ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

First administration of ecallantide in Peru: a case report of a Peruvian patient with hereditary angioedema with normal C1-inhibitor

Primeira administração de ecalantida no Peru: relato de caso de paciente peruano com angioedema hereditário com inibidor de C1 normal

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ABSTRACT

Ecallantide is a specific treatment currently indicated for acute crisis of hereditary angioedema (HAE) due to C1-inhibitor deficiency. Our objective is to report the first administration of ecallantide (Kalbitor®) in Peru, where the treatment was used in an HAE patient with normal C1-inhibitor and no F12 gene alteration. We report the case of a 32-year-old postpartum patient with HAE with normal C1-inhibitor who belongs to the Peruvian Association of Patients with Hereditary Angioedema. During pregnancy, she had increased frequency and intensity of abdominal pain and facial edema crisis and received maintenance treatment with tranexamic acid and spasmolytics, with moderate response. One month postpartum, the patient showed respiratory symptoms and tested positive for coronavirus disease (COVID-19) in a polymerase chain reaction (PCR) test, without any HAE crisis during the infectious process. Three months postpartum, she had an acute laryngeal edema crisis with difficulty breathing and speaking, nausea, and vomiting, triggered by nonsteroidal anti-inflammatory drugs (NSAIDs). The patient then received treatment with antihistamines, corticosteroids, and adrenaline, without improvement; for that reason, the allergist administered ecallantide (Kalbitor®) with good response within the first 15 minutes of administration. Some Peruvian HAE patients have developed mild-to-moderate facial and peripheral edema crisis after NSAID intake, without improvement after administration of allergy treatment. In our patient, HAE crisis was not triggered by COVID-19. The patient showed worsening HAE crisis during pregnancy. The first administration of ecallantide (Kalbitor®) in Peru had good response and tolerance to the treatment as shown in this report.

Keywords: Hereditary angioedema types I and II, hereditary angioedema type III, tranexamic acid.

RESUMO

Ecallantide é um tratamento específico totalmente indicado na crise aguda de deficiência de inibidor de C1 HAE. Nosso objetivo é relatar a primeira administração de Ecallantide (Kalbitor®) no Peru, um caso de paciente peruano com EH com inibidor C1 normal sem alteração genética F12. Relatamos o caso de uma paciente de 32 anos, pós-parto, com HAE inibidor de C1 normal, pertencente à Associação Peruana de Angioedema Hereditário de Pacientes. Durante a gravidez, a paciente apresentou aumento na frequência e intensidade das crises de edema abdominal e facial e recebeu tratamento de manutenção com ácido tranexâmico e espasmolítico, com resposta moderada. Um mês após o parto, a paciente apresentou quadro respiratório e teste de PCR molecular positivo para Doença do Coronavírus (COVID-19), sem crise de AEH durante o processo infeccioso. Três meses após o parto, a paciente apresentou crise de edema agudo de laringe com dificuldade para respirar e falar, náuseas e vômitos, desencadeado por AINH. A paciente recebeu tratamento com anti-histamínicos, corticosteroides e adrenalina sem melhora, por isso o alergista administrou Ecallantide (Kalbitor®) com boa resposta nos primeiros 15 minutos após o início da administração. Alguns pacientes peruanos com AEH desenvolveram crises de edema facial e periférico leve a moderado após a ingestão de AINEs, sem melhora após a administração de tratamento para alergia. Em nossa paciente, a crise de AEH não foi desencadeada por infecção aguda por COVID-19. A paciente apresentou agravamento da crise de AEH durante a gravidez. Apresentamos a primeira administração de Ecallantide (Kalbitor®) no Peru, com boa resposta e tolerância ao tratamento.

Descritores: Angioedemas hereditários, angioedema hereditário tipos I e II, angioedema hereditário tipo III, ácido tranexâmico.

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Introduction

Hereditary angioedema (HAE) is a low-prevalence genetic disease characterized by recurrent episodes of nonpruritic swelling without hives. The estimated frequency ranges from 1 per 50,000 to 100,000 in the general population.[1] Peruvian population is about 33 million. According to calculations, there may be approximately 600 HAE patients in this country.

HAE is underdiagnosed worldwide, which leads to a delay in the diagnosis of patients and causes future complications,[2] sometimes due to the absence of reliable diagnostic tests and poor knowledge of the disease. HAE can be classified into C1-inhibitor deficiency or normal C1-inhibitor levels.[3] Ecallantide is an under-the-skin (subcutaneous), on-demand treatment for HAE attacks that targets and inhibits plasma kallikrein, which stops the production of bradykinin to reduce the pain and swelling. It is a specific treatment currently indicated for acute crisis of HAE due to C1-inhibitor deficiency.[4] There is limited literature reporting its use in other bradykinin-mediated angioedema. Our objective is to report the first administration of ecallantide (Kalbitor®) in Peru. The treatment was used in a Peruvian HAE patient with normal C1-inhibitor and no *F12* gene alteration who belongs to the Peruvian Association of Patients with Hereditary Angioedema.

Case report

We report the case of a 32-year-old female patient who had facial edema and abdominal and pelvic pain episodes during the menstrual periods since she was 18 years old. She experienced two or three intense episodes that lasted 2 to 5 days. Conventional medications (spasmolytics, antihistamines, corticosteroids, adrenaline) for allergic angioedema were prescribed, but no improvement was observed in the patient's condition.

The patient gave birth twice, the first time 4 years ago. During that pregnancy, she had abdominal pain crises and moderate-intensity uterine contractions. Spasmolytics were administrated but did not provide her with relief. She had a vaginal full-term delivery and exclusively breastfed for the first 6 months, experiencing a slight crisis of abdominal pain and facial angioedema.

In the next 2 years, slight abdominal pain crises persisted, and the patient reported a particular HAE crisis triggered by family stress and showing the following symptoms: intense abdominal pain, facial angioedema, and hives associated with itching. In this episode, she was evaluated for the first time by an allergist, who administered antihistamines and tranexamic acid with moderate/good response for the hives and angioedema, respectively. In the next occasions, facial angioedema without hives was treated with tranexamic acid, with good response as well. In the previous episode, the allergist ordered blood tests, and the diagnosis of HAE with normal C1-inhibitor and no *F12* alteration was established.

Laboratory findings

- C4 complement: 21 (range, 10-40).
- C1-inhibitor esterase: 40 (range, 8 – 50).
- Total immunoglobulin E (IgE): 188.0 (< 100).
- Genetic test: no alterations for *SERPING1* and *F12*.

Her second pregnancy was recent, in the coronavirus pandemic year. She presented with increased frequency and intensity of abdominal crisis and showed signs of threatened preterm labor since the 6th month of pregnancy. The patient received maintenance treatment with tranexamic acid 500 mg/8 hours with moderate response.

The patient delivered vaginally at the 8th month of pregnancy without any serious HAE complications. One month later, she experienced one day of high fever, general malaise, and respiratory symptoms, similar to a cold. She received treatment with antipyretics and hydration that helped improve her health status in the next days. Chest radiography compatible with pneumonia and a positive polymerase chain reaction (PCR) test for COVID-19 confirmed the infection by SARS-CoV-2. However, during the infectious course, no HAE crisis was triggered.

Three months postpartum and 8 weeks after the respiratory crisis episode, the patient had an acute laryngeal edema triggered by intake of naproxen 550 mg and acetaminophen 500 mg for abdominal pain. After 6 hours, the patient experienced difficulty breathing and speaking due to a sensation of having a foreign body in her throat. She also had nausea and vomiting, and developed similar slight episodes without improvement after allergic treatment.

The patient decided to seek medical emergency care and received treatment with antihistamines, corticosteroids, and adrenaline, which did not

improve her health status. After 1 hour and a half, the allergist administered ecallantide (Kalbitor®) 30 mg subcutaneously with good response, as she showed improved breathing within the first 15 minutes. The patient was observed in the emergency room during 4 hours and was then discharged with indications and control by the allergist.

Discussion

HAE is one of the so-called "rare diseases" that might cause death by suffocation during an acute attack; thus, it is imperative that patients have specific rescue treatments in public and private centers worldwide. In Peru, few medical centers can give support to HAE patients; tranexamic acid is used as an alternative treatment for acute crisis and, recently, ecallantide (Kalbitor®) was registered in the country.

The Peruvian Association of Patients with Hereditary Angioedema has 23 patients diagnosed with HAE, of which 19 have C1-inhibitor deficiency and four have normal C1- inhibitor values. The mean age of onset of symptoms in 18/20 patients was 13.8 years (range, 7-26), and the others presented the first symptoms before 5 years of age. The mean age at the time of the current diagnosis was 30.2 years (range, 8-60). All of them receive tranexamic acid treatment for acute crisis and maintenance with mild-to-moderate response.

In Peru, HAE patients have reported mild-to-moderate peripheral and cutaneous edema and abdominal pain crisis after intake of nonsteroidal anti-inflammatory drugs (NSAIDs), which, as in our patient, did not show improvement after allergic treatment administration.

There is limited literature about HAE crisis triggered by COVID-19. In Peru, three HAE patients (one with C1-inhibitor deficiency and two with normal C1-inhibitor) have been infected with coronavirus, and they had no HAE crisis during the respiratory infection period.

Because our female patient started monitoring her illness with an allergist experienced in HAE treatment, she received tranexamic acid as treatment for acute crisis and maintenance during pregnancy, with moderate control. In Peru, there are no specific treatments available that can be used during pregnancy in HAE patients.

The findings of the present case report can be used in future studies of the Peruvian HAE patients.

Conclusions

We report the first administration of ecallantide (Kalbitor®) in Peru, with good response and tolerance to the treatment.

Tranexamic acid is an alternative treatment for HAE crisis in the country.

There is a need to expand the studies of HAE crisis triggered by NSAIDs in Peruvian patients, given that this group of drugs produce frequent reactions in our general population.

COVID-19 did not trigger any HAE crisis during the course of the disease, but further investigation must be conducted in this field.

Report from the Peruvian Association of Patients with Hereditary Angioedema.

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