Nonallergic angioedema: role of bradykinin

Angioedema is an underestimated clinical problem. Many cases are nonallergic reactions, e.g. bradykinin-induced angioedema caused by genetic defects and angiotensin-converting enzyme (ACE) inhibitors. This difference is crucial for successful therapy, in particular when complete emergency care is not available. Five important forms of nonallergic angioedema can be distinguished: hereditary (HAE), acquired (AAE), renin-angiotensin-aldosterone system (RAAS)-blocker-induced (RAE), pseudoallergic angioedema (PAE) and idiopathic angioedema (IAE). Some angioedema are present in the larynx and may cause death. A vast majority of nonallergic angioedema are RAE, particularly those caused by ACE inhibitors. It appears important to emphasize that in patients with complete intolerance to RAAS-blockers, cessation of RAAS-blockers is likely to be associated with increased cardiovascular risk. Currently, there is no published algorithm for diagnosis and treatment. Angioedema is usually treated by a conservative clinical approach using artificial ventilation, glucocorticoids and antihistamines. Today, a plasma pool C1-esterase inhibitor (C1-INH) concentrate is the therapy of choice in HAE. The current pharmacotherapy of nonallergic angioedema is not satisfactory, thus requiring the identification of effective agents in clinical trials. Recently, several new drugs were developed: a recombinant C1-INH, a kallikrein inhibitor (ecallantide) and a specific bradykinin-B2-receptor antagonist (icatibant). According to currently available reports, these drugs may improve the treatment of kinin-induced angioedema.

Form of angioedema

In general, angioedema can be allergic or nonallergic, which basically means immunoglobulin (Ig) E-mediated or not IgE-mediated, respectively. Nonallergic angioedema might be caused by hereditary disposition or is of iatrogenic origin, and can be divided into five different types (Fig. 1): hereditary (HAE), acquired (AAE), RAAS-blocker-induced (RAE), pseudoallergic angioedema (PAE) and idiopathic angioedema (unknown cause, IAE). A vast majority of these forms of angioedema are induced by increased bradykinin levels (2) and are the focus of this review. In contrast, many angioedema must be classified as IAE. For example, patients with chronic urticaria develop nonallergic angioedema in the absence of drug therapy or C1-INH deficiency (3). Pseudoallergic angioedema is a different form of drug-induced nonallergic angioedema and is mediated by a so-called pseudoallergic process which is presumably linked to the mechanism of action of the triggering drug. For example, the pseudoallergic reaction to aspirin is thought to be a result of the inhibition of cyclo-oxygenase and subsequently increased generation of cysteinyl-leukotrienes (4).

Epidemiology of angioedema

In people with HAE, heterozygous C1-INH deficiency results in autosomal-dominant inheritance with an incidence of 1:50 000 and there are no differences depending on ethnic groups or sex (5). In contrast, AAE is a rare condition (6, 7). The incidence of RAE induced by ACEi has been estimated with great variety which is most likely due to race differences. For example, in white Caucasians,
the frequency of ACEi-induced angioedema is reported to range between 0.1% and 0.7% (1, 2, 5, 8, 9), while Black people show a much greater susceptibility (10). In fact, a recent meta-analysis investigating adverse reactions to drugs used in cardiovascular medicine found a relative risk of 3.0 for the development of ACEi-induced angioedema among Black compared to White people (11).

Based on roughly 6.5 million users of ACEi in Germany and on an average frequency of angioedema of 0.3%, approximately 20,000 cases of ACEi-induced angioedema will be expected to occur. Thus, the calculated incidence approaches 1:4000 demonstrating that ACEi-induced angioedema, which represents the majority of RAES, appears to be much more frequent than HAE (12). Interestingly, AT-1-blockers appear to induce RAES but with a lower frequency than ACEi (2) and this estimation has been confirmed in large clinical trials (13).

There are no data on the epidemiology of angioedema caused by pseudoallergic reactions to drugs.

**Bradykinin in the human body**

The kallikrein-kinin system

The discovery of the kallikrein-kinin system dates back to 1909, when Abelous and Bardier demonstrated the hypotensive effect of urine (14). Kinins are pharmacologically active peptides released into body fluids and into tissues as a result of the enzymatic action of kallikreins on kininogens. Kinins are a family of peptides, including bradykinin, kallidin and methionyl-lysyl-bradykinin, of which kallidin and methionyl-lysyl-bradykinin are converted very rapidly into bradykinin via the action of aminopeptidases present in the plasma and urine (15).

Tissue kallikrein (EC 3.4.21.35), which differs significantly from plasma kallikrein, is encoded by the KLK1 gene located on human chromosome 19q13.2–q13.4 and mouse chromosome 7 (16). It is expressed in several tissues like kidney, blood vessels, pancreas, gut salivary, spleen, adrenal and neutrophils (17–20). From a cardiovascular viewpoint, the kallikrein-kinin system is thought to antagonize the effects of the RAAS, and is closely related to this system (Fig. 2). The functional coupling between the two systems is illustrated by angiotensin-converting enzyme (ACE) whose two active sites are able to generate angiotensin II from angiotensin I and to degrade kinins into inactive peptides (21, 22).

**Bradykinin receptors and signal transduction**

Kinin receptors are cell surface, G-protein-coupled receptors of the seven-transmembrane family. So far, two subtypes of the receptor – the bradykinin receptor type 1 (BKR-1) and the BKR type 2 (BKR-2) – are identified, based on their pharmacological properties (23–26) and on expression cloning (27–29). The human BKR-2 gene is located on chromosome 14q32 (30), whereas the BKR-1 has been mapped to chromosome 14q32.1–q32.2 (31). At the amino acid level, the BKR-1 and the BKR-2 share only 36% sequence homology (29). The BKR-1 is synthesized in a variety of different organs de novo following tissue injury (31, 32), whereas the BKR-2 is constitutively expressed in a larger number of tissues (33).

Bradykinin is thought to be one of the most potent vasodilatators, as it is capable to liberate three important endothelium-derived vasodilatory mediators: NO, prostacyclin (PGI₂) and endothelium-derived hyperpolarizing factor (EDHF; 34). It is generally accepted that the activation of the BKR-2 on endothelial cells leads to an activation of phospholipase C gamma via a transient tyrosine phosphorylation (Fig. 3), followed by an increased formation of inositol 1,4,5-triphosphate (IP₃) and diacylglycerol (35, 36). As a consequence of an elevated IP₃ concentration, intracellular calcium rises by...
liberalization from internal stores or by an increased Ca\(^{2+}\) influx (37), finally leading to an activation of the Ca\(^{2+}\)-sensitive endothelial nitric oxide synthase (eNOS). In addition, the elevated intracellular Ca\(^{2+}\) activates the Ca\(^{2+}\)-sensitive phospholipase A\(_2\), which hydrolyses membrane phospholipids liberating arachidonic acid, which is the rate-limiting step in the synthesis of PGI\(_2\) (38).

Beside these calcium-regulated signalling pathways, recent studies also explored the importance of signalling pathways depending on phosphorylation. Ju and colleagues demonstrated that bradykinin activates tyrosine kinase 2 (Tyk2) of the Janus-activated kinase (JAK) family, resulting in subsequent tyrosine phosphorylation and nuclear translocation of STAT3 (39). Using similar approaches, it could be demonstrated that bradykinin also activates protein kinase A leading to an acute increase of NO due to a phosphorylation of eNOS at Ser\(^{1179}\) (40).

Physiological actions of bradykinin

Much progress in understanding the physiological role of kinins has been made in the 1980s, when different selective antagonists of BKR-1 and BKR-2 were discovered (26). More recently, the development of C1-INH- and BKR-2-transgenic mice provided important knowledge concerning the role of kinins in vivo (41, 42). The effect of bradykinin on vascular permeability was demonstrated by targeted disruption of C1-INH (42). Bradykinin was shown to dilate peripheral and coronary vessels, may decrease arterial blood pressure in normotensive animals, and exert antithrombogenic, antiproliferative and antifibrogenic effects (Fig. 4; 33, 43–47).

Cardiovascular actions of bradykinin are believed to be mainly mediated by the activation of BKR-2 on endothelial cells leading to the release of NO, PGI\(_2\) and EDHF (48–52) and to the liberation of tissue plasminogen activator (53). Bradykinin is also shown to be involved in the cardioprotective effect of preconditioning on myocardial ischaemia/reperfusion injury (54). It can reduce the infarct area (55, 56) and has a growth inhibitory effect to cardiomyocytes (57, 58). Additionally, kinins can evoke contractions of human bronchi smooth muscles (59), suggesting that bradykinin mediates dry cough induced by ACEi. Indeed, experimental data suggest that bradykinin might be a key substance in the pathomechanism of coughs associated with ACE inhibitors (60, 61). In addition, local accumulation of bradykinin may lead to the activation of proinflammatory peptides and local release of histamine, inducing a cough reflex hypersensitivity (62).

The kallikrein-kinin system also plays an important role in handling sodium and water metabolism. The
natriuretic and diuretic effects of endogenous kinins are documented by several approaches, including BKR-2 gene inactivation in transgenic mice: these animals are prone to salt-sensitive hypertension (63, 64). However, this effect of bradykinin could not be confirmed in another knockout strain (64). There is compelling evidence linking bradykinin to pathophysiological processes that induce tissue damage and inflammation, hyperaemia, leakage of plasma proteins, bone resorption induced by inflammation and pain; besides, many of these activities follow stimulation of BKR-1 (65–71). Bradykinin is also involved in the production of pain and hyperalgesia by direct activation of BKR-2 receptors on primary nonmyelinated sensory neurones and thus participates in the direct pain response (65). When inflammation is prolonged, BKR-1, which are not expressed in healthy tissues to a significant degree, also play an important role in the maintenance of hyperalgesia. In vivo evidence for this was obtained in BKR-1 knockout mice which exhibited a reduced inflammatory response and hypoalgesia (72, 73). Transgenic mice with overexpression of BKR-1 developed exacerbated paw oedema, induced by polyaccharide carrageenan, and were more susceptible to leakage of plasma proteins, bone resorption induced endotoxic shock, supporting the notion that BKR-1 plays an important role in modulating inflammatory responses (74).

Finally, bradykinin has been shown to increase the release of insulin from pancreatic β-cells through the increase of intracellular calcium in response to hyperglycaemia (75, 76) and enhance insulin-dependent glucose transport (77). Other data revealed that bradykinin released locally can regulate the uptake and availability of glucose in target tissues independently of the release of insulin (78, 79). These data suggest that decreased degradation of bradykinin contribute to the beneficial effects of ACEi in cardiovascular patients, such as reduced complications related to diabetes and a reduction of new cases of diabetes type 2 (80).

**Pathophysiology of bradykinin-induced angioedema**

**Hereditary angioedema**

In 1882, Heinrich Irenäus Quincke described an acute and clearly circumscribed oedema. Although other case reports on such oedema had already been published, it was his real reward having accurately described this disease and separated it from urticaria (81). Today, the so-called Quincke oedema is synonymous with angioedema, and is still used to describe a circumscribed oedema without urticaria and/or pruritus.

It is known that the serine protease inhibitor (serpin) C1-INH has a variety of biological activities (82). Of these, the disrupted inhibition by C1-INH deficiency of several proteases of the complement and the contact system and of kallikrein appear to be of particular importance for the development of angioedema. The underlying mechanisms were extensively discussed and reviewed previously (9, 83). Briefly, disrupted inhibition by C1-INH deficiency of the serine proteases C1s and C1r promotes activation of the complement system. In addition, the inhibition by C1-INH of two proteases of the coagulation system, namely factor XIIa (Hagemann factor) and kallikrein appears important. As discussed above, the kallikrein activity is a major player in the synthesis of bradykinin. In particular, the vasodilator activities of bradykinin and its potency to promote and induce increased vascular permeability are well consistent with its putative role in the pathophysiology of angioedema.

According to our current knowledge, a deficiency of C1-INH due to genetic defects plays a causal role in HAE (9). The human C1-INH gene has been mapped to chromosome 11 (11q12–q13.1; 5). Two variants of HAE have been described: HAE type 1 with decreased C1-INH levels and functional deficiency (85% of cases) and HAE type 2 with normal protein concentration but a functional defect (15% of cases; 84). Recently, a first case of homozygous C1-INH deficiency with the mutation c. 1576T>G was reported (85). Targeted disruption of C1-INH in mice resulted in increased vascular permeability as evidenced i.v. injection of Evans blue in the tail and this was reversed by treatment with human C1-INH (42). Other data obtained with this transgenic mouse strain provided strong additional evidence for a crucial involvement of BKR-2 in the pathogenesis of angioedema. For example, increased vascular permeability was strongly reduced by treatment with the BKR-2 antagonist icatibant or by simultaneous homozygous disruption of the BKR-2 gene.

**Acquired angioedema**

AAE develops on the basis of nongenetic C1-INH deficiency, which primarily affects adults or elderly patients (9). This might be a result of various conditions, including severe illness such as malignancies. Patients with lymphoproliferative diseases may develop angioedema associated with decreased C1-INH plasma levels and activity (7, 86). In contrast to HAE where the synthesis of C1-INH is defective, AAE is characterized by large numbers of idiotype-anti-idiotype immunocomplexes (autoantibodies) consuming the Clq molecules and subsequently C1-INH (87). Thus, C1q levels are normal in HAE, but decreased in AAE. In addition, C4 levels are low and C3 levels are normal in AAE. Other diseases such as hepatocellular carcinoma and liver cirrhosis might be associated with decreased C1-INH plasma concentration or activity, but subsequent angioedema has not been described (88, 89). There is also a report on a lymphoma-associated angioedema with a normal plasma concentration of C1-INH (90), and a recent characterization of a new C1-INH mutation, leading to strong inhibition of monocyte C1-INH secretion (91).
RAAS-blocker-induced angioedema

An essential component of the RAAS is ACE (carboxypeptidase, kininase 2, EC 3.4.15.1), an enzyme with two major proteolytic tasks: generation of angiotensin II and degradation of bradykinin. In addition, ACE also degrades substance P (92, 93). Treatment with ACEi increases the plasma levels of bradykinin and the biological activity of bradykinin is crucially involved in the actions of ACEi. For example, it has been shown that permanent blockade of BK1-2 by icatibant (formerly Hoe 140) halved the reduction of blood pressure inducible with captopril in hypertensive patients (94). ACEi-induced angioedema are perhaps caused by decreased degradation of bradykinin (95). Interestingly, combined inhibitors of neutral endopeptidase and ACE, such as omapatrilat showed a dramatic fourfold increase of angioedema when compared to the ACEi enalapril (2.17% vs 0.68%: 96). Bradykinin might also be involved in dry cough, a typical side effect of ACE inhibitors (93).

AT-1-blockers appear to induce angioedema with a lower frequency than ACEi (2, 13). Again, these angioedema appear to be caused by bradykinin. It was shown recently that AT-1-blockers increase bradykinin levels in hypertensive patients (97). This effect was associated with an increased ratio of bradykinin and its degradation product BK1-7, suggesting that AT-1-blockers may inhibit ACE by a mechanism different from ACE-inhibitors. The circulating levels of angiotensin II increase in response to AT-1-blocker therapy, because these drugs interrupt the physiological feedback mechanism regulating angiotensin II synthesis by the release of renin (98). At the same time, all other AT-1 receptors are also blocked, leaving much room for the activation of angiotensin II type 2 receptors, which, in turn, might inhibit the degradation of bradykinin by inhibition of ACE or of neutral endopeptidase (97). However, previous animal studies showed the stimulation of angiotensin II type 2 receptors might actually stimulate bradykinin production so further studies are required to justify the hypothesis given above (99). Nevertheless, AT-1-blockers should be used with caution in patients who have experienced ACEi-induced angioedema (100).

ACEi and AT-1-blockers are widely used as level I evidence drugs to treat hypertension, myocardial infarction, heart failure and type I diabetic nephropathy (101–103). The beneficial effects of these drugs in heart failure and after a myocardial infarction include improvements in survival, the rate of hospitalization, symptoms, cardiac performance, neurohormonal levels and reverse remodelling (101, 102). Thus, in patients who develop RAE, the cessation of RAAS-blocker therapy is, over the long term, likely to be more important problem than is angioedema itself. The availability of an easy-to-use oral or s.c. standby medication which can be self-administered whenever an attack is recognized by the patient might be a promising future approach to maintain RAAS-blocker treatment in severely ill cardiovascular patients who developed RAE. However, new s.c. drugs emerging to treat angioedema (see below) are being evaluated in HAE but not in RAE.

Factors triggering angioedema attacks

Numerous factors have been reported by patients with HAE as triggers or inducers of angioedema attacks. These include exposure to cold, mechanical trauma, tissue compression, prolonged sitting or standing, certain foods (e.g. eggs), infections, concomitant diseases, contact to pesticides or chemicals either directly or via new products or clothes, excitement/stress and certain drugs, such as ACEi and oestrogens (9). However, these anecdotic reports have never been systematically investigated and appear to depend on the patient’s individual characteristics. One exception is the use of contraceptive oestrogens and hormone replacement therapy with oestrogens. It has been shown that some female HAE patients respond to physiologically (first manifestation after menarche, menstrual cycle and pregnancy) and/or pharmacologically increased serum oestrogen (contraceptive oestrogen/gestagen combinations and hormone replacement therapy with oestrogen) with an increased frequency of attacks (104, 105). Other researchers found similar cases in men and women after antiandrogenic treatment with cyproterone (106). Likewise, a significant correlation between the attack frequency and serum progesterone levels was evident in 44 female HAE patients, but not in the 34 male patients of this study cohort (107).

The molecular mechanisms of triggering factors are largely unknown. One exception is the use of ACEi in HAE patients, which further raises plasma and tissue bradykinin (see above). Thus, it is not surprising that HAE patients sensitively respond to ACEi with an increase of their attack frequency (108, 109). A similar mechanism is probably driving angioedema attacks in cardiovascular patients without HAE. However, important questions remain to be clarified. For example, why do only <1% of the patients taking ACEi develop angioedema, while bradykinin levels are increased in all ACEi-patients? Furthermore, what is the reason that some patients develop angioedema within a few days after starting the ACEi therapy, whereas others have their first attack after years of uneventful treatment (110)?

It might be speculated that a variety of endogenous factors counterbalance angioedema-inducing biological activities of bradykinin. In contrast, other factors might create a tissue environment that disrupts this balance and induces angioedema. As many of the above-mentioned triggering factors are associated with an activation of inflammatory pathways, it appears promising to look for an association between inflammatory plasma markers and the development of angioedema. Recent findings may shed some light on such potential trigger factors. In a
cohort of 43 non-HAE male and female patients suffering from an acute angioedema attack, 25 were taking ACEi and their attack completely resolved following drug cessation, while the other 18 cases showed no physical, biochemical or genetic signs allowing classification of their attack and were thus assigned to the group of IAE. Determination of acute-phase proteins during the acute attack revealed striking differences between these two groups (Fig. 5). Patients on ACEi treatment had strikingly and significantly increased plasma levels of C-reactive protein and of fibrinogen (111).

It should be added that in all these ACEi-treated patients, the levels of acute-phase proteins returned to normal as measured 3–6 months after the attack. Furthermore, the determination of acute-phase proteins in 21 cardiovascular patients treated with ACEi who never experienced angioedema showed normal values as well. A subsequent laboratory investigation showed not only potent in vitro vasodilator effects of fibrinogen in human artery rings, but also a strong potentiation of the vasodilatory efficacy of bradykinin (M. Bas and G. Kojda, unpublished results). Taken together, these results may point to a contribution of the inflammatory process to the pathophysiology of angioedema. However, it is still not clear whether or not acute-phase proteins are truly triggering angioedema.

Basic principles of diagnosis

One of the most important procedures to diagnose oedema (see Fig. 6) is to separate allergic from nonallergic angioedema and to exclude other pathologies such as infection, inflammation, tumours and diseases of large salivary glands. These procedures usually follow the initial emergency care, e.g. monitoring of vital functions, determination of the status of angioedema, intubation, oxygen supply and pharmacotherapy with antihistamines, nebulized adrenaline and corticosteroids (1, 9). Beside a detailed physical examination preferably including laryngoscopy, several blood measurements, some imaging procedures and an extensive anamnesis focusing on the patient’s family history and current medications should be performed.

A detailed physical examination should reveal whether the swelling is itchy or painful, which indicates allergic angioedema or inflammatory conditions, respectively. Signs of urticaria usually exclude nonallergic angioedema. Blood measurements must include the determination of C1-INH activity, and, eventually, C1-INH concentration and markers of inflammation (e.g. C-reactive protein, leucocyte count). A reduced activity of plasma C1-INH is indicative of either hereditary or AAE, and should be examined further, e.g. by genotyping or determination of accompanying diseases such as lymphoma (please see ‘Case report: Acquired angioedema’). In some assumed drug-induced cases (ACEi), it might also be helpful to determine serum ACE activity. As for diagnostic imaging procedures, ultrasound visualization of the oedema region is usually sufficient, but uncertain cases and/or abdominal pain should undergo magnetic resonance tomography.

Figure 5. Plasma levels of (A) C-reactive protein and (B) fibrinogen in patients with RAAS)-blocker-induced caused by ACEi and patients with angioedema of unknown cause [data adopted from Ref. (111)].

Figure 6. Algorithm for the diagnosis of angioedema.
A first suspicion of HAE is given by mucosal swellings and/or unclear abdominal pain in patients at a young age and those with a family history, a lack of concomitant drug therapy and the absence of urticaria as well. Following eventually necessary emergency treatment, the diagnostic procedure for HAE (type 1 and type 2) requires the measurement of both C1-INH serum concentration and function (112). Furthermore, plasma levels of the complementary factor C4 in the serum are reduced in a vast majority of the cases. This factor is frequently reduced to approximately 25% of the normal value during the acute episode of angioedema (81, 113). Furthermore, other rare conditions, such as Crohn’s disease of the mouth and lips, facial cellulitis and the superior vena cava syndrome should be excluded (5). An illustration of different manifestations of bradykinin-induced angioedema is depicted in Fig. 7.

**Current treatment of angioedema**

**Basic emergency treatment**

Depending on the symptoms and clinical findings, emergency treatment consists of oxygen application, pharmacotherapy, intubation and, in severe cases, a tracheotomy (84). Currently, in most medical institutions, pharmacotherapy of acute pharyngolaryngeal angioedema consists of i.v. antihistamines (e.g. clemastine 2 mg), i.v. glucocorticoids (e.g. methylprednisolone 250–1000 mg) and/or adrenaline inhalation. The application of antihistamines in nonallergic angioedema may work in IAE but is ineffective and hence superfluous in RAE, AAE and PAE (2). This therapy is due to the fact that in an emergency situation – a patient with potentially life-threatening dyspnoea – the doctor may not be able to entirely exclude an allergic background. Similarly, glucocorticoids are not proven to be effective in kinine-induced angioedema (108). However, glucocorticoids still belong to the standard for treatment of angioedema (114). Principally, this medication should lead to a decrease in mucosal swelling. However, a clinical study showing a beneficial effect in patients with angioedema is lacking. It also has to be considered that this medication is used ‘off label’ and may induce adverse effects, e.g. increased blood pressure. Thus, consequent monitoring of blood pressure and pulse are required. Inhaled adrenaline may also be effective in laryngeal oedema or other severe forms, but this is not based on evidence and adrenaline inhalation is not labelled for this indication.

In case of a progressive course of pharyngolaryngeal angioedema, it may be necessary to temporarily bypass the airflow via intubation or tracheotomy. During the acute angioedema episode, it is technically difficult to insert a ventilation tube and thus this attempt should be performed in the presence of an experienced head-and-neck surgeon able to quickly perform a tracheotomy.
In cases with extensive cervical swelling it might be difficult to identify the trachea and thus an emergency c声iotomy (between the cricoid and thyroid cartilage) might become necessary. Taken together, the current pharmacotherapy of acute nonallergic angioedema is not satisfactory, thus requiring the identification of effective agents in clinical trials.

Hereditary and acquired angioedema

As extensively reviewed recently (84), both types of angioedema are characterized by C1-INH deficiency, and usually respond rapidly to treatment with therapeutic C1-INH, which is currently the ‘gold standard’ of pharmacotherapy. It is not available in the USA, where HAE is treated with the alkylated androgens stanzazolol and danzol (see Case report AAE). This i.v. substitution therapy with C1-INH concentrate derived from human plasma pools might also be used to prevent acute angioedema attacks (9). Although there is theoretical risk of infection with viruses such as HIV, the product has been proved to be safe, as there is not one known case of viral infection despite many million applications. However, in view of the uncomfortable i.v. application route this approach may be difficult to manage for the patient (9). In contrast, drugs such as danazol (see Case report AAE) and tranexamic acid are available in oral form, and are used as a preventive pharmacotherapy to reduce the frequency of attacks.

Tranexamic acid is a fibrinolytic drug used for short- and long-term prophylactic pharmacotherapy in HAE, as it can reduce the number and severity of attacks in HAE (113). Tranexamic acid is structurally related to the amino acid, lysin and saturates lysin-binding regions in plasminogen by forming a reversible complex. This inhibits the binding of plasminogen and plasmin to fibrin, disturbs the proteolytic activity of plasmin and subsequently inhibits fibrinolysis (115). An accompanying effect of this action of tranexamic acid is the reduced consumption of C1-INH, and this effect is used in the treatment of HAE (9, 113). The potency of tranexamic acid in preventive pharmacotherapy in HAE patients is reported to be low, particularly among children (113, 116). Its important side effects include gastrointestinal symptoms, such as nausea, vomiting, diarrhea and rare cases of thrombotic/embolic events (117, 118). In addition, visual impairment and vertigo have been noted after long-term use of tranexamic acid. An annual fundoscopy is a recommended check for any impairment of visual function, including retina tumours (113).

RAAS-blocker-induced angioedema

RAE is basically treated as described in the section Basic Emergency treatment (see above). Furthermore, the immediate cessation of RAAS-blockers is mandatory. Later on, the RAAS-blockers need to be replaced by other antihypertensive drugs. As described above, AT-1-blockers should not be used routinely to replace the much more commonly used ACEi (please see ‘Case report: RAAS-blocker-induced angioedema’) (100, 119, 120). For example, the patient described in the RAE case below received amlodipin to replace candesartan, and this might be sufficient, as long-acting dihydropyridines have beneficial effects on the prognosis of patients with hypertension (101). However, this is strikingly different in patients with a history of myocardial infarction or heart failure (101), where no equally effective drug is available. One possible approach to treat such patients in the future would be to provide a safe and easy-to-use stand-by medication which can be self-administered whenever an attack is sensed by the patient.

Case report: Acquired angioedema

A 65-year-old female patient with a history of surgically treated Morbus Crohn presented at the emergency department of the university hospital in Duesseldorf, Germany, with recurrent angioedema located on her right arm, hips and legs. A detailed diagnostic procedure revealed a strongly decreased C1-INH activity (27%, norm: 70–100) but no mutations in the C1-INH gene. Other abnormal laboratory findings were: increased C-reactive protein of 1.3 mg/dl (norm: <0.5), increased fibrinogen of 471–530 mg/dl (norm: 180–350) and increased alkaline phosphatase of 120 U/l (norm: 35–104).

Further examinations were carried out to look for lymphoproliferative diseases which have been reported to induce C1-INH deficiency (see above). Computerized tomography showed no signs of splenomegaly or abnormal lymph nodes, and blood leucocyte counts were normal. A bone marrow biopsy revealed an infiltration with a non-Hodgkin lymphoma. Histology showed a 20% CD20- and CD43-positive infiltration and a cell population expressing CD23 and CD38. A bone marrow B-cell non-Hodgkin lymphoma was diagnosed. A specific treatment was not necessary, but the patient was advised to return for further bone marrow biopsy and to avoid ACEi. Her acute angioedema attacks were treated with C1-INH concentrate and danazol (200 mg/day) was prescribed to prevent further attacks. Her repeatedly measured C1-INH plasma concentration after 20 months of danazol therapy was 0.11 g/l (norm: 0.17–0.44) and C1-INH activity was 34% (norm: 70–100). Despite this apparent lack of a danazol-effect on C1-INH concentration and activity, the patient experienced no further angioedema attacks. The non-Hodgkin lymphoma did not progress after that.

Short discussion

Angioedema might be the first sign of a lymphoproliferative disease, as was evident in the present case. In this
case, successful treatment with danazol, a steroid which stimulates the synthesis of C1-INH, and of C4 and which is capable of reducing the frequency of angioedema attacks in AAE (121), was successful. The drug is available in several European countries and in the USA but no longer in Germany. In the USA, danazol and its congenere, stanozolol, are widely used to treat angioedema, including acute attacks in children. Interestingly, this case also disputes the assumed mechanism of action of danazol and indicates that an increase of C1-INH concentration and activity are accompanied by other yet unknown activities which interrupt the pathophysiology of angioedema. For example, in women, danazol induces deprivation of oestrogen, a well-known trigger of angioedema. Another interpretation is that danazol is not the underlying cause for the cessation of angioedema. It is known that angioedema might not occur for many months despite continuously decreased plasma C1-INH (9). However, long-term use of danazol may induce rare but severe side effects, e.g. liver diseases such as hepatic necrosis or cholestasis, adenomas and eventually carcinomas (9, 122). Of the many other side effects, some may result from oestrogen deprivation in women.

Case report: RAAS-blocker-induced angioedema

A 62-year-old male patient presented to the emergency department with dyspnoea and diffuse swelling of his tongue that had developed within a few hours. Transnasal flexible endoscopy revealed an oedema of the hypopharynx. He had no known history of allergies. He was taking enalapril (5 mg daily) for the past 7 years to treat hypertension (admission blood pressure 130/80 mmHg). Furthermore, the patient was wearing an atrial pacemaker, had an operation with aortic valve replacement 7 years ago and was suffering from hypothyroidism. Additional prescription drugs are: phenprocoumon (INR 3,1), sotalol mite (160 mg b.i.d.), l-thyroxine (150 mg daily) and tamsulosin (0.4 mg daily). Furthermore, pharmacotherapy with atorvastatin (20 mg/day) was initiated. A routine laboratory investigation on admission showed increased values of fibrinogen (549 mg/dl; norm: 180–350) and leucocytes (11 900/μl; norm: 4000–11 000/μl). All other routinely determined values were normal.

The patient was again treated with 250 mg i.v. methylprednisolone, 2 mg i.v. clemastine, 5 mg nebulized adrenaline and oxygen supply and recovered within 24 h. On being discharged, he was advised to avoid both types of RAAS-blockers, ACEi and AT-1-blockers. Subsequently, candesartan was replaced by 5 mg/day amlodipin, 50 mg/day triamterene and 25 mg/day hydrochlorothiazide.

Short discussion

This case demonstrates that RAE can include severe laryngeal oedema, which can induce life-threatening breathing impairment eventually requiring tracheotomy (110). Furthermore, this case is an example for recurrent RAE when an ACEi was replaced by an AT-1-blocker. In a large controlled clinical trial the frequency of angioedema induced by captopril (0.5%) was higher than that induced by a valsartan (0.2%) (13). However, patients with previous ACEi-induced angioedema might be more susceptible to angioedema induced by AT-1-blockers (see section RAAS-blocker-induced angioedema), although previous investigations on this matter do not support this view (99, 123). Thus, further clinical studies are necessary to estimate this risk more accurately. However, it appears necessary to precisely inform about this potentially life-threatening side effect, including a clear information for patients. Finally, this case matches similar cases registered worldwide and support the warning that AT-1-blocker should be used with caution in patients with previous ACEi-induced angioedema (124).

Special considerations in paediatric treatment of angioedema

In children, the main cause of kinin-induced angioedema is HAE. Insufficient C1-INH function as a result of autoimmunity is also rare in children. It is likely that HAE is under-diagnosed in childhood and adolescence. It is estimated that 85% of the patients with HAE show symptoms before they are 20 years old. In contrast, only 35% are diagnosed at that age. The clinical diagnosis of HAE is difficult in children because they may present with symptoms that are very common in childhood. Among these symptoms is: abdominal pain, swelling of the extremities, difficulties to swallow, hoarseness or acute
C1-INH is a plasma product and expensive, it is not discontinued and is then usually given lifelong. As difficult to establish criteria when to initiate long-term prophylaxis in children, systematic data from large cohorts and registries that report their paediatric data or consensus conferences (9, 84, 113).

Education of parents and the patients (once they are adolescents)

First of all, medical education is of key importance. If the parents are informed about the disease early diagnosis will be possible and unnecessary operations like appendectomy in case of intra-abdominal oedema will be avoided. This point cannot be stressed enough, because in our own experience, unnecessary operations have been performed although parents knew about the diagnosis of HAE in their children but not about their possible manifestations. Avoidance of oral contraceptives in adolescent girls should be a part of counselling. An important part in the education of patients is the knowledge of and contact with patient initiatives, in particular self-regulating communities which can be easily identified by their web pages. Parents need to be informed with emergency lots of C1-INH concentrate for their home refrigerator and their family doctor needs to be well informed about the disease. Moreover, parents and patients need to carry medical information cards with information about the diagnosis in different languages.

Treatment of acute attacks

Acute HAE attacks are successfully treated by infusion of 10–30 units C1-INH concentrate/kg body weight, usually 500–1000 units. If this is not effective within 30–60 min, another 500–1000 units are to be administered. This treatment is usually effective within <2 h, save and well tolerated. Any swelling in the head-and-neck area, unexplained hoarseness or dyspnoea or acute abdominal pain should be treated with C1-INH promptly.

Short-term prophylaxis

Short-term prophylaxis is achieved by the infusion of 500–1000 units within 30–60 min before a planned intervention. It should be done in any surgical procedure, dental intervention or trauma in the head-and-neck region.

Long-term prophylaxis

In children, systematic data from large cohorts and controlled or randomized studies are lacking. There are no established criteria when to initiate long-term prophylaxis. Once it is initiated, it is very difficult to discontinue and is then usually given lifelong. As C1-INH is a plasma product and expensive, it is not convenient for the use in long-term prophylaxis. Choices to C1-INH include antifibrinolytic agents like tranexamic or 1-aminocaproic acid or danazol. The antifibrinolytic agents appear not to be an alternative because they cause adverse effects like myalgias and myonecrosis, abdominal pain, hypotension and thromboses. In a study by a Hungarian group, 26 children from 1 to 15 years of age are reported (9, 116). Of them, 11 children were put on long-term prophylaxis with 1–2 g tranexamic acid because of frequent or life-threatening attacks. This proved to be ineffective in eight of the 11 and, therefore, the remaining eight children where put on danazol 100–200 mg/day, which the authors report to be effective and without serious side effects (with the exception of one girl with a delayed menarche). However, this series reports only a small number of children (n = 8) and the potential long-term side effects of androgens in children (premature epiphysial closure with growth arrest, liver damage and hepatocellular adenoma, development of secondary sexual characteristics, hirsutism and many more) make many paediatricians very cautious about their use.

In conclusion, appropriate education of parents and patients is mandatory. C1-INH concentrate has been shown to be effective and save children with acute attacks and for short-term prophylaxis as well. Management of long-term prophylaxis is difficult. Both antifibrinolytic agents and attenuated androgens cannot be recommended, although both are used where C1-INH concentrate is not available. Therefore, the development of new drugs is particularly important for children, who need long-term prophylactic pharmacotherapy.

Future directions – new treatment options

Significant adverse reactions, an uncomfortable route of administration (i.v. infusion) and the lack of a proven preventive pharmacotherapy may affect the quality of life of patients with HAE. These call for new options to treat HAE as also AAE and RAE. Fortunately, there are three new pharmacotherapeutic options which are currently investigated in clinical trials (Fig. 8): (1) recombinant C1-INH, (2) the kallikrein inhibitor ecallantide and (3) the BKR-2-antagonist icatibant.

rhC1-INH

Recombinant human C1-INH (rhC1-INH; Pharming Group, Leiden, the Netherlands) is extracted from the raw milk of transgenic rabbits. The gene-encoding human C1-INH is functionally linked to an extra bovine milk-specific promoter sequence (alpha-S1 casein) in the rabbit DNA, thus leading to the secretion of C1-INH into the milk. rhC1-INH is expected to act in HAE the same way as native C1-INH: it inhibits factor XIIa and
kallikrein, and blocks the formation of bradykinin (Fig. 8). Nevertheless, the half-life of rhC1-INH is approximately 3 h which is much shorter than the half-life of native C1-INH (125). rhC1-INH is currently tested in phase III trials on humans as listed in the web register of the U.S. National Institute of Health (http://www.clinicaltrials.gov; accessed 16 April 2007). In contrast to the plasma pool C1-INH, which is still the therapy of choice, the use of rhC1-INH will reduce the small but significant risk for the transmission of diseases elicited by contaminations of human plasma with so far unknown pathogens, such as viruses and prions. The virtual unlimited availability of recombinant proteins such as rhC1-INH may also reduce the still immense costs for C1-INH therapy.

Ecallantide

Ecallantide (DX-88, Dyax Corp., Cambridge, MA, USA) is a recombinant 60 amino acid protein that specifically inhibits the plasma kallikrein. By blocking kallikrein, the formation of bradykinin from its precursor high-molecular kininogen is downregulated (Fig. 7), suggesting that ecallantide roughly mimicks the physiological actions of C1-INH. However, there are many differences to the biological activity of C1-INH. For example, although ecallantide potently inhibits plasma kallikrein, it shows a much less inhibitory activity against C1r, C1s, plasmin, factor XIIa and factor XIa (126). Ecallantide has been tested in several phase I and phase II trials, and is currently in a phase III trial for treating HAE. In a phase II trial in 48 patients with HAE administered i.v. DX-88 significantly improved symptoms compared to placebo (126). The primary end point was the proportion of patients reporting a significant improvement 4 h after the administration. Overall, ecallantide is described to be well tolerated. Some reported side effects were dizziness, fatigue, headache, nausea, vomiting and elevations of the liver function test.

In addition, a prolongation of aPTT was observed. This is not surprising, as kallikrein and the Hagemann factor (factor XIIa), which autoactivate one another, are initial players in the clotting cascade. This action of ecallantide might be a matter of concern and might cause significant interactions with commonly used drugs, such as aspirin or heparin. However, it was suggested that prolongation of aPTT by ecallantide is not likely to represent an increased risk of bleeding (126). Another concern eventually limiting the use of ecallantide is the formation of antibodies as well as the occurrence of anaphylactic reaction against this protein. Both events were observed during treatment with ecallantide in a HAE patient, and may raise safety concerns in terms of hypersensitivity reactions (127).

Icatibant

Icatibant (Jerini AG, Berlin, Germany) is a synthetic decapeptide (MW: 1304.6 Da) with a similar structure than bradykinin, but with five nonproteinogenic amino acids. It is a potent, specific and selective BKR-2 antagonist that does not interact with other peptide receptors, e.g. angiotensin II, substance P and neurokinin A (128). Intranasal single-dose administration of icatibant, at doses up to 500 µg and prior to kinin challenge, proved to inhibit bradykinin-induced symptoms in a dose-dependent manner (129). Icatibant has been administered so far to more than 1350 subjects in phase I–III trials (A. G. Jerini, personal communication). In an open-label, proof-of-concept, phase II study, icatibant was administered either i.v. (0.4–0.8 mg/kg) or s.c. (30–40 mg) to 15 HAE patients with 20 attacks (130) . Symptom intensity significantly decreased within 4 h after the administration of icatibant, and a recent case report of treatment of HAE with icatibant supports these results (131).

Icatibant caused no treatment-related serious adverse events or withdrawals. Local rapidly disappearing cutaneous reactions (erythema) occur following s.c. injection (131). However, the upcoming results of two double-blind, randomized phase III studies (FAST 1 and 2) have to be awaited before the safety profile of icatibant can be further determined. In these studies, the efficacy of a single s.c. dose (30 mg) of icatibant in moderate-to-severe HAE attacks of the skin or the abdomen was tested. The primary efficacy end point was the time to the onset of symptom relief assessed by the patient using a visual analogue scale. The secondary end points of the double-blind, either placebo-controlled (FAST 1) or tranexamic acid-controlled (FAST 2), randomized multicentre study included the response rate (the rate of onset of symptom relief within 4 h after application), the time to the complete alleviation of symptoms, and the safety and tolerability of treatment. The results of these recently finished studies have not yet been published.
References


