

Successful Desensitization in a Patient with Hypersensitivity Reaction to Laronidase

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Mucopolysaccharidosis I (MPS I) is a rare, recessively inherited, lysosomal storage disorder caused by deficiency of the enzyme α -L-iduronidase. Scheie syndrome is the least severe form of MPS I. Patients can be diagnosed in the adolescent age group. Enzyme replacement therapy with laronidase is the best treatment option in Scheie syndrome and is generally well tolerated by patients. Anaphylaxis and other immediate hypersensitivity reactions to laronidase are very rare. Immediate hypersensitivity reaction to laronidase and successful desensitization with laronidase have only been described in 2 pediatric patients. We herein report the first case of a severe immediate hypersensitivity reaction to laronidase in an adult patient with MPS-I disease, who was successfully treated with a laronidase desensitization protocol.

Keywords: drug hypersensitivity, desensitization, laronidase

Introduction

MUCOPOLYSACCHARIDOSIS I (MPS I) is a rare, recessively inherited, lysosomal storage disorder caused by deficiency of the enzyme α -L-iduronidase and characterized by a progressive multisystem disease with ophthalmologic, cardiac, gastrointestinal, pulmonary, skeletal, and nervous system involvement.¹ Scheie syndrome is the least severe form of MPS I. Diagnosis of the syndrome can be delayed into the second decade due, in part, to patients' mildly affected facies. Joint stiffness is one of the most frequent presenting features of the syndrome. Life expectancy is longer than with the other MPS I subtypes. Some patients have a normal life span. Enzyme replacement therapy (ERT) with laronidase, recombinant human α -L-iduronidase (Aldurazyme), has become the standard of care for Scheie syndrome patients.² Laronidase infusions are generally well tolerated. Infusion-associated reactions, which occur in approximately half of patients, are mostly mild and easily managed. However, immediate hypersensitivity reaction to laronidase and successful desensitization with laronidase have only been described in 2 pediatric patients.^{3,4} Herein we also report the first case of a severe immediate hypersensitivity reaction to laronidase in an adult patient with MPS-I disease, who was successfully treated with a laronidase desensitization protocol.

Case Report

The patient had been diagnosed with Scheie at the age of 19, at which time he had joint stiffness and numbness in his hands. He had been started on laronidase (6,500 U, once a week) 10 weeks previously. He received treatment for 9 courses without any problem. He experienced facial erythema with swelling and itchiness, dyspnea, and nausea and vomiting 1 h after starting infusion during the tenth course. He was referred to our clinic for evaluation of hypersensitivity reaction to laronidase. He had no history of any other drug allergies or allergic disease. Due to the fact that there was no concomitant drug use that could account for the reaction observed, and the occurrence of symptoms within 1 h after starting the infusion, laronidase was considered the causal drug. As part of the allergy workup, he underwent skin prick tests (SPTs) with undiluted laronidase (Aldurazyme 100 U/mL)[®] solutions and intradermal tests with laronidase (1:10,000, 1:1,000, 1:100 diluted solutions), with negative results in the case. Laronidase is the first-line therapy for the disease. Therefore, we used the 12-step, 3-bag rapid drug desensitization (RDD) recommended by Castells to continue treatment with laronidase (Tables 1 and 2). Premedication with diphenhydramine 45.5 mg, methylprednisolone 1 mg/kg, and ranitidine 50 mg was given 1 h before starting the RDD. The starting dose was 0.1625 U of laronidase (1/40,000 of the

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TABLE 1. DESENSITIZATION PROTOCOL FOR LARONIDASE IV (6,500 U = 13 VIAL): SOLUTION PREPARATION

	Volume	Concentration, U/mL	Total amount of drug in each solution, U
Solution 1	250 mL (25 mL Sol 2 + 225 mL SS)	0.26	65
Solution 2	250 mL (25 mL Sol 3 + 225 mL SS)	2.6	650
Solution 3	250 mL (100 U/mL iduronidase 65 mL) + 185 mL SS)	26	6,500

SS, saline solution.

therapeutic dose), and doses were doubled every 15 min. The patient successfully completed the protocols in 504 min, with no adverse reactions observed. The patient is still receiving the drugs with just antihistamine premedication without any reaction.

Discussion

ERT for MPS I is performed by intravenous administration of laronidase, a protein analogous to human iduronidase produced by genetic engineering in a Chinese hamster ovary cell expression system.⁵ ERT with laronidase was approved for the treatment of patients in the United States in 2003, and in Europe in 2003. Laronidase treatment is the best therapeutic option for patients with MPS-I. The most common adverse events with laronidase therapy are infusion-associated reactions, which are typically mild in severity, and include flushing, arthralgia, and headache. However, severe anaphylactic reactions with laronidase have been described in 1 patient.⁶ In addition, immediate hypersensitivity reaction to laronidase and its desensitization have been described in just 2 pediatric patients with MPS-I.³ Herein we have reported the first suc-

cessful desensitization in an adult patient with severe immediate hypersensitivity reaction to laronidase.

The immediate type hypersensitivity reaction to laronidase was shown with a positive skin test by Ensina et al.³ SPT is a reliable method to diagnose immunoglobulin (Ig) E-mediated drug allergy. In our case, due to the lack of any other factor (food allergy, acute infectious diseases) or concomitant drugs that could account for the reaction observed, and the occurrence of symptoms after starting the infusion, laronidase was considered as the causal drug, even though skin test positivity was not shown. In addition, although immediate hypersensitivity reactions with some other ERTs have been reported, IgE-mediated immune mechanisms were not shown with positive skin tests in some of them.^{7,8}

Immediate hypersensitivity reactions to drugs can occur within minutes to hours after exposure. The IgE-mediated mechanism is responsible for this reaction in most cases. The reactions manifest clinically as anaphylaxis, urticaria, angioedema, bronchoconstriction, and rhinitis. Although our patient's symptoms were suggestive of immediate hypersensitivity reaction, skin testing with laronidase was found to be negative. The negative SPT and intradermal test results with laronidase in the patient seemed to suggest non-immunological mast cell degranulation as the underlying mechanism. However, a negative skin test does not exclude the possibility of an IgE mechanism for this reaction. Therefore, we cannot claim that this immediate reaction was not due to an IgE-mediated mechanism as the specificity and sensitivity of skin testing with laronidase are not known.

Once a patient has presented a hypersensitivity reaction, re-exposure of IgE- and non-IgE-sensitized patients to their allergenic medication can lead to the sudden systemic release of inflammatory mediators from activated mast cells and/or basophils, thus inducing hypersensitivity reactions.⁹ RDD is indicated for individuals who require the medication to which they have previously experienced a reaction and no alternative medication is available. RDD for non-IgE-mediated drug hypersensitivity reactions has also been described for various drugs. Therefore, we considered desensitization treatment with laronidase because the patient requires treatment with the implicated medication and alternative medication is not possible. RDD is a treatment modality by which mast cells are rendered hyporesponsive.¹⁰ Desensitization protocols have been developed to help deliver full

TABLE 2. PROTOCOL FOR INTRAVENOUS DESENSITIZATION WITH LARONIDASE

Step	Solution	Rate, mL/h	Time, min	Amount per step, mL	Administered dose, U	Cumulative dose, U
1	1 (0.26 U/mL)	2.5	15	0.625	0.1625	0.1625
2	1 (0.26 U/mL)	5	15	1.25	0.325	0.4875
3	1 (0.26 U/mL)	10	15	2.5	0.63	1.1175
4	1 (0.26 U/mL)	20	15	5	1.26	2.3775
5	2 (2.6 U/mL)	5	15	1.25	3.25	5.6275
6	2 (2.6 U/mL)	10	15	2.5	6.5	12.1275
7	2 (2.6 U/mL)	20	15	5	13	25.1275
8	2 (2.6 U/mL)	40	15	10	26	51.1275
9	3 (26 U/mL)	10	15	2.5	65	116.1275
10	3 (26 U/mL)	20	15	5	130	246.1275
11	3 (26 U/mL)	40	15	10	260	506.1275
12	3 (26 U/mL)	45	339	232.5	6.045	6551.1278

Target dose: 6,500 U, Total time: 504 min.

therapeutic doses of drug allergens in an incremental, step-wise manner without eliciting life-threatening symptoms.¹¹ The most commonly used protocol is based on 3 bags and 12 steps, with 3×10 -fold diluted solutions at escalating rates.^{12,13} The desensitization protocol for this drug has been published for only 2 case reports.^{3,4} We based our protocol on the recommendations of Ensina et al. and Castells.^{3,14} The case reported by Ensina was treated weekly for 8 months without any reactions. However, during the 28th desensitization therapy, after a dose adjustment for patient weight, the patient experienced urticaria at step 12. The protocol had been amended by adding antihistamine before step 9 and laronidase had been tolerated in weekly infusions, which were adjusted to her weight using the amended protocol without any reactions. Therefore, we also extended the step 12 infusion time of RDD, taking into consideration the patient's weight and age. The patient responded well to the desensitization procedure and safely completed the protocol.

In conclusion, we have herein reported the first successful desensitization in an adult patient with a severe immediate hypersensitivity reaction to laronidase. The desensitization protocol worked well and can therefore be recommended for cases of immediate hypersensitivity reactions to laronidase in adult patients.

Author Disclosure Statement

No competing financial interests exist.

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