Elevations in Serum Creatinine Concentration: Concerning or Reassuring?

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The use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) has significantly reduced morbidity and mortality across the continuum of vascular disease. The utilization of these agents, however, remains suboptimal. The drugs are not prescribed in many patients because of concerns regarding their effects on renal function. Despite overwhelming evidence in favor of renoprotection, it is not uncommon for the glomerular filtration rate (GFR) to decrease shortly after starting treatment with an ACE inhibitor or ARB. This response is functional in nature and should be expected based on renal physiology and its dependence on the renin-angiotensin system to maintain GFR. Unfortunately, this phenomenon sometimes is viewed as an adverse effect or an indicator of underlying pathology. Although somewhat counterintuitive, early elevations in serum creatinine concentration are associated with improved long-term renal outcomes in patients with renal insufficiency and thus support, rather than condemn, continued treatment. Clinicians should be aware of the physiologic course associated with blockade of the renin-angiotensin system so that these agents will not be withheld unnecessarily.

Key Words: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, creatinine, renin angiotensin system, ACE-I, ARB.

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The renin-angiotensin system (RAS) plays a central role in the initiation and progression of cardiovascular disease. Attenuation of this cascade with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) decreases morbidity and mortality in the post–myocardial infarction setting and in patients with a spectrum of vascular diseases, including heart failure, coronary artery disease, diabetic nephropathy, cerebrovascular disease, and peripheral vascular disease.1–12 Nevertheless, underutilization of ACE inhibitors is well documented and remains an area of meticulous investigation.13–16

In recent years, proteinuria has been implicated as an independent risk factor for stroke, myocardial infarction, end-stage renal disease (ESRD [i.e., dialysis]), and death in patients with diabetes mellitus. Accordingly, interventions aimed at impeding the progression of microalbuminuria have moved into the forefront of cardiovascular protection.17–21 Angiotensin-converting enzyme inhibitors and ARBs significantly reduce the composite end point of doubling of serum creatinine concentration, progression to ESRD, and death in patients with diabetic nephropathy.22–24 Ironically, patients with kidney dysfunction experience a decrease in glomerular filtration rate (GFR) shortly after ACE inhibitor or ARB therapy is initiated. Unfortunately, this decline, which is merely functional in nature, is misinterpreted by some clinicians as harmful and may inappropriately provoke discontinuation of therapy. In the context of a recent article that was published in

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The Renin-Angiotensin System and Renoprotection

In the 1980s, the detection of even minute quantities of protein in urine was shown to inexorably predict progression to overt proteinuria. Because proteinuria foreshadows renal failure and is associated with an increased risk for cardiovascular events, considerable resources have been allocated to identifying interventions that prevent microalbuminuria or slow its progression. In patients with type 1 diabetes mellitus who have a daily urinary protein excretion of 500 mg or higher, compared with placebo, the ACE inhibitor captopril was shown to reduce the risk of the combined end point of death, dialysis, and kidney transplantation by 50%, independent of blood pressure reduction.27

The Heart Outcomes Prevention Evaluation (HOPE) trial examined the effect of ramipril in 9297 high-risk patients who were at least 55 years of age and had evidence of vascular disease or diabetes mellitus plus one other cardiovascular risk factor, excluding heart failure.28 A substudy nested within HOPE—Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO)-HOPE—examined the effect of ramipril on the risk of nephropathy in 3577 patients with diabetes mellitus.29 Ramipril decreased the frequency of overt nephropathy by 24% in patients without evidence of proteinuria at baseline. The risk of dialysis did not change significantly; however, the events were scarce and precluded meaningful interpretation.

Aside from the HOPE substudy, MICRO-HOPE, the effect of ACE inhibitors on important clinical end points has not been studied systematically. However, smaller trials have evaluated surrogate end points such as doubling of serum creatinine concentration, reduction in proteinuria, and change in GFR.30–34 Trials of this nature have extended the notion of renoprotection with ACE inhibitors to patients with type 2 diabetes. For example, during a 6-year follow-up, patients were randomized prospectively to lisinopril, atenolol, or either verapamil or diltiazem.30 The mean rate of decline in creatinine clearance was greatest in the atenolol arm and significantly less in the lisinopril and non–dihydropyridine calcium channel blocker (NDCCB) arms. Likewise, proteinuria was reduced significantly more in patients receiving lisinopril and NDCCBs compared with those receiving atenolol.

The effect of ACE inhibitors versus conventional antihypertensives (i.e., atenolol, usually in combination with a diuretic) on the rate of decline in renal function in patients with type 2 diabetes was evaluated.32 Urinary albumin excretion was reduced significantly more compared with baseline in patients taking lisinopril than in those receiving conventional agents.

On the other hand, the renoprotective effects of ARBs have been studied nearly exclusively in patients with type 2 diabetes. Evidence in this population is robust, demonstrating a clear diminution in renal protein excretion accompanied by a delay in the progression of nephropathy to ESRD. In the Irbesartan in Diabetic Nephropathy Trial (IDNT), 1715 hypertensive patients with nephropathy due to type 2 diabetes were randomized to treatment with irbesartan, amlodipine, or placebo.22 The primary composite end point was doubling of baseline serum creatinine concentration, development of ESRD, and death from any cause.

A similar study, the Reduction of Endpoints in NIDDM (non-insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan (RENAAL) study, evaluated identical outcomes among patients randomly allocated to losartan or placebo.23 Both trials showed statistically significant reductions in the primary end point (16% reduction in RENAAL and 20% in IDNT). These results were driven mainly by large reductions in the number of patients whose serum creatinine concentrations doubled during follow-up; however, the rate of ESRD was also significantly reduced in RENAAL.

The mechanism for renoprotection has not been fully elucidated but probably reflects a combination of hemodynamic and nonhemodynamic effects. The contribution of hemodynamics was recently described.25 Briefly, ACE inhibitors and ARBs decrease intraglomerular pressure, which minimizes hydraulic forces and protein handling (i.e., work) in the nephron. This is analogous to unloading the left ventricle in patients with heart failure or decreasing myocardial oxygen demand in patients with ischemic heart disease.35 In addition, blockade of the RAS has been shown to provide nonhemodynamic effects such as stabilization of endothelial function, augmentation of insulin sensitivity, decreased oxidative stress, and reduced levels of tumor necrosis factor α, plasminogen activator inhibitor-1, and transforming growth factor β.36–41 These pleiotropic
actions mitigate the inflammation, hypercoagulability, and cellular proliferation that contribute to organ damage in patients with diabetes.

Renal Hemodynamics During Renin-Angiotensin System Blockade

In an article in *Pharmacotherapy*, Drs. Wargo, Chong, and Chan described a case of acute renal failure secondary to the ARB losartan in a patient with renal artery stenosis. They then reviewed the literature pertinent to the case. In their conclusion they warned providers that elevations in serum creatinine concentration soon after initiation of an ARB may signify renal artery stenosis. They cautioned that failure to withdraw RAS blockade in a timely manner could result in acute renal failure and the need for dialysis. Although renal artery stenosis is a rare cause of acute renal failure and should be considered in the differential diagnosis in certain circumstances, it is essential to distinguish between azotemia that results from extensive atherosclerosis in the renal arteries and that which is solely a manifestation of hemodynamics. This distinction has profound implications because the former necessitates immediate discontinuation of the offending agent and precludes its subsequent use, whereas the latter serves as a marker of successful therapy and appears to correlate with improved long-term outcomes.

Renal artery stenosis is a relatively infrequent cause of renal failure in patients who begin ACE inhibitor or ARB therapy, eliciting the greatest concern when it affects either both or a solitary functioning kidney. Conversely, it is not uncommon for drugs that block the RAS to provoke nonpathologic increases in creatinine among patients with chronic renal insufficiency or diabetes despite patent renal arteries. Usually, when mean arterial pressure (MAP) is decreased, the glomerulus responds by constricting the efferent arteriole, thus modulating peritubular Starling forces and augmenting intraglomerular pressure to preserve GFR. The ARBs and ACE inhibitors weaken the pressure head in the renal arteries by decreasing MAP, thus reducing intraglomerular pressure while simultaneously thwarting the ability of the glomerulus to respond by blocking angiotensin II–mediated vasoconstriction in the efferent arteriole. As a consequence, GFR declines temporarily and the serum creatinine concentration can rise within days after administration of the agent. This pattern has been documented in trials demonstrating renoprotection.

In patients with chronic renal insufficiency, renal autoregulation adapts to elevated intraglomerular pressure and eventually varies more directly with systemic arterial pressure, thus exacerbating this phenomenon (Figure 1). Nevertheless, the degree of baseline renal impairment predicts the magnitude of benefit conferred by ACE inhibitors and ARBs such that patients with more severe disease derive the greatest long-term benefit (Figure 2). There appears to be an equal but inverse relationship between the initial elevation in serum creatinine concentration and long-term renoprotection, indicating that patients with larger initial spikes in creatinine concentration experience the greatest reduction in disease progression. Together, these observations suggest that whereas patients with more severe renal impairment might experience larger increases in creatinine initially, they are also likely to derive the greatest long-term renal benefit.

Although baseline renal function must be taken into consideration, it has been suggested...
that a transient elevation in serum creatinine concentration up to 30% above baseline after initiation of an ACE inhibitor or ARB should not elicit concern. The serum creatinine concentration should plateau in 2–4 weeks, provided that the patient is euvoletic, experiencing normal oral intake, and has not recently begun therapy with a nonsteroidal antiinflammatory drug (NSAID) or had their diuretic dose recently increased (Figure 3). This sequence of events (elevation in creatinine concentration after initiation or dose escalation of an ACE inhibitor or ARB followed by a plateau) should serve to reassure clinicians because it indicates decreased intraglomerular pressure and protein load, both of which are believed to contribute to renal injury.

Renal Artery Stenosis

Indeed, a dramatic rise in serum creatinine concentration may be the initial manifestation after administration of an ACE inhibitor or ARB to a patient with renal artery stenosis. The vastly different approaches to managing azotemia in the case of renal artery stenosis versus functional renal insufficiency during ACE inhibitor or ARB administration underscore the importance of understanding the contribution of renal hemodynamics to GFR. Oftentimes, clinicians will discontinue ACE inhibitors or ARBs reflexively in a patient whose serum creatinine concentration has climbed significantly above baseline. Regrettably, the drug may not be restarted, or worse, the patient could be labeled as ACE inhibitor or ARB intolerant, both of which have profound implications for a patient’s future cardiorenal health. Thus, pharmacists can intervene in such circumstances by explaining the mechanism and reassuring physicians when renal artery stenosis is unlikely and the benefit of continued treatment outweighs any potential harm.

When is renal artery stenosis the likely culprit? The probability of renal artery stenosis increases with advanced age, particularly in patients with diabetes, aortoiliac occlusive disease, coronary artery disease, or hypertension, and in the presence of an abdominal bruit. When these risk factors are present, the threshold for suspecting renal artery stenosis should be lowered. Administering an ACE inhibitor or ARB to a patient with bilateral renal artery stenosis results in a large, protracted increase in serum creatinine concentration that does not remit. Thus, if the serum creatinine concentration increases much more than 30%, taking into account the baseline level, or if it fails to stabilize in the 4 weeks after starting an ACE inhibitor or ARB, causes for azotemia other than renal artery

Figure 2. Change in glomerular filtration rate (GFR) and proteinuria stratified according to baseline renal impairment. Changes in GFR among patients with creatinine clearances of 13–24 ml/minute from the Modification of Diet in Renal Disease (MDRD) trial as a function of the different levels of proteinuria. The largest reduction in proteinuria occurred in patients with the most severe renal dysfunction at baseline. MAP = mean arterial pressure. (Adapted with permission from reference 35.)

Figure 3. Expected change in serum creatinine concentration after renin-angiotensin system blockade in patients with heart failure and volume depletion. Possible changes in serum creatinine concentrations in (A) individuals with normal renal function and volume depletion, heart failure, or bilateral renal artery stenosis started on therapy with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB); (B) individuals with chronic renal insufficiency started on therapy with an ACE inhibitor or ARB, without conditions noted in case A; and (C) individuals with normal renal function started on therapy with an ACE inhibitor or ARB. (Adapted with permission from reference 35.)
steno- 
sis should be ruled out first (e.g., dehydration, NSAID use, heart failure exacerbation). In patients with risk factors for renal artery stenosis and no other identifiable causes of azotemia, either the dose of the ACE inhibitor or ARB should be lowered or the agent should be discontinued temporarily until renal artery stenosis can be ruled out.

On the other hand, a self-limited increase in serum creatinine concentration shortly after the start of ACE inhibitor or ARB therapy can be viewed as therapeutic success. If the serum creatinine concentration increases after the patient has been treated for a substantial period of time, extrinsic factors usually can be identified. Two common scenarios that result in a patient presenting with azotemia during long-term ACE inhibitor or ARB therapy are dehydration secondary to illness (e.g., viral gastroenteritis) or iatrogenic azotemia when a patient ingests an NSAID or is excessively diuresed. Both of these situations mandate either reduction in the dose of the ACE inhibitor or ARB or a brief hiatus from therapy until the underlying cause can be corrected.

Conclusion

Elevations in serum creatinine concentration are not necessarily cause for concern after initiation of drugs that block RAS. On the contrary, transient, self-limiting increases up to 30% above baseline should serve to reassure clinicians that the deleterious actions of angiotensin II have been circumvented. Alternatively, large increases in serum creatinine concentration that do not plateau within 2–4 weeks should alert providers to the possibility of dehydration, pharmacodynamic drug-drug interactions (e.g., NSAIDS), poor cardiac output (e.g., heart failure), or renal artery stenosis. In patients with risk factors or signs of RAS and a larger increase in serum creatinine concentration shortly after initiation of an RAS antagonist, a lower threshold for discontinuing the drug and pursuing a diagnosis should be considered. Clinicians should be aware of the physiologic course of RAS blockade to avoid withholding these extremely valuable pharmacologic agents.

References


40. Brewster UC, Setaro JF, Perazella MA. The renin-angiotensin-

Authors' Reply

The comments provided by Dr. Epstein in response to our case report describing acute renal failure secondary to angiotensin II receptor blockade in a patient with bilateral renal artery stenosis are informative and appreciated. In our case report, acute renal failure occurred secondary to a combination of supratherapeutic doses of the angiotensin receptor blocker (ARB) losartan (100 mg twice/day) and the patient's history of bilateral renal artery stenosis. Based on that information, the ARB was discontinued, as the risk of continuing treatment outweighed the benefit. As Dr. Epstein points out, for patients with larger increases in serum creatinine concentrations after initiation of an RAS antagonist in the presence of renal artery stenosis, a lower threshold for discontinuing the
drug should be considered. The question then arises, after this incident occurred in our patient, should he receive an ARB or an angiotensin-converting enzyme (ACE) inhibitor again? In our opinion, based on the patient's comorbidities, an ACE inhibitor or ARB would be an optimal agent to use; however, they should be used with extreme caution and at appropriate dosages. Perhaps a trial of a low-dose ARB would be appropriate and beneficial in this patient. As Dr. Epstein recommends, clinicians should be aware of the physiologic course of RAS blockade to avoid withholding these extremely valuable pharmacologic agents.

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