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Drug-Induced Angioedema without Urticaria

Incidence, Prevention and Management

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Contents

Abstract

Angioedema without urticaria is a clinical syndrome characterised by self-limiting local swellings involving the deeper cutaneous and mucosa tissue layers. Most occurrences of angioedema respond to treatment with a histamine H_1 receptor blocker (antihistamine) because they are an allergic or parallergic reaction. A small number of cases do not respond to antihistamine treatment. Such cases tend to occur in patients with deficiency or dysfunction of the inhibitor of the first component of the complement (C1-INH), but more rarely can occur in patients with other conditions and as an adverse drug reaction.

Angioedema is well documented in patients taking ACE inhibitors. Considering that 35 to 40 million patients are treated worldwide with ACE inhibitors, this drug class could account for several hundred deaths per year from laryngeal oedema. ACE inhibitors certainly do not mediate angioedema through an allergic or idiosyncratic reaction. For this reason the relationship with this drug is often missed and consequently quite underestimated. Rare instances of angioedema have also been reported with angiotensin II receptor antagonists. This adverse effect seems to occur less frequently with angiotensin II receptor antagonists than with ACE inhibitors. However, we do not know whether this adverse effect has the same mechanism with the 2 classes of medications. Some cases of severe angioedema have been recently reported after treatment with fibrinolytic agents. Scattered reports suggest the possibility of angioedema associated with the use

of estrogens, antihypertensive drugs other than ACE inhibitors, and psychotropic drugs. Angioedema can also occur with nonsteroidal anti-inflammatory drugs.

Prevention of angioedema relies first on the patient history. Estrogen and ACE inhibitors should be avoided in a patient with congenital or acquired C1-INH deficiency. In the case of ACE inhibitors, the appearance of angioedema following long term treatment does not lessen the probability that such an agent could be the cause. The most important action to take in a patient with suspected drug-induced angioedema is to discontinue the pharmacological agent. Epinephrine (adrenaline), diphenydramine and intravenous methylprednisolone have been proposed for the medical management of airway obstruction, but so far no controlled studies have demonstrated their efficacy. If the acute airway obstruction leads to life-threatening respiratory compromise an emergency cricothyroidotomy must be performed.

The following definition of an adverse drug reaction has recently been proposed: 'An appreciable harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product'.[1] This definition improves the old definition of the World Health Organization,[2] which has been in use for about 30 years and in some instances is not sufficiently clear and can be ambiguous. Angioedema without urticaria falls into such a definition. It is a clinical syndrome characterised by self-limiting local swellings involving the deeper cutaneous and mucosal layers. The condition can be drug-induced, most notably with ACE inhibitors. The aim of the present report is to describe the incidence and mechanisms involved in drug-induced angioedema and how this condition can be prevented and managed.

The literature reviewed in this article was obtained from a search of Medline (from January 1990 to September 2000) for articles referring to the appearance of angioedema without urticaria as an adverse drug reaction. We do not discuss angioedema associated with antibacterials and radiographic contrast media since it only rarely occurs without urticaria with such agents.

1. Aetiology, Presentation and Diagnosis

Most of occurrences of angioedema without urticaria are caused by an allergic or parallergic reaction. Histamine is the main mediator of the reaction and the condition resolves following treatment with histamine H^1 antagonists (antihistamines). However, in a small percentage of patients with angioedema without urticaria their condition does not respond to antihistamine treatment and such patients represent a tough diagnostic and therapeutic challenge for the physician.

Typical cutaneous angioedema differs from urticaria because it usually last longer (2 to 4 days instead of a matter of hours) and it is nonpruritic, nonpainful and non-erythematous.[3] Nonhistaminergic angioedema can be localised to the face (distorting the patient's aspect), genitals, extremities and trunk and resolve without sequelae. If the mucosa is affected the upper airways and gastrointestinal tract become involved and this can lead to life-threatening asphyxia and violent abdominal pain, vomiting and/or diarrhoea, respectively. The causes of nonhistaminergic angioedema without urticaria are listed in table I.

This syndrome is most often seen in patients with hereditary deficiency or dysfunction of the inhibitor of first component of the complement cascade (C1-INH) or with an acquired impairment of this protein, generally caused by the presence of autoantibodies against C1-INH.[4,5] A third clinical condition of recurrent familial and estrogen-induced angioedema has been described in women and it has been considered estrogen-dependent.[6-8] In a fourth clinical condition, called idiopathic

Table I. Causes of nonhistaminergic angioedema without urticaria

Hereditary deficiency or dysfunction of C1-INH
Acquired impairment of C1-INH, generally attributed to the presence of autoantibodies
Recurrent familial and estrogen-induced in women
Idiopathic
Adverse drug reaction
Other diseases (infections, autoimmunity)

C1-INH = inhibitor of the first component of the complement.

nonhistaminergic angioedema, symptoms are similar to the ones already described, but no biochemical defect has so far been discovered.[9] Finally, similar clinical features may be the consequence of adverse drug reaction (table II).

Drug-induced angioedema without urticaria may be caused by an immunoglobulin E-mediated allergic reaction, but for the majority of the reactions the pathogenesis remains unclear. Therefore, since no immunological mechanism has been identified, skin tests and antibody determinations are typically unreliable for diagnosis.[10]

2. Drugs That Induce Angioedema without Urticaria

2.1 ACE Inhibitors

Angioedema is a well documented adverse event in patients taking ACE inhibitors. A complete review of reported cases of angioedema related to ACE inhibitor treatment published from January 1966 to June 1997, was presented in 1998 by Vleeming et al.[11] This adverse effect only occurs in 0.1 to 0.5% of patients taking these drugs.[12] However, it represents the most frequent cause of recurrent drug-induced angioedema. Considering that, at present, 35 to 40 million patients worldwide are treated with ACE inhibitors, this drug class could account for several hundred deaths per year due to laryngeal oedema.[13]

The cutaneous, abdominal and laryngeal manifestations of angioedema associated with the use of ACE inhibitors are similar to those observed in patients with C1-INH deficiency, but they differ in so far the angioedema is more frequently localised to the head and neck and because of the rare, though possible, involvement of the intestine.[14,15] Reports indicating the existence of a partial defect of C1-INH have not been confirmed.[14] The pathogenetic mechanism appears to be linked to the decreased degradation of bradykinin (BK), a potent vasodilating peptide. ACE, also known as kininase II, does not just act on angiotensin I, but it is also a major inactivator of BK. Pharmacological inhibition of ACE leads to increased plasma levels of BK[16] and high levels of BK have been demonstrated in plasma during an acute episode of angioedema.[17] However, BK degradation is blocked in all patients treated with ACE inhibitors, but angioedema appears inconstantly and just in a small percentage of such patients. Therefore it is likely that factors, other than impaired BK degradation, are involved in the development of angioedema.

Studies aimed to identify factors predisposing patients to ACE inhibitor–induced angioedema focused their attention on the discovery of abnormalities in enzymes involved in BK catabolism, particularly carboxypeptidase N (CPN), which is also known as kininase I. In a large cohort of patients[18] with ACE inhibitor–related angioedema mean plasma levels of CPN were slightly reduced compared with patients who did not develop this adverse effect.[18] However, the large overlap of CPN levels between the 2 groups limits the value of CPN measurement to predict the risk of ACE inhibitor–related angioedema.[18] Moreover, we have shown that during angioedema associated with ACE inhibitors, BK plasma levels increased; however, contrary to what happens in hereditary angioedema, no cleaved high molecular weight kininogen (HK), the precursor of BK, was detectable in plasma.[14] This finding supports the hypothesis that the pathogenetic mechanism of ACE inhibitor–related angi-

Table II. Drugs associated with angioedema without urticaria

ACE inhibitors
Angiotensin II receptor antagonists
Fibrinolytic agents
Estrogen
Nonsteroidal anti-inflammatory drugs
Other drugs

oedema lies in the catabolic site of BK metabolism.[14] Marcic and Erdös[19] have recently suggested the existence of an intermediate component involved in the action of ACE inhibitors to enhance the release of vasoactive mediators by BK. According to Blais et al.[20] half of the patients with ACE inhibitor–related angioedema have a defect of a serum enzyme, which involves des-Arg BK metabolism leading to its accumulation.

A 4-fold increase in the risk of ACE inhibitor–induced angioedema has been reported in Black American patients[21] as the result of differences in the kallikrein-kinin system with increased sensitivity to BK. Although angioedema related to ACE inhibitors has not been shown to be dose-dependent, low doses of ACE inhibitors in Nigerian patients are associated with a frequency and severity of angioedema that is lower than expected from their reported heightened racial susceptibility.[22] On the other hand gender and age have no effect on the frequency or severity of ACE inhibitor–associated angioedema.

A difficult task when evaluating the prevalence of ACE inhibitor-induced angioedema is caused by the fact that angioedema can first manifest anything from a few hours to 8 years after an ACE inhibitor was first taken. Such a delayed onset accounts, in part, for the long time lag between appearance of angioedema and withdrawal of the ACE inhibitor (range 1 day to 10 years).[14] It is surprising that a large number of physicians fail to recognise the association between ACE inhibitor treatment and angioedema despite the fact that this adverse effect is well known and always listed among the adverse effect of the drug. Actually, physicians expect angioedema, generally allergic or idiosyncratic in nature, to occur in close temporal relationship to the time that the causative drug is taken. Angioedema associated with ACE inhibitors not only can start years after beginning the treatment, but then it recurs irregularly while under treatment and some cases of late onset of angioedema have also been observed weeks after discontinuation of the ACE inhibitors.

In fact, ACE inhibitors certainly do not mediate angioedema through an allergic or idiosyncratic reaction: they rather seem to facilitate angioedema in predisposed individuals. For this reason the relationship with this drug is often missed and consequently quite underestimated. It is was stated in a recent review of the assessment of drug-induced disease that 'A drug that has been taken for several years in unlikely to be the cause of the reaction'.[23] This is not true for ACE inhibitor-related angioedema whose correct diagnosis is clearly a problem. Gabb et al.[24] found that in more than 50% of the cases of ACE inhibitor–associated angioedema, ACE inhibitor therapy has been continued.

2.2 Angiotensin II Receptor Antagonists

While ACE inhibitors reduce blood pressure through the reduction of circulating levels of angiotensin II, angiotensin II receptor antagonists block the effects of angiotensin II at the receptor level and should not increase BK plasma levels. Nevertheless, rare instances of angioedema have also been reported with angiotensin II receptor antagonists, suggesting the possibility of a class effect. We found reports of angioedema during treatment with an angiotensin II receptor antagonist in 20 different patients.[25-32] In some of these patients there was a history of ACE inhibitor–induced angioedema and they had reveived such treatment for more than 1 year. Seven of the reports were case reports of single patients[25-31] and 13 were reports of angioedema associated with the use of losartan that had been received, between 1995 and May 1997, by The Netherlands Pharmacovigilance Foundation and by the Drug Safety Unit of the Inspectorate for Healthcare in The Netherlands.[32] One of these patients had a clear history of recurrent angioedema for 4 months while receiving losartan and disappearance upon withdrawal of the drug. In the remaining 19 patients, the angiotensin II receptor antagonist was stopped immediately after the onset of angioedema. Such a prompt withdrawal of the drug makes it difficult to exclude an allergic/parallergic reaction, as such a reaction is possible with almost any medication. These avail-

able data suggest that angioedema occurs less frequently with angiotensin II receptor antagonists than with ACE inhibitors.[12,33,34] However, we do not know whether this adverse effect has the same mechanism with the 2 classes of medications. More importantly, we have no convincing data to conclude whether patients with a history of ACE inhibitor–induced angioedema will also experience this effect with angiotensin II receptor antagonists. Theoretically, angiotensin II receptor antagonists have a different adverse effect profile than ACE inhibitors, as is well documented with the lower incidence of cough. Since angiotensin II receptor antagonists do not interfere with the kallikrein-kinin system, the pathogenetic mechanism of angioedema attributable to angiotensin II receptor antagonists remains unexplained. If the growing clinical experience with angiotensin II receptor antagonists leads to the conclusion that angioedema complicates their use with the same characteristics as it does that of ACE inhibitors, we will either have to reconsider the effect of angiotensin II receptor antagonists on the metabolism of BK[35,36] or to envisage the possibility that reduced BK catabolism is not the major mechanism leading to ACE inhibitor–related angioedema.

2.3 Fibrinolytic Agents

Some cases of severe angioedema have been recently reported after treatment with fibrinolytic agents (streptokinase and the recombinant tissue plasminogen activator, alteplase) in patients with acute myocardial infarction, acute ischaemic stroke and deep vein thrombosis.[37-42] The pharmacological actions of fibrinolytic agents require massive formation of plasmin in order to dissolve fibrin. Nevertheless plasmin facilitates generation of BK from HK by 2 mechanisms: it can activate contact system by converting factor XII into its active form and can increase susceptibility of HK to the cleavage by kallikrein.[43,44] It is possible that predisposed individuals develop angioedema through this pathway. The incidence of angioedema seems to be higher in thrombolytic therapy of ischaemic stroke than of myocardial infarction. According to Rudolf et al.[37] this indicates that disruption of autonomic pathways may contribute to the development of angioedema with cerebral ischaemia, but the paucity of reports does not justify any limitation for using thrombolytic agents for acute ischaemic stroke therapy.

2.4 Estrogen

Three papers have been published describing a familial form of angioedema affecting just women.[6-8] In some of these patients episodes of angioedema were closely related to estrogens either exogenously administered, as contraceptive pills or substitution therapy, or endogenously produced i.e. during pregnancy. Some of these patients recognised they were pregnant because they developed angioedema. The disorder is inherited and its restriction to women suggests an X-linked dominant mode of inheritance. However, an autosomal dominant transmission with hormonal control of the expression of this tract cannot be totally excluded although the appearance of symptoms in childhood makes this possibility unlikely. C1-INH has been extensively studied in these individuals without any evidence of abnormality. Thus, the biochemical defect remains at present unknown and it is also possible that different mechanisms could be involved in each family. In addition to familial angioedema in women, sex hormones can intervene as triggers of episodes of angioedema. This is well known in C1-INH deficiency where women receiving oral contraceptive treatment experience an increase in attack frequency and severity.[5] The negative effect of estrogens in this condition is further highlighted by the recent observation of a woman with asymptomatic hereditary C1-INH deficiency who developed her first episode of angioedema aged 50 when she started to take estrogen replacement therapy.[45] Moreover 5 women who received an antiandrogen and who had recurrent angioedema were described possibly because of an effect of these drugs on C1-INH functional levels.[46,47]

The relationship between sex hormones and angioedema is further highlighted by the fact that an-

drogen treatment effectively prevents attacks in patients with hereditary angioedema (HAE) and at high dosages increases C1-INH plasma levels. A report demonstrated that danazol, an attenuated androgen widely used in patients with HAE, decreases transcription of the estrogen receptor gene in human monocytes.[48] If this observation can be confirmed it could shed some light on the understanding of the role of sex hormones in angioedema.

2.5 Nonsteroidal Anti-Inflammatory Drugs

Angioedema occurring with nonsteroidal anti-inflammatory drugs (NSAIDs) is discussed in allergy textbooks and for this reason we will just briefly refer to it here. Angioedema induced by aspirin (acetylsalicylic acid) and other NSAIDs is probably the best known form of drug-induced angioedema.[10,49] It may occur with or without urticaria and there is cross reactivity among all cyclooxygenase inhibitory drugs. As with other adverse effects of these drugs, a possible cause is the shunting of arachidonic acid metabolites from the cyclooxygenase pathway to the lypoxygenase pathway such that leukotriene production is increased. Accordingly, leukotriene receptor antagonists have been successfully used in the prevention of NSAID-related urticaria[50] and the newly introduced selective inhibitors of cyclo-oxygenase 2 appear to represent a safer alternative in these patients.[51]

2.6 Other Drugs

Scattered reports describe angioedema without urticaria with a number of other drugs.

Other than with ACE inhibitors, angiotensin II receptor antagonists and fibrinolytic agents, angioedema has been seldom reported with other drugs used for cardiovascular diseases. A severe angioedema reaction was reported in 1 patient after intravenous administration of metoprolol.[52] This patient had experienced previous episodes of angioedema following treatment with ACE inhibitors and the complement components were not studied. An isolated report describes the occurrence of angioedema in 2 patients following the use of 2 different calcium channel antagonists.[53] A case of amiodarone-induced angioedema has also recently been reported.[54]

Psychotropic drugs as risperidone and paroxetine can induce episodes of angioedema.[55-57] It seems that these drugs can induce angioedema in patients already predisposed to develop this adverse effect.

3. Preventing Drug-Induced Angioedema

The first criterion for prevention relays on taking the patient's history. As a general rule, patients with a previous history of angioedema call for particular attention. Thus, estrogen and ACE inhibitors should be avoided in a patient with congenital or acquired C1-INH deficiency and ACE inhibitors should also be avoided in patients who have experienced idiopathic angioedema. In these patients caution should also be used when fibrinolytic agents, or angiotensin II receptor blockers are needed. However, one of our patients with acquired C1-INH deficiency has been treated with alteplase without any problem (unpublished observation). Two patients with hereditary angioedema began angiotensin II receptor antagonist therapy and did not register any worsening of angioedema symptoms (unpublished observation). However, because experience is still limited, no conclusion can be draw so far and careful surveillance is needed.

In the case of ACE inhibitors it should be emphasised that angioedema has to be considered a class effect and no attempt to switch to another compound of the same class should be made in patients developing angioedema. Moreover, long term treatment before the appearance of angioedema does not lessen the probability that this drug could be the cause.

Since the risk for developing ACE inhibitor–related angioedema in the majority of patients cannot be predicted, all patients who begin such therapy should be made aware of the possibility of this complication and of the need to immediately refer to their doctor if angioedema develops. Pretreatment screening to identify asymptomatic carriers of C1-INH deficiency does not seem to be neces-

sary because of the rarity of such condition and the cost of an exhaustive screening. Studies investigating molecular markers for the risk of angioedema may change this situation in the future.[11]

4. Managing Drug-Induced Angioedema

The most important measure to take in a case of suspected drug-induced angioedema is to discontinue the pharmacological agent.

In a few instances when the use of a drug that causes angioedema is absolutely necessary, measures can be taken in order to prevent the adverse effect. We already mentioned the use of leukotriene receptor antagonists for aspirin sensitivity. Desensitisation with increasing doses has been performed to induce tolerance in individuals with aspirin sensitivity.[58] A similar approach has been used to continue azathioprine treatment in a patient with a transplant who had experienced angioedema due to this drug.[59]

In case of airway obstruction, medical management with epinephrine (adrenaline), diphenydramine and intravenous methylprednisolone has been proposed, but the use of these drugs has not been shown to shorten recovery time and so far no controlled studies have demonstrated the efficacy of these agents in this setting.[11] In case of acute airway obstruction inducing life-threatening respiratory compromise, an emergency cricothyroidotomy must be performed since oral intubation of the trachea is associated with too much risk.[60]

5. Conclusion

The main point emerging from such a review is that angioedema represents an adverse effect associated with a number of different drugs. The mechanism involved could be different. However, one major difficulty is the possible absence of a close chronological relationship between the appearance of angioedema and the intake of the drug, as it is clearly apparent in ACE inhibitor treatment. In this situation the diagnosis of drug-related angioedema can be missed with serious consequences for the patients. Expanded clinical observations could be helpful in detecting other drugs predisposed to cause angioedema. In order to obtain significant data we must stress the importance of reporting all instances of angioedema occurring with any drug to drug monitoring centres.

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