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ACE Inhibitor–Induced Angioedema

Incidence, Prevention and Management

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Summary

Available information from 1980 to 1997 on angiotensin converting enzyme (ACE) inhibitor–induced angioedema and its underlying mechanisms are summarised and discussed. The incidence of angioedema is low (0.1 to 0.2%) but can be considered as a potentially life-threatening adverse effect of ACE inhibitor therapy. This adverse effect of ACE inhibitors, irrespective of the chemical structure, can occur early in treatment as well as after prolonged exposure for up to several years. The estimated incidence is quite underestimated. The actual incidence can be far higher because of poorly recognised presentation of angioedema as a consequence of its late onset in combination with usually long term therapy. Also, a spontaneous reporting bias can contribute to an actual higher incidence of this phenomenon. The incidence can be even higher (up to 3-fold) in certain risk groups, for instance Black Americans. Treatment includes immediate withdrawal of the ACE inhibitor and acute symptomatic supportive therapy followed by immediate (and long term) alternative therapy with other classes of drugs to manage hypertension and/or heart failure.

Preclinical and clinical studies for the elucidation of the underlying mechanism(s) of ACE inhibitor–associated angioedema have not generated definite conclusions. It is suggested that immunological processes and several mediator systems (bradykinin, histamine, substance P and prostaglandins) are involved in the pathogenesis of angioedema. A great part of all reviewed reports suggest a relationship between ACE inhibitor–induced angioedema and increased levels of (tissue) bradykinin. However, no conclusive evidence of the role of bradykinin in angioedema has been found and an exclusive role of bradykinin seems unlikely. So far, no clear-cut evidence for an immune-mediated pathogenesis has been found. In addition, ACE gene polymorphism and some enzyme deficiencies are proposed to be involved in ACE inhibitor–induced angioedema. Progress in pharmacogenetic and molecular biological research should throw more light on a possible genetic component in the pathogenesis of ACE inhibitor–associated angioedema.

Angiotensin converting enzyme (ACE) inhibitors are used to treat hypertension and congestive heart failure.[1] Recent guidelines on the treatment of hypertension recommend diuretics and β-blockers as first line antihypertensives, or the choice of one agent from the major classes of antihypertensives, according to the patient's co-existing condition.[2,3]

The list of agents that are suitable for initial monotherapy has been expanded from diuretics, β-blockers and calcium antagonists to ACE inhibitors.[2,3] Most guidelines acknowledge that ACE inhibitors have similar efficacy to other antihypertensives. They are less likely to produce sedation, diminished exercise capacity and sexual dysfunction. In fact, postmarketing surveillance of ACE inhibitors indicates that they frequently improve well-being.[4-6] Their overall favourable adverse effect profile makes it likely that their clinical use will increase in future despite the absence of long term outcome studies in hypertension on the effect of ACE inhibitors on mortality.

Adverse effects that have been described with ACE inhibitors include dizziness (4%), dry cough (3%), headache (2.5%) and hypotension.[7] In addition, angioedema is a less common but potentially life-threatening adverse effect of ACE therapy. It has been associated with all ACE inhibitors commercially available and is estimated to have an incidence of 0.1 to 0.2% among the Caucasian population,[7-9] whereas a higher incidence has been reported for Black Americans.[10,11]

The purpose of this article is to review available information on ACE inhibitor–induced angioedema and its hypothesised underlying mechanism(s).

1. Methods

All publications, without any exclusion criteria, on ACE and angioedema reported from January 1966 to June 1997 were identified through Medline using the key-words 'ACE' and 'angioedema'. Further information not obtained from the Medline search was derived from the references cited in these publications. When reports were conflicting or inconclusive, an additional literature search was done on specific items.

2. Pharmacological Properties of ACE Inhibitors

Although the mechanism of action of ACE inhibitors has not been fully elucidated, their major foci involve both local and systemic ACE and thus prevention of the conversion of angiotensin I to angiotensin II as well as degradation of bradykinin (see fig. 1). As a consequence of ACE inhibition, circulating and tissue levels of angiotensin II are decreased and those of bradykinin are increased.

It has been shown that vascular tissue ACE inhibition may be more important than plasma ACE inhibition with respect to the general pharmacological aspects of ACE inhibitors.[12-14] Therapeutic consequences of ACE inhibitor therapy mainly rely

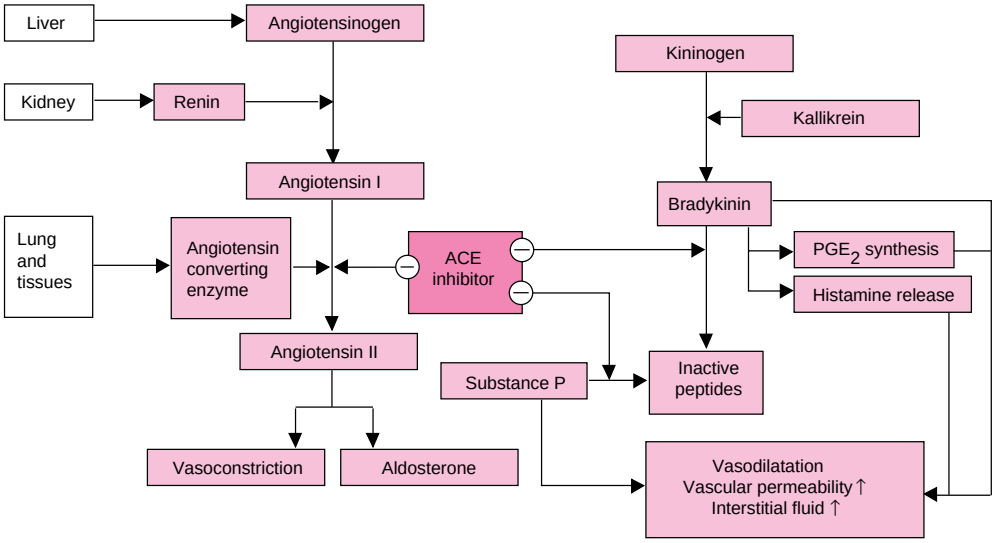

Fig. 1. A schematic portrayal of the pharmacological sites of action of ACE inhibitors. *Abbreviation and symbols:* PGE_2 = prostaglandin E_2; – = inhibition; ↑ = increased.

upon prevention of angiotensin II formation. However, inhibition of bradykinin degradation and stimulation of prostaglandin (PG) synthesis may contribute to it.[15-18] Another mechanism probably involved in ACE inhibitor action may be inhibition of calcium mobilisation in vascular tissue.[19]

ACE inhibition also reduces the cleavage of peptide substrates such as enkephalins, neurotensin, substance P and luteinising hormone–releasing hormone.[20,21] Dzau[13] and Ideishi et al.[22] suggested that during ACE inhibition other angiotensin II–generating enzymes, such as a chymostatin-sensitive angiotensin–generating enzyme (CAGE), kallikrein, trypsin, cathepsin G and tonin, may be important.

ACE inhibitors can be divided into 3 structurally different groups, the sulphydryl compounds (e.g. captopril, zofenapril), the carboxyalkyldipeptides (e.g. enalapril, lisinopril) and the phosphoric acid compounds (e.g. fosinopril).[23,24] Binding with zinc, an important component of the active site of ACE, is critical for the inhibitory activity of these drugs.[24] The -SH group of the sulphydryl compounds, the carboxyl group of the carboxyalkyldipeptides and the phosphonic acid group of phosphorus-containing compounds interact with the zinc ion.

Because of oral bioavailability problems, most ACE inhibitors are prodrug esters and must be hydrolysed to the acid form *in vivo* for inhibitory activity. The lipophilicity of the active drug is important for its ability to diffuse into tissues.[25,26]

3. Angioedema

The first description of angioedema was published in 1882 by Quincke.[27] Osler[28] differentiated the hereditary form after a review of 5 generations of one family experiencing this condition. Angioedema might be caused by the same pathological alterations that produce urticaria, a cutaneous wheal-and-flare-type reaction.[29] However, angioedema occurs deeper in the dermis and subcutaneous tissue, and thus swelling is the dominant feature.

Angioedema is a vascular reaction characterised by nonpitting oedema of the dermis and subcutaneous fat. Any area of the body may be involved but most common sites are the tongue, lips, throat, nose or other parts on the face, extremities, genitalia and viscera, with consequent presentation

of diarrhoea, nausea, abdominal pain and acute abdomen. Angioedema of the upper respiratory tract can result in serious acute respiratory distress, airway obstruction and death. The above-mentioned clinical symptomatology has much resemblance to the symptoms observed with the overwhelming majority of reported case studies regarding ACE inhibitor–related angioedema.

3.1 Incidence and Onset

Angioedema with ACE inhibitors was first reported in 1980 by Wilkin et al.[30] and since then there has been an increase in reports. Hedner et al.[31] observed that angioedema cases in relation to ACE inhibitors were reported more commonly in men than in women. Occasionally, deaths have been reported.[32-36]

While the majority (60%) of the reactions occur in the first week after starting ACE inhibitor therapy, often within hours of the initial dose,[8,33] a significant number become manifest after a more prolonged course of therapy,[37-40] even after 3 years[41] or longer.[42]

Some cases of late onset of angioedema have also been reported after discontinuation of ACE inhibitors.[43,44] Indeed, the early series of ACE inhibitor–associated angioedema emphasised the early onset of the reaction. More recent reports suggest that delayed onset of the reaction is common[37-40] and that the reaction may occur any time during therapy. This is an important clinical point as it appears that ACE inhibitor–associated angioedema is poorly recognised clinically, and part of the reason for this may be the delayed onset. From table I the estimated incidence of ACE inhibitor–associated angioedema is 0.1 to 0.2%.

This estimate of the incidence of angioedema with ACE inhibitors arises from studies that did not assess risk as a function of duration of therapy.[33] This is inappropriate, considering that there is evidence that the onset of ACE inhibitor–associated angioedema may be delayed. Given that knowledge of adverse drug reactions often develops from spontaneous reports it would be expected that initial reports would emphasise the early onset of reaction, as reactions occurring close to the initiation of therapy are more likely to be recognised. This might have led to an underestimation of ACE inhibitor–associated angioedema.

Kostis et al.[40] and Maier[45] found an incidence of about 0.4% in patients followed for an average of about 40 months. This equates to an incidence of approximately 0.1% per year. Taking into ac-

Table I. Angioedema associated with ACE inhibitor therapy reported between Jan 1980 and Jun 1997[a]

Agent	Year	Patients		Reference
		total[b]	with angioedema	
C	1980	12	2	30
C	1984	4 000	1.0%	46
E		1 900	0.1%	46
C	1985		4	47
C or E or L			6	48
C	1986	700	0.1%	49
E		2 677	0.2%	49
C		11 539	0.1%	50
E		11 710	<0.1%	50
C	1987	67 698	16	51
L		1 326	0.5%	52
C or E			19	8
E	1988	12 000	0.1%	33
E		1.2 million	138	33
C			0.1%	53
C or E or L			7	33
L	1989		15	54
C or E or L	1990		12	34
C or E or L			4	55
E			3	56
C or E or L			4	58
C or E or L			8	59
E	1991		25	61
C or E or L			2	63
C or E or L	1992		5	64
C or E or L			60	65
C or E or L			38	37
C or E or L			5	66
L			9	68
E or L	1993		12	38
C or E or L			36	71
R or L	1994		2	76
C or E or L	1995		3	78
C or E or L			2	80
C or E or L	1996	27 834	82	11
C or E or L			2	84
E		3 382	12	40

a A number of single case reports have also been reported in the literature.[35,36,41-45,50,57,60,62,67,69,70,72-75,77,79,81-83,85-92]

b Totals given for studies only.

Abbreviations: C = captopril; E = enalapril; L = lisinopril; R = ramipril.

count that ACE inhibitors are given long term, and patients may develop angioedema any time during therapy, the risk may therefore be as high as 1% for patients after 10 years' treatment.

Another aspect which should be emphasised is the fact that rates of spontaneously reported adverse drug reactions are not representative of the actual rates of occurrence.[33] A controlled study with enalapril showed that the occurrence of angioedema was at least 10 times more frequent than could be derived from spontaneously reported occurrences.[33] Reports of ACE inhibitor–induced angioedema are summarised in table I. Since both reviews and single publications are given in the table, a repetitive presentation of cases cannot be excluded.

3.2 Clinical Presentation

It is crucial that physicians not only treat angioedema but also recognise its aetiology.[38,41] There are a number of case series in the literature demonstrating that ACE inhibitor–associated angioedema is responsible for a significant proportion (10 to 25%) of angioedema presentations.[38,93]

These series also illustrate that this adverse reaction is extremely poorly recognised. In one series of 6 patients with ACE inhibitor–associated angioedema who presented to emergency departments on 9 occasions, the role of ACE inhibitors was recognised on only 1 occasion.[93] Moreover, it was reported that a patient presented with angioedema 18 times during a 3-year period before qualified emergency physicians correctly diagnosed that it was ACE inhibitor induced.[41] So, many cases illustrate the difficulties associated with diagnosis and management of angioedema secondary to ACE inhibitor therapy.

3.3 Risk Factors and ACE Inhibitor–Induced Angioedema

Several risk factors have been proposed for the induction of ACE inhibitor–associated angioedema. Most of them are derived from anecdotal reports without controls. The most important predisposing risk factor, evidenced by case-control studies, appears to be ethnic differences. Previous tolerance for an ACE inhibitor does not exclude the risk for angioedema when therapy is modified to another ACE inhibitor.[33,94]

3.3.1 Black Race

The influence of Black race on the incidence of ACE inhibitor–induced angioedema has been studied by several investigators.[10,11,95] These studies showed that this population may be at greater risk of angioedema than Whites[10,11] and that this increased risk cannot be attributed to an effect of dose, specific ACE inhibitor, or concurrent medications.[11] Although the mechanism of angioedema is not certain, bradykinin has been implicated in its pathogenesis (see section 4.3). Because urinary kallikrein levels are decreased in African Americans with hypertension it was hypothesised that endogenous bradykinin levels may be decreased in this population and that they therefore may be more sensitive to ACE inhibitor–induced increases in bradykinin[96] and thus to the induction of angioedema.

3.3.2 Risk Factors Derived from Anecdotal Reports

Various uncontrolled case reports have suggested a number of factors which could be involved in an increased risk of developing angioedema with ACE inhibitors: a history of idiopathic angioedema,[58,97] head-neck surgery[66,76,98] and allergy to sea food.[41] Furthermore, emotional stress,[62] local anaesthetics,[62] antihypertensive drugs,[31] antibacterials,[31] nonsteroidal anti-inflammatory drugs,[31] autoantibodies against complement 1 esterase inhibitor (C1-EI),[99] mutation in the gene for C1-EI,[100-103] mutation of serpins and serpin polymerisation,[104,105] complement activation,[106,107] parvovirus[108] and haemodialysis membranes[109,110] have also been mentioned as triggering angioedema.

4. Mechanisms Involved in ACE Inhibitor–Induced Angioedema

The mechanism for ACE inhibitor–induced angioedema is not understood. Angioedema reported with other types of drug is generally mediated by

immunological factors.[29] Other rare adverse effects of ACE inhibitors (e.g. pemphigus, lupus erythematosus, rash) have been associated with formation of antibodies to the ACE inhibitor.[111] The development of angioedema caused by ACE inhibitors may be related to the effect of ACE inhibitors on the metabolism of bradykinin and substance P.[112-115] Proposed causes of angioedema are summarised in table II.

4.1 Immunological Effects

The allergic form of angioedema is presumably the most common form and is associated with preformed immunoglobulin (Ig) E antibodies.[117] However, an actual increase in IgE levels in ACE inhibitor induced–angioedema has never been observed.[58,59] Long term administration of ACE inhibitors, especially captopril, has been shown to induce tissue-specific autoantibodies (53% for captopril and 8% for enalapril)[111] and antinuclear antibodies[48] in some patients. Captopril-protein conjugates are immunogenic.[118] IgG anti-captopril antibodies have been detected in the serum of 2 of 45 patients receiving captopril 25 to 75 mg/day.[119]

Lymphocytes withdrawn from patients with captopril-induced rash have been stimulated with captopril but not enalapril, implicating the sulphydryl group of captopril as a crucial component regarding cutaneous adverse effects.[47,120,121] The sulphydryl group of penicillamine[122] and of captopril[123] has also been implicated in the pathogenesis of drug-induced IgA deficiency. Their adverse effects may therefore share a common mechanism.

On the other hand, drugs without a sulphydryl group have also been shown to induce IgA deficiency,[123] and cutaneous reactions also occur (although less frequently) with ACE inhibitors that do not contain this group.[120,124,125]

There are reasons to believe that the incidence of skin reactions (other than angioedema) associated with the use of captopril is dose dependent.[48,124,126] For example, 10% of patients receiving captopril ≥450 mg/day developed skin rash, but less than 5% developed a rash at a dosage of 150 mg/day. The total dose of captopril administered to patients who developed pemphigus and lupus was 4 times higher than patients without these adverse effects.[49,127]

Although an immune-mediated pathogenesis has been suggested for the adverse cutaneous effects of ACE inhibitors,[48,126,128] the specific mechanism for the development of angioedema may be quite different from other adverse effects because it involves only the mucous layer. Furthermore, many times the onset of angioedema occurs so rapidly after the start of therapy that it cannot be immunologically mediated.

Considering the above-mentioned data, which are mainly focused on captopril and the fact that angioedema has been described with all marketed ACE inhibitors irrespective of chemical structure, it is most likely that angioedema is related more to their pharmacological mechanisms of action rather than being triggered by type I immune responses. Nevertheless, the fact that in some cases angioedema is related to the development of drug-specific antibodies in genetically or otherwise susceptible predisposed individuals cannot be fully ignored.

Table II. Causes of angioedema[116,117]

Allergy (drugs, chemicals, foods, inhalant allergens and parasitic infections)
Hereditary angioedema: insufficient synthesis of complement (C) C1 esterase inhibitor (85%) synthesis of dysfunctional C1 esterase inhibitor (15%)
Acquired C1 esterase inhibitor deficiency
Chemical histamine releasers (e.g. morphine, codeine, contrast media)
Presumed circulating immune complex diseases
Physical stimuli (cold, heat, sunlight, pressure, oxygen, water, vibration)
Rare miscellaneous causes (parvovirus, snake bite, haemodialysis membranes, serpin polymerisation and mutation in serine protease inhibitors)
ACE inhibitor therapy related
Idiopathic angioedema

4.2 The Complement System

Although very speculative, an interaction between ACE inhibitors and the complement system can be anticipated because some preclinical[129] and clinical studies[50,59] indicate an interference with components of the complement enzyme cascade, which consists of 9 major components designated from C1 to C9. Angioedema can occur in persons with either hereditary or acquired deficiency of (functional) C1-EI.[130-132] C1-EI inhibits the cleaving of the first component of the complement into its active form which then activates C4, C2 and the rest of the complement cascade. It also inhibits the functions of activated C1, factor XIIa (Hageman factor), factor Xla of the clotting cascade, kallikrein and plasmin.[106,107,133-135]

Molecular pathways in angioedema are shown in figure 2. Patients with hereditary angioedema are functionally deficient in C1-EI, with values 20 to 30% of normal.[130-132]

Acquired deficiency of C1-El,[16] for example, as a result of consumption of C1-El by factors generated by malignant cells[136] or via autoantibody-antigen complexes[99,137-139] or mutation in the gene for C1-EI,[100-102,140] can also result in its functional depletion. In patients with low levels of C1-EI, local levels of C1-EI may become exhausted by consumption via plasma enzymes such as factor XIIa. In this case, kallikrein may become activated, resulting in generation of bradykinin.[135] Furthermore, because formation of C1r and C1s is out of control, activation of early complement components together with activation of plasminogen to plasmin produces a pathological factor C2 kinin. This factor, in association with bradykinin, produces angioedema.[135]

In those studies which have failed to find decreased C1-EI or diminished activity in patients with ACE inhibitor–induced angioedema it can also be hypothesised that ACE inhibitors (or their metabolites) could cause a C1-EI deficiency by inactivation or inhibition of the action of C1-EI in susceptible individuals (for example, patients with borderline values of C1-EI), thereby allowing unopposed action of C1 in the complement cascade and other loci. In fact, the interaction of ACE inhibitors with activators of factor XIIa has been demonstrated in the rat paw oedema model.[129]

The deficiency of C1-EI as assessed by its biological activity may be a more important determinant than the total protein measured antigenically. This may have been the case in 6 patients with ACE inhibitor–induced angioedema who had normal C1-EI levels measured antigenically[59] or in 1 patient on captopril in which the C1-EI level was elevated 2- to 3-fold.[50] In the latter case, the method of measurement was not given but the normal values quoted are similar to the antigenically determined levels.[141] In this patient, antibodies to captopril of class IgG, IgM, or IgE were not detectable. The angioedema resolved after withdrawal of captopril, but reappeared when the patient was given enalapril.

Future research directed to the understanding of the underlying mechanism of ACE inhibitor–associated angioedema should indicate the relative importance of such an interaction of ACE inhibitors with this part of the immune system.

4.3 Bradykinin

ACE inhibitors not only block the conversion of angiotensin I to angiotensin II but also the degradation bradykinin leading to enhanced levels of this nonapeptide in humans and experimental animals.[142,143] In healthy and hypertensive humans ACE inhibitors potentiate the blood pressure lowering effect of bradykinin approximately 20- to 50-fold.[144,145] Bradykinin increases vascular permeability and causes vasodilatation.[114,146,147] It is 10-fold more potent than histamine in this respect.[147]

Bradykinin has a major role in the generation and maintenance of inflammation.[142] It stimulates the release of tumour necrosis factor, interleukin-1 and nitric oxide.[148-150] Intradermal injection of bradykinin evokes cough in healthy volunteers taking ACE inhibitors.[151] The wheal formation induced by intradermal injection of bradykinin is potentiated by pretreatment of healthy volunteers or hypertensive patients with antihypertensive doses

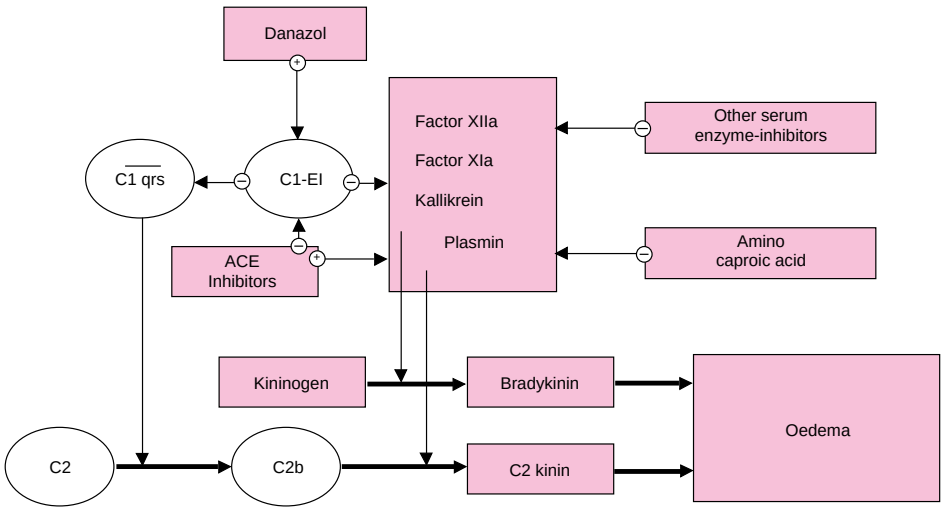

Fig. 2. Molecular pathways in angiodema. In patients with hereditary angioedema the levels of complement 1 (C1) esterase inhibitor (C1-EI) are low, and become locally exhausted by consumption via different plasma enzymes such as factor XIIa or inactivation or inhibition of C1-EI by ACE inhibitors or their metabolites. In this case kallikrein may become activated resulting in generation of bradykinin. There is no serpin available to control C1r and C1s. In this case a pathological factor C2 kinin may be generated by the action of plasmin or C2b. This, in association with bradykinin, produces oedema. Therapy is aimed at increasing C1-EI or reducing activity of enzymes including plasmin and immediate withdrawal of ACE inhibitors (after Roitt et al.,[135] with permission) *Symbols*: + = stimulation; – = inhibition.

of ACE inhibitors.[114,151-153] Bradykinin also produced facial flushing in volunteers pretreated with enalapril or captopril but not placebo.[114,151,152] ACE inhibitors increase bradykinin-induced foot pad oedema in the rat.[154]

These reports provide some evidence for bradykinin as a cause of angioedema in patients who receive ACE inhibitor therapy.

Bradykinin levels increase excessively during dialysis with AN69 membranes in combination with ACE inhibitor therapy, and patients will experience severe anaphylaxis.[109,110,155-157] There is evidence that the AN69 membrane activates factor XIIa which could then generate kallikrein from prekallikrein.[158] Kallikrein in combination with ACE inhibitor therapy would lead to unopposed bradykinin generation from kininogen.[109,110,157,159]

Bradykinin accumulation, associated with ACE inhibitor therapy and anaphylactic reactions, has also been reported with the use of PMMA membranes,[160] with the reuse of capillaries[161] and during low density lipoprotein apheresis using dextran sulphate for hypercholesterolaemia.[162,163] Hypotension seems to be more important than angioedema during anaphylactic reactions induced by haemodialysis membranes.

Symptoms of angioedema observed in patients with hereditary angioedema have been reproduced in healthy volunteers by infusion of bradykinin.[164,165] Bradykinin induces bronchospasm in susceptible and healthy volunteers,[152,166] and bradykinin-induced bronchoconstriction in guinea-pigs is enhanced by captopril.[167] These observations are in line with the hypothesis that angioedema from ACE inhibitors could be related to accumulation of bradykinin. However, data on the effect of ACE inhibitor therapy on circulating bradykinin levels and its role in precipitation of angioedema are conflicting and inconclusive. At therapeutic doses, plasma concentrations of ACE

inhibitors are usually not high enough to cause accumulation of circulating bradykinin.[168-170] Bradykinin has a short half-life, for example, 90% is inactivated during one single passage through the lung.[17,143]

There is evidence that ACE therapy induces bradykinin-inactivating enzymes, such as prolyl-endopeptidase.[171] Long term ACE inhibitor therapy results in normalisation of serum ACE levels in humans,[172-175] which in turn might not permit accumulation of bradykinin. In that case, an increase in bradykinin levels depends on interference by ACE inhibitors with the complement system. It is likely, however, that tissue levels of ACE may remain suppressed by long term administration of ACE inhibitors and that circulating levels of bradykinin may not reflect levels in tissue.[170]

Patients with a syndrome of ACE dysfunction characterised clinically by periodic paralysis, hypokalaemia, alkalosis and high plasma levels of renin, angiotensin I, and bradykinin do not develop angioedema despite high plasma bradykinin levels.[176,177] Also, patients with the syndrome of idiopathic bradykininism do not have angioedema as part of their symptom complex.[178] Anaphylactic reactions during haemodialysis in the presence of ACE inhibitors are characterised by high levels of bradykinin but the predominant symptom is hypotension and not angioedema.[110]

Thus, accumulation of circulating bradykinin does not necessarily have an important role in the induction of angioedema by ACE inhibitors.

In support of the minor importance of bradykinin in ACE inhibitor–associated angioedema is the observation that compounds of a new class, the angiotensin II antagonists (e.g. losartan potassium), have been associated with angioedema, albeit at a lower frequency.[179-184] In fact, these drugs provide a mechanism for blocking the renin-angiotensin system without an effect on bradykinin, possible providing some evidence against the bradykinin hypothesis.

4.4 Histamine

Bradykinin can cause histamine release from mast cells.[115,185] Histamine could also be involved in the development of angioedema, since the wheal and flare response to histamine is potentiated by captopril.[30] However, Anderson and de Shazo[114] did not find significant changes in the size of histamine wheal and flare reactions in 10 patients after captopril administration.

In humans, enalapril increases bronchial reactivity during histamine bronchoprovocation.[115] In guinea-pigs, intraperitoneal pretreatment with enalapril potentiated the skin reactions induced with allergens and capsaicin, which are possibly mediated by histamine.[186] Enalaprilat increased skin content of histamine in guinea-pigs.[115,185] Morphine and codeine, as well as iodinated contrast media have been shown to cause angioedema by direct histamine release.[116]

4.5 Substance P

Substance P is a peripheral and CNS neurotransmitter found in small unmyelinated fibres of sensory nerves and is implicated as a mediator of inflammation.[187] It has been shown that ACE inhibitors block the degradation of substance P allowing accumulation.[113] Ramiprilat and enalaprilat, but not cilazaprilat, increased the skin content of substance P,[115,185] and enhanced erythema evoked by substance P in sensitised guinea-pigs.[188] In rats, captopril caused a 4-fold increase in renal substance P clearance while plasma levels remained unaffected, suggesting that ACE inhibition may increase local levels of this peptide.[189]

4.6 Genetically-Determined Mechanisms

A familial deficiency of carboxypeptidase N has been described for a patient who had episodes of angioedema. Mathews et al.[190] and Slater et al.[33] have speculated that susceptibility to ACE inhibitor–associated angioedema may be greater in patients with this deficiency. Furthermore, a case report described a patient with angioedema and normal levels and function of C1-EI, but with hereditary

deficiency of α_1-antitrypsin (PI-ZZ type) and partial deficiency of complement C4.[191] The role of these proteins in the development of ACE inhibitor–induced angioedema is unknown.

A large study described a familial association with plasma ACE levels suggesting the occurrence of a genetic effect.[192,193] In Japanese and Chinese patients, genetically determined reduced tissue ACE levels[194] in combination with ACE inhibitor therapy may decrease tissue ACE to a critical level which causes cough.[195-198]

Both the amount of immunoreactive ACE,[194,199] and catalytic activity[198] are related to I/D genetic polymorphism. In Chinese patients there is evidence that genetic polymorphism is associated with a structural alteration in ACE.[198] Others were unable to confirm an association between ACE genetic polymorphism and ACE inhibitor–related cough in French and British patients.[200,201] An effect of ACE genotype on myocardial risk[202,203] and hypertension[204,205] has also been suggested.

4.7 Role of Trauma in ACE Inhibitor–Induced Angioedema

Acute external trauma can recruit vasoactive substances, either through activation of factor XIIa or through a direct release from cells. This may contribute to the development of angioedema, especially in combination with ACE inhibitor therapy or in predisposed patients.[117] It has also been suggested that loss of tissue angiotensin II during ACE inhibitor therapy leads to vasodilatation, fluid extravasation and angioedema.[117]

By stimulation of phospholipase A_2 or C, bradykinin could augment levels of platelet-activating factor (PAF) and arachidonic acid metabolites such as prostaglandins (PGs) and leukotrienes. The role of PGs in ACE inhibitor–induced angioedema is based on the observation that ACE inhibitors enhance urinary excretion of PGE_2 in humans.[206] PGE_2 stimulates C-fibres, resulting in cough.[207] Captopril increases the release of PG-like substances from guinea-pig lungs;[167] nonsteroidal anti-inflammatory agents suppress ACE inhibitor-induced cough in humans;[208-211] captopril stimulates PG levels in plasma and bradykinin enhances ACE inhibitor–induced hypotension in rabbits, dogs and rats, which is markedly attenuated by indomethacin.[17]

A role for leukotrienes C and D and PAF in ACE inhibitor–induced angioedema has been suggested but not clarified.[17,55] Although ACE inhibitors decrease plasma atrial natriuretic peptide (ANP) levels, a role of ANP in angioedema remains unlikely.[189]

5. Management of Patients with ACE Inhibitor–Induced Angioedema

If angioedema develops, treatment mainly consists of immediate withdrawal of the ACE inhibitor and maintenance of adequate airway function. In cases where ventilation is threatened, subcutaneous injection of 1 : 1000 aqueous epinephrine (adrenaline) 0.01 ml/kg is indicated and may be repeated every 15 to 20 minutes as needed. The patient should be observed and hospitalised for at least 12 to 24 hours.[37,117] Intravenous or intramuscular diphenhydramine (1 to 2 mg/kg up to a maximum dose of 50mg) can be useful and intravenous saline should be started if hypotension is present.

Allergic-like reactions may be diminished by the short term use of antihistamine drugs and intravenous methylprednisolone (40 to 120mg) or oral prednisone (30 to 50mg every 12 hours). However, so far no controlled studies have demonstrated the efficacy of these agents in ACE inhibitor–related angioedema.[117]

This therapeutic approach can be considered as a standard acute treatment for general angioedema. The most important measure to take in ACE inhibitor–associated angioedema is to discontinue the ACE inhibitor. Of note is that other investigators reported that after discontinuation of the ACE inhibitor the angioneurotic oedema resolved within 72 hours and that additional therapeutic measures (glucocorticoids, antihistamines, epinephrine, C1 inhibitors) did not shorten the recovery time.[76]

Alternative therapy with another class of drugs should be immediately started to treat the underlying disease (hypertension and or heart failure). For

the long term treatment of hypertension a choice can be made from a wide range of antihypertensive drugs, for example, β-blockers, calcium antagonists and angiotensin II antagonists (e.g. losartan).

Alternative therapy for heart failure is more limited but from large studies it has been established that hydralazine and organic nitrates are suitable alternative medications. The value of angiotensin II antagonists in this indication is still under investigation.

All patients starting ACE inhibitor therapy should be made aware of the possibility of angioedema and told to inform their doctor of any lip swelling, difficulty in breathing or swallowing, or episodes of muffled voice.[76] Where ACE inhibitors are thought to have been responsible for angioedema it is important to ensure that the patient will never receive any similar drugs in the future.[50] In such cases alternative treatment will be required.

6. Experimental Models

In general, experimental models focus on ACE inhibitor–induced potentiation of skin reactions evoked by inflammatory mediators. ACE inhibitor–induced potentiation of the histamine bronchoprovocation test has also has been used as a model. Subjects include (sensitised) animals, as well as healthy and cough-sensitive hypertensive humans. All currently used and tested ACE inhibitors demonstrate pro-inflammatory reactions at least in one of these models. It is therefore believed that ACE inhibitor–induced cough, increased bronchial reactivity, adverse skin reactions and angioedema are related to the pro-inflammatory profile of this class of drugs. However, in clinical practice these adverse effects do not occur simultaneously or with a similar frequency, indicating that susceptibility is a major factor involved. To our knowledge there is no model of susceptible animals available that can be used for a clear risk evaluation of development of angioedema by ACE inhibitors.

7. Conclusion

ACE inhibitors are important in long term treatment of hypertension and heart failure. This review on population studies and case reports concerns the epidemiology, possible underlying mechanisms and management of ACE inhibitor–associated angioedema as a life-threatening adverse effect.

General angioedema is characterised by non-pitting oedema of the dermis and subcutaneous fat. The most affected sites are the tongue, lips, throat, nose or other parts of the face, extremities, genitalia and viscera, with consequent abdominal complaints. Angioedema of the upper respiratory tract can result in serious acute respiratory distress, airway obstruction and death. Part of this symptomatology resembles the clinical presentation of ACE inhibitor–related angioedema. It has been shown that 10 to 25% of angioedema presentations can be ascribed to ACE inhibitor therapy, although from many cases it is illustrated that ACE inhibitor–associated angioedema is extremely poorly recognised.

The incidence is thought to be about 0.1 to 0.2%, mainly based on studies in the Caucasian population. During the last decade it has become more clear that angioedema caused by ACE inhibitors can have a much later onset, even after several years. Considering that ACE inhibitor therapy is usually long term, a 1% incidence over 10 years can be calculated: the incidence can be much higher in at-risk groups. Recent evidence indicates that the incidence in African Americans can be 3 times higher than in the Caucasian population. A lot of other risk factors have been suggested but are as yet either unclear or unproved because of the uncontrolled nature of the case reports.

It should also be emphasised that rates of spontaneously reported adverse drug reactions are not representative of the actual rates of occurrence which have been shown in a controlled study with enalapril to be at least 10 times higher. Thus, the actual number of angioedema cases in relation to ACE inhibitor treatment might be considerably underestimated. Finally, it can be expected that better

recognition by physicians in future will contribute to a much higher incidence than is reported now.

Initially, many studies with the first ACE inhibitor captopril indicated that the mercapto (-SH) group might be responsible for the induced angioedema. However, later studies with various ACE inhibitors lacking this group suggest the reaction can occur irrespective of the chemical structure. Also, the most recent experiences with a new class of compounds, the angiotensin II antagonists, speculatively indicate that interruption of the renin-angiotensin system might be related to the occurrence of angioedema.

During the last 2 decades a lot of mechanistic research has been performed on the role of the immune and complement system, bradykinin, histamine, substance P, PGs and bradykinin in ACE inhibitor–associated angioedema. Despite these efforts, angioedema remains an incompletely understood phenomenon. A great part of the preclinical and clinical studies have focused on ACE inhibitor–induced angioedema and increased levels of tissue bradykinin. An exclusive role for bradykinin in angioedema, however, has not been proven and seems unlikely.

In support of the minor importance of bradykinin is the observation that angiotensin II antagonists can also induce angioedema, even though these drugs block the renin-angiotensin system without affecting bradykinin. Accumulation of inflammatory mediators is another general phenomenon in ACE inhibitor therapy. However, ACE inhibitor–induced angioedema only occurs in a small subset of patients, and it is unlikely that inflammatory mediators cause angioedema independent from other factors.

New insights into this complex issue are necessary to define the pathogenic value of kinin accumulation and eicosanoid generation in ACE inhibitor–induced angioedema. Progress in this field of mechanistic research, however, will be strongly hampered by the lack of suitable preclinical models of angioedema.

Additionally, ACE gene polymorphism and some enzyme deficiencies may be involved in ACE inhibitor–induced angioedema. A genetic predisposition cannot therefore be excluded. Progress in pharmacogenetics and molecular biology can deepen insight into the genetic component of ACE inhibitor–induced angioedema.

At present the management of ACE inhibitor–induced angioedema involves immediate discontinuation of the ACE inhibitor and acute symptom treatment. Alternative therapy with another class of drugs should be immediately started: e.g. β-blockers and calcium antagonists for hypertension, and hydralazine and organic nitrates for heart failure are suitable alternative medications. Angiotensin II antagonists might be useful but their value in the treatment of heart failure is still under investigation.

There are several reasons why further study of ACE inhibitor–induced angioedema is needed. First, it is a serious adverse effect. Secondly, this effect occurs with a relatively high incidence. In view of the substantial use of ACE inhibitors, several hundreds of cases may be anticipated. Thirdly, ACE inhibitors were introduced fairly recently, which means they will be in use for another few decades. As ACE inhibitors encompass a very important group of therapeutic agents the identification of risk factors is important. Further study should focus on epidemiology and pharmacogenetics in patients with angioedema taking ACE inhibitors. One of the problems, however, may be that it concerns a group effect, which could mean that some may not consider it justified to force one particular marketing authorisation holder to study this adverse reaction. In that case, further study should consider public funding.

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