



# Successful Idursulfase Desensitization Experience in a Pediatric Patient

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To the editor,

Mucopolysaccharidosis Type II (Hunter Syndrome) (MPS-Type 2) is a rare but progressive lysosomal storage disease caused by iduronate-2-sulfatase deficiency that catalyzes the hydrolysis of sulfate groups including dermatan sulfate and heparan sulfate. Pathological accumulation of glycosaminoglycans (GAG) that cannot be degraded due to lack of this enzyme in the respiratory, cardiovascular, neuronal, and musculoskeletal systems leads to a severe clinical picture presenting with organ dysfunctions (1). Symptoms usually appear in the first few years of life. Patients with a mild clinical form survive until the fifth or sixth decade, whereas in patients with central nervous system involvement, death generally occurs in the second decade of life (2,3). Since 2006, enzyme replacement therapy (ERT) with disease-specific recombinant intravenous idursulfase (Elaprase<sup>®</sup>; Shire, Lexington, MA, USA) has been used in patients with MPS-Type 2. Idursulfase has been shown to improve the natural course of the disease by reducing somatic signs and symptoms, and it should be initiated as soon as possible before the development of any irreversible organ damage (4).

In a study evaluating the idursulfase-related allergic reactions, it has been reported that 3 of 34 (8.8%) patients developed infusion-related anaphylaxis, and contrary to previous studies, specific IgE antibodies to idursulfase have been detected. It has been reported that these three patients, aged 10, 13, and 15, developed urticaria and respiratory distress associated with ERT treatment (5). Here we present a pediatric case of idursulfase-related anaphylaxis that was successfully desensitized.

A 14-year-old male patient with the diagnosis of MPS-Type 2 was being followed at the Department of Pediatric metabolism of our hospital and was receiving idursulfase (Elaprase) treatment for 12 years (at a dose of 0.5 mg/kg administered weekly as a three-hour infusion). There has been no allergic reaction related to this drug before.

Idursulfase was administered as with weekly infusion with premedication (antipyretic and antihistamine). Near the end of the three-hour infusion, the patient developed widespread itching, redness, angioedema in the eyes, ears and lips; tachycardia (130/min), nausea, cramping abdominal pain, and sudden defecation. Therefore, idursulfase infusion was immediately discontinued close to the completion time. The patient was diagnosed with anaphylaxis with these symptoms and administered 0.01 mg/kg intramuscular adrenaline, 1 mg/kg methylprednisolone, and 50 mg pheniramine maleate treatment.

A skin prick test using undiluted idursulfase (2 mg/ml) and intradermal tests with 1/1000, 1/100, 1/10, and 1/1 dilutions were performed 14 days after this reaction, and the results were found to be negative (6). Since the patient's current illness required the continuation of idursulfase treatment and there was no alternative therapy, the drug was planned to be administered following desensitization.

A desensitization protocol with a total of 16 steps was prepared with a solution of idursulfase in 4 different dilutions (0.0001 mg/mL, 0.001 mg/mL, 0.01 mg/mL, and 0.1 mg/mL). Each solution contained four steps as a 15-minute infusion, and the total infusion time was determined as five hours and 25 minutes (Table I). The desensitization process was carried out under continuous

medical observation and with the decision of an experienced pediatric allergy and immunology specialist, in the presence of intervention possibilities against all kinds of reactions. Informed consent was obtained before both the skin prick tests and the desensitization procedure. Desensitization was successfully completed before the adverse events developed. Weekly drug administration was then continued with the same protocol and six-week treatment has been completed so far without any allergic reaction.

Infusion-related reactions are frequently reported during the course of idursulfase therapy. Infusion-related reactions are very similar to allergic hypersensitivity reactions and usually develop in the first three months of treatment. Cutaneous findings (flushing, rash, and mild urticaria), headache, hypertension, and fever are most frequently defined reactions and mostly mild to moderate. The recommended treatment is premedication (antipyretic, antihistamine) and/or prolonging the infusion time (7). Yagmur et al. have reported two pediatric cases who developed urticaria during idursulfase infusion where treatment was continued without

additional reaction by prolonging the infusion time and with premedication (8). In the case reported here, a severe clinical picture involving more than one system was found to be compatible with anaphylaxis, and the infusion was discontinued and adrenaline was administered. In this situation, desensitization is crucial and helps to complete the treatment without any problems.

Reactions that develop within the first hour after drug administration are defined as early hypersensitivity reactions. Skin prick and intradermal tests are used in the diagnosis of early reactions (9). Skin tests were administered in our case and negative results were obtained. Similarly, skin tests were performed before the desensitization protocol were reported by Serrano and Gomez and were found negative (6). In the study of Kim et al., skin prick tests performed in three patients who developed anaphylaxis were found to be positive (5). This may be due to the lack of a standard for skin test doses and timing. According to skin testing for evaluation of IgE-mediated hypersensitivity suggested by Broyles et al., it is best not to perform skin testing within the first four-six weeks following anaphylaxis due to the potential for

**Table I: Intravenous desensitization protocol of Idursulfase.**

Desensitization step	Solution type	Concentration	Infusion duration (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	A	1/1000	15	1	0.0001	0.0001
2	A	1/1000	15	2	0.0002	0.0003
3	A	1/1000	15	4	0.0004	0.0007
4	A	1/1000	15	8	0.0008	0.0015
5	B	1/100	15	1.5	0.0015	0.003
6	B	1/100	15	3	0.003	0.006
7	B	1/100	15	6	0.006	0.012
8	B	1/100	15	12	0.012	0.024
9	C	1/10	15	2	0.02	0.044
10	C	1/10	15	4	0.04	0.084
11	C	1/10	15	8	0.08	0.164
12	C	1/10	15	15	0.15	0.314
13	D	1/1	15	3	0.3	0.614
14	D	1/1	15	6	0.6	1.214
15	D	1/1	15	12	1.2	2.414
16	D	1/1	100	215	21.585	24

Solution A is 2 mL of B solution + 18 mL of 0.9% NaCl (concentration, 0.0001 mg/mL).

Solution B is 3 mL of C solution + 27 mL of 0.9% NaCl (concentration, 0.001 mg/mL).

Solution C is 4 mL of D solution + 36 mL of 0.9% NaCl (concentration, 0.01 mg/mL).

Solution D is 20 mL of Idursulfase (24 mg) + 220 mL of 0.9% NaCl (concentration, 0.1 mg/mL).

mast cell mediator depletion that may temporarily lead to false-negative reactions (10). However, in patients with severe conditions such as cancer, cystic fibrosis, or other disorders in which delaying treatment would adversely affect survival, skin testing may be performed two-three weeks after the initial hypersensitivity reaction, bearing in mind that a false negative result is possible. The test was performed two weeks later in our patient due to the necessity of continuing enzyme replacement therapy. We conclude that test negativity may be related to this.

In the absence of alternative therapy, desensitization induces temporary tolerance to a drug that causes severe hypersensitivity reactions, such as anaphylaxis, thus allowing continued treatment. However, since it is a high-risk procedure, it is recommended to prefer previous protocols that have been successfully applied (11). According to the desensitization protocol in immediate reactions, which is the recommendation of Broyles et al., the 16-step protocol is employed for patients with Grade 3 reactions including anaphylaxis who are at higher risk during desensitization (10). Our patient's reaction was described as Grade 3 in severity according to the grading system for generalized hypersensitivity defined by Brown (12). For this reason, we conducted the 16-step protocol for our patient. There was no recommendation about the 16-step protocol in the English literature. Therefore, the protocol recommended by Mezzano et al. was taken as a reference (13).

Idursulfase is a treatment option that has no alternative and increases survival in patients with MPS-Type-2. With this case report, we intend to add data to the literature that currently lacks sufficient data regarding idursulfase desensitization.

#### Conflict of Interest

The authors have no conflicts of interest to declare.

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#### Author Contributions

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