

# Angioneurotic Edema Attributed to the Use of Losartan

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**Background:** Angioedema is a well-known adverse effect of angiotensin-converting enzyme inhibitors. The bradykinin accumulation as a result of the decreased degradation of bradykinin is thought to be the causal mechanism. Angiotensin II antagonists seem to have no effect on the degradation of bradykinin. Therefore, it was expected that angioedema would not occur during treatment with losartan potassium, the first orally active angiotensin II antagonist.

**Methods:** We reviewed the 13 case reports of angioedema associated with the use of losartan reported to Lareb (Netherlands Pharmacovigilance Foundation, Den Bosch) and to the Drug Safety Unit of the Inspectorate for Health Care, Ryswyh, in the Netherlands since the introduction of losartan in 1995 until May 1997.

**Results:** In all 13 cases, a diagnosis of angioedema attributed to the use of losartan seems to be very plau-

sible. In 7 cases the diagnosis could not be confirmed by a physician because the symptoms had already been resolved, but the signs and symptoms clearly indicated angioedema. The adverse reactions occurred within 24 hours to 16 months after the initiation of losartan therapy. Three patients had previously experienced angioedema during treatment with an angiotensin-converting enzyme inhibitor. Eleven of the patients involved were women and 2 were men.

**Conclusions:** Our observations strongly suggest that the onset of angioedema was associated with the use of losartan. Physicians and pharmacists should be aware of this potentially life-threatening complication. It may be advisable not to prescribe angiotensin II antagonists to patients with a history of angioedema (of whatever origin).

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**A**NGIOEDEMA, or angioneurotic edema (Quincke edema), is a well-demarcated, nonpitting edema of the skin and subcutis. It mostly affects the mouth, tongue, pharynx, and eyelids, but may also affect the hands, feet, genitals, and mucous membranes.<sup>1,2</sup> Angioedema of the upper respiratory tract may cause serious laryngeal obstruction and may lead to life-threatening situations.<sup>1,2</sup> In 1% of the cases, angioedema is associated with a hereditary deficiency of the functional enzyme C1 esterase inhibitor (hereditary angioedema) or with an acquired deficiency of this enzyme. In the majority of the cases, however, angioedema is idiopathic. Angioedema may also be induced by several classes of drugs, such as angiotensin-converting enzyme (ACE) inhibitors or nonsteroidal anti-inflammatory drugs.<sup>1-5</sup> Studies have shown that angioedema occurs in 0.1% to 1% of the users of ACE inhibitors.<sup>5,6</sup>

Angioedema caused by the use of ACE inhibitors is thought to be related to the pharmacological actions of this class of drugs. However, the exact mechanism of angioedema attributed to ACE inhibitors is still unknown. It is assumed that

the inhibiting effect of ACE inhibitors on the degradation of bradykinin is the most plausible explanation for the occurrence of angioedema.<sup>2-4,7</sup> The increased bradykinin level may also cause a cough in 0% to 39% of the patients who are treated with ACE inhibitors.<sup>6,8</sup>

As a result of the pharmacological effects of losartan potassium, the first orally active angiotensin II receptor antagonist, it was expected that both cough and angioedema would occur less frequently. Indeed, the incidence of cough attributed to losartan use was found to be comparable with that attributed to the use of diuretics.<sup>9</sup> However, a few case reports of angioedema associated with the use of losartan have been published recently.<sup>10,11</sup>

Since the introduction of losartan in the Netherlands in 1995 until May 1997, 13 reports of angioedema associated with the use of losartan have been received by the Netherlands Pharmacovigilance Foundation and by the Drug Safety Unit of the Inspectorate for Health Care in the Netherlands (**Table**). In all 13 patients, the causal relation between the use of losartan and the occurrence of angioedema was considered to be at least probable. To illustrate the putative relation between lo-

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**Cases of Angioedema Associated With the Use of Losartan Reported to the Netherlands Pharmacovigilance Foundation and the Drug Safety Unit of the Inspectorate for Health Care in the Netherlands**

Patient No./ Age, y/Sex	Daily Dose, mg	Interval*	Symptoms	Previous Episode of Angioedema
1/39/F	100	16 mo	Edema of the face and pharynx; sore throat	No
2/51/F	50	<24 h	Edema of the lip and face	No
3/42/M	25	11 mo	Recurrent edema of the lip	No
4/68/F	50	6 wk	Edema of the tongue	Yes†
5/65/F	50	7 d	Edema of the lip, throat, and face; dizziness	Yes†
6/47/M	50	<24 h	Edema of the lips; headache; nausea; vomiting	No
7/53/F	50	10 mo	Edema of the face	No
8/51/F	50	<24 h	Edema of the lips and oropharynx; dyspnea	Yes†
9/81/F	25	3 d	Edema of the tongue and lips; pruritus	Unknown
10/58/F	50	14 d	Edema of the upper lip and eyelids; cough	No
11/60/F	50	2 d	Edema of the tongue; dermal reactions	No
12/72/F	50	2 mo	Edema of the face	Unknown
13/57/F	50	3 wk	Edema of the face	Unknown

\*Period between start of treatment and appearance of symptoms.

†History of angioedema associated with the use of angiotensin-converting enzyme inhibitors.

sartan use and angioedema, we describe 3 of the patients in this case series in more detail.

**REPORT OF CASES**

**CASE 1**

A 39-year-old woman visited her general practitioner with a 2-hour history of swelling of her face and throat, sore throat, and dyspnea. For 16 months, she had been taking losartan potassium (50 mg twice daily), amiloride hydrochloride (5 mg/d), and bumetanide (5 mg/d) for essential hypertension. She had also taken dexfenfluramine hydrochloride (15 mg twice daily). Her general practitioner diagnosed an allergic reaction, immediately administered 2 mg of clemastine fumarate intramuscularly, and then referred her to an otolaryngologist, who diagnosed angioneurotic edema and prescribed terfenadine (60 mg twice daily) and prednisone (starting at a dosage of 50 mg/d, which was gradually reduced over 6 days). Determination of complement did not reveal a C<sub>1</sub> esterase deficiency. Losartan therapy was discontinued. The angioneurotic edema disappeared within a few days, and the patient recovered completely.

**CASE 2**

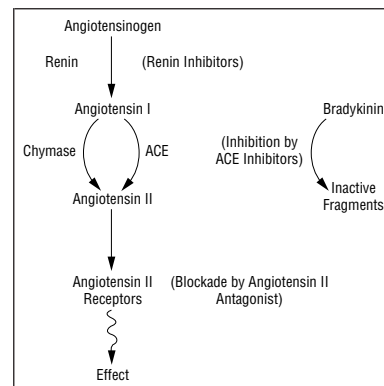
A 51-year-old woman was taking losartan potassium (50 mg/d) to con-

trol hypertension. She also used a combination of estradiol valerate and medroxyprogesterone acetate as hormone replacement therapy. Within 1 day after ingesting the first dose of losartan, she developed edema of her lip and face and was absent-minded. The next day, she stopped taking losartan without consulting her general practitioner. Within a few days, all symptoms resolved.

Three days later, the patient decided to resume the use of losartan. The above described symptoms recurred within 1 day, after which she decided to stop taking losartan permanently. All her symptoms resolved within 3 days. She had never had similar symptoms before, nor did she have a history of food allergy or previous treatment with ACE inhibitors.

**CASE 3**

A 42-year-old man visited his general practitioner with complaints of swelling of the lower lip. He had never experienced this symptom before. He had no history of food allergy. For 11 months, he had been taking losartan potassium (25 mg/d) and metoprolol succinate (100 mg/d) for hypertension. He had also taken acetosal (80 mg/d) after a previous myocardial infarction. The general practitioner diagnosed angioedema and administered 2 mg of clemastine fumarate intravenously. The patient's swelling of the lower lip gradu-



The enzymatic cascade of the renin-angiotensin system showing potential points of therapeutic intervention. Renin inhibitors slow down the conversion of angiotensin I from angiotensinogen. Angiotensin-converting enzyme (ACE) inhibitors slow down the conversion of inactive angiotensin I into active angiotensin II. The alternative route, with the enzyme chymase as a catalyst, is particularly of significance for the formation of angiotensin II in cardiac tissues. This process is not suppressed by ACE inhibitors. Angiotensin II antagonists block the effects of angiotensin II at the receptor level (from van Zwieten and Lie<sup>18</sup>).

ally diminished. However, the swelling of the lip recurred on a weekly basis. These episodes of angioedema were treated with 1-mg tablets of clemastine fumarate.

Four months after the patient's first episode of angioedema, the general practitioner decided to discontinue the losartan therapy. The patient's symptoms disappeared completely within 2 weeks and did not recur.

**COMMENT**

Losartan potassium is the first of a series of nonpeptide angiotensin II antagonists that are suitable for oral administration.<sup>7,8,12</sup> Others are candesartan, irbesartan, and valsartan. Angiotensin II antagonists, like ACE inhibitors, interfere with the renin-angiotensin system. Angiotensin-converting enzyme inhibitors inhibit the formation of angiotensin II from angiotensin I. Angiotensin II antagonists, however, block the effect of angiotensin II at the level of the angiotensin II receptor (**Figure**).

Two disadvantages to the use of ACE inhibitors are a troublesome cough (in 0%-39% of the patients)<sup>6,8</sup> and angioedema (in 0.1%-1% of the patients).<sup>5,6</sup> Although angioedema is rare, it may be life-threatening.<sup>1-5</sup> The exact mechanism of angioedema at-

tributed to ACE inhibition is not known. Apart from the conversion of angiotensin I into angiotensin II, ACE inhibitors also slow down the degradation of bradykinin into its metabolites (Figure). It is assumed that the inhibiting effect of ACE inhibitors on the degradation of bradykinin is the most plausible explanation for the occurrence of angioedema.<sup>2,4,7</sup> The accumulation of bradykinin as a result of this inhibition not only leads to vasodilation, but also to increased vascular permeability.<sup>1</sup> Experimental studies have proved that bradykinin can induce edema.<sup>13</sup> Losartan seems to have no influence on the degradation of bradykinin.<sup>14</sup> However, the 13 cases discussed herein and the few case reports in the literature suggest that angioedema may occur during losartan use.<sup>10,11</sup>

There are a number of reasons to consider a pharmacological rather than an immunological cause for the angioedema that may occur during the use of losartan. First, in a number of cases, there has been a short lagtime between start of the therapy and the occurrence of angioedema. However, like ACE inhibitor-associated angioedema, losartan-associated angioedema may appear after more than 1 year of treatment. Second, 3 of the patients in our series had previously developed angioedema during use of an ACE inhibitor. Finally, it is notable that angioedema has also been reported with the use of valsartan, another angiotensin II antagonist (package insert, Ciba-Geigy Corp, Summit, NJ).

Eleven (84.6%) of the 13 patients in our series were women. A similar pattern has been reported in cases of angioedema associated with ACE inhibitors in the Netherlands.<sup>3</sup> The observation that angioedema also seems to be associated with the use of losartan suggests that the pathophysiological mechanism might be basically similar for both ACE inhibitors and angiotensin II antagonists.

However, a direct effect of losartan on the degradation of bradykinin has not been demonstrated.<sup>14</sup> Therefore, the underlying mechanism of angioedema is probably unrelated to bradykinin excess, and additional studies are needed to clarify the role of bradykinin in the development of angioedema caused by

ACE inhibitors and angiotensin II antagonists. Other possible mechanisms, such as the potential role of histamine and the inactivation or inhibition of C<sub>1</sub> esterase inhibitor,<sup>6</sup> should also be the subject of further research. It is conceivable that a decreased stimulation of the angiotensin II receptor may lead to angioedema in some patients.

Because of the possible complications of angioedema and the considerably varying lagtime between the initiation of losartan therapy and the occurrence of angioedema (<24 hours to >1 year), it is of major importance that physicians and pharmacists are aware of this adverse effect. Gabb et al<sup>15</sup> concluded that there is clearly a problem with the recognition of ACE inhibitor-associated angioedema. They found that in more than 50% of the cases of ACE inhibitor-associated angioedema, ACE inhibitor therapy had been continued.

It is important that swelling, particularly in the area of mouth and throat, is recognized as a possible adverse reaction to angiotensin II antagonists and ACE inhibitors. This symptom should be included in the patient information leaflet, and patients should be strongly advised to contact their physician immediately when any such swelling occurs.

In most cases, discontinuation of the treatment with the angiotensin II antagonist is sufficient to make the swelling disappear. In serious cases, epinephrine and corticosteroids can be administered. Timely intubation should be considered in life-threatening situations.<sup>1</sup>

Although ACE inhibitor-associated angioedema is not considered a contraindication to the use of angiotensin II antagonists, it may be advisable not to prescribe them for patients with a history of ACE inhibitor-associated angioedema until its pathogenesis has been established. The same caution should be observed in cases in which the patients have a history of hereditary or idiopathic angioedema, in whom the use of ACE inhibitors is contraindicated.<sup>4,16,17</sup>

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