ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should an ACE inhibitor be stopped if signs of renal insufficiency appear?

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A small increase in creatinine does not mandate stopping the ACE inhibitor

A: NOT NECESSARILY. Whether to stop the drug depends on several questions. How significant is the decline in renal function? And what are the benefits of continuing the medication?

WHY IS THE PATIENT RECEIVING THE DRUG?

Since their introduction in the late 1970s, angiotensin-converting enzyme (ACE) inhibitors have achieved broad applications. Use of ACE inhibitors has become standard in chronic heart failure with systolic dysfunction, in type 1 diabetic nephropathy, and in left ventricular hypertrophy after cardiac ischemia. They have special indications in proteinuric states in the presence or absence of hypertension, in hypertension coexistent with diabetes, and perhaps in most patients with cardiovascular disease, based on recent findings from the HOPE trial.[1]

DECLINE MAY BE SELF-LIMITING

With the first dose of an ACE inhibitor, renal plasma flow and the glomerular filtration rate decrease in most patients.[2] After about a week the decrease in arterial pressure is often associated with an increase in renal plasma flow and a stable glomerular filtration rate. With long-term therapy, the decrease in renal vascular resistance increases the glomerular filtration rate and renal plasma flow, although they may not increase if the mean arterial pressure falls below a critical renal perfusion threshold.

A 30% increase in serum creatinine is generally regarded as clinically significant. This would need to be assessed, but it may not progress or require that the drug be stopped.[3]

Effect of ACE inhibitors on the kidneys

ACE inhibitors are not nephrotoxic per se, at least not the way drugs such as cyclosporine or aminoglycosides are. Rather, they alter the hemodynamics within the glomerulus.

ACE inhibitors prevent the conversion of angiotensin I to angiotensin II, thus releasing the vasoconstriction of the efferent glomerular arterioles, with a subsequent decrease in the glomerular hydrostatic pressure.[4] With less glomerular hydrostatic pressure, there is less glomerular filtration.

Beneficial renal effects of ACE inhibitors. ACE inhibitors attenuate expansion of the mesangial matrix. They also reduce proteinuria, possibly by selectively decreasing the permeability of the glomerular membrane to protein through direct inhibition of transforming growth factor beta.[5] This effect stabilizes the glomerular basement membrane.

ARE OTHER FACTORS PRESENT?

ACE inhibitors induce renal insufficiency in conditions in which angiotensin plays a crucial role in maintaining the glomerular filtration rate, including the following:

- **Bilateral renal artery stenosis,**[6] under which glomerular filtration is maintained by angiotensin-mediated autoregulation involving preglomerular vasodilation and postglomerular vasoconstriction; ACE inhibitors block this autoregulation, with a concomitant drop in mean arterial pressure.[4]
- **Severe volume depletion**
- **Hyponatremia** (which activates the renin-angiotensin-aldosterone axis)
- **Other conditions** (TABLE 1).

Of importance, the degree of reduction in

TABLE 1

ACE inhibitors reduce renal function in:

- Renal artery stenosis
- Volume depletion
- Hyponatremia
- Autosomal-dominant polycystic kidney disease with very large kidneys
- Severe congestive heart failure
- Cirrhosis
- Intrarenal vascular disease
  - Hypertensive arteriolar nephrosclerosis
  - Polyarteritis nodosa with systemic vasculitis
- Diffuse small-vessel disease
- Acute tubular necrosis
- Acute interstitial nephritis
- Advanced age with intercurrent illness

the glomerular filtration rate under these circumstances is not fully predictable and does not usually progress. It is typically a resetting.

OTHER ACE INHIBITOR SIDE EFFECTS

Elevated creatinine at baseline is not a contraindication to ACE inhibitors

ACE inhibitors are generally well tolerated by most patients. Besides the decline in renal function, other adverse effects include:

- Cough
- Allergic reactions
- Angioedema
- Hyperkalemia, which is related directly to the decreased production of aldosterone, therefore impairing urinary potassium excretion. This mainly happens in patients with renal insufficiency, the elderly, and those taking nonsteroidal anti-inflammatory drugs or calcineurin inhibitors such as cyclosporine. Hyperkalemia can frequently be circumvented by reducing dietary potassium or by giving diuretics
- Hypotension, which can be reduced by avoiding excessive volume depletion and by starting at low doses in patients with chronic heart failure.[7]

RECOMMENDATIONS

- Recognize that ACE inhibitors are mandated in situations such as heart failure and type 1 diabetic nephropathy.
- By itself, elevated creatinine at baseline is not a contraindication to ACE inhibitors. These patients should have close monitoring of serum potassium levels, however.
- Assess renal function and electrolytes before and 1 or 2 weeks after starting an ACE inhibitor.
- Start the ACE inhibitor at a low dose to avoid hypotension and hyperkalemia.
- If problems ensue, consider alternatives to stopping the ACE inhibitor, such as adjusting the diet or other medications.
- Small, self-limited reductions in glomerular filtration rate may occur in some patients, as with any antihypertensive drug, but do not require stopping the ACE inhibitor.
- Unilateral and bilateral renal artery stenosis are not absolute contraindications to the use of ACE inhibitors. If in doubt, get a noninvasive assessment of renovascular disease such as a duplex ultrasound. (However, this test is markedly operator-dependent and requires much experience and skill.)
- A 30% increase in serum creatinine is generally regarded as clinically significant. This would need to be assessed, but may not progress or require stopping an ACE inhibitor.[3]

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