What Should the Physician Do When Creatinine Increases After Starting an Angiotensin-Converting Enzyme Inhibitor or an Angiotensin Receptor Blocker?

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Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are generally well tolerated and are used extensively in the treatment of hypertension and heart failure and in patients with renal disease for the reduction of proteinuria.[1–3] A common clinical problem arises when these renin-angiotensin system–blocking drugs are started and the serum creatinine becomes elevated above the patient's baseline level. This may cause concern and may lead to stopping the ACE inhibitor or ARB. Here, we offer our clinical approach to this problem.

ACE inhibitors prevent the conversion of angiotensin I to angiotensin II by inhibiting the ACE inhibitor enzyme complex, while ARBs inhibit the binding of angiotensin to its AT1 receptor. Angiotensin II constricts both the afferent and efferent arterioles, but it preferentially increases efferent arteriole resistance. When an ACE inhibitor or ARB is used, there is a decrease in resistance at the efferent (postglomerular) arteriole; this lowers intraglomerular pressure and reduces the glomerular filtration rate (GFR).[4] In patients with chronic kidney disease (CKD) and heart failure, the GFR is often even more dependent on an angiotensin II–induced increases in resistance at the efferent arteriole. Patients with heart failure and CKD and patients who are volume-depleted often due to over enthusiastic diuresis may be more susceptible to these hemodynamic effects.[5]

Both the serum creatinine and potassium levels should be checked from 3 days to a 1 week after an ACE inhibitor is started, particularly in patients who might be considered susceptible to the hemodynamic effects of an ACE inhibitor or an ARB. The rise in serum creatinine values usually begins a few days after beginning therapy with an ACE inhibitor or an ARB, as angiotensin II levels are rapidly reduced or blocked from binding.[6] This results in efferent arteriolar dilatation and decreased effective GFR.

So what is an acceptable increase in creatinine level? An increase in creatinine concentration of about 25%–30% above baseline is acceptable (eg, creatinine level of 1.2 mg/dL increasing to 1.5 mg/dL). Frequently, creatinine levels will return to baseline or below if blood pressure is lowered, despite the continued use of a renin-angiotensin-aldosterone system inhibitor. A larger rise in creatinine level is likely to occur in patients with bilateral renovascular disease, CKD, and heart failure.

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What should be done when a creatinine increase exceeds this threshold after a recent medication adjustment? If a decrease in systolic pressure >20 mm Hg has occurred and the ACE inhibitor or ARB was recently added to a diuretic or the dose of ACE inhibitor ARB was increased, the ACE inhibitor or ARB dosage should be reduced or stopped and therapy restarted at a lower dosage later. If the diuretic dosage was recently changed, particularly if the patient lost weight as a result, it may be prudent to temporarily withhold the diuretic and restart at a lesser dose. These are empiric approaches, but the key is to distinguish a large pharmacodynamic effect due to renin-angiotensin system blockade from subtle or overt volume depletion from the diuretic. In our experience, the volume depletion may be so subtle that neither orthostasis in blood pressure nor a detectable increase in heart rate is evident. The important issue in patients with marginally or overtly impaired renal function is to check the creatinine level. In a minority of cases in our experience, substantial increases in creatinine values may be from bilateral renal artery stenosis. Like blood pressure, the biochemical changes induced with medication may be substantial while patients remain clinically asymptomatic.

References

1 Materson BJ, Preston RA. Chronic renal diseases: renoprotective benefits of renin-angiotensin system inhibition. *Arch Intern Med*. 1994;154(5):513–523.

2 The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;316(23):1429–1435.

3 Remuzzi G, Ruggenenti P, Perico N. Chronic renal diseases: renoprotective benefits of renin-angiotensin system inhibition. *Ann Intern Med*. 2002;136(8):604–615.

4 Rose BD, Post TW. *Clinical Physiology of Acid–Base and Electrolyte Disorders*. 5th ed. New York: McGraw-Hill; 2001.

5 Toto RD, Mitchell HC, Lee HC, et al. Reversible renal insufficiency due to angiotensin converting enzyme inhibitors in hypertensive nephrosclerosis. *Ann Intern Med*. 1991;115(7):513–519.

6 K/DOQI Clinical Practice Guidelines on Hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*. 2004;43(5 suppl 1):S1.