Emergency treatment of acute attacks in hereditary angioedema due to C1 inhibitor deficiency: what is the evidence?

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SUMMARY
Hereditary angioedema (HAE) is caused by a deficiency in C1 esterase-inhibitor (C1-INH) and is characterised by skin swelling, abdominal pain and episodes of upper respiratory tract obstruction. Oedema of the larynx can result in rapid asphyxiation and requires emergency treatment. Three treatment options for emergency treatment of HAE are reviewed: fresh frozen plasma, solvent/detergent-treated plasma and C1-INH concentrate. It is concluded that while all three treatment options are theoretically effective in the emergency treatment of HAE, C1-INH is the treatment of choice.

Keywords: Hereditary angioedema; C1 esterase inhibitors; plasma

INTRODUCTION
Hereditary angioedema (HAE) is an autosomal dominant disease characterised by skin swelling, abdominal pain and episodes of upper respiratory tract obstruction (1). These episodes of angioedema result from swelling within the deeper dermis or mucous membranes (2). The underlying cause of HAE is a deficiency in C1 esterase-inhibitor (C1-INH), which has a key role in controlling the early complement and kallikrein systems, as well as factor XII (FXII) and the fibrinolytic system.

Manifestations of the disease vary from patient to patient, with some patients having more frequent or severe attacks than others. Triggers vary but stress appears to be an important factor in many cases – up to 30–40% of attacks are precipitated by emotional stress (3,4).

The most dangerous aspect of HAE is the risk of oedema of the larynx, which can result in rapid asphyxiation – the most frequent cause of death in these patients. Without therapy, it has been estimated that lifetime mortality can be as high as 30%, due to laryngeal oedema (5). Therefore, it is important that people with HAE are identified, in particular by tracing family members of patients diagnosed with HAE. Because of ‘hidden’ cases of HAE within the population, the exact prevalence is unknown but is thought to be between one in 10,000 and one in 50,000 persons worldwide (1).

THERAPEUTIC OPTIONS
Because of the life-threatening nature of laryngeal oedema, establishing the best approach to emergency management of HAE is important, in particular to avoid inappropriate emergency treatment, such as administration of corticosteroids and antihistamines. Serious attacks of acute HAE (laryngeal or abdominal) should be treated by raising serum levels of C1-INH sufficiently to prevent ongoing bradykinin and complement activation, thus preventing further oedema, reducing pain and preventing asphyxiation in laryngeal oedema.

C1-INH can be administered in different forms: fresh frozen plasma (FFP), solvent/detergent-treated plasma (S/D plasma) or as C1-INH concentrate. These three treatment options are reviewed below and their key characteristics are summarised in Table 1. This discussion also has some relevance for other diseases with treatment options of whole plasma vs. purified concentrated plasma products.

EFFICACY
All three treatment options (FFP, S/D plasma and C1-INH concentrate) have been used in the emergency treatment of HAE-associated laryngeal oedema, but efficacy data from clinical trials are available only for C1-INH concentrate. In a double-blind, placebo-controlled trial of C1-INH substitution

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**Table 1** Treatment options in acute hereditary angioedema (HAE) attacks: summary of key characteristics

| Treatment options                        | Fresh frozen plasma (FFP)                        | Solvent/detergent-treated plasma (S/D)                | CI-INH concentrate                      |
|------------------------------------------|-------------------------------------------------|-----------------------------------------------------|----------------------------------------|
| Efficacy                                 | Case reports available                          | Case reports available                                | Proven in clinical trials, including a prospective, randomised, double-blind study |
| Composition/concentration                | Non-standard composition and non-standard concentration of CI-INH. Introduction of other complement proteins may intensify HAE | Standardised composition but CI-INH content not standardised. Introduction of other complement proteins may intensify HAE | Standardised composition and CI-INH activity; CI-INH content is a release criterion for the product |
| Viral safety                             | Serological testing for viral markers only      | S/D treatment inactivates enveloped viruses but not non-enveloped viruses like hepatitis A or parvovirus 19 | Two viral inactivation steps (pasteurisation and chromatography) Clinical viral safety shown by pharmacovigilance studies Dose is not limited by the risk of hyervolaemia |
| Risk of hyervolaemia                     | Large volumes can overload the circulatory system | Large volumes can overload the circulatory system     | Lower allergenic potential than FFP due to fewer components |
| Allergenic potential                     | Large number of potentially allergenic constituents | Large number of potentially allergenic constituents | Lower allergenic potential than FFP due to fewer components |
| Time to intervention and speed of action | Requires thawing – delays time to treatment. Large infusion volume delays action | Requires thawing – delays time to treatment. Large infusion volume delays action | Rare reports of allergic-anaphylactic reactions Lyophilisate is readily reconstituted – no need to thaw More rapid action due to small infusion volume |
| Drug cost                                | Relatively inexpensive                         | Relatively expensive                                  | Relatively expensive                   |
| Therapy cost                             | Unpredictable                                  | Unpredictable                                         | Foreseeable                            |
| Availability                             | Widely available – but stock precious as needed for many applications | Not available in all countries                        | Available in all countries on request*, except the US. Suitable for emergency supplies for patients |
| Indicated for treatment of acute HAE attacks | No                                             | No                                                   | Yes                                    |

*Supplies available on named patient basis from the manufacturer (UK: ZLB Behring, Aventis House, Market Place, Haywards Heath, W Sussex). †Registered indication where product licensed.
in 22 HAE patients, 69% of those treated with C1-INH began to improve within 30 min of infusion, and 95% responded within 4 h (4). In comparison, only 12% of patients in the placebo group had responded in 4 h. A more detailed analysis (6) showed that the time to relief of symptoms over 166 attacks was significantly faster in the C1-INH group than in the placebo group; the mean time to relief was 7.62 vs. 15.35 h, respectively (p = 0.007). In a retrospective analysis of 13 patients, the mean duration of attacks in seven who were treated with C1-INH concentrate (7) was 50 min, with a range of 15–150 min. This contrasted strongly with the typical attack duration of 1–4 days without the use of C1-INH. All patients who used C1-INH concentrate in this study were content with the rapid alleviation of their symptoms (7). Likewise, in 193 episodes of laryngeal oedema, symptoms started to resolve between 30 and 60 min after the administration of C1-INH concentrate (Figure 1) (1); the mean interval between injection and the onset of efficacy was 42 min. The mean duration of symptoms in treated patients was 15 vs. 101 h for untreated patients.

FFP and S/D plasma are known to be effective in the emergency treatment of HAE (J. Gooi, personal communication), but trials are lacking to show comparative efficacy of these products. In addition, C1-INH is supplied at a standardised concentration/activity (50 U/ml), while the exact composition of FFP is not standardised or determined. In this respect, it is also worth noting concerns that the S/D treatment process may conformationally alter or inactivate C1-INH to some degree as has been shown for other similar plasma proteins (serpins) (8). Additional studies of S/D-treated plasma are needed to establish its efficacy as a FFP substitute, as well as its efficacy for treatment of HAE attacks, where only anecdotal evidence exists.

SPEED OF AVAILABILITY

One of the major advantages of C1-INH concentrate over FFP and S/D plasma is that it is available for use more quickly. Unlike plasma, it does not require time-consuming thawing and the lower infusion volume saves additional time. This time saved can be of vital importance, as in some cases, the time from symptoms to death has been very short. A retrospective analysis showed that, although the average time between the onset of laryngeal oedema and asphyxiation was 7 h, in two cases it was 1 h or less. One 9-year-old boy with no previous clinical signs of HAE died just 20 min after the initial onset of symptoms (9). He belonged to a family with five other HAE sufferers and had previously been shown to have C1-INH deficiency.

Another case, with a rapidly progressing airway obstruction over 5 min to the brink of respiratory arrest, has also been reported (10). Although in most cases the time available for therapeutic intervention is longer, it is not possible to predict which episodes will deteriorate quickly; therefore, every case of laryngeal oedema should be treated without delay. These data also support the approach of providing HAE patients with a supply of C1-INH for emergency treatment, as utilised in one clinical study (11). This potentially life-saving approach would not be possible with FFP.

In addition, some patients report that the symptoms persist for longer if they wait to obtain a transfusion, which may suggest that early and appropriate treatment could not only limit distress to the patient but also potentially reduce the total volume transfused (7). These data all support the conclusion that early and appropriate management is extremely important in emergency treatment of HAE (9).

VIRUS SAFETY

Physicians and patients are very concerned about the risk of transmission of viruses (particularly viral hepatitis and HIV) when using blood products (7). It is therefore important to be able to reassure all concerned that they are receiving the safest product available.

In Europe, it is a regulatory requirement (12) (Directive 98/463/EC) that every plasma donor undergoes a comprehensive health screen, which includes questioning about risk factors for infection before every donation; each donation
is screened with serological methods for the presence of human immunodeficiency virus-1 and 2 (HIV-1/2), hepatitis C virus (HCV) and hepatitis B virus (HBV). In addition, for plasma-derived medicinal products (such as C1-INH concentrate) or virus-inactivated pooled plasma products (such as S/D plasma), it is recommended (in CPMP/BWP/269/95 rev. 3) that all plasma pools undergo additional testing with polymerase chain reaction (PCR) for HCV.

Additional Safety Measures

Many manufacturers of plasma-derived products voluntarily exceed the basic requirements of these safety regulations. For example, in the case of the most widely available C1-INH concentrate:

1. donations of first-time donors are quarantined and released for production only when the donor’s second plasma donation has also tested negative for the above-mentioned viruses;
2. donations from repeat donors are stored for a minimum of 60 days prior to use as part of a ‘look-back’ process (allows exclusion of donations from donors later found to have risk factors for infection);
3. individual plasma pools undergo further testing with PCR to exclude the presence of HIV-1, HBV, hepatitis A virus (HAV) and parvovirus B19 (in addition to HCV) (13).

It is only this highly screened plasma that enters the manufacturing process where it then undergoes further specific virus inactivation/removal steps.

Virus Inactivation: One- or Two-Step Process?

In the case of virus-inactivated plasma, this virus inactivation step comprises treatment with solvent/detergent. However, while effective in inactivating enveloped viruses such as HIV, this treatment is less effective at inactivating non-enveloped viruses such as HAV and parvovirus B19. The latest European Committee for Proprietary Medicinal Products Note for Guidance on Plasma-Derived Medicinal Products (CPMP/BWP/269/95 rev. 3) states that:

‘For all plasma-derived medicinal products, it is an objective to incorporate effective steps for inactivation/removal of a wide range of viruses of diverse physico-chemical characteristics. In order to achieve this, it will be desirable in many cases to incorporate two distinct effective steps, which complement each other in their mode of action such that any virus surviving the first step would be effectively inactivated/removed by the second. At least one of these steps should be effective against non-enveloped viruses. It is probably for this reason that many manufacturers of plasma-derived products that previously employed only solvent/detergent virus inactivation methods are adding a second virus inactivation step, often dry heat treatment, to the manufacturing process. Unfortunately, heat treatment cannot be applied to plasma, as it changes the conformation of many plasma proteins making them far less active.’

Conversely, the most widely available C1-INH concentrate undergoes pasteurisation (heat treatment in aqueous solution at 60 °C for 10 h) as a specific virus inactivation step. During the fractionation and purification processes, it is also subjected to additional measures, such as chromatography, that have also been shown to remove a wide range of viruses. This is in line with the CPMP guidelines, which (subsequent to the above) state:

‘Where a process step is shown to be reliably effective in inactivating/removing a wide range of viruses including enveloped and non-enveloped viruses of diverse physico-chemical characteristics and the process contains additional stages reliably contributing to the inactivation/removal of viruses, a second effective step would not be required. Long-term data on the virus safety of pasteurised C1-INH have shown no cases of hepatitis or HIV transmission; however, numbers are small (14–16). In vitro studies suggest that including a pasteurisation step is effective at removing both enveloped and non-enveloped viruses and is superior to S/D treatment at removing non-enveloped viruses (17–19). The pasteurised plasma-derived products that have been most widely tested are for haemophilia. Extensive clinical trials in haemophiliacs treated with FVIII concentrates, produced using a pasteurisation step in a method similar to C1-INH, have shown these products to be safe (20–22).

Both the prescribing doctor and the patient can be reassured by the fact that, since its introduction in 1985, approximately 196,000 standard doses (500 U) of this C1-INH concentrate have been sold worldwide and no proven cases of virus transmission have ever been reported (personal communication, ZLB Behring GmBH).

Tolerability/Adverse Reactions

Another aspect of patient safety is the unnecessary infusion of other plasma proteins that occurs with FFP and S/D plasma. As well as C1-INH, other complement factors and kinins will be introduced simultaneously when FFP or S/D plasma is used. These proteins may exacerbate the symptoms of HAE (23) by increasing the amount of inflammatory substrate available. In addition, there is a small risk of reactions such as non-cardiogenic pulmonary oedema after the administration of FFP (24,25). It has also been shown that elevated anaphylotoxin concentrations are frequently found in FFP (25).

The following reactions after infusion of plasma have also been described (26): febrile non-haemolytic transfusion reaction, post-transfusion purpura, transfusion-related acute lung
injury: graft-vs.-host disease, and fibrinolysis during liver transplantation (27).

Allergic/anaphylactic reactions are also possible with C1-INH concentrate, but such reports are extremely rare (28). This is not surprising given the purified nature of the product, with a greatly reduced amount of potentially allergenic compounds as compared with whole plasma.

In addition, there is a risk of volume overload with plasma administration (6). One unit (1 U) of C1-INH is equivalent to the C1-INH activity of 1 ml of FFP. C1-INH is infused at a concentration of 50 U/ml (23), and therefore at least 50 times the volume of plasma must be used to achieve similar levels of C1-INH. If C1-INH concentrate is unavailable, and FFP or S/D plasma must be used, then a dosage of 10–15 ml/kg body weight is recommended (23) to avoid volume overload.

In terms of general tolerability, C1-INH has been well tolerated without adverse events (4,5,7). This favourable adverse event profile is probably related to the highly specific and purified nature of the product.

Cost

Detailed economic analysis has not been undertaken. Although the unit cost of C1-INH concentrate is greater than FFP or S/D plasma, the use of FFP or S/D plasma is likely to incur significant additional hidden costs, which in many cases will negate any saving made by using these treatments. These hidden costs include the slower time for therapeutic action, lower potential efficacy, the risk of hypervolaemia, the higher risk of viral contamination and the extra time in hospital that may result from less appropriate therapy. Ideally, one should also consider the cost to the patient and to society: e.g. quality-of-life costs, days lost from work or education, resulting in loss of earnings, reduced productivity and reduced future earning power. The real costs of therapy with FFP or S/D plasma are therefore not certain.

Short-Term Prophylaxis

Because of the risk of laryngeal oedema in HAE, prophylaxis is necessary prior to dental manipulation, endoscopy or endotracheal intubation. The importance of this has recently been highlighted by four deaths from asphyxiation after tooth extraction in HAE patients (29). In contrast, short-term prophylaxis has led to uncomplicated maxillofacial surgery using short-term C1-INH replacement therapy (30). C1-INH concentrate has been shown to compare favourably with FFP in this situation: the mean plasma level of C1-INH more than tripled (from 26 to 85% of normal levels) after the initial prophylactic infusions of the C1-INH concentrate.

By contrast, the levels only increased 1.5 fold after prophylactic infusion of FFP (4,31).

CONCLUSIONS

FFP, S/D plasma and C1-INH are all theoretically effective in the emergency treatment of HAE. Clinical evidence from a prospective, controlled, double-blind trial is only available for C1-INH concentrate. Furthermore, the more specific nature of C1-INH, having been tailored to treat this disease, makes it a more directed therapy, with potentially fewer adverse consequences. As early as 1992, Prof. Angelo Agostoni, a European authority on HAE, declared that ‘FFP treatment of HAE is obsolete’ (5). If one draws a comparison with the treatment of haemophilia A and B, where both FVIII/FIX concentrates and cryoprecipitate can be used for treatment, one would not consider the use of cryoprecipitate except as a last resort. The same should be true for the treatment of HAE: C1-INH concentrate is the state-of-the-art treatment for acute attacks in HAE.

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