CURRENT OPINION

Drug Safety 2002; 25 (2): 73-76
0114-5916/02/0002-0073/$25.00/0

Can Angiotensin Receptor Antagonists Be Used Safely in Patients with Previous ACE Inhibitor-Induced Angioedema?

Laurence G. Howes[1,2] and *Diane Tran*[1]

1 Department of Clinical Pharmacology, University of New South Wales, Sydney, Australia
2 Department of Clinical Pharmacology, St George Hospital, Kogarah, Sydney, Australia

Abstract

Angioedema is an uncommon but potentially life-threatening adverse event associated with ACE inhibitor therapy which is believed to be due to potentiation of the vascular effects of bradykinin. Angiotensin receptor antagonists were not expected to produce angioedema, as they do not inhibit the catabolism of bradykinin. However, it is now apparent that angioedema is occasionally associated with angiotensin receptor antagonist therapy and may be more likely to occur in patients who have previously experienced angioedema while receiving ACE inhibitors. Angiotensin receptor antagonists cannot be considered to be a safe alternative therapy in patients who have previously experienced ACE inhibitor-associated angioedema.

Angiotensin receptor antagonists are a relatively new class of cardiovascular drug, which are gaining widespread use for the treatment of hypertension. They also have a potential although unproven role in the treatment of cardiac failure. Angiotensin receptor antagonists are at least as effective as ACE inhibitors in lowering blood pressure while having an adverse event profile similar to that of placebo.[1] In particular, angiotensin receptor antagonist therapy is associated with a lower incidence of cough than ACE inhibitors and, at least theoretically, may be associated with a lower incidence of angioedema.[1] The mode of action of ACE inhibitors and angiotensin receptor antagonists is illustrated in figure 1. ACE inhibitors act by inhibiting ACE, a nonspecific dipeptidase involved in the conversion of angiotensin I to angiotensin II. This enzyme is also involved in the inactivation of other peptides such as bradykinin, substance P and neurokinin A. The potentiation of these peptides contributes to both the beneficial and the adverse effects of ACE inhibitors.[2] It is widely believed that potentiation of bradykinin is responsible for angioedema associated with ACE inhibitor therapy. Angiotensin receptor antagonists act by selectively blocking the angiotensin type 1 (AT_1) receptor

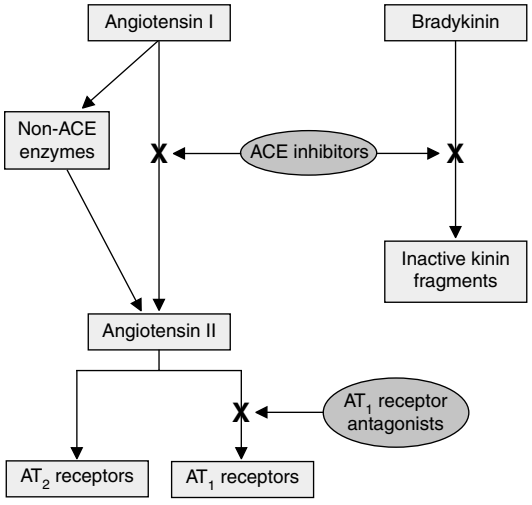

Fig. 1. Sites of action of ACE inhibitors in the metabolism of angiotensin II and bradykinin and the site of action of angiotensin (AT_1) receptor antagonists.

which is responsible for most of the deleterious actions of angiotensin II, including blood pressure elevation. Unopposed activation of angiotensin type 2 (AT_2) receptors during AT_1 receptor blockade may produce beneficial effects by promoting vasodilation, lowering blood pressure and reducing the trophic cardiovascular effects of angiotensin II.[1]

1. ACE Inhibitor-Associated Angioedema

Angioedema is an uncommon but potentially life-threatening adverse event associated with ACE inhibitor therapy. Angioedema was first described in 1882 by Quincke.[3] It is a vascular reaction characterised by nonpitting oedema of the dermis and subcutaneous fat. Any area of the body may be involved but the most common sites are the tongue, lips, throat, nose or other parts of the face, extremities, genitalia and viscera. Visceral involvement may present as diarrhoea, nausea, abdominal pain and acute intestinal obstruction. Angioedema of the upper respiratory tract can lead to acute respiratory distress due to airways obstruction and result in death.[4] Angioedema associated with ACE inhibitor therapy was first reported in 1980 by Wilkin et al.[5] Occasional deaths due to angioedema have been associated with ACE inhibitor therapy.[6-10] While most (60%) episodes of angioedema occur during the first week of ACE inhibitor therapy, a significant proportion occur following prolonged therapy of months or even years. The often unpredictable nature of recurrent angioedema is another factor that may make the association with ACE inhibitor therapy less apparent and delay the diagnosis. The reported incidence of ACE inhibitor-associated angioedema varies between <0.1 and 1.0%, although most of the large studies indicate an incidence of about 0.1 to 0.2%.[4] The true incidence may be higher, as spontaneous reporting of adverse events may be more likely during the earlier stages of drug therapy, when the relationship with therapy would be more apparent. The risk of ACE inhibitor-associated angioedema appears to be 4.5-fold higher in African Americans than Caucasians.[11,12]

2. Potential Mechanism Involved in ACE Inhibitor-Associated Angioedema

The precise mechanism responsible for ACE inhibitor-associated angioedema is not known. However, the most widely held theory is that it results from the reduced inactivation of bradykinin by ACE inhibitors. Bradykinin increases vascular permeability and causes vasodilation. This occurs as a result of arteriolar vasodilation (mediated by the β_2-adrenoceptor) and venule constriction (mediated by the β_1-adrenoceptor), leading to an increase in capillary pressure. The release of other factors that increase capillary permeability, including nitric oxide, interleukin-1 and tumour necrosis factor, are also probably involved.[13] Plasma bradykinin levels have been reported to be elevated during episodes of angioedema (due to any cause) and to be markedly elevated during an attack of angioedema in a patient receiving an ACE inhibitor.[14] However, only a very small proportion of patients who receive ACE inhibitor therapy develop angioedema, suggesting that other factors such as inher-

ited abnormalities of bradykinin metabolism must play a role. An enzyme defect resulting in the delayed catabolism of the synthetic bradykinin analogue *N*-Arg9-bradykinin has been described in 50% of 21 patients who developed angioedema while receiving ACE inhibitors.[15] African Americans with hypertension have been reported to have a lower urinary excretion rate of the enzyme kallikrein, which converts kininogen to bradykinin.[4] It is been hypothesised that African Americans with hypertension may therefore have lower endogenous bradykinin levels and may be more sensitive to ACE inhibitor-induced increases in bradykinin than Caucasians.[16]

Several rare abnormalities of enzymes involved in the metabolism of bradykinin or components of the complement system have been described in patients with angioedema, including C_1 esterase deficiency,[17] familial deficiencies of carboxyalkyldipeptide N,[18] deficiency of α_1-antitrypsin and a partial deficiency of complement C4.[19] While it is theoretically possible that persons with these disorders may be at greater risk of developing angioedema during ACE inhibitor therapy, it is unlikely that the occurrence of these rare deficiencies accounts for the majority of cases of ACE inhibitor-associated angioedema. Other possible mechanisms for ACE inhibitor-associated angioedema include alterations in immune responses, enhancement of substance P formation and bradykinin-induced histamine release.[4]

3. Angioedema Associated with Angiotensin Receptor Antagonist Therapy

While it was initially hoped that angiotensin receptor antagonist therapy would not be associated with angioedema, this is now known not to be the case. The true incidence of angioedema associated with angiotensin receptor antagonist therapy remains uncertain and it is unclear whether the incidence of angioedema varies between the individual drugs in this therapeutic class. The angiotensin receptor antagonists that have been used clinically in Australia are presented in table I, along with a number of reports of angioedema associated with their use in Australia up to April 2001. Most reports of angioedema have occurred during therapy with losartan or irbesartan. However, this may merely reflect the fact that these agents have been used more widely than other members of the class.

There is evidence that angioedema associated with angiotensin receptor antagonist therapy may be more likely to occur in patients who have experienced angioedema while taking ACE inhibitors. A review of 19 patients who developed angioedema while receiving either losartan or valsartan found that 32% had a prior history of ACE inhibitor-associated angioedema.[20] Another review of 13 patients who experienced angioedema during losartan therapy found that three patients had previously experienced angioedema while receiving ACE inhibitors, and in a further three patients a history of potential adverse events during ACE inhibitor therapy had not been obtained.[21]

Angioedema has been described as early as 30 minutes after the administration of a single dose of losartan, suggesting a causal relationship independent of immune mechanisms which would require prior exposure.[22] If angiotensin receptor antagonists produce angioedema in susceptible individuals, particularly in individuals who have previously experienced angioedema while receiving

Table I. Angiotensin receptor antagonists licensed for marketing in Australia and the number of reports of angioedema[a] associated with their use up to April 2001 (data obtained from ADRAC, Therapeutic Goods Administration, Canberra, Australia)

Angiotensin receptor antagonist	Reported cases of angioedema
Losartan[b]	28
Irbesartan	63
Telmisartan	5
Eprosartan	2
Candesartan	0
Valsartan[b]	0

a Angioedema was considered to be all reports described as either angioedema, face oedema, larynx oedema, periorbital oedema or tongue oedema.

b Losartan and valsartan have marketing approval in Australia but are not currently marketed. Losartan was marketed briefly but subsequently withdrawn; valsartan has been used in clinical trials.

ACE inhibitors, possible mechanisms are not readily apparent. Angiotensin receptor antagonists do not appear to increase the levels of bradykinin or other peptides that may be involved in the production of angioedema.[23] However, there is increasing evidence that unopposed activation of AT_2 receptors by angiotensin II during angiotensin receptor antagonist therapy may produce vasodilation and increases in vascular permeability through mechanisms which involve nitric oxide release and potentiation of the effects of bradykinin.[24]

4. Conclusions

The incidence of angioedema in patients receiving angiotensin receptor antagonists is uncertain but appears to be lower than in patients receiving ACE inhibitor therapy. However, there is evidence to suggest that a significant number of patients who develop angioedema while receiving angiotensin receptor antagonists have previously experienced angioedema during ACE inhibitor therapy. As angioedema is potentially life threatening, angiotensin receptor antagonists should be used with extreme caution in patients who have previously experienced angioedema while receiving ACE inhibitors. Angiotensin receptor antagonist therapy should be contemplated in these patients only if there is no other alternative.

References

1. Howes LG, Christie N. Angiotensin receptor antagonists and ACE inhibitors. Aust Fam Physician 1998; 27: 914-21
2. Linz W, Wiemer G, Gohlke P, et al. Contributions of kinins to the cardiovascular actions of angiotensin converting enzyme inhibitors. Pharmacol Rev 1995; 47: 25-49
3. Quincke H. Über akutes umschiebenes Hautödem. Monatsschr Prakt Dermatol 1882; 1: 129
4. Vleeming W, van Amsterdam JG, Stricker C, et al. ACE inhibitor-induced angioedema. Incidence, prevention and management. Drug Saf 1998; 18: 171-88
5. Wilkin JK, Hammond JJ, Kirkendall WM. The captopril induced eruption. A possible mechanism: cutaneous kinin potentiation. Arch Dermatol 1980; 116: 902-5
6. Suarez M, Ho PW, Johnson ES, et al. Angioneurotic edema, agranulocytosis, and fatal septicemia following captopril therapy. Am J Med 1986; 81: 336-8
7. Slater EE, Merrill DD, Guess HA, et al. Clinical profile of angioedema associated with angiotensin converting enzyme inhibition. JAMA 1988; 260: 967-70
8. Barna JS, Frable MA. Life threatening angioedema. Otolaryngol Head Neck Surg 1990; 103: 795-8
9. Ulmer JL, Garvey MJ. Fatal angioedema associated with lisinopril. Ann Pharmacother 1992; 26: 1245-6
10. Oike Y, Ogata Y, Higashi D, et al. Fatal angioedema associated with enalapril. Intern Med 1993; 32: 308-10
11. Burkhart GA, Brown NJ, Griffin MR, et al. Angiotensin converting enzyme inhibitor associated angioedema: higher risk in blacks than in whites. Pharmacoepidemiol Drug Saf 1996; 5: 149-54
12. Brown NH, Rat WA, Snowden M, et al. Black Americans have an increased rate of angiotensin converting enzyme inhibitor associated angioedema. Clin Pharmacol Ther 1996; 60: 8-13
13. Regoli D. Neurohumoral regulation of precapillary vessels: the kallikrein-kinin system. J Cardiovasc Pharmacol 1984; 6 Suppl. 2: S401-12
14. Nussberger J, Cugno M, Amstutz C, et al. Plasma bradykinin in angioedema. Lancet 1998; 351: 1693-7
15. Blais Jr C, Rouleau JL, Brown NJ, et al. Serum metabolism of bradykinin and des-Arg9-bradykinin in patients with angiotensin converting enzyme inhibitor associated angioedema. Immunopharmacology 1999; 43: 293-302
16. Gainer JV, Nadeau JH, Ryder D, et al. Increased sensitivity to bradykinin among African Americans. J Allergy Clin Immunol 1996; 98: 283-7
17. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema; the clinical syndrome and its management. Ann Intern Med 1976; 84: 580-93
18. Mathews KP, Pan PM, Gardner NJ, et al. Familial carboxypeptidase N deficiency. Ann Intern Med 1980; 93: 443-5
19. Vaith P, Bender K, Peter HH. Angioneurotic edema in hereditary alpha-1-antitrypsin deficiency. Immun Infekt 1991; 19: 27-9
20. Warner KK, Visconti JA, Tschampel MM. Angiotensin II receptor blockers in patients with ACE inhibitor induced angioedema. Ann Pharmacother 2000; 24: 526-8
21. Van Rijnsoever EW, Kwec-Zuiderwijk WJ, Feenstra J. Angioneurotic edema attributed to the use of losartan. Arch Intern Med 1998; 158: 2063-5
22. Acker CG, Greenberg A. Angioedema induced by the angiotensin II blocker losartan [letter]. N Engl J Med 1995; 333: 1572
23. Blais Jr C, Leclair P, Molinaro G, et al. Absence of effect of chronic angiotensin II type 1 receptor blockade on endogenous kinin concentration-induced paw edema model in the rat. Peptides 1999; 20: 343-52
24. Sosa Canache B, Cierco M, Gutierrez CI, et al. Role of bradykinins and nitric oxide in the AT2 receptor medicated hypotension. J Hum Hypertens 2000; 14 Suppl. 1: S40-6

Correspondence and offprints: Professor *Laurence G. Howes*, Department of Clinical Pharmacology, St George Hospital, Kogarah, Sydney, NSW 2217, Australia.