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C1-inhibitor concentrate home therapy for hereditary angioedema: a viable, effective treatment option

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Summary

Economic and political factors have led to the increased use of home therapy programmes for patients who have traditionally been treated in hospital. Many patients with hereditary angioedema (HAE) experience intermittent severe attacks that affect their quality of life and may be life-threatening. These attacks are treated with C1-inhibitor concentrate which, for most patients, is infused at the local hospital. Home therapy programmes for HAE are currently being established. This paper reviews the extent of use of these programmes and summarizes the advantages and potential disadvantages of the concept so far.

Keywords: C1-inhibitor deficiency, emergency treatment, hereditary angioedema, home therapy, quality of life

Introduction

Hereditary angioedema (HAE) is an autosomal dominant condition resulting from partial deficiency of C1 inhibitor (C1-INH) [1]. It is a rare disease, thought to affect between one in 10 000 and one in 50 000 people worldwide [2]. Acquired angioedema (AAE), which is also due to C1-INH deficiency, is phenotypically similar to HAE, although it is associated typically with lymphoproliferative disease, or with autoantibodies to C1-INH [3].

Patients with C1-INH deficiency have reduced amounts of functional C1-INH, which at times of physiological or psychological stress is insufficient to control local inflammatory pathways. The complement and contact systems are activated, and excess bradykinin is generated [4]. It is this increased bradykinin production that is believed to be the main factor in the development of local oedema [4]. Oedema may occur at any site, but most commonly affects the subcutaneous tissue, causing swelling of the limbs, face, trunk or genitalia [1]. Oedema can also affect the mucous membranes of the gastrointestinal (GI) tract, causing abdominal pain, often with diarrhoea and/or vomiting, and the mucous membranes of the larynx, causing laryngeal oedema, which may lead to death by asphyxiation [5–7].

Economic and political factors have contributed to the increased use of home therapy programmes for patients who would have been treated previously in hospital. One group of patients who may benefit from home therapy is those with HAE. This paper uses published data (Medline) to assess the use of C1-INH concentrate home therapy in patients with HAE, and includes evaluations of both the recommendations for patient selection for home therapy and the documented benefits of self-administration of C1-INH replacement therapy.

Methods

Data have been collected from a Medline search of the English language literature to identify papers that included information on the use of C1-INH concentrate as home therapy in patients with HAE. The search included the years from 1985, the year that pasteurized C1-INH concentrate replacement therapy was introduced, to August 2006. The keywords used for the search were 'C1-inhibitor', 'C1-inhibitor concentrate', 'C1-esterase inhibitor', 'C1-esterase inhibitor concentrate', 'C1-INH', 'C1-INH concentrate', 'C1EI' and 'C1EI concentrate', combined with 'C1-inhibitor deficiency', 'C1-esterase inhibitor deficiency', 'C1EI

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Table 1. Papers detailing the use of C1 inhibitor (C1-INH) concentrate home therapy in patients with hereditary angioedema (HAE)*.

Author	Publication	No. of patients	Home therapy programme entry requirements	Regimen	Outcome
Levi *et al.*	Basic & Clin Immunol 2006	43 (31 HAE, 12 AAE)	Attack frequency > 1/3 weeks (on-demand treatment), > 1/10 days (prophylaxis) Proven C1-INH deficiency Completion of education programme	C1-INH on demand ($n = 31$) C1-INH every 5–7 days ($n = 12$)	Decreased time to onset of relief and attack duration (on-demand group) Decreased frequency of attacks (prophylaxis group)
Rusicke *et al.*†	JACI 2006 Abstract	163 (HAE and AAE, exact numbers not stated)	Not stated 50% of clinic HAE cohort included	C1-INH on demand (first line for children) or prophylactically (interval not stated)	Reduced consumption of C1-INH Prevention of severe attacks Reduced hospitalization Reduced absence from school or work
Bork *et al.*	Transfusion 2005	25	Attack frequency > 1/month	C1–INH on demand	Not stated but short onset-to-treatment time associated with less severe and shorter duration of attacks
Kreuz *et al.*	Blood 2004 Abstract	23	Intolerant of, or resistant to danazol		Improved QoL Reduced frequency of attacks Reduced frequency of life-threatening attacks No adverse events
Kreuz *et al.*†	Biomed Progress 1999	5	Not stated	C1-INH every 3–4 days	Reduced frequency of attacks 'Largely symptom free'
Bork & Witzke	JACI 1988	2 (1 HAE, 1 AAE)	Optimal oral prophylaxis Attack frequency > 1/week Proven C1-INH deficiency	C1-INH every 4–5 days	Reduced attack frequency and severity Limited duration of benefit in patient with AAE

*Patients suffered from HAE unless otherwise stated. †Reporting on the same cohort.

deficiency', 'hereditary angio(o)edema', 'HAE', 'hereditary angioneurotic (o)edema' and 'HANE'. These groups of keywords were then put together, alone and in combination, with the search terms 'home', 'self-administration', 'self-administered', 'outpatient' and 'home-based'. The articles were retrieved and analysed. Pertinent articles known to the authors but not appearing in the Medline search results were also analysed.

Results

We found six relevant papers: two case series [8,9] with two and 43 patients, respectively; two further papers [10,11] which included information describing patients on home therapy (although this was not the main focus of the papers); and two further case series, which were available in abstract form only [12,13]. The papers are detailed in Table 1.

Patients were treated with C1-INH, given either on demand at the onset of an attack or as regular prophylaxis. C1-INH was self-administered or infused by a family member at home. The results showed that where prophylactic C1-INH was given, patients experienced improved quality of life (QoL) and reduced severity, duration and frequency of attacks. In addition, C1-INH had an excellent safety profile.

Discussion

Treatment of hereditary angioedema

Frequent or severe HAE attacks are disabling for the patient. Consequently, such attacks are an indication for regular prophylaxis, usually with attenuated androgens such as danazol that increase hepatic production of C1-INH [14,15]. However, attenuated androgens may cause unacceptable side effects such as virilization [16] or hepatic abnormalities [17], or may be contraindicated otherwise, for example in women who wish to become pregnant [18]. Fibrinolytic agents such as tranexamic acid or epsilon aminocaproic acid are alternative prophylactic agents, although the evidence base for their use is less certain [19,20]. Despite prophylaxis, many patients continue to experience intermittent severe attacks that interrupt their activities of daily living and may be life-threatening. These attacks are treated with C1-INH concentrate, which in most cases brings about a response within 30–90 min [21]. Licensed C1-INH products are available in

Germany, Austria, Switzerland, France, Hungary, Argentina, Japan (Berinert P®, ZLB Behring, Marburg, Germany) and the Netherlands (Cetor®, CLB, Amsterdam, the Netherlands). In other European countries, including the United Kingdom, and in the United States, C1-INH is used on a named-patient basis, or is completely unavailable.

C1-INH infusion is administered traditionally in hospital, usually in the emergency department. However, this approach can lead to delays in administering treatment. Emergency department staff may be unfamiliar with HAE and patients may not be triaged as urgent. Delays may occur in locating C1-INH, which is not a routine stock item for most hospitals. Such delays necessitate higher C1-INH doses to control the attack, unnecessary hospital admissions and, occasionally, severe adverse incidents, including death [5,8,22]. Death rates from HAE-related laryngeal oedema of 30–40% have been reported. Although the majority of deaths occur in undiagnosed patients, there remains an avoidable mortality in those who are diagnosed [1,5].

Children with C1-INH deficiency are not usually considered for home therapy in the United Kingdom, as there are no paediatric home therapy programmes. Fortunately, HAE is usually mild in preadolescence. However, prophylactic options are limited: long-term attenuated androgens present significant risks, including growth retardation, and are not recommended [23,24]. Our literature search revealed that one German centre does provide home therapy for children severely affected with HAE, suggesting that this option is feasible for selected cases. Rusicke *et al.* describe how on-demand C1-INH therapy is their first-line therapy for children, with regular prophylaxis for those who experience very frequent attacks [13]. More than 50% of their cohort of 325 patients infuse at home, although the proportion of these who are children is not stated. The authors claim that severe attacks are prevented, and hospital time and absence from school is reduced (although detailed figures are not supplied).

Recently, consensus documents providing recommendations on the management of HAE have been published by expert panels in Canada and the United Kingdom [18,25]. Both the Canadian and UK documents recommend offering patients the option of home therapy. In spite of a recent increase in interest in home therapy in those countries where C1-INH is available [9], there is little published literature on this topic and a relative lack of information available for health-care professionals.

The need for home therapy in hereditary angioedema

As C1-INH can be difficult to obtain at short notice, practitioners are strongly recommended to ensure that patients have a supply of C1-INH to keep in the refrigerator at home [5,18,25,26]. For the majority of patients, who have infrequent attacks, C1-INH is taken to the local hospital for infusion. For those patients experiencing more than one attack per month, repeated hospital admissions result in severe disruption to everyday life, affecting the ability to work and carry out domestic duties, impairing patients' confidence to travel too far from the local hospital and creating anxiety. For these patients, or for patients living in remote areas where access to a hospital may be difficult, home therapy (self-infusion or infusion by a family member) is usually the best option and is likely to result in greatly improved QoL.

Patient selection for home therapy in hereditary angioedema

The available data suggest that patients included on C1-INH home infusion programmes must fulfil certain criteria [8–13]: patients must have proven C1-INH deficiency as determined by typical symptoms, low C1-INH protein or function and low C4 complement. Genetic diagnosis is not widely available, but may be useful where diagnosis is unclear. Oral prophylaxis must be optimized. Patients must have sufficiently frequent attacks; the recommended frequency varies between centres, but is usually a minimum of one attack every 3 months [18]. However, patients with less frequent attacks may also benefit from home therapy and should be considered on an individual basis. Patients should be motivated to comply with the home therapy programme and be fully informed as to the risks and benefits. C1-INH should be stored at 2–8°C, although limited data suggest that lyophilized C1-INH concentrate may be stable at room temperature (25°C) for up to 6 months [26]. Twenty-four-hour access to help and advice should be available, including the option of emergency hospital treatment [18].

Training programmes in the United Kingdom and the Netherlands include practical aspects of C1-INH administration: hygiene and cannulation techniques, as well as indications for C1-INH infusion and management of emergencies [9,18]. Attacks should be severe enough to warrant C1-INH treatment – usually severe abdominal pain or orofacial oedema – but not so severe as to require hospitalization; for example, attacks causing symptoms of laryngeal obstruction. However, if airway obstruction is imminent, treatment may be expedited by home administration of C1-INH concentrate while awaiting the arrival of ambulance transport to hospital. Patients should be advised to consult a physician if the symptoms of an attack are atypical, as the onset of an appendicitis or GI infection may present with symptoms similar to abdominal attacks of HAE.

Government directives supporting home therapy

In many countries, the relationship between patient and medical professionals is changing. Nurses and paramedics are taking on tasks that were previously the responsibility of doctors, and many patients expect to take an active role in their own management. Facilitated by the internet, the

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growth of self-help groups such as the UK Primary Immunodeficiency Association (PiA) and HAE International (HAEI) has enabled patients to 'network' on a far wider scale than previously. Patients are increasingly aware of initiatives that can improve their QoL and, as a result, many patients are requesting the option of home therapy. Initiatives such as the UK NHS Plan and 'Expert Patient' programmes seek to give patients the knowledge and confidence to take a more active role in their own management [27,28].

Established home therapy programmes

Intravenous home therapy programmes exist for a variety of conditions, including intravenous immunoglobulins for antibody deficiency [29,30] and intravenous antibiotics for patients with a variety of underlying conditions [31–36]. These programmes have helped establish the feasibility and cost-effectiveness of home therapy. However, perhaps the closest parallel with C1-INH home therapy programmes is haemophilia home therapy. Like C1-INH, clotting factors for haemophilia can be used prophylactically or as an emergency treatment.

Home therapy has been available in haemophilia since the 1980s and is now considered 'routine'. Most paediatric patients are receiving home therapy by 18 months of age, as it is impractical for them to attend hospital several times a week for treatment or preventative therapy [37]. For children at high risk of bleeding, regular prophylaxis with clotting factors can be given; for others, prompt treatment of any bleeds or prophylaxis of high-risk events is preferable. Current UK guidelines [38] suggest regular prophylaxis for those who have declared themselves phenotypically severe (by virtue of two of more haemarthroses) and, for the others, access to coagulation factors for administration at home, a local hospital or a haemophilia centre.

Benefits of home therapy

The results of our Medline search included a recent paper by Levi *et al.*, who reported the experiences of 31 patients with C1-INH deficiency who were trained to self-administer C1-INH [9]. Patients, who all suffered from frequent, severe angioedema attacks, self-administered 1000 units of C1-INH concentrate shortly after the onset of severe abdominal, orofacial or laryngeal attacks. Twelve patients, who had very frequent attacks (> 1 every 10 days) were treated additionally with prophylactic C1-INH concentrate every 5–7 days. Mean follow-up was 3·5 years (range 0·9–5·1). All patients were trained successfully, and reported very low levels of technical failure with venepuncture (< 2%). There were no adverse events of sufficient severity to require medical assistance.

Self-administration of regular prophylactic C1-INH concentrate resulted in a significant reduction in attack frequency, with seven of 12 patients reporting complete freedom from attacks. Patients self-treating attacks reported a significant reduction in time to start of symptomatic relief, and in time to complete resolution of the attack, compared with the five 'historical control' attacks immediately prior to entry into the self-administration programme. Historical control attacks did not respond significantly differently to C1-INH concentrate compared with attacks in control patients who did not self-administer. The authors attributed the reduction in time to onset of relief and attack duration to the reduced attack-to-treatment time associated with self-administration. These observations are in accordance with Bork's observational study, which reported that abdominal attacks treated with C1-INH concentrate within 2 h of onset showed significant reduction in time to onset of relief compared with attacks where treatment was delayed [11]. This study did not report separate outcomes on the subgroup of 25 patients who self-infused. However, Rusicke *et al.* [13] commented on the reduced attack-to-treatment time associated with home therapy. Reduced attack frequency was also reported by Bork *et al.* [11], Kreuz *et al.* [12] and Rusicke *et al.* [13] in patients who infused prophylactically.

Reports from other home therapy programmes also indicate major benefits. Immunoglobulin home therapy is associated with greater patient independence, convenience, comfort and economic benefit [39,40]. A recent study showed that home therapy significantly improved health, school/social functioning (in children) and significantly reduced emotional distress and limitations on personal time [40]. In a similar study, home therapy with immunoglobulin significantly improved QoL [41]. Patients in both surveys preferred home- to hospital-based therapy [40,41]. For patients with haemophilia, home therapy is associated with reduced pain and disability, improved QoL and reduced hospitalization and time off work or school [38]. The availability of home therapy has also been associated with improved life expectancy [42]. Two of the case series in our analysis mentioned improved QoL for HAE patients with access to home therapy, although formal studies are lacking [12,13].

A major issue for patients with HAE is the delay and difficulty in accessing emergency care. Better awareness of HAE among medical staff and better liaison with emergency departments is important, but can be difficult when medical staff change frequently, as is the case in most emergency departments. Patient education is important to ensure prompt attendance at hospital at an early stage of the attack. However, travelling time is likely to be a limiting factor. For those patients with rapid-onset attacks, or who live far from the hospital, the resulting delay may pose a significant risk. Access to emergency treatment can often be expedited only by self-infusion/home therapy.

Home therapy for acquired angioedema

Interestingly, the Levi study group included three patients with AAE, whose benefit did not differ significantly from those with HAE. C1-INH concentrate appears effective in

the management of acute attacks of AAE, even when C1-INH antibodies are present, although some patients may require higher doses or become resistant to treatment [1,3]. Bork and Witzke reported a patient with frequent AAE attacks who was treated with C1-INH 1000 units every 5 days [8]. Treatment was initially successful, but after 10 months the patient became progressively resistant (Table 1). Despite reservations about its durability, C1-INH home therapy remains an option for patients with AAE.

Funding and resources

C1-INH is currently considered an expensive treatment option (approximately £290/€425 for 500 units). Home therapy has the potential to increase overall use of C1-INH by treating attacks that would previously have gone untreated, although published data do not suggest that this is the case when compared with optimum hospital-based treatment [9].

However, untreated attacks are costly in social, pharmacoeconomic and QoL terms. HAE is a lifelong condition, which usually becomes symptomatic in adolescence. Attacks may be precipitated by emotional stress, minor infections or oestrogens [18,43]. Consequently, young adults are particularly at risk of frequent attacks and the lifetime economic cost of disrupted education and employment is likely to be considerable. Additionally, under-treated attacks – where the patient presents late – have major direct costs, as higher doses of C1-INH are required and hospital admission is more probable [11]. Studies in antibody therapy and haemophilia show that home therapy is the most cost-effective option for delivering this type of care [44–46]. Cost–benefit studies in HAE are required urgently.

Funding of treatments is coming under increased scrutiny in both insurance-based and taxation-based health-care systems. C1-INH is unlicensed in several countries. In the United States it is not Food and Drug Administration (FDA) approved, but can be administered for compassionate use. Without FDA approval, HAE sufferers must pay the entire cost of the therapy themselves. Licensing studies are under way for both plasma-derived and recombinant C1-INH and for other therapies for acute attacks of HAE. Access to C1-INH, whether hospital- or home-based, is likely to remain suboptimal until licensed products are available. Even if licensed, the manufacturing costs of plasma-derived C1-INH are likely to be out of reach for many middle- and low-income countries. In the long term, recombinant C1-INH or inhibitors of the bradykinin–kallikrein pathway may provide a solution [47–49]. In theory, kallikrein- or bradykinin-pathway inhibitors also provide an option for patients with AAE who are resistant to C1-INH.

Safety of C1-inhibitor concentrate

Products used for home infusion need to demonstrate a high standard of safety with respect to immunological or allergic reactions. C1-INH is extremely well tolerated [1,50,51], and our analysis did not reveal any treatment-related adverse events [8–13]. However, because it is a plasma product, C1-INH raises particular concerns for patients and physicians regarding virus transmission, particularly viral hepatitis and HIV [52]. It is a regulatory requirement in Europe [53] for plasma donors to undergo a comprehensive health screen. Each donation is then screened using serological methods for the presence of HIV, hepatitis B (HBV) and hepatitis C (HCV). All plasma-derived medicinal products such as C1-INH concentrate are also recommended to undergo additional testing for HCV using the polymerase chain reaction (PCR).

The most widely available C1-INH concentrates undergo several additional voluntary safety checks, including the testing of individual pools via PCR for HIV-1, hepatitis A, HBV and parvovirus B19 [54,55], in addition to HCV. The plasma then enters the manufacturing process, where it undergoes further virus inactivation and removal steps. Inactivation is via pasteurization and removal via chromatography, in accordance with the Committee for Proprietary Medicinal Products' guidelines. Since its introduction in 1985, approximately 200 000 standard 500 unit doses of the most widely available pasteurized C1-INH concentrate have been sold globally, and no apparent cases of virus transmission have ever been identified [8,11,12,56].

Conclusion

Recent UK and Canadian consensus documents providing recommendations on the management of HAE have endorsed the option of home therapy for HAE patients. This choice should potentially be made available to all HAE patients, including those who suffer only infrequent attacks, and children. The opportunity for patients to manage their health enriches QoL, as the now-routine home administration of home haemophilia and immunoglobulin replacement therapies have shown. However, C1-INH is still an expensive treatment option. Therefore, prophylaxis should be optimized in HAE patients, especially those who have frequent, severe or rapid onset of attacks. If prophylaxis is ineffective, such patients should be prioritized for C1-INH home therapy.

Many patients are now requesting home therapy, as awareness of its advantages increases through self-help networking, and this should be encouraged. C1-INH is currently not licensed in many European countries, including the United Kingdom or the United States, and many physicians and funding authorities are reluctant to endorse new initiatives for rare diseases. However, given the proven efficacy and safety of C1-INH, licensing concerns can be overcome by referring patients to specialist HAE centres, who retain overall responsibility for clinical management and who have access to training programmes.

A review of the current situation in HAE management suggests that home therapy is indeed a viable and effective option that should be considered highly beneficial for patients, their families/carers and associated health-care professionals.

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