

Long-Term Prophylaxis of Hereditary Angioedema with a Pasteurized C1 Inhibitor Concentrate

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Established Facts

- Hereditary angioedema is a genetic disorder; the most frequent type is caused by a deficiency of C1 esterase inhibitor.
- Hereditary angioedema causes significant morbidity and can be life-threatening in cases of laryngeal edema.
- Long-term prophylaxis for hereditary angioedema with androgens is effective but may be associated with significant side effects.

Novel Insights

- Berinert® P, a C1 esterase inhibitor concentrate that is indicated for acute attacks of hereditary angioedema, was used as long-term prophylactic home therapy to successfully treat hereditary angioedema in a patient with previously unresponsive disease.

Key Words

C1 inhibitor deficiency • Hereditary angioedema • Pasteurized C1 inhibitor concentrate • Berinert® P

Abstract

Hereditary angioedema (HAE) is a relatively rare genetic disorder caused by a deficiency of C1 esterase inhibitor (C1-INH). Common clinical presentations are abdominal pain and localized edema of the skin, with laryngeal edema being potentially life-threatening. Replacement therapy with C1-INH

concentrate is recommended for treatment of acute HAE attacks and results in rapid resolution of symptoms. C1-INH concentrate can also be used for prophylaxis of HAE and is recommended in cases where standard prophylactic agents are ineffective or not tolerated. This case study describes the use of C1-INH concentrate as a home therapy for on-demand and prophylactic self-administration in a patient with HAE. This treatment approach was well tolerated and effective, leading to a dramatic improvement in symptoms and improved quality of life.

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Introduction

Hereditary angioedema (HAE) is a relatively rare inherited or acquired genetic disorder caused by a deficiency of functionally active C1 esterase inhibitor (C1-INH). C1-INH deficiency affects approximately 1 in 50,000 people, although this may be an underestimate as there is considerable misdiagnosis and underreporting [1]. Relapsing skin swellings and abdominal pain are the most common presentations of HAE [2, 3]. Attacks may also affect the upper airway and can be life-threatening [4]. Edema attacks typically last for 1–7 days, followed by disease-free intervals of variable duration. This results in uncertainty as to when the next attack may occur or which site will be affected.

Replacement therapy with intravenous pasteurized C1-INH concentrates is currently recommended for acute HAE attacks [5–7]. Since being introduced in the mid-1980s, pasteurized C1-INH concentrates have been shown to be effective in treating laryngeal edema and abdominal pain and are now considered first-line treatment [8–12]. C1-INH concentrates have also been used for short- and long-term prophylaxis and have been investigated for home therapy when standard prophylactic agents such as attenuated androgens or antifibrinolytic agents have proved ineffective or are not tolerated [6, 7].

C1-INH concentrates are currently licensed in most European countries, Japan and Argentina, are authorized for temporary use in France and are available under Special Access Programs in Canada and Australia. They have also recently been approved for use in the USA. Where not approved, they are available on a named patient basis [4]. Even before C1-INH concentrates were licensed in Sweden, their proven benefit in treating HAE led to increased usage. Berinert® P (CSL Behring, Marburg, Germany) is a highly purified, human plasma-derived C1-INH concentrate administered by slow intravenous infusion. The following case report illustrates the use of Berinert P for HAE and investigates its role in long-term prophylaxis.

Case Report

A 17-year-old male was first admitted to the emergency department of Ystad Hospital in 1992, with skin swelling in the legs and pain and tenderness in the abdomen. The patient's medical history revealed a few episodes of skin swelling from the age of 11, mainly affecting the lower extremities and lasting for a few hours. The patient's twin brother suffered similar, but fewer, attacks, while the father, grandfather and 3 other close relatives also suffered from attacks of localized edema.

The patient was diagnosed with suspected HAE due to C1-INH deficiency, with low levels of C1-INH subsequently demonstrated. The patient's condition remained stable without treatment until 1995, when localized edema began to occur more frequently, necessitating repeat emergency ward visits. Subcutaneous ephedrine (0.5 mg) was administered for acute attacks with only a modest effect on symptoms. Tranexamic acid, 1.5 g 3 times daily (Cyklokapron®, Pfizer, Sandwich, UK), was then initiated for prophylaxis and was reduced to 1 g once daily upon symptom control. During a severe edema attack of the upper airway 3 years later, 1,000 U of C1-INH (Berinert P) was given for the first time and led to resolution of symptoms within 30 min.

In 1999, the patient began to experience more severe acute attacks involving the mouth, lips and, at times, the tongue. The patient was a dedicated footballer, and his involvement in the sport repeatedly led to attacks of swellings. The frequency of attacks also increased to several per week, with 1 in 10 requiring hospital treatment. Danocrine prophylaxis was suggested, but the patient declined because of safety concerns.

In May 2000, treatment was converted to C1-INH concentrate given as home therapy, with the patient's wife taught how to administer treatment via the cubital vein. Initially, 1,000 U of Berinert P was administered upon onset of swelling, resulting in rapid resolution, although the frequency of attacks remained unchanged. In 2003, the patient's father died of cerebral asphyxia following severe edema of the throat and larynx. The patient then suffered increasing anxiety and more frequent HAE attacks. This led to the decision to initiate C1-INH for prophylaxis; Berinert P (1,000 U) was administered 3 or 4 times per week via the cubital vein. Prophylaxis was successful, with only a single mild attack reported. However, a year later, it became increasingly difficult to access the peripheral veins, and administration via a venous implantable access system was suggested. A portacath catheter was inserted into the upper chest, and the patient's wife was taught how to inject by this method; the patient was also able to inject himself at times. The patient has been on his current treatment for 5 years and receives 1,000–1,500 U of Berinert P 3 times a week, which has resulted in total freedom from symptoms; the patient is now free from swellings and has been for 4.5 years and is able to play football without problems. In May 2007, the patient's portacath was replaced following damage by a football accident, with no associated problems. In the 4 years since starting C1-INH prophylaxis, no acute attacks requiring emergency treatment have been reported. Mild swellings and epigastric pain have been infrequent and were successfully treated by administration of an additional 1,000 U of Berinert P at onset. The patient is more secure and relaxed about his condition and experiences less anxiety. Previously reported psychogenic triggers of edema attacks have also diminished. The patient's twin brother has also been fitted with an implantable venous device and receives C1-INH prophylactically, keeping him free of symptoms.

Discussion

Acute attacks of HAE severely impact on the quality of life of patients and their families. C1-INH concentrates have demonstrated good efficacy and tolerability after 25 years of clinical experience [3, 9, 11, 13–16]. Treatment of

acute attacks is associated with rapid symptom relief, typically within 30–150 min, although some patients experience relief as early as 10 min after treatment [11], with complete resolution seen from approximately 1 h, but typically within 4 h, particularly with early treatment [11, 13]. Adrenaline, antihistamines and corticosteroids are not effective for acute HAE attacks [17]. Because of the potential for viral contamination, the tolerability of C1-INH has been extensively investigated, with no viral transmission reported [18]. Furthermore, side effects are extremely rare, with fewer than 30 events reported from 300,000 treatments, only 10 of which were thought to be related to treatment [5, 11].

Due to the frequency and potential severity of HAE attacks, prophylaxis is often recommended, especially prior to dental surgery, which may exacerbate laryngeal edema attacks, or in cases of very frequent and severe attacks [4, 6, 7]. Long-term prophylaxis commonly involves the use of attenuated androgens or antifibrinolytic agents. Attenuated androgens increase plasma levels of C1-INH [19], but long-term treatment may be associated with side effects such as weight gain, menstrual irregularities, virilization, muscle pains, headaches, depression, fatigue and nausea [20, 21]. Liver tumors have also been observed [22], while liver enzymes and lipid levels may increase [23]. Antifibrinolytics, such as tranexamic acid, reduce the number and severity of HAE attacks and are associated with fewer side effects but are not as effective as attenuated androgens [24]. The patient described herein initially received prophylaxis with tranexamic acid, which was stopped after 3 years when C1-INH treatment led to superior resolution of symptoms within 30 min, an observation consistent with the recent International Multicenter Prospective Angioedema C1 Inhibitor Trial [8].

Experience of prophylactic treatment with C1-INH concentrates has been limited until recently and although currently only indicated for treatment of acute attacks, successful prophylaxis with Berinert P has now been described in a number of cases. This has resulted in reduced severity, duration and frequency of attacks, with potential for an associated reduction in mortality [22].

A number of guidelines recommend home treatment programs with C1-INH concentrates for HAE prophylaxis in patients experiencing more than one attack per month or for those living in remote areas where repeated hospital admissions would significantly disrupt everyday life [6, 7, 22]. At EUR 700 for 500 U of Berinert P, the cost of treatment is relatively high; however, the benefits of home treatment are far-reaching, including improved quality of life, reduced frequency of attacks and greater

patient independence and convenience. Some countries, such as the Netherlands and the UK, are introducing training programs covering practical aspects of C1-INH administration [22]. Although Berinert P was not licensed in Sweden when the home therapy described here was initiated, the body of evidence for C1-INH concentrates in the treatment and prophylaxis of acute HAE attacks justified its use on a patient by patient basis. The case described here demonstrates the advantage of training family members in administration of C1-INH concentrates for both on-demand therapy and prophylaxis. The patient responded well to on-demand administration of Berinert P, with rapid resolution of attacks, and prophylactic therapy led to regression of attacks. The treatment regimen allowed the patient to resume activities that had previously aggravated the condition. Although long-term prophylaxis with C1-INH concentrate led to problems accessing peripheral veins, the use of a venous implantable device resolved this issue and also allowed the patient to self-administer treatment. The acceptability of this method to the patient and carer demonstrates that the benefits of home therapy outweigh any difficulties. Furthermore, a study is in progress to assess the efficacy of subcutaneous administration of C1-INH, which, if successful, could eliminate many of the problems associated with venous access [25]. The response to C1-INH concentrate therapy in our patient is in agreement with a number of clinical studies that have evaluated the safety and efficacy of on-demand and prophylactic home treatment with C1-INH [11, 12, 22] and further supports the need to investigate the full potential of C1-INH concentrates in this setting.

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