

# Letters to the Editor

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## Are Angiotensin II Receptor Antagonists Safe in Patients With Previous Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema?

To the Editor:

We describe the results of a literature and pharmacovigilance survey on the clinically relevant problem of whether angiotensin II receptor antagonists (ARAs) can be safely used in patients with previous angiotensin-converting enzyme (ACE) inhibitor-induced angioedema. The results suggest that patients with previous ACE inhibitor-induced angioedema are at increased risk for relapse angioedema during the use of an angiotensin II receptor antagonist, and therefore angiotensin II antagonist should not be considered a safe substitute in patients with previous ACE inhibitor-induced angioedema.

ACE inhibitors (ACEIs) are widely applied as blood pressure-lowering agents. Although ACEIs are generally well tolerated, they are also involved in the activation of bradykinin, enkephalins, and other biologically active peptides, which may result in adverse effects such as cough, increased bronchial reactivity, and angioedema. An attempt to achieve a more specific blockade of the effects of angiotensin II resulted in the introduction in 1995 of angiotensin II receptor antagonists (ARAs), starting with losartan and followed by irbesartan, valsartan, candesartan, and eprosartan. Because the pharmacology of ARAs is substantially different from ACEIs, the adverse effects associated with ACEIs were not anticipated. However, cases of cough and more rarely of angioedema attributed to the use of ARAs have repeatedly been described.<sup>1-6</sup> The pharmacological mechanism of these effects remains to be clarified. Estimates of the incidence of ACEI-associated angioedema vary between 0.1% to 2%. The onset of angioedema after the first intake of ACEIs is usually within the first week of treatment (60%) but may also cover several years. With regard to ARAs, there are as yet not enough data available to reliably estimate the incidence of the development of drug-induced angioedema, but it is thought to be lower than 0.1%. A recent experience in the Academic Medical Center in Amsterdam (The Netherlands), concerning a patient with angioedema during the use of captopril, raised the question whether ARAs are a safe substitute for ACEIs in the treatment of hypertension.

To find the answer to this common and important question, we did a search of the medical literature using PubMed, consulted the national pharmacovigilance center in our country (the Netherlands Pharmacovigilance Foundation LAREB), and contacted the Uppsala Monitoring Center (UMC) of the World Health Organization in Sweden.

In the literature, case studies were found of 23 patients who experienced angioedema during the use of the ARAs losartan or valsartan;<sup>1-6</sup> 7 of these patients appeared to have had previously angioedema while using an ACEI. On the other hand, only 1 patient was known to have used an ACEI without angioedema. In the remaining 15 cases, there was no information with regard to possible previous exposure to ACEIs.

The LAREB Foundation has received a total of 18 case reports from healthcare professionals describing angioedema attributed to the use ARAs. Five of these 18 patients were known to have previously used ACEIs; all 5 had also experienced angioedema during that period.

A search of the database of the WHO-UMC showed that 356 (4.5%) of a total of 7994 reported suspected adverse drug reactions to various ARAs referred to angioedema (the World Health Organization Adverse Reaction Dictionary terms angioedema, larynx edema, face edema, and edema periorbital). Unfortunately, no information could be provided regarding previous use of ACEIs. As a comparison, for ACEIs as a group, the relative reporting of angioedema was 6% (4053 reports of a total of 67 610 suspected adverse reactions).

During clinical trials with ARAs, angioedema has only occurred sporadically. Therefore, the numbers of case reports (in the literature, registered at the LAREB Foundation, and at the UMC) of angioedema occurring during the use of ARAs are much higher than we had expected. The information in the WHO-UMC database leaves no doubt that angioedema does occur during the use of ARAs. The finding that the reporting percentages of ACEIs and ARAs are in the same range does not mean, however, that such reactions occur in similar frequencies. In a study concerning cough in association with losartan and ACEIs by the Drug Surveillance Research Unit, using prescription event monitoring methodology, it was found that losartan had been selectively prescribed to patients with previous cough during ACEI use. Of 101 patients who had discontinued losartan because of cough, 91% had previously been prescribed an ACEI and 86% had previously experienced cough during ACEI use.<sup>7</sup> After adjusting for "carry-over," the rates of cough were substantially lower for losartan as compared with ACEIs.

Although no data are available, we assume that selective prescribing has also taken place because of previous angioedema during the use of ACEIs and that the number of reports of angioedema in association with ARAs in the UMC database reflects that angioedema occurs in increased frequency in patients with previous angioedema during ACEI use. In addition, the number of cases in the UMC database may have been influenced by a relatively high reporting rate.

We conclude that ARAs can cause angioedema, but in the general population, ARAs cause angioedema at lower frequencies than ACEIs. The available evidence suggests, however, that patients with previous ACEI-induced angioedema are at increased risk for relapse angioedema during the use of an ARA. Although it remains to be determined how frequently cross-hypersensitivity occurs, we conclude that ARAs may not be a safe substitute in patients with previous ACEI-induced angioedema.

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1. van Rijnsoever EW, Kwee-Zuiderwijk WJ, Feenstra J. Angioneurotic edema attributed to the use of losartan. *Arch Intern Med.* 1998;158:2063-2065.
2. Cha YJ, Pearson VE. Angioedema due to losartan. *Ann Pharmacother.* 1999;33:936-938.
3. Frye CB, Pettigrew TJ. Angioedema and photosensitive rash induced by valsartan. *Pharmacotherapy.* 1998;18:866-868.
4. Sharma PK, Yium JJ. Angioedema associated with angiotensin II receptor antagonist losartan. *South Med J.* 1997;90:552-553.
5. Rivera JO. Losartan-induced angioedema. *Ann Pharmacother.* 1999 Sep;33:933-935.
6. Schuster C, Reinhart WH, Hartmann K, Kuhn M. Angioedema induced by ACE inhibitors and angiotensin II-receptor antagonists: analysis of 98 cases. *Schweiz Med Wochenschr.* 1999;129:362-369.
7. Mackay FJ, Pearce GL, Mann RD. Cough and angiotensin II receptor antagonists: cause or confounding? *Br J Clin Pharmacol.* 1999;47:111-114.