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New Developments in Angioedema Caused by Angiotensin-Converting Enzyme Inhibitors

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INTRODUCTION

In 1987, Wood et al reported 19 cases of angioedema during treatment with the angiotensin-converting enzyme (ACE) inhibitors (ACEIs) enalapril (13 patients) or captopril (6 patients).[1] This form of angioedema is now identified as acquired angioedema related to an ACEI (ACEI-AAE).[2]

THE SIZE OF THE PROBLEM

The 19 patients in Wood et al's report developed angioedema within a few hours to a maximum of 4 weeks after starting ACEI treatment. Banerji et al analyzed 220 patients who received a diagnosis of ACEI-AAE when seen in 5 emergency departments (EDs). These patients had been taking an ACEI for an average of 6 months (interquartile range, 1-18 months) before developing the angioedema that prompted the ED visit.[3] We now know that ACEI-AAE may develop months and even years after the beginning of treatment.[4] Such a large interval of time delayed the recognition that angioedema could be a drug-related adverse effect.

The incidence of ACEI-AAE is best estimated in studies that considered the occurrence of angioedema in large cohorts of patients. The OCTAVE trial registered adverse effects occurring in 12,557 patients during the first 24 weeks of treatment with enalapril. Angioedema was present in 0.68% with decreasing incidence over time; more than half of the patients had angioedema within the first month.[5] Miller et al studied medical and pharmacy records of people who received first prescriptions for antihypertensive medications from April 1999 through December 2000: 195,192 received ACEIs and 399,889 received other antihypertensive medications.[6] The incidence rate of angioedema per 1000 person-years was 1.97 (1.77-2.18) cases in the ACEI group and 0.51 (0.43-0.59) cases in the other antihypertensive medication group. The adjusted relative risk estimate for ACEIs versus other antihypertensive medications was 3.56 (2.82-4.44). Toh et al conducted a retrospective, observational, inception cohort study of patients who had initiated the use of drugs that target the renin-angiotensin-aldosterone system between January 1, 2001, and December 31, 2010.[7] The incidence rate per 1000 person-years was 4.38 (95% CI, 4.24-4.54) cases for ACEIs, 1.66 (95% CI, 1.47-1.86) cases for angiotensin receptor blockers, 4.67 (95% CI, 1.88-9.63) cases for aliskiren, and 1.67 (95% CI, 1.56-1.78) cases for β-blockers. Black Americans have a nearly 4 times higher risk of ACEI-AAE compared with their white counterparts.[8] Other less-compelling risk factors are also reported.[9] At least 0.4% of patients starting an ACEI may develop angioedema during the first year of treatment . This risk continues in the years that follow, but at a decreasing rate. Overall prevalence of this adverse effect in the general population is not precisely estimated, but is clearly below 1%. The risk of angioedema is drug-class related and 3 times higher with ACEIs than with any other antihypertensive treatment.

PATHOPHYSIOLOGY

ACE (EC 3.4.15.1) is a membrane-anchored enzyme that regulates vasoactive peptides such as angiotensin (Ang) I and bradykinin (BK), which are responsible for the control of blood pressure.[10] Thus, ACE is strategically poised between the renin-angiotensin system and the kallikrein-kinin system. It regulates the balance between the vasodilatory and natriuretic properties of BK and the vasoconstrictive and salt-retentive properties of Ang II. ACEIs alter this balance by decreasing the formation of Ang II and the degradation of BK.[11]

Due to the physiological activity of ACE and to initial findings in angioedema caused by C1-inhibitor (C1-INH) deficiency, BK seemed a natural candidate mediator of ACEI-AAE.[1] It is a nonapeptide (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) and represents 1 of the 3 human kinins recognized, the other 2 being the decapeptide kallidin (KD: Lys-BK) and the C-terminal des-Arg metabolites of BK and KD. BK is released on activation of the intrinsic coagulation pathway from high-molecular-weight kininogen (HMWK) cleaved at 2 sites by plasma kallikrein. A second pathway of kinin generation involves tissue kallikrein that releases KD from low-molecular-weight kininogen. In addition to plasma and tissue kallikreins, the fibrinolytic system may contribute to kinin generation. All these mechanisms are well described by Moreau et al (**Figure 1**).[12]

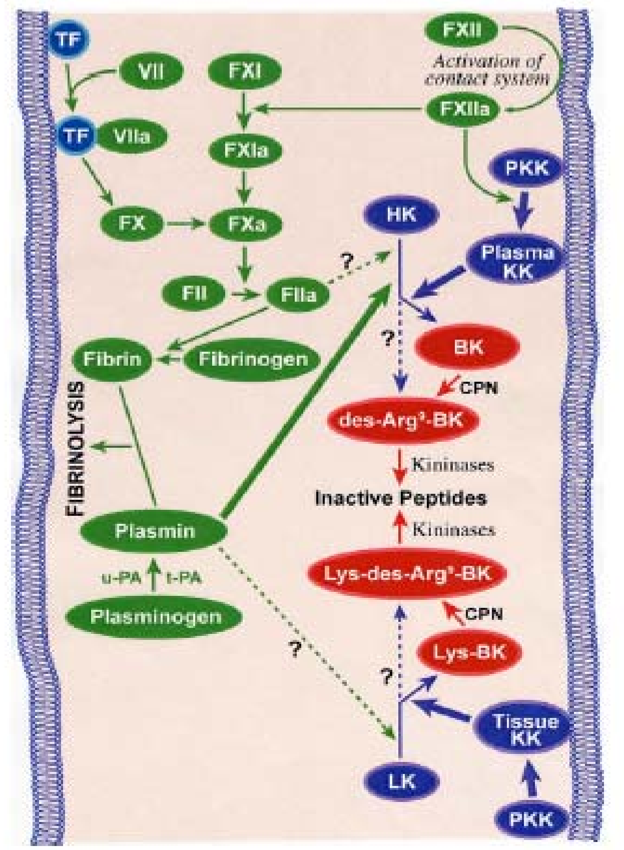

Figure 1. The kinin-forming systems. The kallikrein-kinin system and its interactions with both intrinsic and extrinsic coagulation cascades and fibrinolysis. Solid lines are established pathways, whereas dashed lines are speculative or experimental activation pathways.

TF: tissue factor; PKK: prekallikrein; HK: high-molecular-weight kininogen; LK: low-molecular-weight kininogen; BK: bradykinin; CPN: carboxypeptidase; t-PA: tissue plasminogen activator; u-PA: urokinase plasminogen activator.

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Kinin activities are characterized by the ability to activate endothelial cells—leading to vasodilation, increased vascular permeability, tissue-type plasminogen activator release, production of nitric oxide, and mobilization of arachidonic acid—and they participate in physiological (regulation of blood pressure, renal and cardiac functions) and pathologic processes like inflammation.[12] To respond to kinins, cells express specific membrane receptors (B1R and B2R). The biological relevance of B2R, which is constitutively expressed and binds with high affinity to the natural kinins BK and KD, is well proven. Still controversial is the relevance of B1R, expressed by inflammatory stimuli and evolved across species to respond to kinin des-Arg metabolites. Several lines of experimental evidence indicate that stimulation of B2R by uncontrolled local release of BK is responsible for angioedema in C1-INH–deficient patients.[13] The fact that specific B2R blockade decreases angioedema symptoms in these patients confirms that this mechanism has major pathogenetic relevance.[14] The role of B1R in this setting remains hypothetical, with one in vitro study suggesting that it might act synergistically with B2R.[15] This knowledge can be used to understand ACEI-AAE. These drugs reduce BK catabolism increasing its plasma levels in treated patients.[16] BK levels in the plasma of patients having an angioedema attack related to an ACEI are as high as those found in patients with angioedema due to deficiency of C1-INH , a regulatory protein that controls activation of the kallikrein-kinin system at several steps.[17] Interestingly, in C1-INH–deficient patients, BK increases in plasma during attacks, with a parallel increase in cleaved HMWK, the BK-releasing protein.[18,19] In ACEI-AAE, analogous increases in BK occur without changes in cleaved HMWK, confirming reduced catabolism as a key factor for BK accumulation.[17,20] Polymorphic variants that affect the levels of enzymes contributing to BK catabolism might account for specific phenotypes of susceptibility to ACEI-AAE.[21-23] Low occurrence of these phenotypes accounts for the fact that less than 1% of patients treated with an ACEI experience angioedema. Among BK-degrading enzymes, factors that reduce dipeptidyl peptidase IV activity may predispose individuals to angioedema.[24] Specific inhibitors of these enzymes have been introduced as drugs for type 2 diabetes mellitus, and their association with ACEI treatment should be considered a potential risk factor for angioedema.[25]

CLINICAL PICTURE

ACEI-AAE occurs in the absence of wheals. In our experience, the few patients presenting with both angioedema and wheals while on an ACEI had resolution of angioedema, but not of wheals, on treatment withdrawal.[26] Swellings are more often localized to the face/lips and oropharyngeal mucosa,[5] but the predominant symptom in patients with ACEI-AAE who present to the ED is shortness of breath,[3] suggesting a mortality risk related to angioedema. For the different forms of angioedema, 3 variables affect the risk of death: frequency of laryngeal location, rate of progression, and response to therapy.

ACEI-AAE is a recurrent form of angioedema that should cease after diagnosis and discontinuation of treatment. Therefore, we cannot expect prospective data to define the first of the 3 variables, and retrospective analyses always have critical selection bias. An informative study on this topic was reported by Al-Khudari et al,[27] who prospectively analyzed 40 consecutive patients on ACEIs presenting in one ED in Detroit, Michigan, with angioedema of the head and neck not explained by another cause. Thirty-seven of these patients were black, suggesting that ACEI-AAE occurs not only more frequently but more severely in blacks than in whites. The time from onset of symptoms to therapy ranged from 1 to 10 hours, indicating that angioedema progression occurs in a matter of hours, similar to that in C1-INH hereditary angioedema,[28] and not in minutes as in allergic/anaphylactic reactions. Six patients (15%) needed invasive intervention in the form of nasotracheal fiberoptic intubation. All 40 patients had a complete recovery. It is interesting to compare these data with our experience with 183 patients with ACEI-AAE who were referred to our third-tier angioedema center: only 1 of these patients needed invasive intervention for risk of asphyxia.[29] Comparing Al-Khudari et al's findings with ours, there is a 30-fold difference (15% and 0.5%, respectively) in terms of need for invasive intervention, which demonstrates how recruitment modalities can bias the numbers. We had no black patients (who represent a small minority in Italy), we did not recruit directly from patients arriving in the ED, and we reported retrospective data based on referred histories. Thus, it is important to consider specific settings before merging results from different studies. We listed response to therapy as a third variable influencing mortality from angioedema. For angioedema involving the upper airway, the ED will usually administer antihistamines, corticosteroids, and epinephrine before considering invasive maneuvers. The unresponsiveness of ACEI-AAE, as with other angioedema mediated by BK, to these treatments increases the risk of fatalities unless specific protocols for these types of angioedema are developed.[30,31]

The cardinal symptoms of ACEI-AAE are angioedema of the neck and face with involvement of the tongue.[32] Limbs and trunk are rarely involved, and a small series indicates the possibility that ACEIs induce angioedema of the gastrointestinal mucosa, manifested by severe abdominal pain, similar to angioedema caused by hereditary deficiency of C1-INH.[33-35]

Frequency of symptoms in ACEI-AAE is highly variable. In our experience, patients who do not withdraw from treatment may have more than one angioedema attack per month and a progressive increase in symptom severity.[36] As death from laryngeal edema has been reported,[37] ACEI withdrawal is mandatory as soon as a patient experiences angioedema while on this treatment, independently from the number of years he or she has been on the same medication.

TREATMENT

ACEI withdrawal is the first approach to treatment of ACEI-AAE. With this in mind, we still have to consider 2 therapeutic problems related to this form of angioedema. The first is the need to diagnose ACEI-AAE when a life-threatening laryngeal attack occurs requiring immediate therapy. No trial assessing efficacy of treatments for ACEI-AAE has been published to date. Retrospective case series point to the lack of efficacy of existing anti-allergic therapies: the need for airway intervention in patients presenting with head and neck angioedema related to ACEI ranges from 3.6% to 34.8%.[27,38-42] On the other hand, pathophysiological considerations as well as case reports and small case series raise expectations for BK-targeted therapies.[43-47] These drugs regulate plasma kallikrein to prevent BK release (C1-INH and ecallantide) or by blocking BK receptors (icatibant); all of them are highly effective in hereditary angioedema due to C1-INH, the best characterized form of BK-mediated angioedema.[14,48-51] Theoretical considerations suggest that ACEI-AAE, due to altered BK catabolism without hyperproduction, could be alleviated by the anti-BK receptor icatibant than by plasma kallikrein–controlling drugs. In a case series published by Bas et al, icatibant appeared to be highly effective in resolving acute angioedema related to ACEI, compared with the traditional approach with corticosteroids and antihistamine.[46] Eight patients with ACEI-AAE, who were identified by the investigators on presentation to the ED, were treated subcutaneously with a single dose of 30-mg icatibant. This group was compared with a historical cohort of 47 patients with the diagnosis of ACEI-AAE, consecutively treated in the same clinic for 7 years with methylprednisolone and clemastine. Time to first symptom relief in the icatibant-treated group was 50.6 minutes (±21 minutes), complete resolution occurred in 4.4 hours (±0.8 hours), and no patient needed other therapy or intubation. In the 47 historical controls, complete resolution occurred in 33 hours (standard deviation, 19.4 hours), 3 patients received a tracheostomy, 2 were intubated, and 12 received a second dose of methylprednisolone.

Publication of ongoing clinical trials is expected to confirm these results in controlled settings as well as provide an evidence-based therapeutic approach and an advance from the current use of off-label treatments. However, there is a compelling need to elaborate strategies that prevent fatalities and invasive intervention for patients with ACEI-AAE. An Italian consensus conference for the diagnosis and treatment of angioedema in the ED recommended the use of BK-targeted drugs when angioedema at high risk of laryngeal involvement progresses despite traditional medical approaches.[52] Limited availability of these treatments remains an unsolved major drawback.

The second therapeutic problem related to ACEI-AAE arises when patients continue to have angioedema symptoms after drug withdrawal. Persistence of scattered angioedema episodes is relatively common, but only a minority of patients continue with frequent recurrences.[36] For these patients, the need for a treatment to prevent recurrences may become relevant, particularly in the absence of an effective treatment for acute attacks. Uncontrolled data suggest that the antifibrinolytic agent tranexamic acid effectively prevents recurrences of angioedema that are not histamine mediated but are associated with normal C1-INH plasma levels.[29] However, the potential thrombogenicity of antifibrinolytic agents limits their use, particularly in patients with ACEI-AAE who generally have high cardiovascular risk. The therapeutic approach to these patients, both for acute and prophylactic treatments, remains a major unmet need in the field of angioedema.

In conclusion, ACEI-AAE is diagnosed when patients taking this class of medications present with angioedema that has no other explanation. If treatment is not immediately stopped, angioedema is likely to recur and patients, particularly if they are black, may experience life-threatening situations. BK is very likely the mediator of this form of angioedema that does not respond to traditional anti-allergic medications. Initial evidence for the therapeutic efficacy of BK-targeted drugs needs to be confirmed by controlled studies in order to provide treatment for this condition.

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