ABOUT THE AUTHOR

Chrystyna Kalicinsky, MD

Dr Kalicinsky received her medical degree, as well as specialty training in internal medicine and clinical immunology and allergy from the University of Manitoba. From 2000-2005 she was in community practice. From 2005 onwards, she has been in academic practice at the University of Manitoba where she was the Program Director of the Clinical Immunology and Allergy Training Program at the University of Manitoba from 2009 until 2020. Dr Kalicinsky enjoys teaching medical students and residents, as well as patient education and her clinical interests include immunodeficiency, angioedema, chronic urticaria and mast cell disorders.

BRADYKININ MEDIATED ANGIOEDEMA

A 36-YEAR-OLD FEMALE IS REFERRED WITH RECURRENT ANGIOEDEMA WITHOUT URTICARIA, UNRESPONSIVE TO ANTIHISTAMINES, CORTICOSTEROIDS, AND EPINEPHRINE. HER EPISODES CAN LAST FOR MORE THAN 3 DAYS.

Bradykinin angioedema can affect mucous membranes of the oropharynx, as well as the larynx, subcutaneous tissue, bowel mucosa, and the abdominal wall. Angioedema without urticaria, which is unresponsive to antihistamines, corticosteroids and epinephrine, is presumed to be caused by episodic buildup of bradykinin.

This article will examine the medications known to be associated with bradykinin angioedema and provide an overview on hereditary angioedema (HAE), acquired angioedema (AAE) and idiopathic bradykinin mediated angioedema.

MEDICATIONS

ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI) AND ANGIOTENSIN II RECEPTOR BLOCKERS (ARB)

The incidence of Angiotensin Converting Enzyme Inhibitor (ACEi) induced angioedema is reported to be between 0.1-0.7%. Although it occurs during the first week of exposure in over half of cases, it can occur any time during the course of therapy. A large retrospective study found that two-thirds of ACEi-associated angioedema episodes occur within the first three months of therapy while case reports have documented angioedema episodes that began after years of stable therapy.[1] ACEi angioedema tends to occur more commonly in ACEi users who are female, smokers, or of African-American descent.[2] In both ACEi and angiotensin II receptor blocker (ARB) - related angioedema, the angioedema most commonly affects the head and neck area (tongue>lips>pharynx/larynx).[3] Fatal laryngeal angioedema has been well documented. Therefore, ACE inhibitors should be discontinued in all individuals with angioedema and are absolutely contraindicated in patients with either HAE or AAE. Episodes of angioedema may occur up to 1 month (or sometimes more) after discontinuing the ACE inhibitor.[2] If an episode of angioedema occurs greater than 4 weeks after discontinuation of the ACEi, clinicians may consider a workup for HAE with C4, C1 esterase inhibitor level and function, and follow up for the possibility of HAE (including with normal C-INH level and function), as well as idiopathic bradykinin mediated idiopathic angioedema. The unmasking of these conditions may have occurred due to use of the ACEi.

Two randomized controlled trials (RCTs) and one meta-analysis evaluated ARB use in patients who were intolerant to ACEi. When the trials are analyzed together, there is a 10% or less incidence of cross-reactivity of angioedema in patients who receive an ARB after experiencing ACEi-associated angioedema.[4] In a

meta-analysis of randomised controlled trials of >12 months duration comparing ARBs with placebo or active antihypertensive treatment, the incidence of angioedema with ARBs in patients not previously on ACEi was 0.5%[5]

Other than airway management with acute attacks, there is no approved treatment to hasten recovery. There are conflicting outcomes reported in studies with the use of icatibant in ACEi- induced angioedema. In a phase II RCT of 27 patients, the time to complete resolution of edema was significantly shorter (P=0.002) with icatibant (14 patients; median time to resolution of 8 hours) than with combination therapy of a glucocorticoid and an antihistamine (13 patients; median time to resolution of 27.1 hours).[6] However, in a subsequent study and meta-analysis, icatibant did not seem to shorten the time for complete resolution of ACEi-induced angioedema symptoms compared to placebo or conventional treatment strategies.[7,8]

There are also conflicting results from published case series reports involving the use of C1-esterase-inhibitor concentrate (pdC1-INH) in ACEi- induced angioedema and RCTs with these agents have yet to be undertaken[9,10]

DIPEPTIDYL PEPTIDASE – 4 INHIBITORS (GLIPTINS)

Dipeptidyl peptidase-4 inhibitors are a class of oral diabetic agents that affect bradykinin and substance P degradation and therefore can lead to angioedema. Beginning in 2005, angioedema was specified as a safety event in clinical trials of vildagliptin. Angioedema has also been reported in post marketing surveillance of sitagliptin.[10] Treatment with dipeptidyl peptidase-4 inhibitors must be carefully considered and patients closely monitored especially during concurrent treatment with ACEi or when treating patients with a known predisposition to angioedema.[11]

NEPRILYSIN INHIBITORS

Neprilysin inhibitors are a separate class of cardiac medications, which include sacubitril, and can lead to drug-induced angioedema especially when used in combination with ARBs and ACEi.[13] If the ACEi was chosen purely as an antihypertensive agent, clinicians should consult with the referring physician and may consider substituting with amlodipine. If the ACEi was used for cardio- or nephro-protective reasons, an individual risk assessment should be undertaken with the patient regarding the use of ARBs, given its low risk of cross-reactivity. With respect to neprilysin, clinicians may consider deferring to the patient's cardiologist or seeking a cardiology consult in the event that the patient is not actively followed by a cardiologist.

TISSUE PLASMINOGEN ACTIVATOR (TPA)

Approximately 5% of patients treated with tPA for acute ischemic stroke can develop orolingual angioedema. It is typically mild, transient and contralateral to the ischemic hemisphere.[14]

HEREDITARY AND ACQUIRED ANGIOEDEMA (HAE AND AAE)

HAE

HAE is a rare, autosomal dominant disorder that results in random and often unpredictable attacks of angioedema. Attacks are associated with significant functional impairment, decreased health-related quality of life, and mortality in the case of laryngeal attacks.[15,16]

Function	C4	C1-INH antigen	C1-INH
HAE-1	↓	↓	↓
HAE-2	↓	normal or ↑	↓
HAE-nC1INH variants coagulation factor XII angiopoietin-1 plasminogen unknown	normal	normal	normal

Table 1. Laboratory findings in hereditary angioedema[17]

Table 2. Therapies for HAE supported by high level of evidence[18]

Therapies for HAE supported by high level evidence

HAE-specific treatment	Product name and company	Mechanism of action	Approved indications	Dose and route of administration	County licensed and age indications
pdC1-INH	Berinert®[a] (CSL)	Replaces C1-INH	Acute treatment	20 U/kg intravenous	Australia, Canada, EU, USA (adult and pediatric)
			Pre-procedural	Adults: 1000 U Pediatrics: 15 to 30 U/kg body weight	EU (adult and pediatric)
	Cinryze® (Shire—now part of Takeda)	Replaces C1-INH	Acute treatment	≥ 12 years: 1000 U intravenous 2–11 years: 1000 U (> 25 kg body weight) 500 U (< 25 kg body weight)	Australia (≥ 12 years) EU (≥ 2 years)
			Pre-procedural	≥ 12 years: 1000 U intravenous 2–11 years: 1000 U (> 25 kg body weight) 500 U (< 25 kg body weight)	Australia (≥ 12 years) EU (≥ 2 years)
			Long-term prophylaxis	1000 U intravenous q 3–4 days (6–11 years 500 U q 3–4 days)[b]	Australia, Canada (≥ 12 years) EU, USA (≥ 6 years)
	Haegarda® (CSL)	Replaces C1-INH	Long-term prophylaxis	60 U/kg body weight twice weekly (every 3–4 days)	Australia[c], Canada, EU[d], USA (≥ 12 years)
rhC1-INH	Ruconest® (Ruconest)	Replaces C1-INH	Acute treatment	50 U/kg intravenous (< 84 kg); 4200 U intravenous (≥ 84 kg)	EU (adults), USA (adults and adolescents)
Ecallantide	Kalbitor® (Shire—now part of Takeda)	Selective, reversible inhibitor of plasma kallikrein	Acute treatment	30 mg (3 × 10 mg/1 ml) subcutaneous injections	USA (≥ 12 years)
Icatibant	Firazyr® (Shire—now part of Takeda)	Synthetic selective and specific antagonist of bradykinin 2 receptor	Acute treatment	30 mg subcutaneous injection; dose-adjusted for adolescents < 65 kg and children ≥ 2 years[e]	USA (≥ 18 years) Australia, Canada, EU (≥ 2 years)
Lanadelumab	Takhzyro® (Shire—now part of Takeda)	Fully human monoclonal antibody that binds plasma kallikrein and inhibits its proteolytic activity	Long-term prophylaxis	300 mg subcutaneous injection every 2 weeks a dosing interval of 300 mg every 4 weeks may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months	Australia, Canada, EU, USA (≥ 12 years)

Please refer to current country-specific monographs for further details regarding specific indications and listings of adverse events

[a] Berinert 1500 in EU

[b] Dose-adjustment up to 2500 U q3–4 days for ages 12 and above, and up to 1000 U q3–4 days for ages 6-11, based on patient response

[c] Berinert SC in Australia

[d] Berinert 2000/3000 in EU

[e] 12 kg to 25 kg: 10 mg (1.0 ml); 26 kg to 40 kg: 15 mg (1.5 ml); 41 kg to 50 kg: 20 mg (2.0 ml); 51 kg to 65 kg: 25 mg (2.5 ml); > 65 kg: 30 mg (3.0 ml)

Table 1 differentiates the three forms of HAE, based on deficiency C1 esterase inhibitor antigen (Type 1), C1 esterase inhibitor function (Type 2), and hereditary angioedema with normal C1 esterase inhibitor level and function (HAE nC1-INH). The latter is more prevalent in females but has been reported in males. Three genes have been identified in HAE nC1-INH families (FXII, ANGPT1, PLG) but in the majority of families the pathogenesis is unknown. Type 1 HAE accounts for the majority of HAE cases, with 25% arising from spontaneous mutation and with no family history.

MANAGEMENT OF HAE

ACUTE TREATMENT OF HAE WITH NORMAL C1-INHIBITOR

As per the 2019 International/Canadian Hereditary Angioedema Guidelines, non-randomized, retrospective studies and small case series have shown that intravenous pdC1-INH may reduce the duration and intensity of attacks of angioedema in these patients, despite the fact that the pathogenesis of the angioedema, by definition, is not caused by a deficiency in C1-INH.[19-22]

LONG TERM PROPHYLAXIS (LTP) OF HAE WITH NORMAL C1-INHIBITOR

Although treatments used for LTP for HAE-1 and HAE-2 may potentially be beneficial for patients with HAE nC1-INH, published and peer-reviewed data is lacking and therefore the authors of the International/Canadian Hereditary Angioedema Guidelines could not make a recommendation regarding their use.

PREGNANCY

By unanimous consensus, the authors of the guidelines from 2019 agreed on the use of pdC1-INH during pregnancy to treat acute attacks. Short term prophylaxis is not routinely required prior to vaginal delivery but is recommended with C-section and intra-partum instrumentation.[23]

PEDIATRICS

When children with HAE-1 and HAE-2 are treated with pdC1-INH for HAE attacks, responses are consistent with those seen in adults.[24] Dosing for pdC1-INH is 20 units (U)/kg IV Berinert®(CSL), 500 U IV Cinryze® (Takeda) for children 10–25 kg, or 1000 U IV Cinryze® for children > 25 kg.[18] Icatibant has been approved to treat patients ≥ 2 years of age according to the manufacturer's product monograph.

ACQUIRED ANGIOEDEMA

Acquired angioedema is a very rare condition and can be associated with lymphoproliferative disorders and systemic lupus erythematosus. It usually presents after the fourth decade. As with HAE, deficiency in C1 esterase inhibitor antigen or function can occur. Laboratory differentiation between AAE and HAE is by means of C1q, which is normal in HAE and decreased in 70% of those with AAE. Acute attacks can be effectively treated using pdC1-INH, but some patients become progressively non-responsive, due to autoantibody-mediated rapid catabolism. In these patients icatibant can be effective.[25]

IDIOPATHIC BRADYKININ MEDIATED ANGIOEDEMA

Patients with idiopathic bradykinin mediated angioedema present similar to HAE, with cutaneous, pharyngeal, laryngeal, and abdominal attacks, but without a family history and with normal C1 esterase inhibitor antigen and function. Treatment with tranexamic acid at 1 g p.o. t.i.d. for 3 months, tapered according to its effectiveness has shown benefit in some published case series.[26,27] There are also case reports of icatibant and pdC1-INH use providing benefit.[28]

CONCLUSION

Bradykinin-mediated angioedema results from either overproduction of bradykinin or inhibition of its degradation. Its etiology can be hereditary or acquired and it is a rare disease, which affects the abdomen and/or upper airways. It is known to differ clinically from histamine-mediated angioedema by the absence of urticaria or skin rash and the use of antihistamines and corticosteroids have not been shown to be effective.[29]

References

1. Banerji A, Blumenthal KG, Lai KH, Zhou L. Epidemiology of ACE Inhibitor Angioedema Utilizing a Large Electronic Health Record. J Allergy Clin Immunol Pract. 2017;5(3):744-749. doi:10.1016/j.jaip.2017.02.018

2. Kanani A, Betschel SD, Warrington R. Urticaria and angioedema. Allergy Asthma Clin Immunol. 2018 Sep 12;14(Suppl 2):59. doi: 10.1186/s13223-018-0288-z. PMID: 30263036; PMCID: PMC6157046.

3. Angioedema induced by cardiovascular drugs: new players join old friends. Bas M, Greve J, Strassen U, Khosravani F, Hoffmann TK, Kojda G Allergy. 2015 Oct; 70(10):1196-200.

4. Beavers CJ, Dunn SP, Macaulay TE. The role of angiotensin receptor blockers in patients with angiotensin-converting enzyme inhibitor-induced angioedema. Ann Pharmacother. 2011 Apr;45(4):520-4. doi: 10.1345/aph.1P630. Epub 2011 Mar 22. PMID: 21427294.

5. N. Chapman, F. Dixon, A.K. Gupta, Incidence of angioedema in randomised controlled trials of angiotensin receptor blockers: a meta-analysis, European Heart Journal, Volume 34, Issue suppl_1, 1 August 2013, 1829

6. Baş M, Greve J, Stelter K, Havel M, Strassen U, Rotter N, Veit J, Schossow B, Hapfelmeier A, Kehl V, Kojda G, Hoffmann TK. A randomized trial of icatibant in ACE-inhibitor-induced angioedema. N Engl J Med. 2015 Jan 29;372(5):418-25. doi: 10.1056/NEJMoa1312524. PMID: 25629740.

7. Straka, Ramirez. "Effect of Bradykinin Receptor Antagonism on ACE Inhibitor-Associated Angioedema." Journal of Allergy and Clinical Immunology, vol. 140, no. 1, Elsevier B.V, 2016, pp. 242–248.e2, doi:10.1016/j.jaci.2016.09.051

8. Jeon, Lee. "Effect of Icatibant on Angiotensin-converting Enzyme Inhibitor-induced Angioedema: A Meta-analysis of Randomized Controlled Trials." Journal of Clinical Pharmacy and Therapeutics, vol. 44, no. 5, Wiley Subscription Services, Inc, Oct. 2019, pp. 685–92, doi:10.1111/jcpt.12997.

9. Greve J, Bas M, Hoffmann TK, Schuler PJ, Weller P, Kojda G, Strassen U. Effect of C1-Esterase-inhibitor in angiotensin-converting enzyme inhibitor-induced angioedema. Laryngoscope. 2015 Jun;125(6):E198-202. doi: 10.1002/lary.25113. Epub 2015 Jan 13. PMID: 25583256.

10. Brown NJ, Byiers S, Carr D, Maldonado M, Warner BA. Dipeptidyl peptidase-IV inhibitor use associated with increased risk of ACE inhibitor-associated angioedema. Hypertension. 2009 Sep;54(3):516-23. doi: 10.1161/

11. Scott SI, Andersen MF, Aagaard L, Buchwald CV, Rasmussen ER. Dipeptidyl Peptidase-4 Inhibitor Induced Angioedema - An Overlooked Adverse Drug Reaction? Curr Diabetes Rev. 2018;14(4):327-333. doi: 10.2174/1573399813666170214113856. PMID: 28201967.

12. Perza, Koczirka. "C1 Esterase Inhibitor for Ace-Inhibitor Angioedema: A Case Series and Literature Review." The Journal of Emergency Medicine, vol. 58, no. 3, Elsevier Inc, Mar. 2020, pp. e121–e127, doi:10.1016/j.jemermed.2019.10.031.

13. Hudey, Stephanie N., Emma Westermann-Clark, and Richard F. Lockey. "Cardiovascular and diabetic medications that cause bradykinin-mediated angioedema." The Journal of Allergy and Clinical Immunology: In Practice 5.3 (2017): 610-615.

14. Hill, Michael D., et al. "Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke." Neurology 60.9 (2003): 1525-1527.

15. Agostoni A, Aygören-Pürsün E, Binkley KE, Blanch A, Bork K, Bouillet L, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor defciency workshop and beyond. J Allergy Clin Immunol. 2004;114(3):S51–131.

16. Zilberberg MD, Jacobsen T, Tillotson G. The burden of hospitalizations and emergency department visits with hereditary angioedema and angioedema in the United States, 2007. 2010.

17. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010;6(1):24.

18. Betschel, S., Badiou, J., Binkley, K. et al. The International/Canadian Hereditary Angioedema Guideline. Allergy Asthma Clin Immunol 15, 72 (2019). https://doi.org/10.1186/s13223-019-0376-8

19. Bork K, Wulf K, Steinmüller-Magin L, Brænne I, Staubach-Renz P, Witzke G, et al. Hereditary angioedema with a mutation in the plasminogen gene. Allergy. 2018;73(2):442–50

20. Bork K, Wulff K, Witzke G, Hardt J. Treatment for hereditary angioedema with normal C1-INH and specific mutations in the F12 gene (HAE-FXII). Allergy. 2017;72(2):320–4.

21. Deroux A, Boccon-Gibod I, Fain O, Pralong P, Ollivier Y, Pagnier A, et al. Hereditary angioedema with normal C1 inhibitor and factor XII mutation: a series of 57 patients from the French National Center of Reference for Angioedema: type III hereditary angioedema. Clin Exp Immunol. 2016;185(3):332–7.

22. Veronez CL, Moreno AS, Constantino-Silva RN, Maia LSM, Ferriani MPL, Castro FFM, et al. Hereditary angioedema with normal C1 inhibitor and F12 mutations in 42 Brazilian families. J Allergy Clin Immunol Pract. 2018;6(4):1209.e8–1216.e8.

23. González-Quevedo T, Larco J, Marcos C, Guilarte M, Baeza M, Cimbollek S, et al. Management of pregnancy and delivery in patients with hereditary angioedema due to C1 inhibitor deficiency. J Investig Allergol Clin Immunol. 2016;26(3):161–7

24. Schneider L, Hurewitz D, Wasserman R, Obtulowicz K, Machnig T, Moldovan D, et al. C1-INH concentrate for treatment of acute hereditary angioedema: a pediatric cohort from the I.M.P.A.C.T. studies. Pediatr Allergy Immunol. 2013;24(1):54–60.

25. Cicardi and Zanichelli: Acquired angioedema. Allergy, Asthma & Clinical Immunology 2010 6:14.

26. Cicardi M, Bergamaschini L, Zingale LC, Gioffré D, Agostoni A. Idiopathic nonhistaminergic angioedema. Am J Med. 1999 Jun;106(6):650-4. doi: 10.1016/s0002-9343(99)00123-0. PMID: 10378623.

27. Du-Thanh A, Raison-Peyron N, Drouet C, Guillot B. Efficacy of tranexamic acid in sporadic idiopathic bradykinin angioedema. Allergy. 2010 Jun 1;65(6):793-5. doi: 10.1111/j.1398-9995.2009.02234.x. Epub 2009 Nov 3. PMID: 19886924.

28. Shroba J, Hanson J, Portnoy J. Current treatment options for idiopathic angioedema. Ann Allergy Asthma Immunol. 2015 Nov;115(5):429-33. doi: 10.1016/j.anai.2015.07.023. Epub 2015 Sep 1. PMID: 26341649.

29, Lepelley, Marion, et al. "Update on bradykinin-mediated angioedema in 2020." Therapies 75.2 (2020): 195-205.