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Case Report

Pegvaliase-induced immediate hypersensitivity reaction after the discontinuation of antihistamine therapy in a patient with phenylketonuria – Case report

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ABSTRACT

Phenylketonuria (PKU) is an autosomal recessive inborn error of phenylalanine (Phe) metabolism, resulting from the deficient activity of phenylalanine hydroxylase that converts Phe to tyrosine in the liver, leading to elevated levels of Phe. Pegvaliase is an innovative and effective enzyme replacement therapy for reducing Phe concentration, but it has been associated with severe drug-induced hypersensitivity adverse events (HAEs). Limited data is available on the management of these HAEs, thus, we aimed to present a case report of a successful management strategy.

The patient was a 28-year-old Caucasian male with classical PKU, who was otherwise healthy. Due to poor metabolic control, the pegvaliase treatment was initiated. The titration phase was uneventful, with transient and mild side effects, localized to the injection site. After the patient was on a maintenance dose of pegvaliase and had no reactions to the drug, we discontinued the H1-antihistamine. In the following days, within minutes after receiving the pegvaliase injection, an acute hypersensitivity reaction occurred that required emergency treatment. H1-antihistamine treatment was reintroduced. Four days after the incident he received pegvaliase under medical supervision and did not experience any symptoms.

In conclusion, cautious reintroduction of pegvaliase in a hospital setting can be safely performed after HAE due to the discontinuation of H1-antihistamines. HAEs could be successfully mitigated by scheduling daily antihistamines administration closer to the pegvaliase injection. This approach can enable PKU patients to maintain their access to an effective and quality-of-life-improving therapy.

1. Introduction

Phenylketonuria (PKU) is an autosomal recessive inborn error of phenylalanine (Phe) metabolism and results from variations of the gene encoding phenylalanine hydroxylase (*PAH*) [1]. Due to the deficient activity of PAH that converts Phe to tyrosine in the liver, PKU, when left untreated, leads to elevated levels of Phe in both the bloodstream and the brain, contributing to the development of severe intellectual disability, epileptic seizures and behavioral disturbances [2]. Current standards of care consist of lifelong natural protein intake restriction [3]. Unfortunately, a significant proportion of adults and adolescents with PKU fail to maintain these dietary restrictions, resulting in elevated Phe levels [4].

Pegvaliase is a PEGylated recombinant phenylalanine ammonia lyase (PAL) enzyme, which converts Phe into trans-cinnamic acid and ammonia, both of which are excreted in urine and further metabolized in the liver [5]. Pegvaliase is an innovative enzyme replacement therapy that received approval from both the Food and Drug Administration in

Abbreviations: ASHR, acute systemic hypersensitivity reaction; HAE, hypersensitivity adverse event; PAH, phenylalanine hydroxylase; PAL, phenylalanine ammonia lyase; Phe, phenylalanine; PKU, phenylketonuria.

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2018 and the European Medicines Agency in 2019 [6,7].

Pegvaliase is indicated for PKU patients aged 16 years and older who have uncontrolled disease (Phe levels >600 μmol/L), despite previous treatment efforts [8]. Despite the high effectiveness of pegvaliase in reducing Phe concentrations, cases of severe drug-induced hypersensitivity adverse events (HAEs) have been described [5]. In clinical trials, all subjects treated with pegvaliase developed anti-drug antibodies against the protein PAL and the PEG component, which can lead to HAE [9,10].

In this article, we present a case of pegvaliase-induced HAE with generalized urticaria and angioedema and its successful management.

2. Case presentation

A 28-year-old Caucasian male with classical PKU, who is otherwise healthy with no regular therapy was admitted as an outpatient to our Metabolic Department. His medical history did not include any skin, joint, or muscle conditions, nor any hypersensitivity reactions. Despite his best efforts through dietary measures, the metabolic control was poor with plasma Phe levels averaging 900 μmol/L. We started the treatment with pegvaliase.

The patient started increasing the dose of pegvaliase following the protocol outlined in Table 1. He initiated therapy with a once-weekly subcutaneous injection of 2.5 mg and achieved a daily maintenance therapy of 20 mg after 9 weeks.

At the initiation of therapy, the patient and a family member received education from the professional nurse educator on side effect management and proper use of auto-injectable epinephrine. Additionally, we recommended regular use of preventive H1-antihistamine fexofenadine and instructed relieving muscle pain with acetaminophen. The patient did not take any local or systemic pre-medications, such as H2-antihistamines, corticosteroids, or non-steroidal anti-inflammatory drugs The titration phase was uneventful, with transient and mild adverse effects, such as localized injection site reaction and mild arthralgia. Acetaminophen was regularly administered for approximately two months from pegvaliase initiation and was then discontinued by the patient due to the spontaneous alleviation of the adverse effects.

After 33 weeks of pegvaliase treatment, the patient has remained free of side effects, we recommended discontinuation of antihistamine therapy. Five days after the discontinuation of antihistamine therapy, the patient developed an acute hypersensitivity reaction. Ten minutes after the pegvaliase injection, the patient observed swelling in his right hand, followed by an intensely pruritic rash that quickly spread across his body, along with swelling of his lips. He did not have any other systemic symptoms, such as coughing or wheezing, dyspnea or dizziness. The patient immediately self-administered epinephrine intramuscularly and called the emergency line. He also received intravenous hydrocortisone, clemastine and saline fluid during transport to a nearby emergency department. When the patient arrived, his vital functions were normal, and the symptoms almost completely subsided.

Given the adverse event emerged only after the discontinuation of the antihistamine and considering the observed improvement in the patient's quality of life during the pegvaliase treatment we considered that the potential benefits of continuing pegvaliase treatment outweighed the associated risks. The patient gave consent to continue with the treatment.

Following the event, the patient resumed on fexofenadine120 mg daily. Four days later, he was admitted to the Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Centre Ljubljana, where we rechallenged the patient with pegvaliase (20 mg) under the supervision of medical professionals. We observed no symptoms after the drug application and discharged the patient on the same day.

The patient continued with the same regimen of 20 mg daily. Five days later, a localized urticarial reaction occurred a few minutes after injection. This time the patient chose not to administer an epinephrine injection but instead took another 120 mg tablet of fexofenadine. An hour later the symptoms completely subsided.

We considered the time when the patient took antihistamine (in the morning) and pegvaliase (late in the evening) too long and instructed the patient to take the antihistamine an hour before the pegvaliase injection, after which no adverse reaction has occurred.

Table 1
The titration regimen for pegvaliase in the presented case.

Treatment stage	Dose (mg)	Frequency	Duration
Titration	2.5	once weekly	4 weeks
	2.5	twice weekly	1 week
	10	once weekly	1 week
	10	twice weekly	1 week
	10	four times weekly	1 week
	10	once daily	1 week
Maintenance	20	once daily	from week 10 onwards

3. Discussion

In this case report, we presented a patient with classical PKU, who experienced an immediate episode of generalized urticaria and angioedema after receiving a subcutaneous injection of pegvaliase. The patient underwent the titration phase experiencing only transient and mild side effects primarily localized to the injection site and HAEs occurred only when the H1-antihistamine was discontinued.

Pegvaliase is a pegylated recombinant enzyme, derived from the cyanobacteria *Anabaena variabilis*. As its protein structure is unfamiliar to the human immune system, pegvaliase exhibits high immunogenicity [9]. However, drug-specific IgE have not been detected and anaphylaxis is rarely described [11]. In all patients included in clinical trials, at the initiation of pegvaliase treatment, elevated levels of anti-PEG antibodies and anti-PAL IgM were detected [10], driving the Type III immune complex-mediated reactions. In this type of hypersensitivity response, immune complexes trigger the classical complement pathway, leading to the production of anaphylatoxins which then activate mast cells to release histamine. Histamine induces allergic and inflammatory symptoms by interacting with H1-receptors in nearby or distant body tissues. Type III immune complex-mediated HAEs reach their peak occurrence rate during the initial induction or titration phase of pegvaliase [11]. As therapy continues, the reduction in HAEs during maintenance therapy is thought to be due to improved affinity maturation of anti-drug antibodies (mainly anti-PAL IgG), decreased formation of immune complexes and reduced activation of the complement system over time [10].

There is a common consensus on the clinical treatment measures for HAEs, and many patients have a desire to continue using pegvaliase, even after experiencing initial HAE episodes. As majority of HAEs are restricted to the skin and not life-threatening, the benefits of pegvaliase treatment outweigh the safety concerns. Pegvaliase effectively reduces blood Phe levels to the recommended targets, which can be challenging to maintain through diet alone [5]. To improve drug tolerability, especially during the initial treatment phase when HAEs are most frequent, specific measures can be implemented. One way to minimize the risks associated with initial treatment is by following a well-defined dosing protocol that includes starting with low initial doses and gradually titrating upwards [12].

The implementation of various risk mitigation measures has significantly improved the safety of home treatment with pegvaliase. These measures encompass premedication with H1-antihistamines, which were considered to be most effective [13,14]. Moreover, initial pegvaliase doses should be given under healthcare professional supervision until patients and observers can confidently manage dosing and identify HAE symptoms. To treat a possible acute systemic hypersensitivity reaction (ASHR), all patients using pegvaliase should have access to auto-injectable epinephrine and should be educated about recognizing ASHR

symptoms and administering epinephrine [15,16]. In cases of arthralgia episodes, patients can manage their symptoms with medications, such as acetaminophen [12]. To prevent injection site reactions, patients are encouraged to rotate injection sites. These reactions can be treated with topical H1-antihistamines, topical steroids, or cold compresses [12,17].

The treatment interruption following a HAE is generally less favorable than dose reduction, as it helps maintain continued antigen exposure's 'desensitizing' effect. Temporary dose reduction may be necessary, depending on the severity of the event. This could involve taking one or two steps back in the dosing regimen. This is in line with common practice in allergen immunotherapy [5].

In case of recurrent and severe HAEs, 13-step desensitization may be another approach to management in order to continue the effective treatment [18].

The pharmacokinetic properties of antihistamine drugs play a significant role in mitigating the HAE. In this patient's case, there had been a significant time gap, about 16 h, between pegvaliase and fexofenadine which exceeded the terminal elimination half-life of the latter [19]. The diminished antihistamine effect may have contributed to the residual skin reaction. After changing the time of fexofenadine administration to be closer to the pegvaliase injection, the adverse reaction has not reoccurred.

In conclusion, this case report supports the recommendations that in the case of HAE after discontinuing antihistamines, pegvaliase can be safely reintroduced in a hospital setting. Moreover, scheduling antihistamine administration 1–2 h before the pegvaliase injection could also play a significant role in alleviating HAEs. This approach allows PKU patients to continue pegvaliase therapy.

Compliance with ethics guidelines

The study was conducted in accordance with the Declaration of Helsinki. The study and this paper were approved by the Scientific Committee of the Department of Endocrinology, Diabetes, and Metabolic Diseases, University Medical Centre Ljubljana. Informed consent has been obtained from patient to perform this study, and to publish the results in an anonymized form.

Author contributions

All authors participated in the investigation process and writing of the original draft. Gregoric N. and Sikonja J. conceptualized the study. Gregoric N., Janez A. and Sikonja J. critically reviewed and edited the manuscript. Janez A. supervised the study and drafting of the manuscript. All authors have read and agreed to the published version of the manuscript.

CRediT authorship contribution statement

Nadan Gregoric: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Anita Tara:** Writing – original draft. **Rebeka Kastelic:** Writing – original draft. **Jaka Sikonja:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Conceptualization. **Katarina Peklaj:** Investigation. **Mojca Mesojedec:** Investigation. **Peter Kopac:** Writing – review & editing. **Andrej Janez:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

There is a potential conflict of interest. The Slovenian Osteology Society, of which three of the authors are members (Sikonja J., Janez A., and Gregoric N.), has been granted funds by BioMarin Pharmaceutical, the manufacturer of pegvaliase (Palynziq), to support a clinical program for patients using Palynziq. However, BioMarin Pharmaceutical had no role in the design and conduct of this case report; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Other authors declare no conflict of interest.

Data availability

Data will be made available on request.

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