

Successful Desensitization to Imiglucerase of an Adult Patient Diagnosed with Type I Gaucher Disease

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Established Facts

- To date, only one case of desensitization to imiglucerase has been reported in a child with type 1 Gaucher disease who experienced anaphylaxis due to enzyme therapy.

Novel Insights

- This is the first adult case of successful desensitization to imiglucerase.

Key Words

Anaphylaxis • Desensitization • Gaucher disease • Imiglucerase

Abstract

Gaucher disease is the most common lysosomal storage disorder, and enzyme replacement therapy, such as administration of imiglucerase, is the standard therapy. Anaphylaxis to imiglucerase is rarely reported. Here, we report a 26-year-old female who was diagnosed with type 1 Gaucher disease and referred to our Allergy Outpatient Clinic because of an anaphylactic reaction due to imiglucerase enzyme therapy. A desensitization protocol was administered with two different dilutions with an increasing rate of administration deliv-

ered in 10 consecutive steps by intravenous infusion in an intensive care setting. No reactions occurred during the procedure, and the total final dose of 2,000 U was successfully administered. To our knowledge, this is the first adult case with successful desensitization to imiglucerase. Desensitization protocols to drugs in chronic disease patients for whom no alternative therapies are available can be lifesaving.

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Introduction

Gaucher disease (GD), the most common lysosomal storage disorder, results from an inherited deficiency in lysosomal enzyme glucocerebrosidase [1]. Type 1 GD is

by far the most common form. It is characterized by its variability in the age of onset, clinical signs and progression. It is usually diagnosed in the first or second decade of life, with the appearance of bone pains, splenomegaly and thrombocytopenia, but the disease may be diagnosed at any age between 1 and 73 years. Many adult cases of GD have been reported worldwide [2].

The current standard of care for the treatment of GD is enzyme replacement therapy [3]. Recombinantly produced enzymes imiglucerase, taliglucerase α and velaglucerase are gradually replacing the human placental derived α -glucosidase in the treatment of GD patients [4–6]. Other therapeutic approaches include substrate reduction therapies, such as treatment with miglustat, and an investigational alternative, such as the use of eliglustat tartrate, which reduces intracellular storage of glucosylceramide [7, 8]. Patients with type 1 GD should receive one of these therapeutic options throughout their lives.

An analysis of the long-term clinical records of the safety of imiglucerase therapy demonstrates a stable and low rate of adverse reactions and seroconversion between 1994 and 2005. Decreased spleen and liver volumes combined with increased hemoglobin levels and platelet counts usually occur with enzyme replacement therapy [9]. Frequently reported adverse reactions related to imiglucerase are infusion-associated reactions which are predominantly self-limiting in nature and do not require discontinuation of treatment. Between 1994 and 2005, IgG antibodies to imiglucerase were detected in approximately 15% of treatment-naïve patients [3]. To the best of our knowledge, Aviner et al. [4] described the first case of an anaphylactoid reaction to imiglucerase in a patient who tolerated α -glucosidase.

To date, only one case of desensitization to imiglucerase has been reported in a child with type 1 GD who experienced anaphylaxis due to enzyme therapy [10]. In this document, we report the first desensitization protocol to imiglucerase in an adult patient.

Case Report

A 26-year-old female, diagnosed as type 1 GD at the age of 25 years, was referred to our Allergy Outpatient Clinic because of an anaphylactic reaction due to imiglucerase enzyme therapy. In her detailed history, we learned that she had been diagnosed as GD with hepatosplenomegaly, anemia, thrombocytopenia, numerous Gaucher cells in the bone marrow, and a decrease in leukocyte β -glucocerebrosidase. Replacement therapy with imiglucerase had been started at the age of 25 years and she had been receiving 30

Table 1. Desensitization protocol administered to the patient

Infusion rate ml/h	Duration of infusion, min	Imiglucerase administered U/h	Administered units
Solution 1			
10	30	8	4
20	30	16	8
40	30	32	16
80	30	64	32
160	30	128	64
320	60	256	256
525	60	420	420
Solution 2			
500	30	600	300
375	60	450	450
375	60	450	450

Solution 1: total of 1,000 ml 0.9% NaCl solution = 960 ml 0.9% NaCl solution + 800 U imiglucerase. Solution 2: total of 1,000 ml 0.9% NaCl solution = 940 ml 0.9% NaCl solution + 1,200 U imiglucerase.

U/kg every 2 weeks ever since. During the 8 months of treatment, she developed itching, flushing, hypotension, syncope, dizziness, and headache within 2 h of infusion, which were compatible with an anaphylactic reaction. The infusion was stopped; the patient was treated with antihistamines and intravenous steroids. In a subsequent dose, although enzyme replacement was planned to be administered slowly, she experienced the same complaints within 1 h of the infusion. Therapy was consequently interrupted and her symptoms were treated. After 4 months without treatment, anemia and thrombocytopenia reoccurred, and she was referred to our clinic to be considered for a desensitization protocol to imiglucerase. Her skin prick and intradermal tests, which were started with 1/10,000 dilution and continued with 1/1,000, 1/100, 1/10 dilutions, respectively, revealed no hypersensitivity to imiglucerase. A desensitization protocol with two different dilutions delivered in 10 consecutive steps was planned, as shown in table 1. After written informed consent was obtained, she received 40 mg methylprednisolone (Prednol-L) and 45.5 mg pheniramine (Avil) intravenously 30 min before the procedure, in addition to 500 mg acetylsalicylic acid given orally 1 h prior to treatment. A desensitization protocol was started with fresh diluted imiglucerase (0.8 U/ml) with an increasing rate of administration by intravenous infusion according to the presented scheme (table 1) in an intensive care setting. No reactions occurred during the procedure and the total final dose of 2,000 U was successfully administered.

Two weeks later, a second imiglucerase infusion was administered with the same desensitization protocol. The procedure was successful and the patient subsequently tolerated imiglucerase. The patient has now received imiglucerase successfully every 2 weeks for a period of 3 months with the same desensitization protocol.

Discussion

In this document, we report the first adult patient diagnosed as type 1 GD with a history of anaphylaxis due to imiglucerase administration who has subsequently undergone successful desensitization.

Drug desensitization is the induction, within hours to days, of a temporary state of tolerance to a drug to which the patient has developed a hypersensitivity reaction [11]. Desensitization is a process that aims to remove IgE-induced sensitivity to a particular drug when there is no alternative treatment [12]. Although the term 'desensitization' is generally limited to IgE-mediated reactions, it also describes the nonresponsive condition that occurs as a result of repeated and ever-increasing encounters with a drug. It can also include delayed-type, non-IgE-mediated reactions [12]. Desensitization is a therapeutic modality for drug allergy [11].

To date, only one case of desensitization to imiglucerase has been reported in a child with type 1 GD. This child had anaphylactic hypersensitivity to imiglucerase

therapy. After immune desensitization to imiglucerase using a rush protocol, the patient was able to resume treatment and has not had further hypersensitivity complications.

Our desensitization protocol was completed in approximately 8 h, with the aim to reach the therapeutically effective dosage in the adult patient. As a result, it was longer than the one previously described by Peroni et al. [10]. We premedicated the patient with acetylsalicylic acid, antihistamines and steroids before the procedure because such a procedure had not yet been performed in an adult patient receiving high doses of imiglucerase. Throughout this process, we observed that the patient experienced no complaints or complications during the infusion.

In conclusion, this first report demonstrating a successful desensitization protocol to imiglucerase in an adult patient indicates the importance of desensitization in patients where no alternative therapies are available for chronic diseases.

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