A Case Report of Angioedema During Long-term (66 Months) Angiotensin Converting Enzyme Inhibition Therapy With Enalapril

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We describe a rare case of ACE inhibitor-induced angioedema during long-term therapy in a 51-year-old male patient with essential hypertension; and this is the third case reported of this adverse reaction in Japan. The patient received enalapril for 66 months, and complained of a dry cough which was mild and tolerable. Recently, he noted tenderness of his mouth, face, swelling of lips and tongue for 3 to 4 h after taking his morning dose of enalapril. These symptoms abated spontaneously, so he continued taking the drugs. He again noted similar episodes of angioedema 29 days after the first experience. He had no further episodes of angioedema or dry cough after cessation of enalapril. This case of angioedema developed during long-term therapy with enalapril administered as 19,930 mg of enalapril maleate.

We emphasize that angioedema may occur at any time during the use of enalapril. (*Jpn Circ J* 1996; **60**: 166–170)

ANGIOTENSIN converting enzyme (ACE) inhibitors have been used successfully in the treatment of hypertension and congestive heart failure; however, there are 2 troublesome adverse-reactions: cough and angioedema. Cough induced by ACE inhibitors is more common and is thought to occur in about 5 to 20% of the population^{1,2} while the incidence of angioedema induced by ACE inhibitors has been estimated to be less than 0.7%^{1,4–7}. There have been only 2 reported cases of angioedema induced by ACE inhibitors in Japan^{8,9}. We present here the third case report of a Japanese patient with

angioedema developed during long-term (66 months) treatment with enalapril.

CASE REPORT

The patient was a 51-year-old man. He weighed 75 kg and his height was 178 cm. He had exhibited high blood pressure in several physical check-ups since 1976, at the age of 35. His drug compliance and blood pressure control were not good in the years following. At the age of 42 his blood pressure showed 206/132 mmHg despite 30 mg of propranolol and 2 mg of trichloromethiazide per day. He was referred to our University Hospital in October 1982. He had no family history of hypertension or idiopathic angioedema, and had stopped smoking after a left

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Fig 1. Angioedema of the lips and face 24 h after last dose of enalapril.

upper lobectomy for tuberculosis at the age of 25. He reported no allergy to food. On physical examination, his blood pressure was 230/130 mmHg with marked hypertensive and arteriolosclerotic retinopathy (Keith-Wagener-Barker classification grade III). No edema was observed on his extremities, and a neurologic examination revealed no abnormalities. Neither abnormal heart murmur nor abdominal vascular bruits was heard, and breath sounds were normal, but the scar of lobectomy for left lung was noted. Laboratory findings were as follows. Serum creatinine of 124 $\mu\text{mol/L}$ and uric acid of 512 $\mu\text{mol/L}$ were slightly elevated, but total protein of 74 g/L, aspartate aminotransferase (AST) of 19 U/L, alanine aminotransferase (ALT) of 16 U/L, Na of 142 mmol/L, K of 3.8 mmol/L, Cl of 99 mmol/L, total cholesterol of 5.22 mmol/L, and fasting plasma glucose of 5.44 mmol/L were within normal limits. Plasma renin activity of 1.86 ng/L.s and aldosterone concentration of 766 pmol/L were high, but cortisol was normal

(466 nmol/L). A chest X-ray showed no enlargement in cardiac shadow but did show slight pleural thickening. Electrocardiogram revealed high voltage with inverted T-wave in leads III, aVF, and V_4 to V_6 . Renogram and adrenal scintigram were normal. The patient was diagnosed as having accelerated essential hypertension. He received 40 mg of furosemide, 500 mg of methyldopa, 100 mg of allopurinol and 16 mmol of oral potassium supplement per day, then his blood pressure was controlled between 180–160/110–90 mmHg. In October 1986 he complained of slight fatigue, and the blood laboratory data revealed slight elevations in AST (36 U/L), ALT (37 U/L), and uric acid (595 $\mu\text{mol/L}$), but K (4.2 mmol/L) and creatinine (133 $\mu\text{mol/L}$) were controlled well. Methyldopa and potassium supplement were stopped, and nifedipine 20 mg bid was prescribed with furosemide and allopurinol. Soon after administration of nifedipine he complained of upset stomach, palpitation, and flushing face, so in late February 1987, enalapril 5 mg bid was started instead of nifedipine. Laboratory data just before the administration of enalapril were: red blood cell count $4.41 \times 10^{12}/\text{L}$, white blood cell count $4.9 \times 10^9/\text{L}$ with a normal distribution, hemoglobin 9.25 mmol/L, hematocrit 42.8%, C-reactive protein negative, AST 28 U/L, ALT 22 U/L, alkaline phosphatase 141 U/L, creatinine 115 $\mu\text{mol/L}$, and K 4.1 mmol/L. Blood pressure was controlled between 170–150/100–90 mmHg. A tickling sensation in the throat and mild dry cough developed soon after the administration of enalapril; however, he preferred enalapril to nifedipine. By March 1988, his blood pressure had gradually elevated to 180–160/110–100 mmHg, and the blood laboratory data were: serum creatinine of 97.2 $\mu\text{mol/L}$ and total cholesterol of 5.61 mmol/L. Additionally 10 mg bid of arotinolol, an alpha-beta blocker, was prescribed, and his blood pressure decreased to 160–140/100–90 mmHg. In October 1989, serum cholesterol had risen to 6.28 mmol/L; 5 mg of pravastatin was added. In October 1990, he experienced lumbago several times, and his urine gave positive tests for occult blood and microhematuria without proteinuria. The blood laboratory data were: total protein 76 g/L, creatinine 88.4 $\mu\text{mol/L}$, uric acid

422 $\mu\text{mol/L}$, Ca 2.45 mmol/L, Pi 0.84 mmol/L, alkaline phosphatase 141 U/L, total cholesterol 5.66 mmol/L, and HDL-cholesterol 1.45 mmol/L. He was diagnosed with a urolithiasis in the pelvis of the left kidney, and received ultrasonic urolithiotripsy in March 1991. After this episode his clinical course went relatively well except for the continuous irritating sensation in the throat and mild dry cough, both adverse reactions to enalapril. The blood laboratory data were: white blood cell count $5.7 \times 10^9/\text{L}$ with a normal distribution, total protein 73 g/L, C-reactive protein negative, creatinine 106 $\mu\text{mol/L}$, and K 4.2 mmol/L. His electrocardiogram was improved (high voltage alone without inverted T-waves), and retinal findings had also improved to Keith-Wagener-Barker classification grade II.

After taking the drugs in the morning of July 15th 1992, he noted tenderness of his mouth, face, swelling of lips and tongue. In 3 to 4 h, the symptoms abated spontaneously, and he continued taking the drugs. He again experienced these symptoms, together with dysphagia, on August 13th. When he visited our University Clinic on August 14th, right-sided perioral edema, slight lip swelling, and submandibular swelling were noted (Fig 1). He took the last dose of 5 mg of enalapril 24 h before the visit. Neither edema of the extremities nor skin rash was observed, and the neurologic examination was grossly intact. His breath sounds were normal. He was diagnosed as having perioral angioedema induced by enalapril. To investigate other possible causes of this episode, we referred him to a dermatologist whose diagnosis was "Quinke's edema". The blood laboratory data were within normal limits except for a slightly elevated white blood cell count of $8.7 \times 10^9/\text{L}$ with a slight increase in neutrophils (70.5%). He reported that the symptoms of angioedema disappeared by the next day without any special treatment, but enalapril was stopped immediately and 20 mg of nifedipine-retard bid was prescribed in combination with 40 mg of furosemide, 100 mg of allopurinol, 10 mg of arotinolol bid, and 5 mg of pravastatin per day. He has had no further episodes of angioedema, throat irritation, or mild dry cough in the 23 months since the cessation of enalapril.

DISCUSSION

ACE inhibitors are recommended as one of the first-line drugs for the treatment of hypertension.^{10,11} We have also indicated the possibility to use ACE inhibitors as one of the first-line antihypertensive agents.¹² ACE inhibitors are generally well tolerated and regarded as rather safe drugs with only occasional side effects; however, several adverse reactions induced by ACE inhibitors are also well known, including cough, skin rash, hypotension, angioedema, as in this case, and other side effects such as neutropenia, impaired taste, and proteinuria. Cough induced by ACE inhibitors is the most common,¹ and hence is the usual reason for discontinuation of ACE inhibitors. In the present case, even though the patient noted a tickling sensation in the throat and mild dry cough soon after the administration of enalapril, he preferred enalapril to nifedipine. Similar cases are documented, in which the mild cough induced by ACE inhibitors may be better-tolerated by patients than more serious adverse reactions such as headache, palpitation, flushing face, generalized fatigue, etc induced by the different class of antihypertensive drugs.¹ The first case of angioedema was described by Jett in 1984.¹³ Since then, the reported incidence of angioedema induced by ACE inhibitors has been estimated at less than 0.7%; however, it is alerted that this rare adverse reaction can be severe and potentially fatal when associated with upper (because it may develop) airway obstruction.^{1,3-8,14} It has been reported that the majority (about 60%) of angioedema reactions occur in the first week of ACE therapy, often within hours of the initial dose.^{1,6,15} Since 1978, when the open clinical trial for the first ACE inhibitor, captopril, started in Japan, numerous ACE inhibitors have been evaluated. Captopril, enalapril, alacepril, delapril, cilazapril, lisinopril, benazepril and imidapril have been widely used for the treatment of hypertension and congestive heart failure, but since 1979 there have been only 2 reports^{8,9} in Japan of angioedema induced by ACE inhibitors, including all the records of the clinical trials and post-marketing surveillance studies. The present case is thus the third of its type in Japan. The reason such angioedema

is so rare in Japan is unknown, but it is believed that Japanese physicians, aware of the side-effects of these drugs, circumvent adverse reactions through consideration of many kinds of medical information. In the present case angioedema developed during long-term (66 months) therapy with enalapril which was totally administered as 19,930 mg of enalapril maleate. The patient and his family had no history of allergies or idiopathic angioedema. There are several reports of angioedema developing during long-term (more than 12 months) therapy with ACE inhibitors, and in some cases the symptoms recurred hours after apparent resolution.^{5,16-19} Among these reports, there is the important and interesting case of a patient who received enalapril over 3 years for his hypertension, during which period he experienced 18 separate episodes of angioedema whose etiology escaped the recognition of several physicians.¹⁸ Thus, it should be emphasized that angioedema may occur at any time during the use of any kinds of ACE inhibitor.

There are several hypotheses regarding the mechanisms contributing to the development of angioedema induced by ACE inhibitors, and it is thought to be biochemical rather than immunologic phenomenon.²⁰ The pathogenesis of angioedema induced by ACE inhibitors is believed to be related to the augmentation of bradykinin activity which causes inflammation, vasodilation, and altered vascular permeability.²¹ Bradykinin is metabolized to inactive moiety by 2 proteases, kininase I (carboxypeptidase N) and kininase II (ACE). Development of angioedema in patients receiving ACE inhibitors may be due to accumulation of tissue bradykinin levels through the decrease in the degradation of bradykinin. In fact, Johnston and colleagues have reported that serum bradykinin did not increase after captopril administration;²² however, we have demonstrated that the urinary excretion rate of kinins increased in patients with essential hypertension after a single dose of 10 mg of enalapril.²³ Furthermore, the effects of intradermal injection of bradykinin have been potentiated by ACE inhibitors in hypertensive patients.²⁴ Deficiency of carboxypeptidase N (kininase I) may also be associated with angioedema reactions.^{6,25} In fact, it has

been proposed that ACE inhibitors may be contraindicated in patients with hereditary angioedema or with a history of idiopathic angioedema because they may increase the risk of severe angioedema.^{14,26} Immunologic factors involving mast cell activation or consumption of complement may not contribute to the development of angioedema;²⁷ however, the exact mechanisms of angioedema induced by ACE inhibitors are still unknown.

It is described that angioedema induced by short-acting ACE inhibitors such as captopril is mild, and responds to antihistamine and glucocorticoid treatment; in contrast, angioedema induced by long-acting ACE inhibitors such as enalapril or lisinopril is serious and sometimes requires intubation or tracheostomy.¹⁶ When angioedema develops, it is suggested that treatment includes immediate withdrawal of the ACE inhibitor and maintenance of an adequate airway. To relieve respiratory distress with vocal cords edema and/or airway obstruction, emergency tracheostomy, epinephrine, glucocorticoids and high-flow oxygen may be required! For patients with severe hypertension and cardiac disease not likely to tolerate epinephrine, short-term intubation or tracheostomy should be employed.

In summary, we described a rare case report on the development of ACE inhibitor-induced angioedema during long-term (66 months) therapy in a patient with essential hypertension. The number of patients treated with ACE inhibitors is increasing greatly. Thus episodes of angioedema will increase, because this adverse reaction is not dose dependent. Although such angioedema is rare, it should be emphasized that it may occur at any time during the use of any kind of ACE inhibitor, and physicians must be aware of the development of this potentially life-threatening adverse effect even among patients who, as in this case, have tolerated a prolonged course of ACE inhibitor therapy.

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