ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Rapid idursulfase desensitization tailored to a patient with mucopolysaccharidosis type II

Dessensibilização rápida à idursulfase adaptada para um paciente com Mucopolissacaridose tipo II

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ABSTRACT

Mucopolysaccharidosis type II (MPS II), or Hunter syndrome, is a rare X-linked disease characterized by the accumulation of glycosaminoglycans (GAGs) due to deficiency of the enzyme iduronate-2-sulfatase. Standard treatment is enzyme replacement therapy (ERT) with idursulfase, which, although effective, can cause serious adverse reactions, including anaphylaxis. Desensitization is an option in cases of severe allergic reactions when no viable alternative treatment is available. We report the case of a 9-year-old boy with MPS II who, after 2 years and 9 months of idursulfase use, developed severe allergic reactions during infusion. Skin testing indicated a possible IgE-mediated hypersensitivity reaction. After several attempts to adjust the infusion rate and to use premedication, we decided to perform desensitization using a protocol based on that described by Professor Castells. The first attempt was unsuccessful. However, after adjustments to the infusion rate and use of additional premedication, the patient began to tolerate the full dose of idursulfase weekly. Immediate hypersensitivity reactions to idursulfase are common, and skin testing is useful to identify IgE-mediated reactions. Desensitization was effective in this case, avoiding treatment discontinuation. The adjustments were tailored to the patient's response, highlighting the importance of an individualized approach. Idursulfase desensitization is a safe and effective option for patients with MPS II who experience severe immediate hypersensitivity reactions to ERT. This case contributes to the understanding of the management of allergic reactions during treatment with idursulfase, encouraging future studies to improve the technique.

Keywords: Idursulfase, mucopolysaccharidosis type II, Hunter disease, desensitization.

RESUMO

A Mucopolissacaridose tipo II (MPS II), ou Síndrome de Hunter, é uma doença genética rara ligada ao cromossomo X, caracterizada pelo acúmulo de glicosaminoglicanos (GAGs) devido à deficiência da enzima iduronato-2-sulfatase. O tratamento padrão é a terapia de reposição enzimática (TRE) com idursulfase, que, apesar de eficaz, pode provocar reações adversas graves, incluindo anafilaxia. A dessensibilização é uma opção em casos de reações alérgicas graves quando não há terapias substitutas viáveis. Relatamos o caso de menino de 9 anos, com MPS II, que após 2 anos e 9 meses de uso de idursulfase desenvolveu reações alérgicas graves durante as infusões. Testes cutâneos indicaram uma possível reação de hipersensibilidade mediada por IgE. Após várias tentativas de ajuste da infusão e uso de pré-medicações, optou-se pela dessensibilização, utilizando protocolo baseado no descrito pela Profa. Castells. A primeira tentativa foi malsucedida, porém, após modificações no tempo de infusão e uso de pré-medicação adicional, o paciente passou a tolerar a dose completa de idursulfase semanalmente. Reações de hipersensibilidade imediata à idursulfase são comuns, e os testes cutâneos são úteis na identificação de reações mediadas por IgE. A dessensibilização demonstrou ser eficaz neste caso, evitando a suspensão do tratamento. O protocolo foi ajustado conforme a resposta do paciente, destacando a importância de abordagens individualizadas. A dessensibilização à idursulfase é uma alternativa segura e eficaz para pacientes com MPS II que apresentam reações de hipersensibilidade imediata graves à TRE. Este caso contribui para a compreensão da gestão de reações alérgicas no tratamento com idursulfase, incentivando estudos futuros para aprimorar a técnica.

Descritores: Idursulfase, mucopolissacaridose tipo II, Doença de Hunter, dessensibilização.

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Introduction

Mucopolysaccharidoses (MPS) are rare, heterogeneous genetic diseases characterized by an accumulation of glycosaminoglycans in tissue lysosomes, leading to various systemic manifestations over time.[1,2] Mucopolysaccharidosis type II (MPS II), or Hunter Syndrome, is a recessive disease linked to the X chromosome, which thus primarily affects males.[3,4] The disease's prevalence ranges from 0.38 to 1.07 per 100,000 live births[5], and it was first described by Charles Hunter in 1917 after observing 2 brothers.[6]

In this disease, a genetic alteration occurs in chromosome Xq28, which leads to insufficient levels of the enzyme iduronate-2-sulfase, which is encoded by the IDS gene and is responsible for the degradation of glycosaminoglycans. The lack of this enzyme leads to an accumulation of lysosomal glycosaminoglycans, which results in organomegaly and dysfunction in a number of systems, such as the ocular, central nervous, skeletal, respiratory, cardiac, and gastrointestinal systems. This dysfunction can range from mild (often without cognitive deficit) to severe (with significant cognitive deficit and possible organ failure, especially in the heart).[7-10]

For many years, treatment was limited to supportive and palliative measures. However, this has changed since the genetic and pathophysiological bases of the disease were discovered: bone marrow and hematopoietic cell transplants were introduced in 1980 and enzyme replacement therapy, which remains the most widely used treatment, was introduced in 2006.[11-13]

Idursulfase (brand name Elaprase) provides the deficient enzyme to MPS II patients, resulting in the breakdown of accumulated glycosaminoglycans, which is essential for treatment.[14] This drug is indicated for all symptomatic patients with a confirmed diagnosis of MPS II, although there are still some questions about its long-term benefits.[11,15,16] The major problem with intravenous enzyme replacement therapy is that it does not reach all affected organs, especially the central nervous system, because it does not cross the blood-brain barrier. Thus, it does not reduce cognitive impairment and results in a high rate of adverse reactions during infusion, which affect up to two thirds of patients, especially in the first three months.[11,17]

Most adverse infusion reactions are mild to moderate, such as the appearance of rash, headache, fever, dyspepsia, urticaria, angioedema, abdominal pain, rhinitis and, in some cases, bronchoconstriction.[17,18] These reactions are usually treated or prevented through premedications, such as antihistamines, antipyretics, or corticosteroids, in addition to changes in the infusion speed and interrupting the infusion.[15,17,19] However, anaphylaxis has been reported in the literature, although extreme caution should be used when administering adrenaline in these patients due to the increased risk of coronary disease.[15,20]

Adverse infusion reactions can involve hypersensitivity through IgE- and non-IgE-mediated mechanisms. Although IgG and IgM and IgE anti-idursulfase formation, triggering the complement cascade, cytokine release, direct mast cell activation, immune complex deposition, and T cell stimulation are all possible mechanisms, the exact cause is not yet fully understood.[11,19-24] Desensitization is indicated for severe or recurrent immediate hypersensitivity reactions or when premedication fails to prevent them.[19]

Rapid drug desensitization is used to induce a state of hyporesponsiveness to specific allergens. This treatment involves the gradual controlled administration of the allergen to modify the patient's immune response and inhibit an immediate hypersensitivity reaction. It is indicated when patients have an immediate hypersensitivity reaction to a necessary drug and no viable alternatives are available.[25,26]

Here we report the first description, to our knowledge, of a Brazilian case of desensitization to idursulfase.

Case report

A 9-year-old boy, born and raised in Umuarama, Paraná, weighing 37 kg, was diagnosed with MPS II at 5 years of age. He had been taking idursulfase at a weekly dose of 0.5 mg/kg since the age of 5 years, 4 months. Two years, 9 months after beginning weekly infusions (September 2022), he developed erythema and itching at the application site, minutes after the end of the infusion. At that point, premedication was begun prior to infusion (first-generation antihistamines, intravenous corticosteroids, and nonsteroidal anti-inflammatory drugs), which resolved the reactions.

In December 2022, the patient began reacting again, this time 1 h after the infusion began, resulting in erythema on the face, arms, and trunk, associated

with local itching and extreme irritation. The medication was immediately suspended and the skin symptoms abated without the further medications; the infusion was postponed until the following week. Again the following week, the skin reaction recurred 1 h after the idursulfase infusion began, but it spontaneously improved after the infusion was suspended. The patient received no other medications (Figure 1).

Since then, several infusion attempts have been made, including premedication before and during the procedure and reducing the infusion rate to a maximum of 50 mL/h, although reactions always occurred, causing considerable discomfort for the patient and family. In addition, the required dose of 18 g of medication was not being administered, reaching a maximum weekly tolerated limit of 6 g before infusions were indefinitely suspended.

In April 2023, our team was called to evaluate the case. First, skin tests were performed in a controlled environment to determine whether a specific IgE-mediated immediate hypersensitivity reaction was involved. A skin prick test with idursulfase was applied at a concentration of 2 mg/mL (undiluted), in addition to a negative control (saline solution) and a positive control (histamine). After 15 min the results were negative for idursulfase and the negative control and positive for histamine (3x3 mm). An intradermal test with idursulfase was then performed at dilutions of 1:1000 (0.002 mg/mL), 1:100 (0.02 mg/mL) and 1:10 (0.2 mg/mL), with readings 20 min after each dilution. Only the 1:10 test (0.2 mg/mL) was positive, with the initial papule increasing by 3 mm (3x3 mm to 6x6 mm).

Given that a probable IgE-mediated or mixed-mechanism reaction was observed, it was decided to perform the desensitization procedure. Since the patient had already reacted to a slow infusion at a fixed rate of 50 mL/h, this was set as the maximum achievable value.

The desensitization protocol was based on Castells et al.[27], in which the medication was diluted in 3 100 mL bags of 0.9% saline solution to reach a total final dose of 18 mg (0.5 mg/kg, according to the manufacturer's instructions). Concentration and infusion speed were progressively increased and vital signs were measured between stages (every 15 min) until the final stage was reached: the final speed of bag 3 was 50 mL/h, which was kept constant until the bag was completely drained, as shown in Table 1.

After the first desensitization attempt, which was preceded by premedication (oral H1-antagonist and oral corticosteroid), the patient reacted to a rate of 25 mL/h during the third bag (step 11) and the infusion had to be interrupted. In the second attempt the following week, the protocol was changed, extending step 10 (12.5 mL/h during the third bag) to

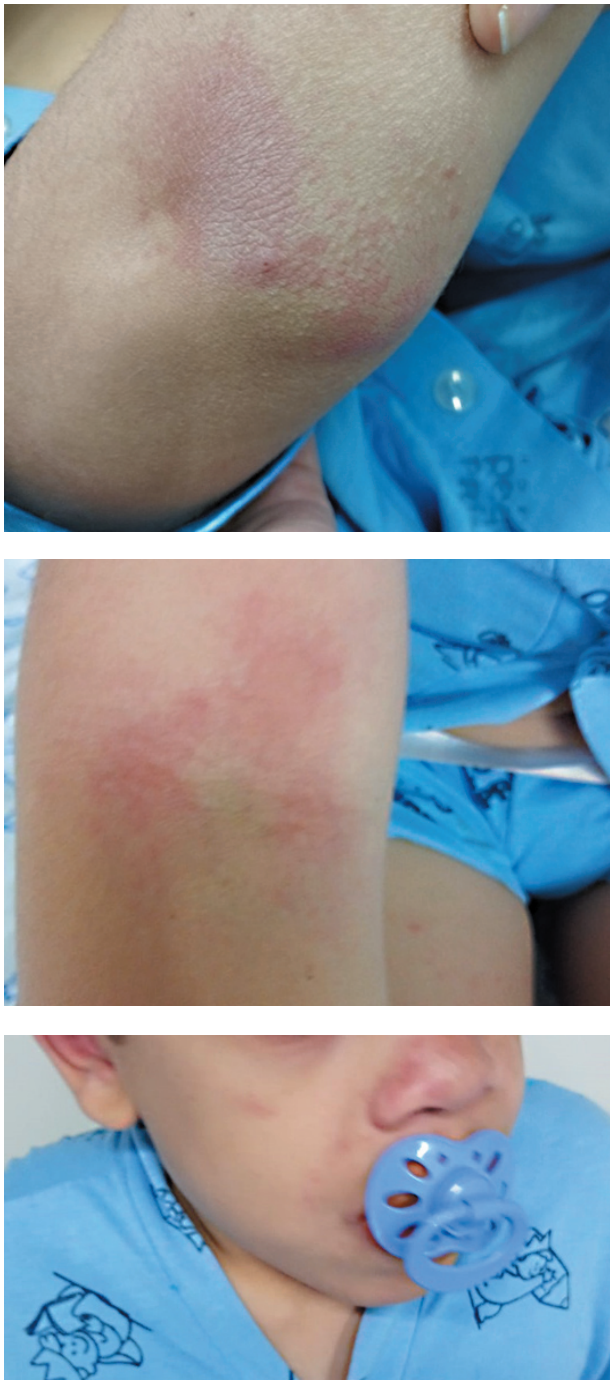

Figure 1
Skin reactions after beginning the idursulfase infusion

30 min and premedicating again after this step. Step 11 (at 25 mL/h) was also extended to 30 min. After these adjustments, the patient no longer reacted to the infusions, and these changes were maintained, subsequently allowing him to receive 18 mg of idursulfase weekly.

Discussion

If an IgE-mediated hypersensitivity reaction is suspected, the first step in the investigation is an allergy skin test involving the medication in question. For idursulfase, positivity appears to correlate well with IgE-mediated reactions. According to Kim et al., a skin prick test with idursulfase had a sensitivity of 66.7% and a specificity of 100% for IgE-mediated symptoms. Of the 34 patients who received the medication, 3 had anaphylactic reactions (8.8%) during the infusions, while the prick test for idursulfase was positive for 4 patients, including all of those who had anaphylaxis (100%). This same study found that ELISA could reveal the presence of anti-idursulfase IgE, with results > 2 SD from the mean of healthy controls in 7 patients with hypersensitivity reactions.[20]

It has been postulated that de novo sensitization occurs due to the high purity of the medication, the dissimilarity of idursulfase's amino acid sequence to other known allergens, and the time required for reactions to begin – several infusions after initiation, as was also observed in our report.[20]

We chose to desensitize the patient to the drug because we considered the benefits of avoiding discontinuation to outweigh the risks, since no other drug with the same function could replace it. The desensitization protocol can vary, depending on the allergen in question, the severity of the immediate hypersensitivity reaction, and patient characteristics.[25-27]

Table 1

Total target dose of 18 mg. The concentration in bag 1 was 0.0018 mg/mL: 0.09 mL of idursulfase (2 mg/mL) in 99.91 mL of 0.9% saline. The concentration in bag 2 was 0.018 mg/mL: 0.9 mL of idursulfase (2 mg/mL) in 99.1 mL of 0.9% saline. The concentration in bag 3 was 0.178 mg/mL: 8.9 mL of idursulfase (2 mg/mL) in 91.1 mL of 0.9% saline

Stage	Bag	Rate (mL/h)	Time (min)	Dose administered at this stage (mg)	Cumulative dose (mg)	Concentration in the bag (mg/mL)
1	1	1.3	15	0.0006	0.00	0.0018
2	1	3.1	15	0.0014	0.00	0.0018
3	1	6.3	15	0.0028	0.00	0.0018
4	1	12.5	15	0.0056	0.01	0.0018
5	2	3.1	15	0.0141	0.02	0.018
6	2	6.3	15	0.0281	0.05	0.018
7	2	12.5	15	0.0563	0.11	0.018
8	2	25.0	15	0.1125	0.22	0.018
9	3	6.3	15	0.2778	0.50	0.178
10	3	12.5	15	0.5556	1.05	0.178
11	3	25.0	15	1.1112	2.17	0.178
12	3	50.0	106.875	15.8341	18.00	0.178
Total infusion time =		271.875				

Serrano reported the first desensitization to idursulfase in 2011. In this case, urticaria began after the sixth infusion. Because the skin tests were negative, it was considered a non-IgE mediated reaction, and an alternative 8-h desensitization protocol was successful.[28]

Bustamante et al. reported that 3 years after starting idursulfase treatment, the patient presented anaphylaxis. Skin tests were performed at the same concentrations we tested, with a concentration of 1:10 (0.2 mg/mL) being positive, which also indicated that it could be an IgE-mediated reaction. In this study, 5 healthy controls were tested with all concentrations of idursulfase to rule out an irritant reaction, and all were negative. Desensitization was performed in 12 steps, as in our report, and occurred without complications.[29]

A patient of Emeksiz et al. had an anaphylactic reaction after 12 years of weekly infusions. Since skin tests were negative, it was considered a non-IgE-mediated reaction and a 16-step desensitization procedure was used for the next infusion. The patient suffered no further reactions during the procedure, and it was repeated for subsequent infusions.[30]

Gragnaniello et al. also desensitized a patient who had a negative skin test, but in this case the symptoms, including fever and vomiting, began 18 h after the first infusion and recurred during the eighth infusion when, 1 h after the infusion began, the patient developed a bilateral malar rash, and it was decided to perform a 7-h, 3-bag desensitization protocol. However, fever and bronchospasm occurred 4 h after desensitization began. The authors were unable to differentiate whether this reaction was due to an infectious process or to a reaction to the medication, although they subsequently collected a positive rhinovirus swab.[24]

In any case, reactions can occur during the desensitization process, and the methods of addressing them vary considerably, depending on the team monitoring the case, since there is no defined consensus on the subject. The protocol can be maintained and the reactions treated, the protocol can be suspended and then modified, or the protocol can be resumed at a lower concentration or speed in a step prior to the reaction, all of which are valid options.[25-27]

Gragnaniello et al. decided to reduce the total dose to 50% of that required in subsequent infusions, following the same 3-bag desensitization process as before and increasing the maximum tolerated dose with every 2 successive infusions, reaching the desired target dose in 1.5 months. The concentration was also progressively increased and the infusion time was reduced to 3.5 h, with no further reactions after 3 months.[24] However, in the present case we modified the protocol by increasing the infusion time during the final steps, in addition to repeating premedication before the step that triggered the reaction in the previous procedure.

Finally, Spataro et al. introduced a new approach to the idursulfase desensitization process. In their report, two patients with MPS II began showing symptoms of an immediate hypersensitivity reaction (hives) 1 year after the start of weekly infusions (first case) and 3 years after the start of infusions (second case). In both patients, the skin test was positive at a concentration of 1:100 and, thus, the reactions were considered to be IgE-mediated. It was decided to perform a 12-step desensitization protocol based on Casells et al. and, as in our case, the patients reacted during the procedure. The first patient reacted during step 12 of the initial desensitization at a rate of 150 mL/h, which was treated with an H1-antagonist and an intravenous corticosteroid. By reducing the infusion rate to 40 mL/h for 60 min, they were then able to resume a rate of 150 mL/h with no further reactions.[31]

The second patient, a 9-year-old boy, was very similar to our case: an initial attempt was made to increase the infusion time and decrease the total dose for several months, but the patient could only tolerate 4 mg of the total required daily dose. When desensitized with a 12-step protocol, with premedication before and between steps 8 and 9, the patient reacted during step 12 with generalized urticaria, being medicated again with an H1-antagonist and an intravenous corticosteroid. The final rate was resumed after the reaction was resolved, with no further complications.[31]

In both patients, after reactions during desensitization, an immunotherapy protocol similar to that for hymenoptera venom was implemented, which was associated with traditional desensitization. The protocol consisted of subcutaneous injections of idursulfase (3 or 4 in each session), intradermal injections spaced 20 min apart every 2 days, with increasing concentrations and volume as the steps progressed for a total duration of 3 weeks. No further reactions occurred in the first patient, so the infusion time was reduced to 3 h and premedication consisted

of oral H1-antagonist alone. It was unnecessary to continue intradermal injections in this patient after the initial 3 months. The second patient, however, continued to react for 2 further desensitization sessions. When the procedure was increased to 4 bags and 20 steps, the patient no longer reacted. Over the following weeks, the immunotherapy protocol was reduced to just 6 steps, 1 bag, and approximately 2 h.[31]

These cases, like ours, show that there are many possibilities for desensitization and that performing the procedure does guarantee a lack of reaction. Our patient no longer experiences reactions with our modified protocol, which is maintained weekly. As a next step, we intend to simplify and shorten our desensitization protocol.

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