

Use of angiotensin receptor antagonists in patients with ACE inhibitor induced angioedema

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Granger et al. recently published the results of their randomized controlled double blind clinical trial comparing the effect of candesartan, an angiotensin receptor antagonist (ARA), with placebo in patients with chronic heart failure and previous intolerance to an angiotensin-converting-enzyme (ACE) inhibitor¹. The results led to the conclusion that candesartan was generally well-tolerated and it reduced cardiovascular mortality and morbidity in this group of patients. This would encourage physicians to prescribe ARAs in patients who have experienced adverse effects during the use of an ACE inhibitor.

By providing additional information on the safety aspects of using ARAs in patients with previous intolerance to ACE inhibitors, we would like to express our concern, especially in the case of those who have suffered from previous ACE inhibitor associated angioedema.

The most prominent side effects associated with ACE inhibitors, non-productive cough and more rarely angioedema, have been attributed to the activation of bradykinin, enkephalins and other biologically active peptides. As ARAs selectively block the angiotensin 1 (AT1) receptor and do not inhibit the catabolism of bradykinin, no such adverse effects were anticipated. However, the number of case reports describing cough and angioedema associated with ARAs has been steadily increasing over the past years², with an incidence that remains lower than for ACE inhibitors. The underlying mechanism remains poorly understood. A role for stimulation of the AT2 receptor by the increased levels of angiotensin II has been proposed³. The function of the AT2 receptor has not been fully elucidated, but its putative effects have been suggested to involve activation of the bradykinin-prostaglandin-nitric oxide cascade^{4,5}. This could account for the occurrence of bradykinin-mediated side-effects with both ACE inhibitors and ARAs and their possible cross-hypersensitivity.

The clinical trial conducted by Granger et al.¹ reports 3 cases of angioedema among the 1,013 individuals in the candesartan group (0.3%). This exceeds the incidence of ARA associated angioedema in the general population and even exceeds the incidence of 0.1–0.2%, reported for the widely recognized ACE inhibitor induced angioedema⁶. Strikingly, all 3 cases occurred in the group of 39 patients with a history of angioedema following the use of ACE inhibitors. This suggests that patients with previous ACE inhibitor induced angioedema are at increased risk for relapse angioedema during the use of an ARA (7.7% in this study). Indeed, we found that an increased risk has been reported consistently in literature (6–13), with estimates of almost half of ARA induced angioedema being preceded by a prior episode of angioedema attributed to ACE inhibitor therapy^{7,10}.

Additional information on the safety aspects of ARAs was provided by the National Pharmacovigilance Center in our country (The Netherlands Pharmacovigilance Centre Lareb) and the Uppsala Monitoring Center (UMC) of the World Health Organization (WHO) in Sweden.

In the period from 1 May 1996 to 1 November 2003, The Netherlands Pharmacovigilance Centre received a total of 47 reports from healthcare professionals describing angioedema attributed to the use of ARAs. Of the patients, 16 were known to have previously used an ACE inhibitor, 11 of whom (8 women and 3 men) had experienced angioedema during that period as well (69%). A search of the international database of the WHO Uppsala Monitoring Centre showed that 907 (7.0%) of a total of 12,881 casereports of suspected adverse drug reactions to various ARAs (single and combination products) referred to angioedema (WHOART: angioedema, face edema, edema periorbital, tongue edema, larynx edema). Unfortunately, no information could be provided regarding the possible previous use of ACE inhibitors in these patients. In comparison, for ACE inhibitors as a group, the relative reporting of angioedema was 9,029 (8.9%) of a total of 100,920 reports of suspected adverse reactions (until 8 November 2003).

The trial performed by Granger et al. showed that candesartan was generally well tolerated and reduced cardiovascular mortality and morbidity in patients with symptomatic chronic heart failure and previous intolerance to ACE inhibitors. This is an important result for patients with a life-threatening condition without other therapeutic options. However, angioedema is also potentially life-threatening. Although the absolute risk is limited, our data indicate that the risk of developing angioedema while using an ARA highly correlates with previous ACE inhibitor induced angioedema. Therefore, we advise extreme caution when prescribing ARAs to patients with a history of ACE inhibitor associated angioedema.

Conflict of interest

None declared.

Funding

None.

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