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Research Article

C1 esterase inhibitor (C1-INH) for the off-label treatment of angiotensin-converting enzyme inhibitor induced angioedema

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Abstract

Introduction: Currently, C1 esterase inhibitor (C1-INH) is indicated for hereditary angioedema (HAE) but is utilized off-label for angiotensin- converting enzyme inhibitors (ACEi) induced angioedema (AAE). There is no standard of care for the treatment of AAE, however patients may receive a combination of epinephrine, corticosteroids, fresh frozen plasma (FFP), tranexamic acid (TXA), and histamine 1 and 2 receptor antagonists (H1RA, H2RA). C1-INH place is therapy is not well defined.

Materials & Methods: A retrospective chart review was conducted from patients at a large academic medical center who received C1-INH for AAE between January 2012 and May 2022. Variables and outcomes of interest were receipt of alternative angioedema treatment prior to C1-INH, time of C1-INH administration, dose of C1-INH, need for intubation or surgical airway placement, duration of intubation, and hospital length of stay.

Results: All patients received additional medications for angioedema prior to C1-INH administration. Steroids and H1RAs were most common. The dose of C1-INH ranged from 11.7 IU/kg to 23.2 IU/kg with an average dose of 19.3 IU/kg. Five patients required airway support with four requiring intubation (30.8%) and one requiring a surgical airway.

Conclusions: This retrospective review of 13 patients showed mixed results for C1-INH to prevent intubation in AAE. Providers should consider limiting the use of C1-INH to patients who remain symptomatic after administering a combination of other therapies when there is an ongoing risk for airway compromise and adequate time for preparation, administration, and effect.

Keywords: C1 esterase inhibitor; ACE inhibitor–induced angioedema; angioedema; adverse drug reaction; Berinert; ACE inhibitors

Introduction

Angiotensin converting enzyme inhibitors (ACEi) may cause rare, but serious and potentially life-threatening angioedema in approximately 1% of patients [1,2]. ACEi-induced angioedema (AAE) may occur at any time during treatment, and the risk may even persist years after ACEi discontinuation [2]. The pathophysiology of AAE is not completely understood, but it is thought to be due to an excessive accumulation of bradykinin as a result of impaired breakdown of bradykinin [1-3]. There is no standard of care therapy for AAE. However, a clinical practice statement from the American Academy of Emergency Medicine stated: "In the absence of high-quality evidence, no specific medication therapy is recommended for its treatment [4]." A French Guideline published in 2013 recommends icatabant 30 mg subcutaneously as a first line option and C1-INH dosed at 20 IU/kg as a second line option [5]. Patients may receive some combination of epinephrine, corticosteroids, fresh frozen plasma (FFP), tranexamic acid (TXA), and histamine 1 receptor antagonists (H1RA) and histamine 2 receptor antagonists (H2RA) as pharmacologic therapies [5,6].

Alternative treatment options for AAE have been proposed and investigated, including agents indicated for the treatment of hereditary angioedema (HAE) such as C1 esterase inhibitors (C1-INH), ecallantide, and icatabant [2,3]. The off-label treatment of severe ACEi-induced angioedema (AAE) with C1-INH addresses the underlying pathophysiology leading many to hypothesize that C1 esterase inhibitors may offer some benefit for AAE [2,3]. Several case reports, case series, and review articles have evaluated the off-label use of C1-INH for ACEi angioedema, however, the evidence of clinical efficacy is conflicting [2-4, 6-14].

This case series' main objective was to evaluate the incidence of intubation for AAE in patients receiving C1-INH. Secondary outcomes included hospital and intensive care unit (ICU) length of stay.

Materials and Methods

A retrospective chart review was conducted at a large academic medical center examining all patients with AAE who received C1-INH treatment

between January 2012 and May 2022. Patients were included if they were at least 18 years of age, current or recent use of ACEi, administration of C1-INH for acute AAE of the head and/or neck region. Patients were excluded if they did not meet inclusion criteria, received C1-INH for hereditary angioedema prophylaxis or treatment, or were pregnant or incarcerated. Data collected included patient demographics, alternative angioedema treatment prior to C1-INH, time of C1-INH administration, dose of C1-INH, need for intubation or surgical airway placement, duration of intubation, and hospital length of stay.

Results

Thirteen patients were identified as receiving C1-INH for AAE in the emergency department at this academic medical center from January 2012 to May 2022. Descriptive statistics were used to evaluate the results of this case series. The majority of patients (n = 9) were male and of African American ethnicity (n = 8). Most patients were currently or had recently received lisinopril or lisinopril-hydrochlorothiazide (n = 12) with the exception of one patient who was taking ramipril. The offending agent was discontinued for all patients, and an allergy was added to the electronic health record. All patients received additional medications for angioedema prior to C1-INH administration. Intravenous steroids were administered in nearly all patients (n = 11). Additional therapies included H1RA (n = 10), H2RA (n = 7), FFP (n = 6), IV/IM epinephrine (n = 3), and tranexamic acid (n = 1). The average dosing weight was 109.6 kg (IQR 75-115.9 kg), and 7 patients (53.8%) eight at least 100 kg. The dose of C1-INH ranged from 11.7 IU/kg to 23.2 IU/kg with an average dose of 19.3 IU/kg. A total of five patients required airway support with four requiring intubation (30.8%) and one requiring the placement of a surgical airway (7.7%). Of the five patients who required airway support, two patients received C1-INH after intubation occurred. The median hospital length of stay was 1.81 days (median IQR 1.28-4.7 days). The median ICU length of stay was 1.34 days (median IQR 0.93-2.27). The summary of these patient demographics and outcomes can be found in Table 1. This case series identified no difference in ACEi length of use before AAE occurred and no difference in incidence of intubation, duration of intubation, and ICU or hospital length of stay.

Patient (Age/Sex)	Time symptom onset to C1-INH, hr	C1-INH dose, IU (IU/kg)	Other Medications	Intubation	Time C1-INH to intubation
51/M	>10	2000 (16)	Steroid, H1RA, H2RA, FFP	No	-
38/M	6-8	2000 (11.7)	Steroid	Yes[a]	80 min before
63/M	4-6	2500 (20)	Steroid, H1RA, H2RA, Epi	No	-
62/M	2-4	1500 (21.6)	Steroid, H1RA, H2RA, tranexamic acid	No	-
59/F	>10	1500 (20)	Steroid, H1RA, H2RA, FFP	Yes	10 min before
63/M	>10	2000 (17.8)	Steroid, H1RA	Yes	3 min after
60/M	< 2	2000 (18.2)	Steroid, H1RA, Epi	Yes	37 min after
67/M	2-4	1500 (24.7)	FFP	Yes	50 min before
50/M	< 2	2000 (23.2)	Steroid, H1RA, H2RA, FFP	No	-
47/M	4-6	2000 (17.3)	Steroid, H1RA, H2RA, FFP, Epi	No	-
66/M	>10	2000 (20)	FFP	No	-
77/F	2-4	1180 (20)	Steroid, H1RA	No	-
62/F	2-4	2000 (18.2)	Steroid, H1RA, H2RA	No	-

Table 1: C1-INH dosing and administration timing, other medications, and intubation instance and timing

Abbreviations:

H1RA, histamine 1 receptor antagonist

H2RA, histamine 2 receptor antagonist

Epi, epinephrine

FFP, fresh frozen plasma

IU, international unit

a. Patient required a surgical airway

Discussion

The only current treatments that have consensus for management of AAE are discontinuation of the offending agent and appropriate supportive care with specific emphasis on airway management [6]. Thus, the investigation of other treatment modalities to effect outcomes is paramount. The pathophysiologic similarities between HAE and AAE warrant further studies into using medications targeting the bradykinin pathway such as C1-INH. In our cohort, the incidence of intubation was higher than the incidence seen in other studies including the retrospective reviews by Mohorn and Greeve [4,12]. The propensity-matched study by Mohorn et al. revealed a 13.6% incidence in intubation (n = 3/22) in the C1-INH group versus 9.1% incidence (n = 2/22) after propensity score matching (*P* >0.999), which was not statistically significant [4]. Another retrospective chart review by Kovaltchouk et al. demonstrated a 77.8% incidence of intubation (n = 8/9) [7]. Other case reports and series have demonstrated a relatively rapid improvement in upper airway swelling that prevented the need for airway support [11,13,15].

Of the five patients in this cohort that required advanced airway support, two patients received C1-INH after intubation. This study, like the study from Perza et al., contains multiple cases in which C1-INH was administered after intubation with similar durations of intubation between the two groups [2]. In our case series, the median duration of intubation was 1.86 days (IQR 1.1-2.53 days), and the surgical airway was utilized for 1.36 days. In the Perza et al study, 4 of 7 patients were intubated for a mean duration of 2 days, and of the 4 intubated patients, 3 received C1-INH after intubation [2].

A variation in C1-INH dosing was seen between patients, with weight-based dosing ranging from 11.7 to 24.7 IU/kg and administered single

dose ranging from 1,180 IU to 2,000 IU. No patients received a second dose. This variation in dosing strategy is seen in the published literature with doses ranging from 500 IU to 2,500 IU as a single dose [2,7,12]. Repeated dosing was not shown to benefit symptom resolution in a previous study [7]. The proof-of-concept case series by Greve and et al. noted that the fixed dose regimen of C1-INH 1,000 IU was too low of a dose to meet the recommended 20 IU/kg dosing approved in HAE [12]. Kovaltchouk et al. did utilize 20 IU/kg with continued ambivalence of the efficacy and role of C1-INH in the treatment of AAE [7].

The strength of this case series includes the focus of the research question and relevant outcomes. This case series has several limitations. As a retrospective chart review, this introduces the potential for information bias, and there was a lack of consistent documentation regarding symptom resolution following medication administration. Providers were inconsistent about the dosing strategy chosen, and some patients received a dose of 2000 IU while others received weight-based dosing at 20 IU/kg. There was a large variation in timing of C1-INH administration with two patients receiving C1-INH after intubation. The use of other medications, such as nonsteroidal anti-inflammatory drugs, that can potentially cause angioedema were not assessed. The potential efficacy of C1-INH is confounded by the administration of multiple other agents targeted at treating undifferentiated angioedema prior to C1-INH administration. Furthermore, the timing between administration of other agents and C1-INH was not collected and likely variable.

Conclusion

This retrospective case review of C1-INH use for AAE presented mixed results. The aforementioned limitations and discussion highlight the variability in the use of other agents targeted at treating undifferentiated angioedema, dose of C1-INH, and timing of C1-INH administration. Providers should limit the This case series demonstrates an ongoing interest in the clinical application of C1-INH in AAE despite a lack of evidence and defined role in therapy, therefore, we the authors recommend C1_INH administration for patients who remain symptomatic after the administration of other medications for edema including H1RA, H2RA, tranexamic acid, FFP, and epinephrine that are at risk of airway compromise. C1-INH should be used when there is a continued risk for airway compromise and there is adequate time for preparation and administration. Consideration should also be given to imminence of intubation; given the significant cost and unclear benefit, C1-INH should not be administered following placement of endotracheal tube or surgical airway.

Data Availability

The data underlying this article are available in the article.

Key points:

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