C1 Esterase Inhibitor for Drug-Induced Angioedema at a Community Teaching Health System

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BACKGROUND

- Acute drug-induced angioedema is a serious emergency that can cause life-threatening symptoms and death if not treated promptly.
- Drug-induced angioedema, particularly angiotensin-converting enzyme inhibitor (ACEi)-induced angioedema, is thought to be caused by excess accumulation of bradykinin due to ineffective breakdown pathways and mainly manifests as upper aerodigestive tract edema.[1-3]
- This pathophysiological mechanism suggests that treatments aimed at preventing the accumulation of bradykinin might be effective in treating drug-induced angioedema.
- Currently, no FDA-approved medications exist to treat drug-induced angioedema.
- Small randomized studies, case reports, and a meta-analysis have evaluated off-label use of icatibant, C1 esterase inhibitor (C1EI), and other therapies with no clear delineation of their role in the treatment of drug-induced angioedema.[2-17]

OBJECTIVE

- To evaluate the use, clinical efficacy, and angioedema-related medication costs of C1EI for drug-induced angioedema

METHODS

- Study Design: IRB approved retrospective, observational study comparing patients who received C1EI to those who did not for drug-induced angioedema from January 2018 to December 2019
- Patient Population:
  Inclusion criteria:
  -Adults > 18 years of age
  -Primary diagnosis of drug-induced angioedema

  Exclusion criteria:
  -Pregnant or incarcerated
  -Received fresh frozen plasma
  -Received C1EI post intubation
- Primary Endpoint: Incidence of intubation secondary to drug-induced angioedema
- Secondary Endpoints: Duration of mechanical ventilation, intensive care unit (ICU) length of stay (LOS), hospital LOS, in-hospital mortality, angioedema-related medication therapy costs, and reported C1EI adverse effects
- Other data points collected included: Age, gender, race, ethnicity, weight, Charlson Comorbidity Index, initial patient disposition, standard of care received (defined as epinephrine 0.2 to 0.5 mg intramuscularly or 0.05 to 0.1 mg intravenously, corticosteroids at ≥ 50 to 100 mg hydrocortisone equivalent, a histamine-1 receptor antagonist, and a histamine-2 receptor antagonist), dose administered of C1EI, history of angioedema, patient reported duration of symptoms, angioedema causative medications, and a validated initial symptoms severity score that has been published elsewhere[7,18]

METHODS (continued)

- Statistical Analysis:
  Sample size calculation: 21 patients in each group would give the study 80% power to detect a 30% between-group difference in the incidence of drug-induced angioedema-related intubation based on previous literature.[17,19,20]

  Propensity scores (using a greedy matching procedure) were used to match patients who received C1EI to a control (a patient who did not receive C1EI).

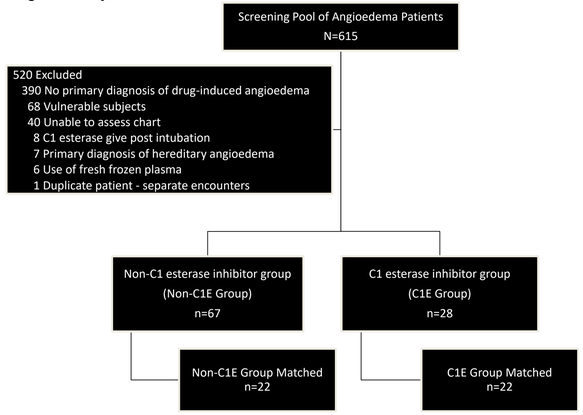
  Categorical variables were summarized using counts and percentages, and comparisons between groups were analyzed using chi-square, Fisher's exact, or McNemar test.

  Depending on data distribution, continuous and ordinal variables were summarized using means or medians, and comparisons between groups were analyzed using Mann–Whitney U, Wilcoxon signed ranks, Student t test, or paired Student t test.

  A 2-sided *p*-value of <0.05 was considered statistically significant. Missing data statistical procedures were not required.

  Statistical analyses were conducted using SPSS 26.0 (Statistical Package for Social Sciences, IBM Corporation, Armonk, NY).

Figure 1. Subject Enrollment



RESULTS

- Overall (n = 95), the mean age was 60.7 (± 13.8) years, and 48 patients (50.5%) were female. The majority of patients were Caucasian (63 patients, 66.3%), had no history of angioedema (84 patients, 88.4%), had a patient-reported duration of symptoms less than three hours (36 patients, 37.9%), had an ACEi as the angioedema-associated medication (82 patients, 86.3%), and were discharged home upon initial presentation (50 patients, 52.6%).

RESULTS (continued)

Table 1. Baseline Characteristics Before and After Propensity Score Matching

	Before Propensity Score Matching (n = 95)			After Propensity Score Matching (n = 44)		
Characteristic	Non-C1EI Group (n=67)	C1EI Group (n=28)	p-value	Non-C1EI Group (n=22)	C1EI Group (n=22)	p-value
Age, years, mean (SD)	59.5 (13.9)	63.6 (13.6)	0.191	62.6 (12.9)	64.2 (14.2)	0.687
Female, n (%)	32 (47.8)	16 (57.1)	0.501	12 (54.5)	14 (63.6)	0.791
Race, n (%)						
Caucasian	48 (71.6)	15 (53.6)	0.101	12 (54.5)	12 (54.5)	>0.999
African American	19 (28.4)	13 (46.4)		10 (45.5)	10 (45.5)	
Ethnicity, n (%)						
Hispanic	0 (0)	1 (3.6)	0.295	0 (0)	0 (0)	-
Non-Hispanic	67 (100)	27 (96.4)		22 (100)	22 (100)	
Initial Patient Disposition, n (%)						
Discharged home	44 (65.7)	6 (21.4)	<0.001	8 (36.4)	6 (27.3)	0.727
ICU	5 (7.5)	12 (42.9)	<0.001	3 (13.6)	7 (31.8)	0.125
General Medicine	8 (11.9)	6 (21.4)	0.340	5 (22.7)	5 (22.7)	>0.999
Med/Surg	5 (7.5)	3 (10.7)	0.690	3 (13.6)	3 (13.6)	>0.999
Observation Unit	5 (7.5)	1 (3.6)	0.667	3 (13.6)	1 (4.5)	0.625
Weight, kg, median (IQR)	89.4 (72.6, 102.4)	91.9 (76.3, 111.8)	0.475	94.4 (77.5, 110.5)	89 (17.1, 112.3)	0.858
Charlson Comorbidity Index, median, (IQR)	2 (1, 4)	3 (2, 4)	0.098	2 (1, 5)	3 (1.7, 4.2)	0.599
Standard of care, n (%)						
Yes	18 (26.9)	8 (28.6)	>0.999	6 (27.3)	7 (31.8)	>0.999
Partial*	49 (73.1)	20 (71.4)		16 (72.7)	15 (68.2)	
History of angioedema, n (%)	6 (9)	5 (17.9)	0.291	3 (13.6)	2 (9.1)	>0.999
Initial symptoms severity score, median, (IQR)	0 (0, 2)	2 (0, 5)	0.005	0 (0, 2.2)	2 (0, 5)	0.183
Patient-reported duration of symptoms, n (%)						
<3 hours	25 (37.3)	11 (39.3)	>0.999	11 (50)	9 (40.9)	0.754
3-6 hours	15 (22.4)	10 (35.7)	0.206	6 (27.3)	8 (36.4)	0.774
>6-12 hours	7 (10.4)	1 (3.6)	0.429	0 (0)	1 (4.5)	>0.999
>12 hours	17 (25.4)	6 (21.4)	0.796	4 (18.2)	4 (18.2)	>0.999
Not documented	3 (4.5)	0 (0)	0.553	1 (4.5)	0 (0)	>0.999
Angioedema-associated medications, n (%)+						
ACEi	57 (85.1)	25 (89.3)	0.749	20 (90.9)	20 (90.9)	>0.999
ARB	3 (4.5)	2 (7.1)	0.630	2 (9.1)	2 (9.1)	>0.999
NSAID	3 (4.5)	1 (3.6)	>0.999	0 (0)	0 (0)	-
BB	1 (1.5)	0 (0)	>0.999	0 (0)	0 (0)	-
Beta-lactam	1 (1.5)	0 (0)	>0.999	0 (0)	0 (0)	-
Other^	4 (6)	1 (3.6)	>0.999	0 (0)	0 (0)	-
Amount of C1 esterase inhibitor given						
Total Units, median (IQR)	-	1800 (1500, 2150)	-		1800 (1450, 2225)	-
Units/kg, median (IQR)	-	19.8 (19.5, 20.3)	-		19.8 (19.4, 20.4)	-

SD, standard deviation; ICU, intensive care unit; IQR, interquartile range; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-2 receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; BB, beta-blocker
*Missing medications: unmatched-epinephrine (n=64), histamine-2 receptor antagonist (n=5); matched- epinephrine (n=29), histamine-2 receptor antagonist (n=2)
+Numbers may not equal total as some patients had more than one angioedema-associated medication
^Other: aripiprazole, levalbuterol, doxazosin, glatiramer acetate, sulfamethoxazole/trimethoprim

Table 2. Study Endpoints Before and After Propensity Score Matching

	Before Propensity Score Matching (n = 95)			After Propensity Score Matching (n = 44)		
Endpoints	Non-C1EI Group (n=67)	C1EI Group (n=28)	p-value	Non-C1EI Group (n=22)	C1EI Group (n=22)	p-value
Primary Endpoint						
Intubation, n (%)	3 (4.5)	5 (17.9)	0.046	2 (9.1)	3 (13.6)	>0.999
Secondary Endpoints						
Duration of mechanical ventilation, days, median, (IQR)	0 (0, 0)	0 (0, 0)	0.036	0 (0, 0)	0 (0, 0)	0.109
ICU LOS, days, median, (IQR)	0 (0, 0)	0 (0, 1.1)	<0.001	0 (0, 0)	0 (0, 0.6)	0.018
Hospital LOS, days, median, (IQR)	0.15 (0.1, 1)	1.4 (0.49, 2.23)	<0.001	0.9 (0.1, 1.3)	1.1 (0.4, 2.1)	0.314
In-hospital mortality, n (%)	0	0	-	0	0	-
Cost of angioedema-related medication therapy, dollars, median, (IQR)	11 (10, 23)	8697 (7243, 10392)	<0.001	11 (10, 23)	8697 (7005, 10750)	<0.001

IQR, interquartile range; ICU, intensive care unit; LOS, length of stay

DISCUSSION

- Any baseline characteristic differences between C1EI and non-C1EI groups were resolved with propensity score matching (Table 1).
- While there was a statistically significant difference in incidence of intubation, duration of mechanical ventilation, and hospital LOS in the unmatched analysis, there was no statistically significant difference between the C1EI and non-C1EI groups after propensity score matching (Table 2).
- ICU LOS was longer in the C1EI group compared to the non-C1EI group both before and after propensity score matching (Table 2).
- Cost of angioedema-related medication therapy was greater in the C1EI group compared to the non-C1EI group both before and after propensity score matching (Table 2).
- No in-hospital mortality was observed and no C1EI adverse effects were reported

CONCLUSION

- This retrospective, observational study suggests that C1EI may not prevent drug-induced angioedema-related intubation while also incurring a larger angioedema-related medication therapy cost.
- Larger, multicenter, randomized controlled trials are needed to further validate the results of this study.

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DISCLOSURE
Authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest on the subject matter of this presentation

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