Incidence and Characteristics of Angioedema Associated With Enalapril

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Background: Angioedema is a rare but potentially serious adverse event of angiotensin-converting enzyme inhibitor therapy. However, no prospective, controlled studies have reported on its incidence and clinical characteristics.

Methods: We studied the occurrence of angioedema in a randomized, double-blind, controlled trial of 12 557 persons with hypertension treated with enalapril maleate, 5 to 40 mg/d, using a prospective ascertainment and adjudication of angioedema by an expert committee.

Results: Angioedema occurred in 86 (0.68%) of the subjects. Stepwise logistic regression identified black race (odds ratio [OR], 2.88; 95% confidence interval [CI], 1.72-4.82), history of drug rash (OR, 3.78; 95% CI, 1.80-7.92), age greater than 65 years (OR, 1.60; 95% CI, 1.02-2.53), and seasonal allergies (OR, 1.79; 95% CI, 1.06-3.00) as independent risk factors for angioedema. The incidence of angioedema was higher after initiation of therapy (3.6/1000 patients per month) and declined to 0.4/1000 patients per month. Treatment was not given in 44 (51%) of the cases; antihistamines were administered in 35 (41%); corticosteroids, in 20 (23%); and epinephrine, in 1 (1%). Two patients were hospitalized but none had airway compromise.

Conclusions: Enalapril-related angioedema is uncommon. Although it is most likely to occur early after initiation of therapy, it may occur at any time. It is more likely to occur in black patients, those older than 65 years, and those with a history of drug rash or seasonal allergies. Fatal angioedema or angioedema requiring airway protection did not occur in this study.

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ANGIOEDEMA IS A RARE AND usually self-limited but potentially serious adverse effect of therapy with angiotensin-converting enzyme (ACE) inhibitors, a widely used class of pharmacologic agents.[1-10] Although the occurrence of angioedema with ACE inhibitor therapy has been widely recognized, no prospective controlled studies have evaluated the occurrence and clinical characteristics of angioedema in large numbers of patients receiving ACE inhibitors. The double-blind Omapatrilat Cardiovascular Treatment Assessment vs Enalapril (OCTAVE) Trial carried out in 12 634 patients randomized to enalapril maleate and 12 668 randomized to omapatrilat was designed to evaluate the safety and efficacy of the 2 agents. The study was designed to have adequate size to evaluate the rate of angioedema with enalapril and omapatrilat and to study the efficacy and safety of the 2 agents in treating patients with a broad spectrum of hypertension.[11] The primary findings with respect to blood pressure and angioedema were reported in the initial publication. This report further analyzes clinically relevant features of enalapril-related angioedema.[11]

METHODS

STUDY DESIGN

The OCTAVE Trial was conducted at 3298 investigative sites in 12 countries under the supervision of appropriate institutional review boards or ethics committees. The study was conducted under the principles of the Declaration of Helsinki and in accordance with local regulations. Written informed consent was obtained from all study participants prior to any study-related procedures. The OCTAVE Trial was sponsored by Bristol-Myers Squibb, Princeton, NJ, and conducted under the auspices of an independent steering committee.

The OCTAVE Trial was a multicenter, randomized, double-blind, active-controlled study. Study subjects had treated or untreated hypertension (systolic blood pressure, ≥140 mm Hg; diastolic blood pressure, ≥90 mm Hg) and were at least 18 years of age. Exclusion criteria con-

sisted of a contraindication to therapy with ACE inhibitors or angiotensin II receptor antagonists; a history of angioedema, anaphylaxis, drug-induced or chronic urticaria, or multiple drug sensitivities; recent hospitalization for myocardial infarction, unstable angina, stroke, transient ischemic attacks, or chronic obstructive pulmonary disease; and recent treatment for a malignancy, chronic renal disease secondary to autoimmune disease, or end-stage renal disease of any etiology. Subjects who met the inclusion/exclusion criteria for enrollment were randomized in equal numbers to receive omapatrilat or enalapril.

After randomization, a 24-week double-blind treatment period included a titration phase (weeks 1-8) in which omapatrilat and enalapril maleate dosages were titrated (5-20 mg/d) as needed to reach the target blood pressure (systolic blood pressure, <140 mm Hg; diastolic blood pressure, <90 mm Hg), and a maintenance phase (weeks 9-24) in which the dosage of the double-blind study drug was maintained and adjunctive antihypertensive therapy was added as needed to reach the target blood pressure. Adjunctive antihypertensive medication could be added to omapatrilat or enalapril therapy at weeks 8 or 16 or at interim unscheduled visits during the maintenance phase to achieve blood pressure control. Key safety objectives included summarizing the incidence of severe adverse events and discontinuations due to adverse events and comparing the incidence and evaluating the severity of angioedema.

ASSESSMENT OF ANGIOEDEMA

All potential angioedema events, including any swelling of the head or neck, were reported as potential study end points. Detailed follow-up information regarding the intensity, clinical features, severity, treatment, outcome, etiology of the event, as well as a description of diagnostic procedures, prodromal symptoms, concomitant medications, and a history of compliance with the study drug were obtained using a structured questionnaire. All data were then reviewed in blinded fashion by the Event Adjudication Committee (a panel of experts in angioedema) to determine whether angioedema had occurred. Three primary adjudicators reviewed each event and met to reach a consensus on the presence or absence of angioedema, the severity class, and the etiology of the event. Agreement by 2 of 3 primary adjudicators was necessary and sufficient to make a determination. Because no standardized or validated classification system for the severity of angioedema is currently available, a classification system was developed for this purpose. This system used treatment variables as the primary basis for classification, in the belief that the treatment provided would reflect the severity and clinical importance of the signs and symptoms of angioedema. Thus, the Event Adjudication Committee classified the severity of angioedema according to an ad hoc scale that used measures of treatment intensity as proxies for severity. Angioedema events were classified by severity as class 1 when patients were given no treatment or were given antihistamines only, class 2 when patients were treated with catecholamines or corticosteroids, class 3 when patients were hospitalized but no mechanical airway protection was given (subclassified to class 3a if patients were hospitalized with no airway compromise or class 3b if they were hospitalized with airway compromise), and class 4 when patients required airway protection or died.

STATISTICAL ANALYSIS

The 2-sided 95% confidence interval for the relative risk of angioedema was calculated using the Fieller theorem. All analyses of angioedema were based on cases confirmed by adjudication. The first coprimary blood pressure objective (comparison of the change in systolic blood pressure from baseline to week 8 within each study group) was evaluated using a 2-sample *t* test; the second coprimary blood pressure objective (comparison of the proportion of subjects adding new adjunctive antihypertensive medications by week 24 within each study group) was evaluated using a Pearson χ^2 test. The OCTAVE Trial was designed to have sufficient power to test the coprimary efficacy objectives and the important secondary objective (comparison of the incidence of angioedema by week 8). The sample size of 25 000 randomized subjects was expected to provide 95% power to exclude a 2-fold increase in the risk of angioedema with omapatrilat relative to enalapril at a 1-sided significance level of $P<.05$, assuming the rate of angioedema with enalapril is 0.4%. For angioedema results, analyses are based on events confirmed as angioedema by the Event Adjudication Committee. For most analyses (including summaries of incidence, time course, dose response, and risk factors), the denominator for all presentations is the total number of subjects treated. For analyses of the features of angioedema (including summaries of treatment, time to resolution, outcome, signs, and symptoms), the denominator for all presentations is the total number of subjects experiencing an angioedema event by treatment group. Investigative sites, subjects, the administrative center, and the angioedema Event Adjudication Committee were blinded to treatment assignments.

RESULTS

Of a total of 25 302 subjects in the OCTAVE Trial, 12 634 were randomized to enalapril. (Seventy-seven subjects who were randomized to receive enalapril did not receive any dose of the medication during the study.) Of the 12 634 subjects randomized, 10% were black and 52% were men. Baseline mean ± SD blood pressure was 155.2 ± 12.8/93.6 ± 8.6 mm Hg, mean age was 56.9 years, approximately 13% of the study population had diabetes, and substantial numbers had a history of overt cardiovascular disease (angina, myocardial infarction, stroke/transient ischemic attacks, heart failure, or renal disease). Sixty-five percent of the subjects had not used ACE inhibitors before entering the study (**Table 1**).

The dose of study drug was increased in 85.1% of subjects with uncontrolled hypertension (13 879/16 306) (blood pressure, ≥140/≥90 mm Hg) at week 4 and 79.0% (10 191/12 904) at week 6. Adjunctive antihypertensive therapy was added in 36.3% of subjects with uncontrolled hypertension (3632/10 011) at week 8 and 13.4% (1117/8307) at week 16. The blood pressure results (a 3.6/2.0–mm Hg greater decrease in blood pressure with omapatrilat than enalaprilat by week 8 and less use of adjunctive antihypertensive therapy by week 24 despite more frequent upward titration of study therapy among subjects randomized to enalapril) have been published elsewhere.[11] The most commonly reported adverse events were headache (8.9%), cough (8.8%), dizziness (5.4%), and upper respiratory tract infection (6.9%).

ANGIOEDEMA AMONG ENALAPRIL-TREATED PATIENTS

Incidence

Angioedema occurred during the 24-week treatment period in 86 subjects (0.68% of the 12 557 subjects given

Table 1. Baseline Characteristics of 12 634 Patients Randomized to Enalapril Maleate

Baseline Characteristic	Finding*
Age, y	
Mean	56.9
Range	18-93
Age groups	
<65 y	9083 (71.9)
65-74 y	2482 (19.6)
≥75 y	1063 (8.4)
Sex	
Male	6558 (51.9)
Female	6069 (48.0)
Race	
White	11 182 (88.5)
Black	1247 (9.9)
Asian/Pacific	170 (1.3)
Other	29 (0.2)
Region	
United States	7416 (58.7)
Europe	4944 (39.1)
Canada	180 (1.4)
Australia	94 (0.7)
Baseline SBP, mm Hg	
Mean (SD)	155.2 (12.8)
Range	104.0-225.0
Baseline DBP, mm Hg	
Mean (SD)	93.6 (8.6)
Range	48.0-148.0
Chronic stable angina	544 (4.3)
Unstable angina	52 (0.4)
MI	387 (3.2)
Cardiac surgery	399 (3.2)
Parental history of MI	837 (6.6)
Congestive heart failure	122 (1.0)
Stroke/TIA	380 (3.0)
Diabetes	1666 (13.2)
Hypercholesterolemia	4031 (31.9)
Renal disease	107 (0.8)
ACE-I use	
Present	2270 (18.0)
Recent past	913 (7.2)
Remote past	1284 (10.2)
Never	8158 (64.6)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; DBP, diastolic blood pressure; MI, myocardial infarction; SBP, systolic blood pressure; TIA, transient ischemic attacks.
*Unless otherwise indicated, data are expressed as number (percentage) of patients. The total number of patients varies because of missing data.

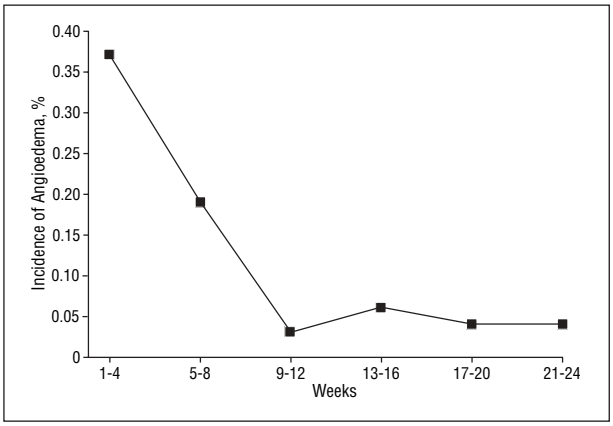

Figure 1. The incidence of angioedema in the weeks after randomization.

Table 2. Incidence of Confirmed Events and Risk of Angioedema by Patient Characteristic by Week 24 of Treatment

Baseline Characteristic	No. of Confirmed Events/ Total No. of Subjects (Incidence, %)*
Age groups	
<65 y	56/9045 (0.62)
≥65 y	30/3512 (0.85)
≥75 y	6/1044 (0.57)
Sex	
Male	35/6510 (0.54)
Female	51/6047 (0.84)
Race	
White	61/11 126 (0.55)
Black	20/1237 (1.62)
Asian/Pacific	3/165 (1.82)
Other	2/29 (6.90)
Comorbidity	
Severe hypertension	27/3680 (0.73)
ISH	8/677 (1.18)
Diabetes	7/1646 (0.43)
CHF	1/122 (0.82)
Atherosclerotic disease	7/1169 (0.60)
Renal disease	5/307 (1.63)
ACE-I use	
Present	15/2253 (0.67)
Recent past (48 h to 6 mo)	8/905 (0.88)
Remote past (>6 mo)	13/1279 (1.02)
Never	50/8119 (0.62)
History of allergy	19/1614 (1.18)
History of rash	8/323 (2.48)
Smoking status	
Never	40/6594 (0.61)
Former	28/3683 (0.76)
Present	18/2233 (0.81)

Abbreviations: ACE-I, angiotension-converting enzyme inhibitor; CHF, congestive heart failure; ISH, isolated systolic hypertension.
*The total number of patients varies because of missing data.

enalapril). The rate for omapatrilat was approximately 3 times higher. At week 8, the incidence of angioedema in enalapril-treated subjects was 0.54%. The incidence of angioedema was not constant over time, with approximately a 10-fold decrease between weeks 1 to 4 and week 24. The incidence of angioedema appeared to stabilize after week 12 to a level of 0.03% to 0.06% (**Figure 1**).

Risk Factors for Angioedema in Patients Receiving Enalapril

Angioedema was about 3 times more likely to occur among black patients (1.62% vs 0.55% for white patients) and slightly more likely in women (0.84% vs 0.54% for men) (**Table 2** and **Figure 2**). A clear effect of age was not observed in univariate analysis. The incidence of angioedema was lower in diabetic patients (0.43%) and higher in participants with renal disease (1.63%) or a history of rash (2.48%). Clear effects of severity of hypertension or the presence of heart failure or atherosclerotic disease on

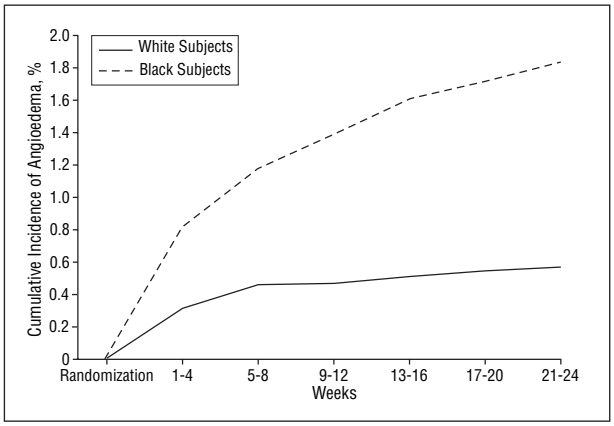

Figure 2. The cumulative incidence of angioedema in black and white subjects.

Table 3. Stepwise Logistic Regression of Risk Factors for Angioedema by Week 24*

Risk Factor	OR (95% CI)	*P* Value
Black race	2.88 (1.72-4.82)	<.001
History of drug rash	3.78 (1.80-7.92)	<.001
Age >65 y	1.60 (1.02-2.53)	.04
Seasonal allergies	1.79 (1.06-3.00)	.03

Abbreviations: CI, confidence interval; OR, odds ratio.
*Includes factors associated with angioedema determined by stepwise logistic regression. The ORs describe the adjusted odds of development of angioedema in the presence vs the absence of each risk factor.

Table 4. Clinical Characteristics and Treatment of Angioedema

Clinical Feature	No. (%) of Subjects With Enalapril Maleate–Related Angioedema (n = 86)
Sites of edema/swelling	
Lips	42 (49)
Face	45 (52)
Neck	16 (19)
Tongue	19 (22)
Eyelids	22 (26)
Pharynx	10 (12)
Mucous membrane	6 (7)
Larynx	2 (2)
Edema in ≥2 sites	51 (59)
Edema in ≥3 sites	22 (26)
Symptoms with flushing or facial redness	24 (28)
Difficulty swallowing	8 (9)
Difficulty speaking	5 (6)
Burning/tearing of eyes	6 (7)
Stridor/dyspnea	4 (5)
Hoarseness	3 (3)
Urticaria	6 (7)
Increased salivation	2 (2)
Difficulty handing oral secretions	2 (2)
Treatment	
None	44 (51)
Antihistamine	35 (41)
Epinephrine	1 (1)
Corticosteroid	20 (23)
Mechanical airway protection	0
Other	9 (11)

incidence of angioedema were not observed. The incidence of angioedema was not affected by prior or current use of ACE inhibitors at randomization. It was similar among participants without a history of ACE inhibitor use, those with a distant history of ACE inhibitor use (>6 months before enrollment), those with a recent history (48 hours to 6 months), and those receiving an ACE inhibitor at enrollment. The incidence of angioedema was higher among smokers in the omapatrilat group but not among smokers in the enalapril group. Stepwise logistic regression considering candidate variables derived from univariate analyses of effects of demographic variables, comorbidity, history of ACE inhibitor use, seasonal allergy, rash, and smoking (Table 1) identified black race, history of drug rash, age greater than 65 years, and seasonal allergies as independent risk factors for angioedema related to enalapril (**Table 3**).

Clinical Characteristics

The most common sites of angioedema were the lips (49%) and the face (52%) (**Table 4**). Swelling of the tongue, neck, or eyelids occurred in approximately 1 of 5 patients with angioedema. In 59% of the patients, angioedema occurred in 2 or more sites, and in 26%, 3 or more sites. Difficulty swallowing was reported in 9%, difficulty speaking (possibly related to tongue swelling) in 6%, stridor/dyspnea in 5%, hoarseness in 3%, and increased salivation and difficulty handling oral secretions in 2% each (Table 4). Urticaria was present in 7%. Although flushing or facial redness was observed in 24 of the 86 patients with angioedema, these symptoms occurred in 103 additional enalapril-treated subjects who did not have angioedema.

SEVERITY

In 65 (76%) of 86 angioedema events, antihistamines or no treatment for angioedema was given (class 1). No treatment was given in about half of the angioedema cases (51%). The most common treatments provided were antihistamines (41%) and corticosteroids (23%); epinephrine was required for 1 patient (1%). Nineteen (0.15% or 1.5/1000) of those given enalapril were treated with catecholamines or corticosteroids (class 2), and 2 (0.02% or 2/10 000) of those given enalapril were hospitalized but did not have airway compromise and did not receive mechanical airway protection (class 3a) (**Table 5**). Angioedema with airway compromise, or requiring mechanical airway protection or resulting in death (class 3b or 4) did not occur in any of the 12 557 enalapril-treated patients (Table 4). Hospitalizations were usually brief, and most patients were discharged from the hospital within 1 day of admission.

TIME COURSE OF ONSET

The incidence of angioedema among patients treated with enalapril was not constant over time (Figure 1 and Table 5). Angioedema occurred on the first day of double-

blind therapy in 3 patients: in 1 patient between 1 and 2 hours and in 2 patients between 6 and 12 hours after the initiation of therapy. Three events occurred on day 1 (0.02%), 43 (0.34%) occurred between day 2 and week 4, and 22 (0.18%) between weeks 5 and 8. The weekly incidence of angioedema was lower thereafter (Table 5). However, angioedema occurred throughout the study, including during the maintenance phase. During the maintenance phase (weeks 9-24), with long-term treatment the risk of angioedema declined progressively to a level of approximately 0.1/1000 patients per week. At any given time, the risk of angioedema was higher in black than in white subjects (Figure 2).

Table 5. Occurrence of Adverse Events by Severity Class

Severity Class*	Treatment Group, No. (%) of Subjects With Angioedema†	
	Omapatrilat (n = 274)	Enalapril (n = 86)
1	161 (1.28)	65 (0.52)
2	94 (0.75)	19 (0.15)
3	18 (0.14)	2 (0.02)
3a	17 (0.13)	2 (0.02)
3b	1 (0.01)	0
4	1 (0.01)	0

*Described in the "Assessment of Angioedema" subsection of the "Methods" section.

†In these analyses, percentages are calculated from the total of 12 609 of the 12 668 patients randomized to omapatrilat and 12 557 of the 12 634 subjects randomized to enalapril maleate who received at least 1 dose of study medication.

COMMENT

Soon after the development of ACE inhibitors, Wilkin et al[12] reported angioedema and proposed enhanced kinin effects from inhibition of kininase II as the underlying mechanism. Later reports of ACE inhibitor–related angioedema estimated an incidence between 1/1000 and 3/1000.[13-15] The lack of clarity on the definition of angioedema has created ambiguity on the true incidence. For example, in the Studies of Left Ventricular Dysfunction (SOLVD) trial, angioedema was ascertained by 2 different methods. In the first 3567 participants, angioedema was not specified in the follow-up forms but could be written in the "other side effects" field. In the remaining 3202 participants, the occurrence of angioedema was elicited by specific inquiry. When compared with a nonspecific question, the reported rate of angioedema was about 10 times higher when a specific question on its occurrence was asked.[16] In the SOLVD trial, the overall incidence of angioedema was approximately 5/1000 in the enalapril group and 1/1000 in the placebo group during an average 40-month follow-up.[17] The incidence of angioedema observed in the present study (6.8/1000 in 24 weeks) is higher than those previously reported, most likely because in previous studies, which did not include prospective adjudication of events, only the more serious cases of angioedema were reported.

In this study, the incidence of enalapril-related angioedema was 3 times higher in black than in white subjects. This is consistent with the 3.1-fold greater incidence observed by Burkhart et al[18] in more than 150 000 Medicare recipients and the 4.5 adjusted relative risk reported by Brown et al.[19] The present study also showed a 4-fold higher incidence of angioedema among patients with a history of drug rash, a 1.5-fold higher incidence in patients older than 65 years, and an almost 2-fold higher incidence in patients with seasonal allergies. The occurrence of angioedema in predisposed subjects has been reported by Agostoni et al.[20]

Angioedema is more likely to occur early after initiation of ACE inhibitor therapy.[14,18-21] Slater et al[14] reported a 14-fold higher incidence of angioedema in the first week compared with later time intervals, and Hedner et al[22] reported that about half of the cases occurred in the first week of therapy. In the present study, the incidence of angioedema was 9 times higher in the first month of therapy. Although angioedema requiring airway protection or death did not occur in the present study, these events have occurred in previous studies and case fatalities have been reported.[21] Slater et al[14] reported 38 angioedema cases with respiratory or life-threatening symptoms (4 requiring airway protection and 1 death) among 1.2 million patients taking enalapril. Also, life-threatening symptoms requiring intubation occurred in 2 of 36 cases of ACE inhibitor–related angioedema reported by Hedner et al.[22]

Limitations of this study include the fact that there is no randomized placebo group and that patients were treated with additional medications for hypertension or other reasons. However, a clear-cut influence of concomitant therapy on the risk of angioedema was not observed. To our knowledge, this is the only large prospective study on the occurrence of angioedema with ACE inhibitor therapy. It indicates that enalapril-related angioedema is uncommon; that although it is more likely to occur early after initiation of therapy, it may occur at any time; and that it is more likely to occur in black patients, older patients, and those with history of drug rash or seasonal allergies.

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