubilizing agent, might be the cause. Herein, we aimed to report our observation of anaphylaxis to intravenous (IV) cyclosporine (Sandimmune[®]; Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA), which was occurred in a recipient of allogeneic bone marrow transplantation (BMT), and resolved readily by its own oral form (Sandimmune[®]). Furthermore, all the probable causative mechanisms involved in this reaction will be discussed in details.

Case Report

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A 19-year-old Iranian female with acute myeloid leukemia was admitted to Hematology-Oncology and Stem Cell Transplantation Department of Shariati hospital, Tehran, Iran. Induction and consolidation chemotherapy was done with cytarabine and daunorubicin in two courses of 7 + 3 and 5 + 2 regimens (the numbers stand for the days of treatment with cytarabine and daunorubicin, respectively). After going into remission, she was prepared for allogeneic BMT from her human leukocyte antigen-identical sibling. She had food and seasonal allergy and also, she had the history of hypersensitivity to vancomycin. As a prevention for graft versus host disease (GVHD), she was treated with IV cyclosporine (Sandimmune®) at a dose of 3 mg/kg/day and methotrexate from the day 3. Cyclosporine was diluted in 100 mL D5W and infused over 2 h in two divided doses. Its serum level was measured twice a week, which always was within the therapeutic range. On the day + 4 of allogeneic BMT, 15 min after the start of cyclosporine infusion, the patient deteriorated suddenly with respiratory distress, tachypnea, decreased arterial oxygen saturation by 84%, tachycardia, flushing, and facial and gum swelling. Cyclosporine infusion was withheld instantly, and oxygen, 10 mg IV chlorpheniramine, and 100 mg IV hydrocortisone were given. All of the symptoms resolved within 1 h. Following cessation of cyclosporine, no subsequent hypersensitivity reaction was observed despite the continuation of other medications including meropenem, calcium gluconate, magnesium sulfate, pantoprazole, fluconazole, and acyclovir. Taking a score of 8 in Naranjo Scale, it was attributed to cyclosporine. Laboratory investigations including electrolytes along with renal function tests and liver function tests were normal at the time of the reaction. One day later, with regard to cyclosporine hypersensitivity, we made the decision to give corn oil-based soft gelatin capsule of cyclosporine (Sandimmune®) at a dose of 150 mg twice daily instead, which was tolerated easily without any reaction. Weekly serum level of cyclosporine showed appropriate dosing. Finally, she was discharged on the day + 15 of allogeneic BMT with normal blood count and successful engraftment. She developed only Grade I dermatologic complication attributed to GVHD, which was controlled with 50 mg of oral prednisolone.

Discussion

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The first evidence of anaphylaxis to cyclosporine traced back to 1984 in a patient who underwent kidney transplantation.[4] Dyspnea, tachypnea, “band-like” chest pain, hypotension, and dizziness occurred immediately after 10th episode of cyclosporine infusion despite premedication with antihistamines and glucocorticoids. All symptoms resolved 30 min after stopping infusion. It is important to note that he showed mild dizziness and hot flush within previous infusions as well. Previous studies indicated less frequent anaphylactic reactions with cyclosporine among transplanted patients compared to nontransplanted ones. An immunosuppressed status might be the rational. Indeed, it is assumed that hypersensitivity to medications such as cyclosporine, tacrolimus, paclitaxel, multivitamins hydrosol, Vitamin K, anesthetics, and anticonvulsant agents is related to castor oil derivative in their formulations. Polyoxyethylated castor oil (Cremophor EL) is a nonionic surfactant, which is extracted from seeds of *Ricinus Communis* and used as a vehicle in hydrophobic medications such as cyclosporine. It may cause itching, erythematous rash, urticaria, angioedema, facial flushing, bronchospasm, dyspnea, nausea, and vomiting following drug infusion.[5] IgE-mediated immune response, complement activity, histamine release by basophils or mast cells, and IgG antibody formation are the probable mechanisms thought of as the pathophysiology to this reaction. Skin test and basophil activity test supported the role of IgE in type-I hypersensitivity, which requires previous exposure to Cremophor.[6]

Although inappropriate mixing, rapid infusion, and infusion without premedication predispose the patient to hypersensitivity, it may occur even in the absence of these factors.

Graft rejection is the main concern in transplanted patients, and the use of immunosuppressant agents is inevitable. Assuming Cremophor as the culprit agent in hypersensitivity with IV cyclosporine, corn oil-based soft gelatin capsule form (Sandimmune®), which contains polyoxyethylated glycolized glycerides, would be a safe alternative in hypersensitivity to other forms of cyclosporine. There has not been any report regarding hypersensitivity to this form of cyclosporine (i.e. corn oil-based soft gelatin capsule Sandimmune®) till now and has been tolerated very well by patients.[7] Polyoxyethylated castor oil (Cremophor EL), polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), and polyoxyethylated oleic glycerides are the vehicles with similar structures in other forms [Table 1] which hypersensitivity to one of them equals reaction to the others.

In switching from parenteral to oral form, some issues should be kept in mind which include increasing the dose (roughly twice the IV dose), taking the drug at definite times with 12 h interval, and checking the serum level in regular periods.

Conclusion

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Based on the present evidence, hypersensitivity reaction to cyclosporine occurs very rarely, and its vehicle Cremophor EL is the causative agent. Soft gelatin capsule form, which is free from this content, is the drug of choice in this situation. Furthermore, in patients with oral intolerance, it may be better to think about new formulations with safe vehicles such as hydroxypropyl-cyclodextrin.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Figures and Tables

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Table 1

Different formulations of cyclosporine

Medication	Brand name	Dosage form	Solvent
Cyclosporine	Sandimmune	Intravenous, 50 mg/mL (5 mL)	Polyoxyethylated castor oil (Cremophor EL)
	Sandimmune	Oral solution, 100mg/mL (50 mL)	Polyoxyethylated oleic glycerides
	Sandimmune	Soft gelatin capsule, 25, 50, 100 mg	Polyoxyethylated glycolysed glycerides
	Neoral	Oral solution, micro emulsion 100mg/mL (50 mL)	Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)
	Neoral	Soft gelatin capsule, micro emulsion 25, 100 mg	Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)

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