PEDIATRIC ALLERGY, IMMUNOLOGY, AND PULMONOLOGY
Volume 27, Number 4, 2014
© Mary Ann Liebert, Inc.
DOI: 10.1089/ped.2014.0422

Treatment of Hereditary Angioedema in the Pediatric Patient

Shana Kalaria, MD, and Timothy Craig, DO

Hereditary angioedema (HAE) is an autosomal dominant disease, with the expectation that there is a risk of 50%, if a parent has HAE, of inheriting the disease. Manifestations of the disease start early in life for some patients, but symptoms frequently increase during the transition from childhood to adolescence. Unfortunately, most medications are not approved for use in children. This requires off-label use for most of the medications that are U.S. Food and Drug Administration approved for HAE. For this reason, we have sought to identify the use of medications approved and unapproved and used off label for children with HAE.

Introduction

Hereditary angioedema (HAE) is a serious condition that usually manifests in childhood (i.e., aged ≤ 12 years) or adolescence (i.e., aged >12 years), and is characterized by edema involving the skin, gastrointestinal tract, and upper airway. HAE is caused by a deficiency of C1-inhibitor (C1-INH), which is the major regulator of early steps of the complement and contact pathways and also has minor effects on the fibrinolytic and coagulation pathways.[1] With a deficiency of C1-INH, there is uncontrolled activation of the contact system either spontaneously or after a traumatic or stressful event, leading to increased production of bradykinin causing the edema typical of HAE.[2]

It is important to treat HAE differently in the pediatric population (i.e., in those aged ≤ 18 years) compared to the adult population. The frequency of attacks are usually less than in adults, and rarely should prophylaxis be necessary. However, early onset of frequent symptoms can predict future severity, and patients with onset of symptoms before the age of 5 years are at greater risk of having more attacks throughout life than those who develop angioedema after 15 years of age.[3] Not only does the frequency of attacks differ in children compared to later in life, but the side-effect profiles of HAE treatments in children, other than for C1-inhibitor, is not well defined. Also, the metabolism and pharmacokinetics of the drugs in most cases have not been assessed in children. Most importantly, with the exception of C1-INH from CSL Behring and recombinant C1-INH (rcC1-INH) from Pharming, the other approved therapies are not based upon weight, making it difficult to treat very small or young children.[4]

HAE treatments are categorized by their indication and include acute treatment, often referred to as ''on demand,'' short-term prophylaxis, and long-term prophylaxis. In this article, we discuss the use of fresh frozen plasma (FFP), androgens, tranexamic acid, epsilon-aminocaproic acid, ecallantide, icatibant, C1-INH (Berinert and Cinryze), and rcC1-INH by their indication. The dosing, use, approval by the United States Food and Drug Administration (FDA), advantages and disadvantages, and experience in the pediatric population are compared for each of these treatments.

What We Reviewed

We researched the literature for treatment of HAE in the pediatric population by searching Google, PubMed, and Ovid for ''pediatrics and hereditary angioedema,'' ''icatibant and children,'' ''ecallantide and children,'' ''C1-inhibitor and children,'' ''recombinant C1-inhibitor and children,'' ''fresh frozen plasma and children,'' and ''androgens and children.'' The Internet search for ''pediatrics and hereditary angioedema'' returned 68 articles, which were reviewed to be included in this article. The other search terms rarely produced studies not included in the ''pediatrics and hereditary angioedema'' search. Unfortunately, evidence-based literature is lacking in this age group, making dosing difficult. For this reason, we reviewed available information, and merged this with our clinical experience to develop suggestions for the care of patients aged 18 years and younger with HAE. Most of the suggestions are not FDA approved.

Treatment of HAE

The only FDA-approved medications in the United States for HAE in the pediatric population are (Table 1):

- Ecallantide: 30 mg SQ for patients aged ≥ 12 years for acute attacks.

College of Medicine, Penn State University, Hershey Medical Center, Hershey, Pennsylvania.

Table 1. Approved Medication in the United States for Use in Pediatric Patients with Hereditary Angioedema (HAE)

Approved medications for	*Indication*	*Dose*	*Benefits*	*Main disadvantages*
C1-inhibitor (Cinryze[T])	Prophylaxis for patients aged ≥12 years	1,000 IU twice a week i.v.	Reduces attacks by 50%	Requires i.v. injection, associated with thrombosis
C1-inhibitor (Berinert[T])	On demand for HAE attacks for patients aged ≥12 years	20 IU/kg i.v.	Long half-life, years of experience from Europe, and weight-adjusted dosing	Requires i.v. injection, associated with thrombosis
Ecallantide	On demand for patients aged >15 years	30 mg s.c.	s.c.	Short half-life, anaphylaxis, no self-treatment

[T]Trade name. Used as both medications are C1-inhibitors but approved for different indications.
i.v., intravenous; s.c., subcutaneous.

- C1-INH (Berinert): 20 IU/kg intravenously (i.v.) for adolescents and adults for acute attacks.
- C1-INH (Cinryze): 1,000 IU/kg i.v. every 3–4 days for prophylaxis for adolescents and adults for acute attacks.

For this reason, which is also noted above, we discuss off-label uses and make some inference and assumptions for the treatment of pediatric patients, especially those younger than 12 years of age in Table 2.

Treatment of pediatric HAE, like HAE in adults, began with the wide use of FFP. The recommended dose is 10 mL/kg i.v. for use in acute treatment of HAE as well as short-term prophylaxis. Active C1-INH is a component of FFP, and for this reason is expected to be effective, and preliminary data suggest that it is. However, controlled data proving the efficacy are lacking. FFP is widely available and inexpensive. However, it has become a less favorable drug for treatment of HAE due to risks of viral transmission potential, immune sensitization, lack of controlled data, and a possible but rare worsening of HAE attacks when used for acute treatment. Despite possible potential of worsening an acute attack, triggering a new attack when used for prophylaxis has never been reported.[5,6] The positive attributes are that it is readily available and inexpensive, dose is based upon weight, and it can be used for both short-term prophylaxis and therapy for acute attacks.[5,6]

Androgens are frequently used in adults. However, they are used less in the United States than in the past, but are still used in many countries worldwide for short- and long-term prophylaxis. The recommended dose of danazol is 2.5–10 mg/kg per day orally for short- and long-term prophylaxis. Stanozolol and oxandrolone are alternative androgens, but stanozolol is no longer manufactured. A safe dose of oxandrolone in children has not been investigated. However, many experts suggest oxandrolone has less adverse events associated with its use in the pediatric patient. Androgens are used for treatment of HAE because they increase C1-INH levels in the blood and may also have a direct effect on the contact system, are available orally, are readily available, and are inexpensive. However, androgens are associated with significant adverse events and risks, especially when used before puberty. The adverse effect profile includes liver toxicity, vascular disease, weight gain, virilization, dyslipidemia, hypertension, and premature closure of growth plates.[7] Guidelines suggest the dose should not exceed 200 mg a day for chronic long-term prophylaxis in adults.[7] A safe dose in children has not been determined, and research in this area would be considered unethical due to the adverse effect profile. Despite the risk for long-term prophylaxis, the risk in short-term prophylaxis—that is, for 5 days before and 2–3 days after dental work or surgery—poses little risk, even when used before puberty. The benefits of androgens are their availability, weight-based dosing, inexpensive price, and effectiveness as determined by controlled studies.[7,8] The adverse events are not the only limiting factor in prescribing androgens to children for chronic prophylaxis. In addition, recent guidelines based on expert opinion discourage the use of androgens in adults and pediatric patients, especially in females.[1]

In children, since androgens for long-term prophylaxis are relatively contraindicated, antifibrinolytic agents, such as epsilon-aminocaproic acid and tranexamic acid, are often used. The exact mechanism of action of antifibrinolytics in HAE is unknown. However, they are thought to decrease consumption of C1-INH. The recommended dose of epsilon-aminocaproic acid is 0.17–0.43 g/kg per day orally for long-term prophylaxis.[9,10] Tranexamic acid is preferred over epsilon-aminocaproic acid because of its better tolerability and fewer side effects. Tranexamic acid is not approved by the FDA for use in children in the United States. The manufacturer's recommended dose of tranexamic acid for adults in the package insert is 0.5–3 g orally divided across one to three dosages, with maximum dose of 1 g three times a day. In Hungary, weight-based dosing for children with HAE is 20–40 mg/kg divided across two to three dosages to a maximum of 3 g a day divided into three dosages.[9] While both antifibrinolytics are available orally, their disadvantages include multiple dosing per day, cardiac toxicities, and questionable efficacy. The advantages are affordability, availability, and oral dosing.[9–11]

Other treatments include kinin pathway modulators such as ecallantide and icatibant. Ecallantide's mechanism of action is inhibition of kallikrein, which causes a reduction of bradykinin production with the result being a reduction of edema during HAE attacks. Ecallantide is approved for use in the United States for treatment of acute HAE attacks in patients aged 12 years and older. The recommended dose of ecallantide is 30 mg subcutaneously (s.c.) as 3–10 mg injections. The dose is not weight adjusted. The advantage of ecallantide is that it can be administered s.c. The disadvantages are that it has a short half-life, a small risk of anaphylaxis (3%), insufficient data for its use in patients

Table 2. Comparing Medications Approved in the United States for HAE in Adults and Their Use in Children

Drug classification	*Dosage and route of admin*	*Acute treatment*	*Short-term prophylaxis*	*Long-term prophylaxis*	*Advantages*	*Disadvantages*	*Experience in peds*
Fresh frozen plasma/ solvent detergent treated plasma	10 mL/kg, i.v.	X (off-label)	X (off-label)		Inexpensive, widely available	Viral potential, may worsen attack	Frequently used in the past due to lack of other medication. Being displaced by the other therapies over the past 5 years.
Androgens	2.5–10 mg/kg daily, oral for short-term prophylaxis		X (off-label for peds)	X (off-label for peds)	Easy to take, oral, inexpensive	Liver toxicity, vascular disease, other adverse events	Adverse reaction profile similar to adult population
Tranexamic acid	20–40 mg/kg daily divided across two to three dosages, oral	X (off-label)		X (off-label)	Oral	Multiple toxicities, limited effectiveness	Low efficacy in ped population
Epsilon-aminocaproic acid	0.17–0.43 g/kg per day, oral			X	Oral	Multiple dosing, multiple toxicities	Low efficacy in ped population
Ecallantide (kinin modulator)	30 mg s.c. (as three injections)	X (on-label)			s.c.	Short half-life, risk of anaphylaxis	Insufficient data of use in patients <16 years
Icatibant (kinin modulator)	30 mg s.c. (single injection)	X (on-label)			s.c., room temperature stable	Local pain and burning at injection site, short half-life	Lack of studies in ped population
Berinert (plasma C1-INH)	20 IU/kg i.v.	X (on-label)	X (off-label use)	X (off-label use)	Replaces deficient protein, long half-life, use for >30 years	Viral transmission possible, i.v. only, expensive	Similar efficacy to use in peds and adults
Cinryze (plasma C1-INH)	1,000 IU (two vials) IV	X (on-label)	X (on-label)	X (on-label)	Replaces deficient protein, long half-life	Viral transmission possible, i.v. only, breakthrough attacks occur, expensive	Similar efficacy to use in peds and adults
Recombinant C1-INH	50 IU/kg i.v.	X (off-label)	X (off-label)		No viral risk	Short half-life, i.v. only, potential for allergic reaction	Minimal data on ped use

X, effective; ped, pediatric patient.

younger than 12 years of age, and a fixed dose that is not weight based. Although the risk of anaphylaxis is low, the drug should be administered under the supervision of a licensed healthcare professional trained to treat anaphylaxis.[12]

Icatibant inhibits bradykinin activity by binding in a competitive inhibitory fashion with bradykinin for the bradykinin-B2 receptor. Icatibant is given in a 30 mg s.c. dose as a single injection. An additional and very positive benefit of icatibant is that it is stable at room temperature and is approved for self-administration. The disadvantage of icatibant is that 97% of patients will have redness, pain, and burning at the injection site. Additional disadvantages of icatibant are that it has a short half-life and needs to be redosed in approximately 10% of patients, the dose is fixed and not weight-based, and there is a lack of efficacy and safety data in the pediatric population.[13]

The first FDA-approved medication for the treatment of HAE in the United States was plasma-derived C1-INH concentrate (Cinryze) for long-term prophylaxis. Berinert was FDA approved shortly after for the treatment of acute HAE attacks. Both C1-INH can be used interchangeably, but are suggested to be used for their FDA-approved indication. The recommended dose of Berinert is 20 IU/kg i.v. and Cinryze is 1,000 IU/kg i.v. Plasma-derived C1-INH has been used for more than 30 years for the treatment of HAE in Europe and has been used safely in children, during lactation, and in pregnancy. The advantages are that it has a long half-life, controlled studies demonstrating the efficacy, can be used for prophylaxis and for acute therapy, and there is a vast amount of literature published supporting its use and safety. The disadvantages are it requires i.v. injection, it is expensive to produce, it is not available in many countries, and it has the remote but possible risk of viral transmission. The advantage of C1-INH for children is that controlled studies have demonstrated that dosing by weight is effective.[14] For children, the WAO guidelines recommend C1-INH as the preferred therapy for both treatment of attacks and, if needed, short- and long-term prophylaxis at 20 IU/kg. However, a set dose of 1,000 IU/kg is an alternative. Both C1-INH products are FDA approved for patients aged ≥12 years and are not approved below this age.[1,10,11]

Recombinant human C1-INH (rcC1-INH) has just recently been approved by the FDA, and was approved earlier in the European Union (EU). It is a human C1-INH protein produced from the milk of transgenic rabbits, and differs from native human CI-INH only in terms of glycosylation. Controlled studies demonstrate the effective dose is 50 IU/kg i.v. Although there is no viral risk associated with the drug, it has a shorter half-life and a potential for an allergic reaction in patients allergic to rabbits. Since it is dosed by weight, it is expected to be utilized off label in children for the treatment of acute attacks. The short half-life may limit the use for prophylaxis, but further data are necessary before indicated or excluded for this use.[1,10]

Application of the Above

Children can be screened for C1-INH deficiency after the age of 1 year.[1] Once identified, it is the authors' belief that therapy should be prescribed, since there is no way to predict when the first attack will occur.[14] Since severe disease is uncommon in children, chronic prophylaxis is rarely necessary. When prophylaxis is indicated in children, C1-INH at 20 IU/kg is preferred.[1] Some children can be taught to self-administer C1-INH after the age of 8 years, but for most young children, a family member would be the preferred person for the i.v. injections of C1-INH. Serial assessment of HIV, hepatitis C and B, and administration of hepatitis B vaccine are recommended by some experts, since there is a remote risk, though never reported with the C1-INH currently marketed, of viral transmission.[1]

Most children in our experience will be able to maintain a quality life by early use of ''on demand therapy,'' and WAO guidelines recommend C1-INH at 20 IU/kg.[1] Recombinant C1-INH is expected to be safe in children, and since the dose is weight based (50 IU/kg), there is guidance on how much to give to children. The use of icatibant and ecallantide are limited by fixed dose (30 mg s.c. for attacks) and lack of safety data in children. We expect both will be safe, but dosing needs to be explored to ensure the 30 mg doses are safe in young children. Similar to adults, all pediatric patients should have two doses of on-demand therapy at all times, since none of the drugs are 100% effective in stopping an attack, and thus redosing may be necessary. A second reason always to have two doses available is that after use, the shipment of a replacement dose may be delayed, predisposing the children to have inadequate therapy available for an attack.[1,10,15,16]

Short-term prophylaxis can be accomplished with C1-INH, FFP, or androgens. Again, since data exist that 20 IU/kg is effective, most suggest that this should be the dose for short-term prophylaxis for children.[17] Administration should be the day of surgery or dental work, since the benefit lasts for 3 days, and attacks can be triggered as much as 2 days after a procedure. Androgens can be used 5 days before and 2 days after a procedure at a dose of 2–5 mg/kg. Lastly, if C1-INH is not available, FFP at 10 mL/kg can be administered on the day of the procedure.[1,6,10]

The key to successful therapy is encouraging the early use of specific therapies noted above for attacks. All the above therapies work best when used early during an attack. Early therapy also reduces disability, pain, anxiety, swelling, absenteeism, morbidity, and potential mortality. As noted above, backup therapy is essential, since breakthrough attacks may occur despite therapy. An action plan, to include a backup plan and location for treatment, is recommended, since at times self-injection may be impossible. Self-care and home care are preferred to dependence on the emergency department (ED), since ED care often results in delay of therapy and increased cost. Training of the patient and the family can be accomplished by the home infusion specialist provided by the specialty pharmacies in the United States or by physicians and their extenders if home infusion specialists are not available.[1,16,18,19] Despite the potential need for frequent i.v. therapies, central dwelling catheters should be avoided due to the risk of infection and thrombosis associated with indwelling catheters.[20]

The future looks bright in that multiple therapies for prophylaxis are being researched, and we suspect that at least a few of these medications will make it to market and make prophylactic therapy easier with the advantage of improving the quality of life for our patients. These additional new therapies under investigation are further discussed in a separate article in this issue. C1-INH injected s.c. dosed by weight (CSL-Behring) and as a fixed dose (Shire) are being studied for long-term prophylaxis to be

used in place of the i.v. preparations. Dyax is investigating a monoclonal antibody that inhibits kallikrein and is expected to be effective for long-term prophylaxis. Biocryst has completed studies in the EU on an oral preparation for long-term prophylaxis that also inhibits kallikrein. Two other preparations are under very early investigation and include a pegylated-C1-INH and a factor 12 inhibitor, with both being for long-term prophylaxis.[21]

In conclusion, HAE is a chronic disease, and as with all chronic diseases, depression and anxiety are common. Both should be assessed for and treated if indicated. A strong patient–physician relationship is essential for compliance and adherence, and also because frequent attacks may compromise quality of life. Patients should be encouraged to treat as early as possible when attacks occur, since delay in therapy may result in significant morbidity.[18] It has been recommended that reassessment every 6–12 months by an HAE specialist is indicated for HAE patients, and this includes children.[1] It is necessary to avoid estrogens and ACE inhibitors, since both can trigger attacks. As emphasized above, a treatment plan is essential to ensure early and appropriate therapy is initiated.[1]

Author Disclosure Statement

Dr. Craig is a Speaker for CSL Behring, Dyax, Shire, and Viropharma; a consultant for CSL Behring, Dyax, Shire, and Biocryst; and a researcher for CSL Behring, Dyax, Shire, ViroPharma; Pharming. Dr. Kalaria has no competing financial interests to declare.

References

1. Craig T, Pursun W, Bork K, et al. WAO guideline for management of hereditary angiodema. World Allergy Organ J 2012;5:182–199.
2. Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. Lancet 1998;351:1693–1697.
3. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med 2006;119:267–274.
4. Buyantseva LV, Sardana N, Craig TJ. Update on treatment of hereditary angioedema. Asian Pac J Allergy Immunol 2012;30:89–98.
5. Tang R, Chen S, Zhang HY. Fresh frozen plasma for the treatment of hereditary angioedema acute attacks. Chin Med Sci J 2012;27:92–95.
6. Prematta M, Gibbs JG, Pratt EL, et al. Fresh frozen plasma for the treatment of hereditary angioedema. Ann Allergy Asthma Immunol 2007;98:383–388.
7. Craig T. Assessment of danazol and other androgens in the treatment of hereditary angioedema. Allergy Asthma Proc 2008;29:225–231.
8. Bork K, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. Ann Allergy Asthma Immunol 2008;100:153–161.
9. Farkas H. Pediatric hereditary angioedema due to C1-inhibitor deficiency. Allergy Asthma Clin Immunol 2010;6:18.
10. Wahn V, Aberer W, Eberl W, et al. Hereditary angioedema (HAE) in children and adolescents—a consensus on therapeutic strategies. Eur J Pediatr 2012;171:1339–1348.
11. Farkas H, Varga L, Széplaki G, Visy B, Harmat G, Bowen T. Management of hereditary angioedema in pediatric patients. Pediatrics 2007;120:713–722.
12. Cicardi M, Levy RJ, McNeil DL, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. N Engl J Med 2010;363:523–531.
13. Cicardi M, Banerji A, Bracho F, Malbrán A, Rosenkranz B. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med 2010;363:532–541.
14. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J Allergy Clin Immunol 2009;124:801–808.
15. Dispenza M, Gutierrez M, Bajaj P, Craig T. The need for individualized hereditary angioedema acute action plans: two case studies of misdiagnosed attacks and unnecessary surgeries. J Angioedema 2013;1:1–3.
16. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 Recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. J Allergy Clin Immunol Pract 2013;1:458–467
17. Craig T, Schneider L, MacGinnitie A. Plasma-derived C1-INH for managing hereditary angioedema in pediatric patients: a systematic review. Pediatr Allergy Immunol; in press.
18. Craig TJ, Rojavin MA, Machnig T, et al. Effect of time to treatment on response to C1 esterase inhibitor concentrate for hereditary angioedema attacks. Ann Allergy Asthma Immunol 2013;111:211–215.
19. Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. Eur J Dermatol 2009;19:147–151.
20. Kalaria S, Craig T. Assessment of hereditary treatment risks. Allergy Asthma Proc 2013;34:519–522.
21. MacGinnitie A. Future therapies for hereditary angioedema. Pediatr Allergy Immunol Pulmonol 2014;27:177–180.

Address correspondence to:
Timothy Craig, DO
Department of Medicine and Pediatrics
Penn State University
500 University Drive, H041
Hershey, PA 17033

E-mail: tcraig@psu.edu

Received for publication August 10, 2014; accepted after revision December 1, 2014.