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Iatrogenic angioedema associated with ACEi, sitagliptin, and deficiency of 3 enzymes catabolizing bradykinin

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Key words

Iatrogenic angioedema; bradykinin; enzyme deficiency

Summary

New concepts of idiopathic and iatrogenic angioedema underline the role of bradykinin, and the importance of catabolizing enzymes. A case is described of Angiotensin converting enzyme inhibitor (ACEi) and sitagliptin induced angioedema, where AO attacks decreased after the withdrawal of lisinopril but resolved only after the withdrawal of sitagliptin, an inhibitor of dipeptylpeptidase IV. ACE, aminopeptidase P and carboxypeptidase N were decreased down to 17%, 42%, 64% of median references values, and remained low one year after the interruption of these drugs: 56%, 28% and 50%, respectively. The combined deficiency of APP and CPN might enhance the inhibiting effect of the DPP IV inhibitor. The fact that this triple deficiency remained latent before and after the treatment indicates that searching for latent enzyme deficiencies should be carried out when there is intention to treat with a combination of drugs interfering with the bradykinin metabolism.

Introduction

Possible mechanisms of angioedema have greatly benefited from the knowledge of angiotensin-I converting enzyme inhibitors-induced angioedema. The importance of bradykinin and of enzymes catabolizing bradykinin and its active metabolism *des*Arg9-BK has been underlined (1). The ACEi extends the half-life of bradykinin (BK) and kallidin (KD), resulting in vasodilation, vasopermeation and cardioprotection (2). Other substrates of ACEi are *des*Arg9-BK and Substance P. Due to its action on BK degradation, ACE promotes the kininase II pathway that is responsible for 75% of BK and 35% of *des*Arg9BK cleavage (3). The decreased ACE activity and subsequent accumulation of vasoactive kinins is a causative factor for iatrogenic angioedema (AE). In addition to ACE, other metallopeptidases contribute to kinin catabolism: aminopeptidase P (APP), dipeptidylpeptidase-IV (DPP-IV), plasma carboxypeptidase N (CPN) and carboxypeptidase M on endothelium, and Neutral Endopep-

tidase (NEP). APP metabolizes 21% and 65% of circulating BK and *des*Arg9BK respectively (3,4). Decreased APP activity is associated with more severe AE disease (5). Substance P, BK and *des*Arg9BK are also substrates of DPP-IV (6). The DPP-IV inhibitors (also called gliptins) are a new class of active agents for treatment of type 2 diabetes. Recently, Brown *et al.* demonstrated the increased risk of angioedema in patients taking an ACEi and a DPP-IV inhibitor (7).

We report the original observation of a patient suffering from ACEi-AE, secondarily worsened by gliptin and persistent after the withdrawal of ACEi. From the biological investigation of kinin metabolism the patient presented with decreased ACE, APP and CPN activities.

Case Report

In February 2010, a 56-year-old man presented to our Allergology Department with recurrent angioedema episodes. The

patient's medical history included type 2 diabetes, acute coronary syndrome and dyslipidemia. He suffered from moderate seasonal rhinitis that did not require any treatment. There was no family history of AE. His daily treatment included lisinopril 10 mg/day (since 1995), glibenclamide 5 mg/day, metformin 1000 mg/day (since 2003), sitagliptin 100 mg/day (since 2009), flurbiprofen 50 mg/day, atorvastatin 20 mg/day. For more than 10 years he had experienced unpredictable angioedema of the face, uvula and hands, without pruritus or urticaria, on a yearly basis, which developed over 3-4 days, despite oral corticosteroid therapy with prednisolone 60 mg/day. The swelling attacks sometimes occurred during infectious episodes or stress periods. Since 2009, symptoms had worsened: oedema was associated with abdominal pain and increased frequency of attacks (every 6 weeks).

Biological investigations

C1-esterase inhibitor concentrations and function, enzymatic assays for APP, ACE and CPN were studied as previously described (8,9).

Results/Findings

C1-esterase inhibitor concentrations and function were normal. ACE, APP and CPN activities were decreased down to 17%, 42% and 64% of median reference values, respectively (**table 1**). Allergy tests indicated sensitization to ragweed and grass pollens. Serum tryptase was found to be within the normal range (2.7 μg/L; N: < 13).

Lisinopril was withdrawn and only three attacks of AE were observed over nine months (2 episodes of facial swelling and 1 episode of foot swelling). Abdominal pain disappeared. Since total recovery was not obtained, sitagliptin was stopped in November 2010 and the patient did not report any AE attack for 19 months following withdrawal.

The retained diagnosis was iatrogenic BK-dependent AE, dependent on ACEi treatment, further worsened by DPP-IV inhibitor, in a patient with latent deficiency of the enzymes involved in bradykinin catabolism, namely ACE, APP and CPN. Results of DPP-IV assay were not available.

Discussion

The incidence of AE in patients taking ACEi was evaluated at 0.5% to 0.68% or even 0.9% (10,11). The diagnosis of ACEi-induced AE is difficult to make because of the high variability of symptom occurrence from the first day of ACEi introduction up to 8 years of therapy (12). The time lag between initiation of ACEi and onset of AE was estimated as 10.2 months; however, about 25% of AE attacks occurred during the first month of treatment and up to 27% of cases occurred after more than 6 months, or even several years, after ACEi initiation. As for the case reported here, the time of symptom occurrence was estimated as 5 years. The clinical manifestations of AE ranged from tumefaction, more or less severe, of the tongue, lips, other area of the face, hands, feet or rarely bowel, to life-threatening airway compromise. The severity and lethality correlated with the involvement of larynx (13-15). Dysphagia and change in voice or dyspnoea should receive primary attention from the

Table 1 - Successive explorations of patient kinin catabolism.

		February 2010	July 2010	July 2012
Current therapy		Lisinopril, Sitagliptin	Sitagliptin[1]	None[1,2]
C1-INH	Antigenic C1-INH (RV: 210-345 mg/l)	284	ND	262
	Functional C1-INH (RV: 17.2-27.4 U/ml)	23,5	ND	21.7
Aminopeptidase P (RV: 0.21-1.82 nmol/min/ml)		0.30 (42%)	0.36 (50%)	0.20 (28%)
Carboxypeptidase N (RV: 35.7-55.3 nmol/min/ml)		29.2 (64%)	33.3 (73%)	22.8 (50%)
Angiotensin Converting Enzyme (RV: 43-95 IU)		10.6 (17%)	40 (64%)	35 (56%)

The percentages refer to residual activity as compared to median reference value. [1]Lisinopril withdrawn on February 2010. [2]Sitagliptin withdrawn on November 2010. C1-INH, C1-Inhibitor. RV, Reference values. ND, not determined.

physician. ENT injury might be explained by the overexpression of BK-B1 receptors in ENT tissues, a fact demonstrated by animal experiments in ACEi-treated pigs (16). The clinical features reported here were the hallmark of BK-dependent AE, manifesting as a subcutaneous swelling, sometimes highly distorting, that developed over 3 to 4 days, without pruritus and urticaria, and partially refractory to corticosteroids. Episodes of abdominal pain can be intense, leading to suspected occlusion or surgical disease. Their cause is shown by scanner examination, exhibiting specific aspects of oedema of the intestinal walls and/or intra-abdominal effusion. When pain is less severe, symptoms are considered to be functional, as observed in this patient who had been diagnosed with irritable bowel syndrome. The physiopathology of ACE-induced angioedema postulates a deficiency of the catabolism of bradykinin because ACE is the main enzyme implicated in this catabolism. It was confirmed by the study from Agostoni, showing high levels of plasma bradykinin in ACE-induced angioedema (17). A decrease to the normal level is obtained by the withdrawal of ACE inhibitor (18). In addition, it has been shown that, contrasting with the high level of bradykinin, there is no increase of high molecular weight kininogen catabolic products (17).

Six proteases (kininases) are mainly responsible for kinin catabolism: ACE, APP, CPN, CPM, DPP-IV and NEP. During ACE inhibition, BK, *des*Arg9BK and Substance P are metabolized primarily by APP and DPP-IV, respectively. In hypertensive patients who experienced angioedema while being treated with ACEi, decreased APP activity has been demonstrated (3). Patients' APP activity was found to be defective in three successive investigations: 42%, 50% and 28% respectively of the median value. A single nucleotide polymorphism (SNP), c.-2399C>A, in *XPNPEP2*, the X-linked gene encoding for APP, has been reported to be associated with APP activity. In addition, APP activity is lower in men and SNP is associated with an increased risk of ACEi-induced AE in men (odds ratio, OR: 2.17) (19,20). ACE and CPN activities were also found to be decreased when patients were no longer exposed to ACEi (**table 1**).

Individuals suffering from ACEi-induced AE also show a decrease in DPP-IV activity (6,23) and increased levels of Substance P (6). There is a correlation between the degradation half-life of substance P and the level of DPP-IV activity (6). DPP-IV inhibitors (gliptins) have been marketed because they decrease degradation of incretins. These hormones play an important role in glucose homeostasis, stimulating insulin secretion and suppressing glucagon release. Gliptins were then approved for treatment of type 2 diabetes mellitus in 2006 (21). However, they also decrease the degradation of kinins and Substance P. Although no evidence of AE risk was evidenced during phase III studies, the FDA post marketing surveillance of sitagliptin reported 10 cases of AE reactions that occurred within the first 10 months of marketing (22). In a report by the French National Center of Pharmacovigilance, 10 cases of gliptin-induced angioedema have been reported so far: sitagliptin (6 cases), vildagliptin (3 cases), saxagliptin (1 case) (*Communication by the Nancy Regional Centre of Pharmacovigilance*). Brown and colleagues recently presented the results of premarketing surveillance for AE in clinical trials for the DPP-IV inhibitor vildagliptin: the authors reported no association between vildagliptin use and AE; however, vildagliptin use was associated with an increased risk of AE in individuals taking an ACEi (OR: 4.57). The role of Substance P, associated with BK, as a triggering factor of AE could be put forward.

In our case, the AE attacks persisted after several months of ACEi withdrawal. Some AE episodes occurred during gliptin treatment alone, as already documented. We suggest that the combined deficiency of APP and CPN might enhance the effect of the DPP-IV inhibitor since catabolism of bradykinin and substance P might rely predominantly on DPP-IV. A specific interest of this case is that the triple deficiency of enzymes catabolizing bradykinin had been latent and was only revealed by drugs adding their inhibitory action.

Extensive use of the gliptins for treatment of type 2 diabetes and the common association of a DPP-IV inhibitor and an ACEi in diabetic, hypertensive patients, strengthens the need to be aware of their interaction. Even if DPP-IV inhibitors may have differential impact on DPP-IV, as suggested in a paper, the benefit-risk ratio of the combined prescription of an ACEi and a DPP-IV must be carefully assessed (24). This case suggests to search for the levels of kinin catabolism enzymes (ACE, APP, DPP-IV and CPN) when there is intention to treat with combined drugs at risk to interfere with bradykinin metabolism.

Statement of contribution

E. Beaudouin: is the referent allergist in charge of the patient. He wrote a part of the text.
F. Defendi (French Reference Center for Angioedema): dosage of functional activities of bradykinin catabolizing enzymes. She reviewed the text.
J. Picaud: allergist associated with the first author, in charge of the patient. Contributed to the search of references.
C. Drouet (French Reference Center for Angioedema): he participated to the discussion and reviewed the text.
D. A. Moneret-Vautrin: wrote a part of the text, contributed to the discussion, and reviewed the text.

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