ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: At what level of hyperkalemia or creatinine elevation should ACE inhibitor therapy be stopped or not started?

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Check the serum creatinine and potassium levels within 1 week of starting an ACE inhibitor

A: ANGIOTENSIN-CONVERTING enzyme (ACE) inhibitors are a double-edged sword with respect to their potential impact on the kidneys.[1] They can slow the decline in renal function in many patients, yet they can reduce the glomerular filtration rate (GFR) and impair potassium excretion in some patients, especially those with a compromised afferent renal blood supply (eg, due to renal artery stenosis).

I believe that the serum creatinine concentration and the serum potassium level should be checked in all patients within 1 week of starting ACE inhibitor therapy, and rechecked if clinical conditions change or medications are changed. ACE inhibitor therapy should be stopped if the serum creatinine concentration increases by more than 1 mg/dL or if the serum potassium concentration increases to 5.5 mmol/L or higher. Greater caution is needed in patients who are in a high-renin state—eg, hypovolemia, renal artery stenosis, congestive heart failure, or salt restriction—or who are taking a potassium supplement or a potassium-sparing diuretic. In such patients, the risks and benefits must be carefully weighed.

THE RENAL EFFECTS OF ANGIOTENSIN II

Most of our understanding of the role of the renin-angiotensin system in autoregulation of renal blood flow and the glomerular filtration rate (GFR) comes from elegant studies done by Hall et al[2,3] in the early 1970s in dogs. The investigators placed an adjustable clamp on the abdominal aorta and measured the resulting decreases in renal perfusion pressure, renal blood flow, and GFR. The specific effects of angiotensin II were evaluated after intrarenal infusion of an angiotensin II antagonist.

These studies unequivocally showed that a decline in renal arterial perfusion, induced by the adjustable clamp, led to a decrease in intraglomerular pressure and therefore to a decline in GFR, unless there was efferent arteriolar vasoconstriction. This vasoconstriction is necessary to maintain adequate intraglomerular pressure (at least 35 mm Hg) across the ultrafiltration surface.[1] It is mediated by angiotensin II, as demonstrated by a decline in GFR after infusion of an angiotensin II antagonist. In other words, the balance between afferent and efferent arteriolar vasodilation or vasoconstriction regulates the intraglomerular pressure and, consequently, the GFR (FIGURE 1). Therefore, an intact renin-angiotensin system is necessary to maintain GFR when there is a decline in renal arterial pressure (eg, due to hypovolemia, renal artery stenosis, congestive heart failure, or salt restriction). For this reason, frequent monitoring is recommended with the use of ACE inhibitors in these situations.

RISK OF RENAL DYSFUNCTION WITH ACE INHIBITORS

The exact frequency of GFR decline during ACE inhibitor therapy is not known. However, significant deterioration of renal function seems to be limited and, in most instances, temporary.

In a study of 15,169 monitoring reports of prescription-related events in patients taking enalapril,[4] including 1,098 deaths, the serum creatinine concentration increased by more than 50% in only 8.2% of cases.[4] This finding reflects a relatively low incidence in the general population. However, these data are not necessarily applicable to patients with abnormal renal function.

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Renal artery stenosis

A decline in renal function with the use of ACE inhibitors can occur in patients with renal artery stenosis, either bilateral or unilateral in a solitary functioning kidney. Nevertheless, it is in these patients that ACE inhibitors are considered the medical treatment of choice.[5]

The overall frequency of worsening renal function reported in the literature is 5% to 20%. In a prospective study of 49 patients with renal artery stenosis who were treated with enalapril, the incidence of serum creatinine increase was only 20% and rarely limited therapy.[6] The incidence was no different between bilateral or unilateral renal artery stenosis in this series. However, in patients with bilateral renal artery stenosis, a decreased pretreatment GFR was a significant predictor of an increase in serum creatinine. The decrease in GFR usually occurs within days and in most instances is reversible.[1] Therefore, ACE inhibitors can be used with caution in most patients with renovascular hypertension. If renal function drops after starting an ACE inhibitor, the patient should undergo a medical workup to rule out high renin states, including renal artery stenosis.

Left ventricular dysfunction

There are multiple studies of ACE inhibitors in the setting of decreased left ventricular function.[7–11] In these studies the incidence of increased serum creatinine requiring discontinuation of the medication varied from 4.7 % to 10.7%. These studies involved 10,334 patients with a wide spectrum of conditions: symptomatic (as much as New York Heart Association Class IV) or asymptomatic left ventricular dysfunction, myocardial infarction, older age, and serum creatinine concentrations as high as 3.4 mg/dL.

The average increase in serum creatinine seen with ACE inhibitor treatment in these studies[7–11] is difficult to ascertain because each study measured deterioration of renal function differently. The highest incidence, 32.6%, comes from a study by Packer et al[12] in which 104 patients with an ejection fraction of less than 30% and a baseline serum creatinine concentration of 1.6 mg/dL underwent right heart catheterization before and after ACE inhibitor administration. Worsening renal function (defined as an increase in serum creatinine concentration ≥ 0.4 mg/dL or more) occurred in 34 patients (33%). The creatinine clearance declined significantly from 44.9 ± 5.1 to 31.2 ± 2.8 mL/min. The patients in whom renal function declined received higher doses of furosemide and had lower filling pressures. Declining renal function was clinically silent except in patients in whom the serum creatinine concentration increased by more than 1 mg/dL. Most important, declining renal function resolved with lowering the dose of diuretic while maintaining the dose of ACE inhibitor. Diuretic use and advanced age were also found to predict declining renal function in a recent analysis of the Studies of Left Ventricular Dysfunction (SOLVD).[10]

ACE-associated renal function decline is limited, temporary

Diabetic and nondiabetic renal disease

ACE inhibitors slow the progression of diabetic and nondiabetic renal disease.[13–20]

Two landmark studies in patients with diabetic renal disease showed renal benefits of ACE inhibitors.[13,14] Both studies excluded

The role of angiotensin II in maintaining adequate intraglomerular pressure

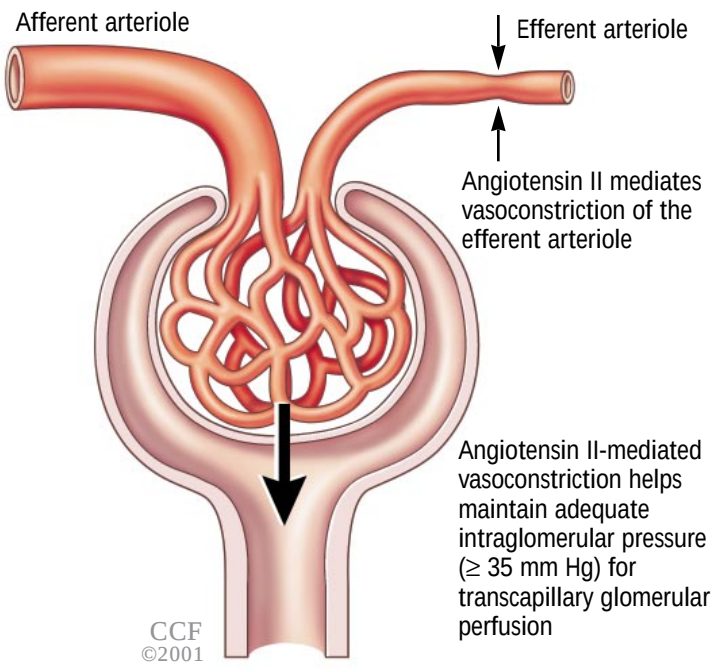

FIGURE 1

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patients with a serum creatinine concentration above 2.5 mg/dL. From these two studies we learned two important lessons. First, the percent reduction in the risk of doubling of serum creatinine was higher in the patients with higher baseline serum creatinine concentrations.[13] Second, out of 400 patients randomized in the United Kingdom Prospective Diabetes Study (UKPDS-39),[14] only 5 stopped taking their ACE inhibitor because of an increase in their serum creatinine concentration. Therefore, the use of ACE inhibitors in diabetic renal disease is advisable, has a beneficial effect on patients with a high serum creatinine concentration, and is safe under most common clinical conditions.

A recent meta-analysis that pooled 1,594 patients with nondiabetic renal disease who were treated with ACE inhibitors concluded that ACE inhibitors are more effective than other antihypertensive agents in reducing the rate of progression of nondiabetic renal disease.[17] More significant to our question, ACE inhibitors did not increase overall mortality (RR 1.24, 95% CI 0.55 to 2.83). The mean serum creatinine concentration at baseline varied from 1.0 to 4.4 mg/dL in the 10 pooled studies. No relation existed between the mean baseline level of renal function and the treatment effect, as seen in diabetic renal disease.[13] Therefore, the investigators suggested that ACE inhibitors could be prescribed early and used throughout the course of renal disease.[17]

Use of ACE inhibitors is advisable in diabetic renal disease

HYPERKALEMIA

The risk of hyperkalemia with the use of ACE inhibitors is well established. Hyperkalemia occurs because of reduced aldosterone levels.[21] However, when this effect is combined with reduced GFR, impaired tubular potassium secretion by the distal nephron (due to interstitial disease, diabetes mellitus, or cyclosporine use), and potassium supplementation, the risk of hyperkalemia can be magnified. Textor et al[21] showed that serum potassium levels during captopril therapy were inversely related to GFR and yet independent of aldosterone levels.

The risk of increased serum potassium levels reported in the randomized trials of patients with congestive heart failure varied from 1.6% to 22.7 %.[7–9,11] However, very few patients needed to stop ACE inhibitor therapy. In other studies,[13–15,17–19,22] the risk of hyperkalemia requiring discontinuation of medication was also very low and not always reported in patients with diabetic and nondiabetic renal disease. In one study,[19] more patients receiving enalapril required sodium polystyrene sulfonate for hyperkalemia than did patients receiving placebo.

EXPANDING INDICATIONS FOR ACE INHIBITORS

The spectrum of benefits from ACE inhibitors continues to expand. Benefits have been shown in patients with decreased left ventricular function,[7] high cardiovascular risk,[23] diabetes mellitus,[13,14] and chronic renal failure with or without proteinuria.[15,22] Because of this, clinicians will continue to be faced with the decision whether to prescribe ACE inhibitors for patients who do not fit the profile of those described in large interventional trials.

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