CME CREDIT

ONE MINUTE CONSULT

BRIEF QUESTIONS AND ANSWERS ON CURRENT CLINICAL CONTROVERSIES

Q: Can angiotensin II receptor blockers be used in patients who have developed a cough or angioedema as a result of taking an ACE inhibitor?

DONALD G. VIDT, MD
Department of Nephrology and Hypertension, Cleveland Clinic; member, Sixth Joint National Committee on Detection, Evaluation, and Treament of High Blood Pressure

A: ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs) appear to be an appropriate alternative for patients who have developed an intolerable cough or angioedema while taking an angiotensin-converting enzyme (ACE) inhibitor. The incidence of these adverse effects is much lower with ARBs than with ACE inhibitors; moreover, small clinical studies have shown that ARBs lower blood pressure just as well as ACE inhibitors. Larger clinical trials that are underway should further clarify the efficacy and safety of ARBs compared with ACE inhibitors.

COUGH IS COMMON WITH ACE INHIBITORS

ACE inhibitor-induced cough occurs twice as often in women as in men and more frequently in nonsmokers. Although post-marketing surveys indicated that cough occurs in only 0.1% to 3% of patients who take an ACE inhibitor, two randomized controlled trials found the incidence to be much higher.[1,2] Conservative estimates suggest that about 10% of patients treated with an ACE inhibitor develop this problem.

The cough usually begins within 1 to 2 months after starting therapy. It is dry, persistent, and mostly nonproductive, and it is often described as a "tickling in the throat." It may occur more frequently when a person reclines, and it usually resolves 5 to 7 days after the drug is discontinued.

The mechanisms responsible for ACE inhibitor-related cough are not fully understood, but kinins and prostaglandins have been suggested as likely mediators.[3] Both bradykinin and prostaglandins are tussive agents, and some prostaglandins have been shown to increase both bronchoconstriction and cough response. These observations seem to mesh with the observed effects of ACE inhibitors, which are associated with an accumulation of bradykinin and substance P and increased prostaglandin production. Evidence suggests that nonsteroidal anti-inflammatory drugs such as sulindac and indomethacin, which inhibit prostaglandin synthesis, can reduce or abolish this adverse effect.[4,5]

ARBs cause fewer side effects than do ACE inhibitors

ANGIOEDEMA: RARE BUT POTENTIALLY LETHAL

ACE inhibitor therapy is one of the most common causes of angioedema—nonpitting edema of vascular origin that is confined to the head and neck. The edema can affect the floor of the mouth, tongue, larynx, lips, and face.[6] ACE inhibitor-induced angioedema occurs most frequently in African American patients.

Generally speaking, angioedema is not a common adverse effect of ACE inhibitor therapy. It is nonetheless important because it can be potentially lethal if it develops in the tongue, glottis, or larynx. For that reason, patients should not be switched to another ACE inhibitor if this complication occurs.

ARBs AS AN ALTERNATIVE

Angiotensin II receptor blockers, a newer class of drugs, are distinct from the ACE inhibitors in that they have no effect on angiotensin-

Downloaded from www.ccjm.org on May 7, 2025. For personal use only. All other uses require permission.

converting enzyme. Rather, they block the diverse physiologic effects of angiotensin II by specifically blocking angiotensin II tissue receptors.[7] Currently, there are 6 ARBs approved by the Food and Drug Administration: candesartan (Atacand), eprosartan (Teveten), irbesartan (Avapro), losartan (Cozaar), telmisartan (Micardis), and valsartan (Diovan).

These drugs are not associated with an increase in circulating bradykinins or an increase in prostaglandin production, so theoretically, they should cause less of a problem with cough. In fact, that is what clinical studies of ARBs have found. Overall, the studies showed that the frequency of cough in patients taking ARBs was statistically significantly lower than that in patients taking ACE inhibitors. The frequency was comparable to that observed in the placebo controls.

Although a few cases of angioedema did occur during clinical trials of the six ARBs, there was no clear pattern of occurrence.[8,9] However, a recent review of case reports documenting ARB-induced angioedema reported that one third of the patients had experienced a prior episode of ACE inhibitor-induced angioedema.[10] In view of these observations, ARBs should be used with caution in patients with a prior history of angioedema.

REFERENCES

1. **Simon SR, Black HR, Moser M, Berland WE.** Cough and ACE inhibitors. Arch Intern Med 1992; 152:1698–1700.
2. **Fletcher AE, Palmer AJ, Bulpitt CJ.** Cough with angiotensin converting enzyme inhibitors: how much of a problem? J Hypertens 1994; 12(Suppl 2):S43–S47.
3. **Lacourciere Y, Lefebvre J, Nakhle G, Faison EP, Snavely DB, Nelson EB.** Association between cough and angiotensin converting enzyme inhibitors versus angiotensin II antagonists: The design of a prospective, controlled study. J Hypertens 1994; 12(suppl 2):S49–S53.
4. **Fogari R, Zoppi A, Tettamanti F, Malamani GD, Tinelli C, Salvetti A.** Effects of nifedipine and indomethacin on cough induced by angiotensin-converting enzyme inhibitors: a double-blind, randomized, cross-over study. J Cardiovasc Pharmacol 1992; 19:670–673.
5. **McEwan JR, Choudry NB, Fuller RW.** The effect of sulindac on the abnormal cough reflex associated with dry cough. J Pharmacol Exp Ther 1990; 255:161–164.
6. **Agah R, Bandi V, Guntupalli KK.** Angioedema: the role of ACE inhibitors and factors associated with poor clinical outcome. Intens Care Med 1997; 23:793–796.
7. **Burnier M, Brunner HR.** Angiotensin II receptor antagonists. Lancet 2000; 355:637–645.
8. **Schuster C, Reinhart WH, Hartmann K, Kuhn M.** [Angioedema under ACE inhibitors and angiotensin II-receptor antagonists: analysis of 98 cases.] Schweiz Med Wochenschr 1999; 129:362-369.
9. **Pylypchuk GB.** ACE inhibitor- versus angiotensin II blocker-induced cough and angioedema. Ann Pharmacother 1998; 32:1060-1066.
10. **Warner KK, Visconti JA, Tschampel MM.** Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. Ann Pharmacother 2000; 34:526-528.

ADDRESS: Donald G. Vidt, MD, Department of Nephrology and Hypertension, A51, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail vidtd@ccf.org.

INTERNAL MEDICINE BOARD REVIEW

Clinical vignettes and questions on the differential diagnosis and treatment of medical conditions likely to be encountered on the Qualifying Examination in Medicine — as well as in practice.
Take the challenge.

IN THIS ISSUE
PAGE 199

Downloaded from www.ccjm.org on May 7, 2025. For personal use only. All other uses require permission.