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REVIEW ARTICLE

CME

Hereditary Angioedema: Current and Emerging Treatment Options

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Angioedema can result from allergic, hereditary, and acquired conditions. Hereditary angioedema (HAE) attacks are disabling at the time of occurrence and can be life threatening; they often result in hospitalization and intensive care unit admission. Although there are several variants of HAE, they share a final common pathway: unopposed activation of multiple kinins and mediators including kallikrein and bradykinin. This leads to increased vascular permeability, which in turn produces the edema after which the condition is named. Older treatment options licensed in the United States, anabolic steroids and antifibrinolytics, have troublesome side effect profiles and may not reverse a severe acute attack. In Europe, C1 esterase inhibitor (C1-INH) concentrates have been used since 1974 for both preventing and terminating attacks. Two of these have now been licensed in the United States for use in HAE patients, one for prophylaxis and the other for treating acute abdominal and facial HAE attacks. The first kinin pathway modulator, ecallantide, has also been licensed recently in the United States for treating HAE attacks. The objective of this article is to describe HAE and review the available options for managing patients, as well as different drugs currently under investigation. Specific attention is given to the perioperative management of patients with HAE. (Anesth Analg 2010;110:1271–80)

Angioedema (AE) is circumscribed, nonpruritic, and nonpitting edema, caused by an increase in vascular permeability.[1] It can result from allergic, hereditary, or acquired conditions. Hereditary AE (HAE) accounts for approximately 2% of clinical AE cases and affects approximately 1 in 50,000 people.[2] It can cause life-threatening injury and often leads to hospitalization and intensive care unit admission; 15 to 30,000 emergency room visits per year in the United States are attributable to HAE.[3] Mortality rates have nevertheless been reduced by improved monitoring and therapy.[4]

ETIOLOGY

In HAE, increased permeability of submucosal or subcutaneous capillaries and postcapillary venules leads to plasma extravasation and subsequent swelling.[5] Deficient C1 esterase inhibitor (C1-INH) activity has long been understood to be the main cause.[6] In healthy individuals, C1-INH inhibits a number of physiological reactions in the plasma. These include the coactivation of coagulation factor XII and prekallikrein, the conversion of high-molecular-weight kinin into bradykinin, the breakdown of fibrin by plasmin, and activation of the complement protein C4 by C1 esterase as shown in Figure 1. Historically, uncontrolled activation of the complement system in the absence of C1-INH was believed to be the primary mediator of AE, but more recent studies suggest that bradykinin is the active substrate in AE attacks.[7–14]

There are several etiological variants of HAE. The most common is type I, which is caused by a deficiency of C1-INH in the plasma and is responsible for up to 85% of all HAE. HAE type I is produced by a mutation on chromosome 11 that renders 1 copy of the *SERPING1* gene nonfunctional. The condition is transmitted through autosomal dominant inheritance with a spontaneous mutation rate of 25%.[15] The frequency and severity of symptoms do not seem to relate to particular mutations.[16,17] There are 2 types of HAE assay available for diagnosis: an antigen test that measures the level of C1-INH protein and a bioassay that quantifies C1-INH functional activity. HAE type I is characterized by low levels of both C1-INH antigen and functional activity. Affected patients have C1-INH plasma levels 5% to 30% of normal.[18] This phenomenon is thought to be caused by both increased consumption and gene down-regulation.[19,20]

HAE type II is clinically indistinguishable from type I and represents 15% to 20% of HAE cases. This type is

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Accepted for publication January 23, 2010.

Jerrold Levy is the Section Editor of Hemostasis and Transfusion Medicine for the Journal. The manuscript was handled by Charles W. Hogue, Jr., Associate Editor-in-Chief for Cardiovascular Anesthesiology, and Dr. Levy was not involved in any way with the editorial process or decision.

Reprints will not be available from the author.

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DOI: 10.1213/ANE.0b013e3181d7ac98

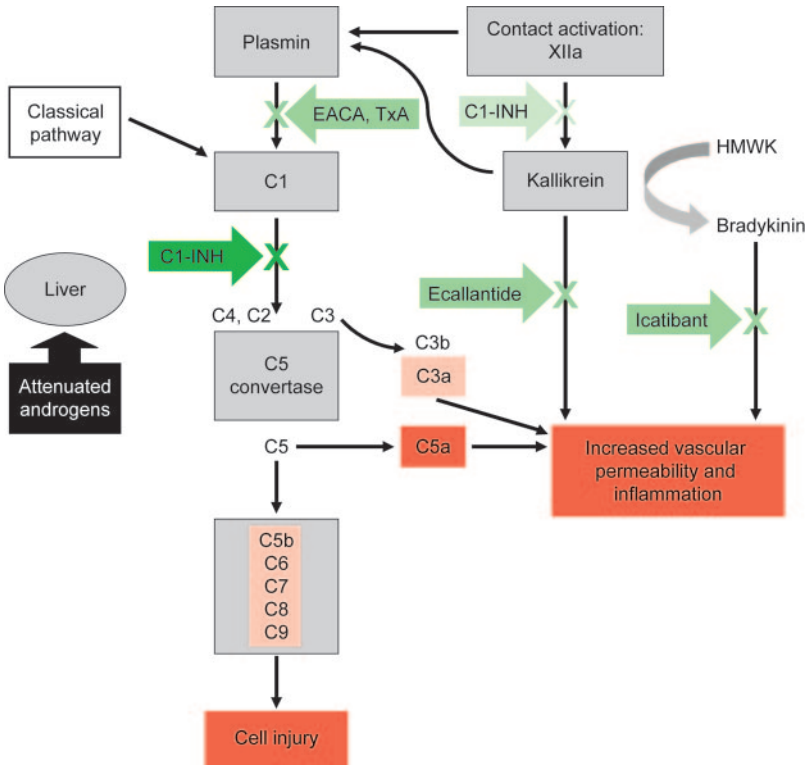

Figure 1. Mechanisms of action for therapeutic agents in treating or preventing hereditary angioedema (HAE). Multiple pathways are capable of activating complement and generating inflammatory mediators including complement anaphylatoxins C3a and to a greater extent C5a, kallikrein, and bradykinin. Activation of the final complement cascade produces a membrane attack complex that produces cellular injury. Angioedema occurs after tissue injury from multiple causes. Tissue injury can activate contact activation (Hageman factor or factor XII) to generate kallikrein from prekallikrein, its precursor. Kallikrein in turn generates and activates plasmin from plasminogen, and plasmin can directly activate the C1 esterase complex to initiate complement activation. Under normal circumstances, the C1 esterase inhibitor (C1-INH) functions to inhibit both complement activation and to a lesser extent modulate contact activation. In HAE, because of quantitative or qualitative C1-INH, the pathway proceeds unchecked generating mediators that increase capillary permeability to produce angioedema. Therapeutic approaches are directed at acutely restoring C1-INH levels, inhibiting kallikrein with ecallantide, inhibiting bradykinin with Icatibant, and inhibiting plasmin with the lysine analogs ϵ-aminocaproic acid (EACA) or tranexamic acid (TxA). Anabolic corticosteroids (attenuated androgens) have been used to increase liver synthesis of C1-INH.

characterized by mutations of the *SERPING1* gene leading to the production of nonfunctional enzyme. Similar to HAE type I, low functional levels of C1-INH are seen in HAE type II. However, in contrast to HAE type I, type II is characterized by C1-INH antigen levels in the normal or even high range.[15]

HAE type III is found predominantly in women and was initially associated with therapeutic estrogen. It has been suggested that HAE type III is caused by activating mutations in the gene for factor XII.[21,22] Activated factor XII cleaves prekallikrein to kallikrein, which in turn generates bradykinin from high-molecular-weight kinin. Factor XII transcription is upregulated by estrogen, which likely explains the female preponderance of HAE type III.[23] HAE type III exhibits dominant inheritance but has a relatively late age of onset (mean 26.8 years).[24]

PRESENTATION AND DIAGNOSIS

HAE is characterized by intermittent swelling of the skin, gastrointestinal tract, and bronchial tree. The average HAE patient has approximately 20 attacks per year.[25,26] These are life threatening if the upper airway is affected: HAE-associated laryngeal edema carries a mortality rate of 25% to 40%.[27,28] Attacks are generally sporadic and unpredictable, but more likely to occur in association with minor trauma, dental procedures (which account for up to half of cases), infection, snoring, daily activities such as typing, and stress.[29–31] The edema develops slowly over a period of up to 36 hours and resolves 1 to 3 days later. Attacks involving the skin may result in patients feeling a sensation of uncomfortable stretching, tightness, or numbness of the tissue. Subcutaneous attacks can occur anywhere on the body, but show a predilection for the extremities, face, and genitalia.[32] Abdominal attacks involving the gastrointestinal tract, which are experienced by up to 93% of HAE patients, bring cramping pain, nausea, vomiting, and diarrhea.[30,33–35] The severe abdominal pain with nausea and vomiting may be extremely difficult to differentiate from an acute surgical abdomen because diagnostic imaging studies and endoscopy frequently yield transient or nonspecific findings.[36–38] As a result, many patients undergo unnecessary surgical procedures (usually in patients with undiagnosed HAE, and by physicians unfamiliar with HAE).[39] However, the most dangerous manifestation of HAE is upper airway obstruction, which has been shown to occur in one-half to two-thirds of patients.[30,34,35] In most cases, further attacks do not occur within a week.[40] Patients with HAE do not present with erythema or hives, nor do they respond to antihistamines, steroids, or epinephrine.

HAE should be suspected in patients with recurring attacks of swelling and abdominal pain without a clear underlying cause. The first diagnostic step in the workup of a patient with suspected HAE is an evaluation of quantitative C4. A normal C4 level makes HAE highly unlikely.[41] If the patient has low C4 or the clinician has a suspicion of HAE in a patient with normal C4, a C1-INH level should be obtained. Alternatively, C4 levels can be retested when the patient is symptomatic. Patients with low C1-INH and C4 levels most likely have HAE type I, although acquired AE (AAE) should be suspected in patients with no family history or late onset of symptoms.[2] A C1q level can be ordered to differentiate between HAE type I and AAE in ambiguous cases because C1q is normal in HAE type I but

Table 1. Existing Treatments for Hereditary Angioedema (United States)

Class/drug	Indication	Dose	Potential side effects
Attenuated androgens	Prophylaxis		Weight gain, acne, alopecia, hirsutism, myalgia, hematuria, nausea, headache, anxiety, hypertension, menstrual irregularities, decreased libido, hepatotoxicity, hepatocellular adenomas, hyperlipidemia
Danazol (Danocrine)		Individualized (start on 200 mg t.i.d. then titrate down)	
Stanozolol (Winstrol)		Individualized (start on 2 mg t.i.d., typical maintenance dose 2 mg/d)	
Antifibrinolytics	Prophylaxis		Muscle weakness, hypotension, headache, dizziness, confusion, diarrhea, nausea, prolonged menstruation, elevated muscle enzymes, impaired vision, thrombosis
Epsilon-aminocapric acid (Amicar)		0.17–0.43 g/kg	
Tranexamic acid		1–1.5 g, 2 or 3 times daily	
C1 esterase inhibitor concentrates	Prophylaxis		
(Cinryze) (Berinert P.)	Treatment of acute attacks	1000 units every 3 or 4 d	Upper respiratory tract infection, sinusitis, rash, headache
Kallikrein inhibitors		20 units per kg body weight	Nausea, dysgeusia, abdominal pain, vomiting, headache
Ecallantide (Kalbitor)	Treatment of acute attacks	30 mg (a second 30 mg dose may be administered within 24 h if an attack persists)	Hypersensitivity reactions including anaphylaxis, headache, nausea, fatigue, diarrhea, upper respiratory tract infection, injection site reactions, nasopharyngitis, vomiting, pruritus, upper abdominal pain, pyrexia

low in AAE. Unfortunately, C1q testing is not yet available in all laboratories.[42]

Those with normal C1-INH antigenic levels should have their C1-INH function evaluated because HAE type II patients present with normal C1-INH protein levels but decreased C1-INH function. Enzyme-based chromogenic assays are most suitable for a diagnostic evaluation of C1-INH activity because they are less likely than other methods to produce false-negative results.[7] A finding of low C4 with decreased C1-INH capacity carries a 98% specificity and a 96% negative predictive value for AE.[43] In contrast, C4 and C1-INH levels and function are generally normal in HAE type III, although C1-INH may be depleted during an attack as a result of enhanced substrate use.[44]

Genetic testing is not recommended as a general screening measure, and it is not needed to establish a diagnosis of HAE. It may, however, be useful in some patients with suspected HAE type III or a borderline presentation for HAE type I versus AAE.[2,43,45] Recently, denaturing high-performance liquid chromatography has shown promise as a rapid, inexpensive genetic screen for *SERPING1* mutations.[46]

PEDIATRIC CONSIDERATIONS

Most patients with AE begin having attacks during childhood,[30] and some as early as infancy.[47] Overall, 40% to 80% of children present with abdominal pain as their main symptom.[48,49] Life-threatening respiratory attacks are less common in children, but nevertheless can occur.[50] The clinician must remain especially vigilant because small children can suffocate quickly because of their small airway diameters.[50,51] Laryngoscopy may be difficult to perform, and any hoarseness, stridor, dyspnea, globus, dysphagia, or voice changes should be seen as evidence of airway involvement.[51] As such, it is recommended that C1-INH and C4 testing be performed early in family members of affected individuals.[52] Diagnosis can be difficult in young children because C4 and C1-INH may not reach adult levels until the age of 3 years.[53] Tests performed during infancy should be repeated after the child reaches the age of 1 year, and young children with a high clinical suspicion of AE should be treated with the assumption that they have the disease regardless of laboratory values.[51,54]

ESTABLISHED (OLDER) TREATMENT OPTIONS

A number of drugs have been available for use in HAE management in the United States for many years. Attenuated androgens, antifibrinolytic drugs, and use of fresh frozen plasma (FFP) are older reported treatments. Each of these will be considered individually.

Attenuated androgens are anabolic corticosteroids that have been shown to decrease the frequency of attacks by >80% in 97% of patients.[34,55] The most frequently used drugs in this class are danazol and stanozolol (Table 1). Both work by increasing the liver's production of C1-INH.[56] Weight gain, cramps, hirsutism, and menstrual abnormalities are common side effects of attenuated androgens (Table 1), although these generally resolve with decreased dosing.[57–62] Most attenuated androgen regimens involve careful tapering after an initial high-dose "run-in" period to gauge response.[63] Some authors have alternatively advocated starting with low doses and titrating up as needed.[39] However, these therapies are not for acute attacks.

HAE patients treated with danazol have been found to have increased low-density lipoprotein and decreased high-density lipoprotein levels, placing them at increased long-term risk of atherosclerosis.[62] It is therefore recommended that patients receiving attenuated androgens have their liver function checked at presentation and every 6

months thereafter. Lipid levels should be checked at baseline, 6 months, 1 year, and then annually if no abnormalities are detected. Because of the risk of hepatic neoplasm, an ultrasound should be ordered at baseline and then every 2 years. After 10 years, hepatic ultrasound should be repeated annually.[2,52] Tibolone (a steroid hormone with mixed properties of estrogen, testosterone, and progesterone) has shown promise in treating HAE patients who might not tolerate attenuated androgens because of their side effect profile. In a pilot study, the drug prevented attacks with similar efficacy to danazol, with fewer side effects.[64]

Antifibrinolytics such as ϵ-aminocaproic acid[51] and tranexamic acid[51,54] work in a certain percentage of C1-INH–deficient states by inhibiting plasmin activity. Plasmin directly can initiate complement activation and consumes C1-INH.[65–67] Inhibiting plasmin-mediated fibrinolysis also prevents the release of vasoactive peptides, thereby decreasing the magnitude of inflammation in tissues.[67] Antifibrinolytics decrease the frequency and intensity of AE attacks,[68–71] but are far less effective than anabolic steroids[34,69] and are therefore usually reserved for HAE patients who cannot tolerate steroids. Side effects (listed in Table 1)[69] are worse in patients taking ϵ-aminocaproic acid, and tranexamic acid is therefore used more frequently.[51] There are case reports linking antifibrinolytics with thrombosis, but causality has not been firmly established.[72,73] Nevertheless, it has been suggested that patients beginning tranexamic acid therapy receive baseline liver function tests and a thrombophilia screen if they have a personal or family history of thromboembolic disease.[52]

FFP is used for the treatment of acute AE attacks, particularly in countries where C1-INH concentrate is not available.[74,75] However, such treatment can potentially worsen an attack because of the high concentrations of complement components in human plasma.[52] Furthermore, there are certain safety concerns with FFP (e.g., transfusion-related acute lung injury, anaphylaxis, and viral transmission), and the need for a relatively large infusion volume is time consuming and can be problematic in the emergency setting or with volume-sensitive patients.[76,77] Therefore, when C1-INH concentrates are available, they are preferred over plasma transfusion.

IMMINENT AND RECENTLY LICENSED THERAPEUTIC OPTIONS IN THE UNITED STATES

C1-INH concentrate has been available in Europe for many years. In the 1970s, when the use of C1-INH was first established, it was considered only as an emergency treatment.[78] After the introduction of purification and virus inactivation steps into the manufacturing process, C1-INH is now regarded as first-line therapy wherever it is available.[52,54,78] Five companies are conducting or finalizing late-stage trials of products, classified as either C1-INH replacement therapies or kinin pathway modulators, with the intention of marketing in the United States.[26] The first C1-INH concentrate was licensed by the Food and Drug Administration (FDA) for prophylactic use in the United States in October 2008, and a second product was licensed 12 months later for the treatment of HAE attacks.

Cinryze (ViroPharma, Exton, PA) is a C1-INH concentrate under investigation, which is similar to a product marketed in The Netherlands for several years. Cinryze is derived from human plasma that has been tested and treated to reduce the possibility of viral infection. All donors are screened for human immunodeficiency virus, hepatitis B and hepatitis C viruses, and parvovirus B19. Subsequently, the product is pasteurized and nanofiltered to further reduce the risks of infectious disease transmission. Phase III trials have demonstrated efficacy for both prophylactic treatment of HAE ($P < 0.0001$) and the treatment of acute attacks ($P < 0.05$).[79] Open-label trials are ongoing in the United States and, although as yet there is little information in the literature, Cinryze was the first C1-INH concentrate to be licensed by the FDA. It is indicated for routine prophylaxis against AE attacks in adult and adolescent patients with HAE, but not for the treatment of acute attacks.

Berinert P (CSL Behring, King of Prussia, PA) is a purified C1-INH concentrate derived from human plasma, and is stored at room temperature. One unit of Berinert P is the amount of C1-INH in 1 mL of human plasma (0.27 mg).[80] The product is tested by polymerase chain reaction (high-titer screening[81]) and pasteurized (60°C for 10 hours in aqueous solution). Specific chromatography is a further virus removal/inactivation step during manufacture.[80] These processes have been shown to preserve clinical efficacy while effectively protecting against transmissible viruses.[82,83] Berinert P is administered IV, and adverse events are uncommon.

More than 20 years of European experience has established the efficacy and safety of Berinert P in clinical use.[76,79,84] In a recent multinational, randomized, placebo-controlled phase II/III trial (IMPACT1), Berinert P produced a significant reduction in the time to symptom relief compared with placebo (30 vs 90 minutes, $P = 0.003$).[85] An open-label extension study (IMPACT2) is currently in progress in the United States, among subjects from both arms of IMPACT1.[86] Interim results have confirmed that Berinert P is effective in treating HAE attacks at all body locations. Median time to onset of symptom relief was 32 minutes for peripheral attacks, 25 minutes for laryngeal attacks, 26 minutes for abdominal attacks, and 32 minutes for facial attacks.[86] Both studies confirm the excellent safety profile of Berinert P.[85,86] Based on these outcomes, in October 2009, Berinert P became the first therapy to be approved by the FDA for the treatment of acute abdominal and facial attacks of HAE. No cases of viral transmission were identified in the recent trials of C1-INH concentrates, indicating the success of viral inactivation during manufacture.

Rhucin (Pharming, Leiden, the Netherlands) is a recombinant C1-INH (rhC1-INH) derived from the milk of transgenic rabbits. The product (dosed at 100 U/kg) has a half-life of only 3 hours because of enhanced catabolism, related to increased glycosylation; however, its inhibitory activity is reported to be comparable with human C1-INH.[87] Rhucin has been shown to increase C1-INH and C4 levels while decreasing cleaved C4 in HAE patients.[87] When given in the context of an acute attack, approximately 80% of patients achieved a symptomatic response

within 2 hours with a median time to onset of 30 minutes. By 12 hours, 80% of patients experienced only minimal symptoms.[88] Open-label studies are ongoing. However, in March 2008, the European Medicines Agency recommended refusal of the marketing authorization for Rhucin because of insufficient evidence of efficacy and safety (e.g., repeated administration poorly studied) and possible impurities from the rabbit milk source.[89] Furthermore, based on insight from other indications, the increased side-chain glycosylation could negatively affect the biological effectiveness of the transgenic molecule.[90,91]

Icatibant (Jerini, Berlin, Germany) is a synthetic protein that blocks the bradykinin receptor B2 with the same affinity as bradykinin itself. It does not interact with B1 receptors or the receptors of similar peptides, nor is it degraded by the enzymes that normally cleave bradykinin.[92] Because AE is currently believed to be mediated by increased activity of bradykinin, this receptor is a logical therapeutic target. Icatibant can be dosed subcutaneously. In the first phase III trial of Icatibant (FAST-1), time to clinically significant relief was 2.5 hours for Icatibant and 4.6 hours for placebo. These results did not achieve statistical significance ($P = 0.142$) because of a greater than expected response to placebo. Time to onset of improvement did, however, favor Icatibant (0.8 vs 16.9 hours, $P < 0.001$).[93] In a second phase III trial (FAST-2), median time to clinically significant relief was 2.0 hours for Icatibant compared with 12.0 hours for tranexamic acid ($P < 0.001$).[93] Approximately 90% of patients in both studies required only a single dose despite Icatibant's short half-life of 1.2 hours. There have been no serious adverse events associated with Icatibant, although local injection has been described as painful in some patients, accompanied by redness and a wheal.[93] Some patients receiving Icatibant treatment have experienced attack recurrence, which may be successfully treated using C1-INH concentrate.[92] In April 2008, the FDA issued a letter of nonapproval in response to the US license application, although the product was approved for use in the European Union in July 2008.

Ecallantide (Kalbitor/Dx-88, Dyax, Cambridge, MA) is a potent and specific inhibitor of plasma kallikrein. Similar to Icatibant, ecallantide may be dosed subcutaneously. Ecallantide is generally well tolerated, but side effects of dizziness, fatigue, headache, nausea, vomiting, increases in liver function tests, and prolonged partial thromboplastin times (an expected finding of a kallikrein inhibitor) have been noted.[94] Rare allergic reactions have been reported with the product, although not in major clinical trials.[94,95] In a placebo-controlled study (EDEMA1), 72.5% of patients treated with ecallantide showed symptomatic improvement within 4 hours, compared with 25% of patients receiving placebo.[96] The authors considered ecallantide to be well tolerated, although there were 4 acute dosing reactions. In a second placebo-controlled, single-dose (30 mg subcutaneously) phase III trial (EDEMA3), the treatment outcome score was significantly better in the ecallantide group than the placebo group (53.8 vs 18.5, $P = 0.021$).[93] The FDA approved ecallantide for treating acute attacks of HAE in December 2009. However, because of the potential risk of anaphylaxis, ecallantide may only be administered by a physician with the support needed to manage anaphylaxis. The approval of this drug was also subject to the establishment of a Risk Evaluation and Mitigation Strategy program, with the aim of communicating the risks of anaphylaxis and the need to differentiate between the symptoms of anaphylaxis and those of an HAE attack.

GENERAL MANAGEMENT OF HAE

Prevention

The foundation of prophylaxis for patients with nonallergic AE is the recognition and prevention of disease triggers. Myriad infections trigger attacks and may even lead to AAE in patients without previously recognized disease. Primary care providers should treat any symptoms of infection aggressively and be aware of dental abscesses and other forms of oral pathology.[31,97–103] Drugs that can cause or exacerbate AE (e.g., angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) should be avoided.[104–107]

Long-term prophylactic treatment is recommended for any patient with >1 episode of severe abdominal pain in a year, any head or neck swellings, >2 attacks per month, or the need for acute treatment more than once annually.[4,26,27] Patients under high psychological stress loads are candidates for prophylactic treatment.[52] Treatment can also be considered in patients whose peripheral attacks are particularly frequent or bothersome. Individuals who do not meet these criteria do not require maintenance therapy. All of the available treatment options may be considered for prophylactic use, although critical assessment of side effects versus benefit is particularly important in this setting.

Attacks are generally less frequent and severe in children, and most will not require long-term prophylaxis.[51] For those who do, antifibrinolytics have been proposed as first-line therapy.[39,49] C1-INH concentrate, administered at the same doses as adults, has been shown to be safe and effective for treating attacks in children, and has also been proposed as a potential long-term prophylactic agent.[83,108]Young people afflicted with HAE should not participate in contact sports, nor should they go to day care before kindergarten because of the risk of acquiring an infection that could cause an AE exacerbation.[51]

There is controversy as to whether pregnant women with HAE can expect an increase in attack frequency or have a higher rate of perinatal complications.[30,34,99] Prophylaxis is generally not recommended in pregnancy, and androgens are contraindicated (although some authors have endorsed their use in the third trimester).[54,109] AE-related obstetric complications are rare but have been documented in the literature.[110,111] Where available, C1-INH concentrate should be on hand during delivery. An initial loading dose of 500 to 1000 U should also be considered during childbirth to reduce the risk of complications.[52]

Treatment

Isolated cases of peripheral AE may not require treatment, except when associated with bothersome symptoms. Antifibrinolytic therapy with tranexamic acid orally every 3 to 4 hours has been suggested for mild AE.[63] Similarly, mild

cases of AE might require no intervention beyond therapeutic oxygen and observation on pulse oximetry.

For severe attacks and those involving the respiratory tract, there is an urgent need for treatment. When patients present with severe abdominal attacks, symptomatic treatment through fluid resuscitation, antiemetics, and analgesics is of immediate concern. Severe cases of AE may necessitate immediate intubation or airway establishment. During emergency laryngoscopy and intubation, the ability to provide a surgical airway should be considered (tracheostomy), as should the prompt administration of C1-INH.[112]

Because of the potential for significant morbidity and mortality in unrecognized cases, the prompt diagnosis and treatment of laryngeal AE is crucial. These attacks usually develop slowly over a median of 8 hours with dysphagia and vocal changes manifesting before airway obstruction.[50] There are, however, reports of rapid onset laryngeal edema, and the physician must be vigilant when dealing with an acute AE crisis.[27,112] Patients taking attenuated androgens as prophylaxis should double their dose for several days upon identifying evidence of an impending AE attack involving any part of the body.[54] When available, an appropriate dose of C1-INH should be given at the earliest suspicion of an AE attack involving the respiratory tract.[54,63,109] The onset of protection is rapid because C1-INH levels increase quickly after the initiation of treatment.[4] In 1 study, 75% of patients with serious laryngeal, abdominal, or facial symptoms responded within 30 minutes of C1-INH administration.[83] Another study showed injection of C1-INH concentrate to halt symptom progression within a mean of 42 minutes and to reduce the mean attack duration from 101 to 15 hours.[113] If no response is observed within 1 hour of administration or if symptoms worsen, an additional dose of C1-INH may be given.[51] The effect of C1-INH infusion has been shown to last up to 2 days.[4,83] Furthermore, case reports have indicated that C1-INH concentrate may be successful in the management of HAE attacks occurring during pregnancy.[114,115]

Home C1-INH therapy (given at the onset of attack) has been shown to decrease attack severity, duration, and time to onset of relief in patients with poorly controlled HAE.[33,116,117] Because most HAE patients experience a life-threatening attack at some point in their lives, home C1-INH should be made available to all individuals able to safely administer the drug and comply with appropriate follow-up.[52]

Perioperative Management of HAE

Because of the high risk of AE exacerbation associated with surgery, dental work, and other procedures, short-term prophylaxis should be given to any HAE patient undergoing anything more invasive than mild dental manipulation.[54] Attenuated androgens can be given 2 days before and after the procedure, or C1-INH can be administered 24 hours in advance of the intervention.[34,52,54] If C1-INH is unavailable, FFP can be given 6 to 12 hours in advance.[75,118]

Endotracheal intubation and laryngeal mask airways should be avoided when possible in AE patients to minimize airway trauma.[112] When endotracheal intubation cannot be avoided, appropriate prophylaxis should be undertaken.[119] Although there are no firm guidelines, reports suggest that anabolic steroids such as danazol 4 mg be given 4 times daily 5 to 7 days before intubation. C1-INH or FFP should also be given immediately before the procedure, with a second dose immediately available.[54,112] Patients undergoing orthopedic and abdominal procedures are unlikely to develop attacks unless they are tracheally intubated.[3,30,120] Although AE patients undergoing surgery have been shown to have good outcomes when given appropriate prophylaxis, sporadic attacks have been reported nonetheless.[30,119] Uncontrolled complement activation has been implicated in at least 1 fatality in an AE patient undergoing cardiopulmonary bypass.[121] A diagnosis of AE should not affect the choice of induction drug, volatile anesthetic, or muscle relaxant.[112,119]

Before surgery, it is necessary to manage patients' C1-INH levels. Normal levels have been suggested as an optimal therapeutic target,[122] and it seems essential to achieve at least a minimal C1-INH level of 39% of normal.[123] Although it may be inconvenient to pretreat patients for 9 to 17 days with androgens before cardiopulmonary bypass and cardiac surgery, this has been recommended in the absence of C1-INH concentrates.[122] Even with prophylaxis, some patients still develop AE.[122] In these patients, the availability of commercially purified C1-INH may be potentially life saving.[122] Patients should be closely monitored in a critical care environment during the postoperative period.

Case reports have indicated the potential success of C1-INH concentrate administered in the perioperative setting. In 1 HAE patient undergoing dental surgery, administration of C1-INH 2 hours before and 50 minutes after the procedure restored C1-INH functional levels to 90% of normal within 30 minutes of administration.[124] There were no complications during the procedure. In another HAE patient, surgery for colorectal intussusception was required.[125] C1-INH concentrate was administered 1 hour before laparotomy and every 30 minutes during the procedure. Both the procedure and the postoperative phase were free from complications. Coronary artery revascularization was scheduled in a 48-year-old man with HAE, and danazol treatment was begun 3 days before surgery.[126] C1-INH was administered 1 hour before the procedure, whenever heparin was administered perioperatively, and every 6 hours postoperatively. This approach proved successful.

CONCLUSION

HAE is still a disabling and potentially life-threatening disorder. Older treatment options in the United States are limited and have potentially serious side effects. C1-INH concentrates have been used for several years in Europe and have excellent efficacy and tolerability records. The safety of these products has increased dramatically with improvements in the manufacturing process. The first C1-INH concentrates were recently licensed for treating HAE patients in the United States, one product for prophylaxis and one for treating HAE attacks. A kinin pathway modulator has also been approved for treating attacks, although this product carries a risk of anaphylaxis. A pathway diagram of where each agent acts in the complement and kinin cascades and the therapeutic sites of interest is shown in Figure 1. The recent developments should help

improve the treatment of acute HAE attacks in the United States, which will be particularly welcomed and valuable in the perioperative management of patients with HAE.

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