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Hereditary Angioedema (HAE)

Introduction

1. HAE results from a deficiency in quantity or function of C1 inhibitor (C1-INH) due to a genetic defect
    a. A rare, autosomal-dominant disorder that manifests in early childhood
2. Swelling in HAE results from excess bradykinin production, which is a potent vasodilatory mediator
    a. Histamine and other mast cell mediators are not directly involved
3. HAE attacks are classified as laryngeal, cutaneous, or gastrointestinal
    a. Laryngeal attacks are the least common but most serious due to possible airway obstruction
4. Treatment involves airway management, empiric treatment, and targeted treatments
    a. Empiric treatment with antihistamines (e.x. IV diphenhydramine and famotidine), corticosteroids (IV methylprednisolone, dexamethasone)
        i. While antihistamines are generally ineffective it is recommended to still do a trial of these medications
    b. IM epinephrine recommended for anaphylaxis, severe laryngeal edema, or respiratory distress
    c. Targeted treatment by C1-INH replacement, Bradykinin B_2 receptor blocker, plasma kallikrein inhibitor

Pharmacology

Medication	C1-INH Concentrates (Berinert®, Cinryze®)	Conestat alfa (Ruconest®)	Icatibant (Firazyr®)	Ecallantide (Kalbitor®)	Fresh Frozen Plasma (FFP)
Dose	20 units/kg over 10 min	50 units/kg over 5 min (max 4,200 units)	30 mg slow (may repeat every 6 hours (max 90 mg/day)	30 mg (may repeat one time within 24 hours)	2 units
Administration	IV	IV	Subcutaneous	Subcutaneously	IV
Mechanism	CI-INH replacement	CI-INH replacement	Bradykinin B_2 receptor antagonist	Plasma kallikrein inhibitor	CI-INH replacement
Onset	30-60 minutes	90 minutes	120 minutes	30 minutes to 4 hrs	2 to 4 hours
Adverse Effects	Headache, skin rash, injection site reactions, thrombotic events	Headache, injection site reactions, thrombotic events	Injection site reactions, increased transaminases, fever	Headache, fatigue, nausea, diarrhea, skin rash	Volume overload
Drug Interactions	Androgens, estrogens, and progestins may enhance effect	Androgens, estrogens, and progestins may enhance effect	May reduce the antihypertensive effect of ACE-inhibitors	No significant interactions	Transfusion-related reactions, thrombotic events, hypocalcemia
Comments	Must be warmed to room temp Preferred therapy for children and in pregnancy	Must be warmed to room temp Maximum of 4200 units in 24 hrs	Indicated in patients > 18 years of age Caution in ischemic heart disease	BBW: Anaphylaxis (must be administered by a medical professional)	Monitor for volume 2nd line to other C1-INH therapies
Price Tag $	~ $3,500 per 500 units	~ $7,100 per 2,100 units	~ $2,000-4,000 per 10 mg	~ $6,000 per 10 mg	~ $ 55 per unit

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Overview of Evidence			
Author, year	**Design/ sample size**	**Intervention & Comparison**	**Outcome**
2017 Li	Randomized, double-blind, placebo-controlled (n=43)	IV **recombinant human C1-INH (rhC1-INH)** 50 units/kg (max of 4,200 units) or **placebo** to patients with a severe HAE attack	RhC1-INH significantly **reduced the time to onset symptom relief (90 min vs 334 min)** and also required less rescue therapy
2017 Farkas	Multicenter, open-label, nonrandomized (n=32)	Pediatric patients (< 18 years old) received subcutaneous **icatibant** (0.4 mg/kg, max 30 mg)	Icatibant was well tolerated, injection-site reactions with erythema and swelling were most common (90.6% of patients)
2014 Riedl	Randomized, placebo-controlled (n=75)	IV **rhC1-INH** 50 units/kg (max of 4,200 units) or **placebo**	RhC1-INH significantly reduced the time to onset symptom relief (90 min vs 152 min) with no differences in adverse events
2011 Lumry	Randomized, double-blind, placebo-controlled (n=93)	Subcutaneous **icatibant** 30 mg or **placebo**	Icatibant significantly reduced median times in symptom severity reduction, the onset of symptom relief, complete symptom relief No difference in the incidence of adverse events
2010 Cicardi	Two randomized, double-blind trials (n=56, n= 74)	Subcutaneous **icatibant** 30 or **placebo** Subcutaneous **icatibant** 30 mg or PO **tranexamic acid** 3 gm	Icatibant significantly reduced time to complete symptom resolution compared to placebo and tranexamic acid
2010 Levy	Randomized, double-blind, placebo-controlled (n=96)	Subcutaneous **ecallantide** 30 mg or **placebo**	Ecallantide significantly mean symptom complex severity score at 4 hours and treatment outcome score throughout 24 hours
2010 Cicardi	Randomized, double-blind, placebo-controlled (n=72)	Subcutaneous **ecallantide** 30 mg or **placebo**	Improvement in patient-reported treatment scores No difference in time to significant improvement or adverse effects

Conclusions

- There is a lack of response to antihistamines and corticosteroids in HAE due to the underlying pathophysiology of the disease
  - While there is no proven benefit it is still recommended to give these agents in case there is an underlying allergic reaction occurring
- FFP is inexpensive but not routinely used in clinical practice for HAE
- Berinert® is the preferred therapy in children < 12 year of age and pregnancy
- Recombinant human C1-INH, Icatibant® and Ecallantide® have provided evidence of safety and efficacy in HAE

References

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