

Ten-year study of causes of moderate to severe angioedema seen by an inpatient allergy/immunology consult service

Aleena Banerji, M.D.,* Eyal Oren, M.D.,* Paul Hesterberg, M.D.,* Yulan Hsu, M.D.,* Carlos A. Camargo, Jr., M.D., Dr.P.H.,# and Johnson T. Wong, M.D.*

ABSTRACT

The causes of angioedema are not well described, especially in the inpatient setting. The purpose of this study was to examine the causes of moderate to severe angioedema in patients requiring inpatient treatment. We performed a retrospective review in patients requiring inpatient consultation by the Division of Allergy and Immunology at our institution between 1995 and 2004. We focused on potential interactions among medications that elicited life-threatening angioedema requiring intubation. The allergy/immunology service was consulted on 69 patients with moderate to severe angioedema. Medications were the most common cause of angioedema ($n = 64$, 93%). In most cases ($n = 46$, 67%), the angioedema was attributed to two or more medications. Patients previously stable on ACE inhibitors (ACEI), aspirin (ASA), or non-steroidal anti-inflammatory drugs (NSAIDs) appeared more likely to develop angioedema soon after the addition of another drug (i.e., ACEI, ASA/NSAIDs, direct mast cell degranulators, and antibiotics). ACEI, ASA/NSAID, and direct mast cell degranulators were contributing causes in 36 patients (56%), 45 patients (70%), and 23 patients (36%), respectively. Twenty patients required intubation, 14 (70%) patients were on ACEI, 12 (60%) patients were on ASA/NSAID, and 7 (35%) patients were on direct mast cell degranulators. ACEI, ASA/NSAID, or direct mast cell degranulators were a cause in 95% ($n = 19$) of patients requiring intubation. The combination of ACEI and ASA/NSAID was the most frequent cause of angioedema among all patients ($n = 17$, 25%) and those requiring intubation ($n = 8$, 40%). Moderate to severe angioedema often is a result of interactions between two or more medications involved in different pathways causing angioedema. In particular, combinations of ACEI, ASA/NSAID, or direct mast cell degranulators may lead to life-threatening angioedema requiring intubation.

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Key words: Allergy, angioedema, angiotensin-converting enzyme inhibitors, aspirin, drug allergy, immunology, intubation, mast cell, NSAID

Angioedema is characterized by swelling of the subcutaneous or submucosal tissues due to vascular leak. The development of angioedema has been attributed to a number of pathophysiological mechanisms including the release of inflammatory mediators from mast cells, as well as the activation of complement or kinin-generating systems.¹ A number of factors have been associated with angioedema, including medication hypersensitivity, food allergy, infection, autoimmunity, malignancy, and hereditary conditions.² However, in many cases the precise cause of the angioedema remains unknown.

Recently, we have seen a rise in the number of consultations for angioedema by the allergy/immunology service of the Massachusetts General Hospital (MGH).

We noticed that many of the severe cases of angioedema requiring intubation occurred in patients on a combination of angiotensin-converting enzyme inhibitor (ACEI) and aspirin/nonsteroidal anti-inflammatory drugs (ASA/NSAIDs) with or without direct mast cell degranulators, *viz.*, opiates, radiocontrast media (RCM), and vancomycin. To formally examine this observation and determine whether similar interactions occur with other drug classes, we investigated all inpatient cases of moderate to severe angioedema for whom consultation by the adult Allergy/Immunology service had been requested at the MGH over a 10-year period.

METHODS

We performed a retrospective chart review of all patients with a diagnosis of angioedema seen by the allergy/immunology inpatient adult consult service at MGH from January 1995 through December 2004. Only patients with moderate to severe angioedema were included in the analysis. If patients did not require any specific medical treatment (*i.e.*, antihistamines, steroids, and/or i.v. fluids) or intervention (*i.e.*, intubation and/or i.v. access) they were considered to have mild

From the *Division of Rheumatology, Allergy, and Immunology, Department of Medicine, and #Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

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Address correspondence and reprint requests to Aleena Banerji, M.D., Allergy Associates, Cox 201, 100 Blossom Street, Massachusetts General Hospital, Boston, MA 02114

E-mail address: abanerji@partners.org

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angioedema and were not included in the analysis. The Institutional Review Board of the MGH approved the study.

We compiled information from the patients' records including age, sex, race, and concurrent medications. With regard to the clinical course, we focused on cases of severe angioedema that required treatment with epinephrine or intubation. We also noted the duration of use of causative medication(s) or other contributing causes as determined by the inpatient allergy/immunology consult service. The service included one allergy/immunology attending and at least one allergy/immunology fellow-in-training who independently evaluated the patient and agreed on the cause of angioedema at the time of consultation. In particular, we focused on potential interactions among medications in eliciting life-threatening angioedema requiring intubation. All cases were evaluated for hereditary and acquired forms of angioedema *via* laboratory assays for complement, C1 inhibitor function/level, and C1q level, where appropriate. Data are described using descriptive statistics. Data are presented as proportions (with 95% confidence intervals [CIs]) or means (with standard deviation [SD]).

RESULTS

Over the 10-year study period, 69 patients with a diagnosis of moderate to severe angioedema required inpatient consultations by the allergy/immunology service. In this population, there was a female predominance with 43 (62%) women and 26 (38%) men. Ages ranged from 18 to 92 years with a mean of 61 years (SD = 16). A significant proportion of the population was white ($n = 46$, 67%), consistent with the racial/ethnic mix of patients at our institution. The second largest group was African American ($n = 14$, 20%), and several patients were of Asian, Hispanic, and Middle Eastern descent.

In 64 patients (93%), the cause of angioedema was attributed to medications by the allergist/immunology consult service. Of the five nonmedication-related cases (7%), 1 patient was diagnosed with hereditary angioedema, 3 patients were diagnosed with idiopathic angioedema (with or without urticaria), and 1 patient was diagnosed with angioedema secondary to hormonal treatment with progesterone. ACEI, ASA/NSAID, and direct mast cell degranulators were the most common medications implicated, leading to 37 (58%), 45 (70%), and 23 (36%) of the cases of angioedema, respectively (Fig. 1). Together, these three groups of medications accounted for 62 (97%) of all cases of medication associated with moderate to severe angioedema. Other antibiotics and antineoplastic and anesthetic agents comprised the other medication-related causes. Of the 64 medication-related cases, 46

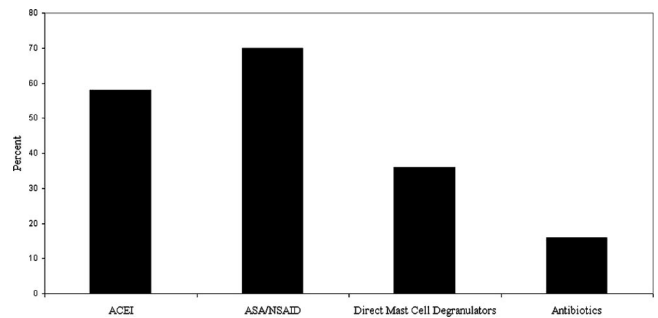


Figure 1. Most common causes of moderate to severe angioedema in the inpatient setting.

were attributed to ≥ 2 medications that have been known to cause urticaria or angioedema.

Angioedema Requiring Intubation

Twenty (31%; 95% CI, 26–34%) of the 64 patients with medication-associated angioedema required intubation. None of the 5 patients with nonmedication-associated angioedema required intubation. Fourteen (70%) of the intubated patients were receiving ACEI, 12 (60%) were receiving ASA/NSAID, and 7 (35%) were receiving an opiate. Of the intubated patients, 6 (30%) were on concurrent ACEI and ASA/NSAID. Two additional patients were on ACEI and ASA/NSAID, but one patient in combination with opiates and the other in combination with an anesthetic. Two (10%) patients were taking ACEI alone and two (10%) patients were taking ASA/NSAID alone. Four patients were taking ACEI with opiates and one patient was on ASA and opiates. The other three patients were on a combination of Cefepime and Tobramycin, ASA and Levaquin and vancomycin with opiates. ACEI, ASA/NSAID, or direct mast cell degranulators alone or in combination accounted for 95% ($n = 19$) of patients requiring intubation. Overall, in 80% ($n = 16$) of patients with angioedema requiring intubation for airway protection, the cause was attributed to more than one drug.

ACEI Angioedema

Of the 64 patients with medication-related angioedema, 37 (58%) were related to ACEI use (in 1 patient, angioedema followed initiation of an angiotensin receptor blocker [ARB] 2 days after an ACEI was discontinued). Of these 37 patients, 6 (16%) developed angioedema while on treatment with ACEI alone. The remaining 31 cases (84%) involved a combination of an ACEI and either ASA/NSAIDs ($n = 23$), opiates ($n = 12$), RCM ($n = 1$), or anesthetics ($n = 1$). One patient developed angioedema with a combination of ARB and ASA.

Fourteen of the patients for whom ACEI was a cause of angioedema required intubation. Only 2 of the intubated patients were on ACEI alone. The other 12 pa-

Table 1 Cause of moderate to severe angioedema

ACEI	ASA/NSAID	Direct Mast Cell Degranulator	Antibiotic	Total Patients % (n)	Intubated Patients % (n)
✓	✓			27 (17)	30 (6)
	✓			16 (11)	10 (2)
✓		✓		10 (7)	20 (4)
✓				9 (6)	10 (2)
✓	✓	✓		7 (5)	5 (1)
	✓	✓		6 (4)	5 (1)
	✓		✓	4 (3)	5 (1)
	✓	✓	✓	3 (2)	N/A

tients were on various combinations of ASA/NSAID ($n = 8$, 57% intubated ACEI patients), opiates ($n = 5$, 36% of intubated ACEI patients), or anesthetics ($n = 1$, 7% of intubated ACEI patients).

Of the 23 patients (36%) who developed angioedema attributed to concurrent use of an ACEI and ASA/NSAID, 6 (25%) were started on either ACEI or ASA/NSAID therapy within 2 weeks of the onset of angioedema. Most of the patients in this category developed a moderate to severe degree of angioedema involving the tongue and throat. None of the patients had any symptoms of flushing, rash, or urticaria if they were not concurrently on ASA/NSAIDs.

ASA/NSAID Angioedema

There were 45 patients identified who developed angioedema while on ASA/NSAID therapy. Eleven of the 45 (24%) patients were on ASA or NSAIDs alone, while in the remaining 34 (76%) patients, angioedema was caused by more than one drug in combination with the ASA/NSAIDs. These 34 patients were on various combinations of ACEI ($n = 23$), opiates ($n = 10$), RCM ($n = 3$), ARB ($n = 1$), and anesthetics ($n = 2$). Several of the patients on ASA/NSAIDs also developed urticaria in addition to angioedema.

Twelve (26% of all ASA/NSAID-associated therapy and 60% of intubated) patients on therapy with ASA/NSAIDs required intubation. Two of the 12 patients (17%) were on ASA/NSAIDs alone. The remaining 10 patients (83%) were on ASA/NSAIDs with various combinations of ACEI ($n = 8$, 67%), opiates ($n = 2$, 17%), antibiotics ($n = 1$, 8%), and anesthetics ($n = 1$, 8%).

Direct Mast Cell Activator Angioedema

Opiates comprised the third largest group of medications causing angioedema, identified in 21 (33%) of the 64 patients in whom medications were the cause of the angioedema. RCM ($n = 3$) and vancomycin ($n = 1$) were much less common causes than opiates. All of the opiate-associated cases involve various combinations

of ACEI ($n = 12$), ASA/NSAIDs ($n = 10$), antibiotics ($n = 7$), or anesthetics ($n = 1$, 5%). There was no case where opiates were the only suspected causative agent. Seven patients on opiates required intubation. They were all concurrently receiving ACEI ($n = 5$), ASA/NSAIDs ($n = 2$), or vancomycin ($n = 1$).

DISCUSSION

In contrast to the overall population of patients who develop angioedema, the subgroup with moderate to severe angioedema requiring inpatient consultation had a cause identified in >90% of the cases (Table 1). At our institution, during the 10-year study period, the most common cause was medication, accounting for 93% (64/69) of the patients. Of the medication-induced angioedema, the majority of cases were caused by a combination of medications. Our study found the usually suspected medications, ACEI (56%) and ASA/NSAIDs (70%), caused a majority of the moderate to severe angioedema. However, a surprising finding was that direct mast cell degranulators also contributed to a significant number of the cases (36%).

ACEIs were the second most common cause of moderate to severe angioedema in our study population, but the most common cause among patients requiring intubation. In that respect, our study is consistent with other studies that have shown ACEIs have become a common cause of angioedema in the hospital and emergency department.³⁻⁶ The literature suggests that the interval between onset of angioedema and duration of ACEI treatment generally is days to weeks, with only a minor subgroup occurring up to several years later.⁷ In this series, the addition of other medications capable of causing angioedema, in particular ASA/NSAIDs and direct mast cell degranulators, appeared to be relevant in patients who had been previously stable on an ACEI. This is consistent with previous case reports that have implicated concurrent medications, dental surgery, local anesthetics, and interruption of ACEI therapy as possible triggers for angioedema in

patients who have previously tolerated ACEI treatment.^{8–13}

In this series, most of the angioedema caused by ACEIs involved the oropharyngeal area and appeared to be a major contributor toward the severity, with a disproportionate number requiring intubation. In part, this reflects the predilection of ACEI-induced angioedema for that area,¹⁴ although the reasons for this predilection remain poorly understood. Patients on ACEI alone did not have urticaria. However, urticaria was noted in several patients taking concurrent ASA/NSAIDs. The numbers were too small to be statistically significant but suggested that ACEIs alone generally do not lead to urticaria, similar to hereditary angioedema.

In our study, ASA/NSAIDs was the most common cause of moderate to severe angioedema and the second most common cause in the subgroup requiring intubation. ASA/NSAIDs are well-known causes of angioedema either with or without associated urticaria. ASA/NSAIDs inhibit cyclooxygenase (COX-1 and COX-2) enzymes, thereby decreasing prostaglandin production and causing increased production of leukotrienes. This may be the dominant mechanism of ASA/NSAID-induced angioedema/urticaria.¹⁵ The incidence is much higher for agents capable of inhibiting both COX-1 and COX-2 compared with those that specifically inhibit COX-2.

Opiates, RCM, and antibiotics such as vancomycin cause direct mast cell degranulation and may contribute to angioedema *via* this mechanism.^{16–18} Other antibiotics cause angioedema by direct IgE-mediated mast cell degranulation. However, there were no patients in this series with angioedema caused by opiates alone, suggesting that in most cases opiates alone are inadequate to cause severe angioedema. Our observations suggest that factors influencing different pathways, as described previously, may synergize to induce angioedema in patients that would otherwise not develop moderate to severe angioedema if only one pathway was affected.

Our study has several limitations. The first is the retrospective and single center design. We compiled 10 years of data to yield 69 cases. More importantly, there are no validated assays for the diagnosis of medication-induced angioedema. The allergy/immunology consultants performed a comprehensive history and physical examination including complete home and hospital medication lists. They combined this knowledge with a full understanding of the current medical literature describing medication-induced angioedema to determine the likely cause. Until assays are available for proposed mediators of medication-induced angioedema (such as aminopeptidase P and dipeptidyl peptidase IV, enzymes known to be involved in the degradation and inac-

tivation of bradykinin),^{19,20} we will be unable to confidently diagnose the cause(s) of angioedema. This makes our findings of multiple medications as likely causes of medication-induced angioedema of more clinical value.

In summary, among cases of moderate to severe angioedema requiring hospitalization and consultation, our findings suggest that medications are the most common cause of angioedema. In particular, ASA/NSAIDs, ACEI, and direct mast cell degranulators are the most common cause of moderate to severe drug-induced angioedema. The addition of a second or third drug known to potentiate angioedema (*i.e.*, ASA/NSAIDs, ACEI, and direct mast cell degranulators) often led to the development of moderate to severe angioedema in otherwise stable patients. Therefore, physicians should focus on ACEI, ASA/NSAID, and direct mast cell degranulators when obtaining a medical history in patients with moderate to severe angioedema and be aware of potential interactions.

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