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Current Concepts of Pharmacotherapy in Hypertension

Domenic A. Sica, MD, Senior Editor

Angiotensin-Converting Enzyme Inhibitors' Side Effects—Physiologic and Non-Physiologic Considerations

Domenic A. Sica, MD

Angiotensin-converting enzyme (ACE) inhibitors are increasingly recognized as having an important role in the treatment of hypertension and/or end-organ disease. The sheer number of ACE inhibitors in the United States—now numbering 10 different chemical entities—has created a sense of comfort with these compounds, which is particularly evident when these compounds are used in the patient with essential hypertension; conversely, when comorbid conditions are present in the ACE inhibitor-treated patient, circumstances change and physician vigilance becomes more of a necessity. ACE inhibitor therapy in patients with either cardiac and/or renal disease is as much an art as it is a science, and even in the most skilled hands can prove a challenging undertaking. This review discusses the physiologic and non-physiologic basis for side effects with ACE inhibition. (J Clin Hypertens. 2004;6:410–416)

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In addition to their antihypertensive properties, angiotensin-converting enzyme (ACE) inhibitors have been widely accepted for their capacity to slow progressive renal, cardiac, and/or vascular disease.[1,2] Outcome studies with a variety of ACE inhibitors have resulted in usage indications in conditions, such as congestive heart failure, post-myocardial infarction, and diabetic nephropathy (Table).[1,2] Most recently, a treatment indication has been granted to the ACE inhibitor ramipril for reducing cardiovascular events in the high-risk cardiac patient without evident left ventricular dysfunction.[3] In consideration of these successes with ACE inhibitor therapy, it comes as no great surprise that the market for this drug class is as expansive as it is. At present there are 10 ACE inhibitors available in the United States and several more to be had worldwide.

ACE INHIBITOR SIDE EFFECTS

ACE inhibition is a sufficiently well accepted treatment modality, and most of the guidelines addressing treatment of hypertension, renal disease, and/or cardiovascular disease have this therapeutic option prominently positioned in the treatment hierarchy.[4–6] Despite the universality of such recommendations, issues remain as to how to most safely utilize these compounds. There remains an art as much as a science to the use of these drugs. The science behind ACE inhibitor use is well accepted, the art, however, is a work in progress, with many subtleties to use that only become evident after extensive usage experience.

Both physiologic and non-physiologic side effects can be the basis for ACE inhibitor intolerance;

Table. United States Food and Drug Administration-Approved Indications for Angiotensin-Converting Enzyme Inhibitors

Drug	HTN	CHF	Diabetic Nephropathy	High-Risk Patients Without Left Ventricular Dysfunction
Captopril	•	• (post-MI) *	•	
Benazepril	•			
Enalapril	•	• **		
Fosinopril	•	•		
Lisinopril	•	• (post-MI) *		
Moexipril	•			
Perindopril	•			
Quinapril	•	•		
Ramipril	•	• (post-MI)		•
Trandolapril	•	• (post-MI)		

HTN=hypertension; CHF=congestive heart failure; MI=myocardial infarction; *captopril and lisinopril are indicated for CHF treatment both post-MI and as adjunctive therapy in general heart failure therapy; **enalapril is indicated for asymptomatic, left ventricular dysfunction

however, what constitutes true ACE inhibitor intolerance is highly subjective, and even when extreme physiologic change (such as an excessive increase in serum creatinine concentration) is the basis for drug discontinuation, there are differing opinions on when to stop (and/or restart) a medication in this class. Alternatively, with the ready availability of a drug class such as the angiotensin-receptor blockers (ARBs), which offer similar benefits for both blood pressure (BP) control and event protection, the decision is simplified as to how long to tolerate a non-physiologic side effect such as cough. As of yet, the available information is less than convincing that ARBs are better tolerated than ACE inhibitors relative to physiologic side effects.[7]

Although certain ACE inhibitor side effects can prove life threatening (such as angioedema) the majority fall into the category of being no more than discomforting; however, in certain instances, ACE inhibitor side effects (such as a suppression in red blood cell production in the setting of erythrocytosis) can prove beneficial. Most ACE inhibitor side effects can be viewed as a class effect.[8] The concept of an intraclass switch to alleviate a side effect has been most commonly applied to the issue of ACE inhibitor-related cough.[9,10] In most instances, a less-than-rigorous trial design proves to be the unmaking of a superiority claim for one ACE inhibitor (over another) for less frequent cough. As such, simply switching from one ACE inhibitor to another will not alleviate the side effect per se.

PHYSIOLOGIC SIDE EFFECTS

The site of ACE inhibitor activity (within the renin angiotensin aldosterone axis) can be pinpointed at the pluripotent ACE, an enzyme known to catalyze the conversion of angiotensin-I to angiotensin-II, as well as to facilitate the degradation of bradykinin to assorted vasoactive peptides.[2,3] The basis for physiologic side effects with ACE inhibitors relates to these aforementioned changes in angiotensin-II (and possibly the increase in bradykinin) and is particularly prominent when the effected system—cardiovascular and/or renal—is heavily dependent on the presence of angiotensin-II for maintenance of function. ACE inhibitor side effects of a physiologic nature are typically worsened when patients are volume depleted, but even in the face of an overly sodium restricted diet, such side effects can develop.[11]

Blood Pressure

Hypotension is not a specific side effect with ACE inhibitors; rather, it is a broadening of the physiologic action of these drugs that occurs most commonly when a patient becomes volume contracted. In the setting of ACE inhibitor-related hypotension, circumstances have evolved in such a way that peripheral resistance (and thereby BP) is dependent on angiotensin-II. As angiotensin-II is subtracted from this hemodynamic equation, there can be a precipitous fall in BP, which is only worsened by the actions of the vasodilator bradykinin.

ACE inhibitor hypotension can present as a first-dose phenomenon or anytime in the course of chronic therapy.[12] Hypotension observed in the first days of treatment with an ACE inhibitor may be best managed with a dose reduction or temporary discontinuation of the drug. Hypotension developing in the course of chronic therapy can be anticipated—such as in heart failure—where oftentimes as much ACE inhibitor is given as BP

permits.[13] In other instances hypotension is coupled to intercurrent febrile or gastrointestinal forms of dehydration and is unexpected. Occasionally, poor glycemic control can induce a sustained osmotic diuresis and, in the process, produce significant enough volume contraction to also exaggerate an ACE inhibitor's effect on BP.

If ACE inhibitor-related hypotension is sufficiently prolonged (days), a meaningful drop in the glomerular filtration rate (GFR) will occur. When such a fall in GFR occurs it limits drug clearance of any renally-cleared compound and, in particular, the clearance of ACE inhibitors (with the exception of fosinopril and trandolapril).[13,14] As such, the drug in question (an ACE inhibitor) will accumulate (if it is being dosed repetitively) and in the process oblige the BP to remain persistently low.

ACE inhibitor-related hypotension is much more common in the setting of heart failure with reduced systolic function, being that BP is typically borderline-low to start in such patients. When hypotension occurs in a non-heart failure setting, the prudent maneuver is to either liberalize the intake of sodium and/or reduce (or temporarily stop) diuretic therapy as the ACE inhibitor is being withheld. On occasion, an ACE inhibitor-treated patient, who routinely undertakes exercise where excessive sweating occurs, needs to have his or her medication dose dissociated from the time of exercise to lessen the risk of hypotension.

If BP, at the time of presentation, is not excessively reduced with ACE inhibitor-related hypotension, oral fluid replacement can suffice to return BP to more normal values; however, the use of oral fluid replacement is a treatment choice where careful outpatient follow-up and/or home BP measurement capacity is close at hand. More commonly with ACE inhibitor-related hypotension, intravenous sodium-containing fluids (preferably normal saline) are needed, an approach which carries the added benefit of rapid volume replacement returning GFR more quickly to baseline values. Any improvement in GFR will increase ACE inhibitor renal clearance (if the ACE inhibitor is one that is renally cleared) and in so doing do away with the original basis for the hypotension.

Renal Function

Soon after their release, a syndrome of functional renal insufficiency was recognized as a class effect with ACE inhibitors.[15] This phenomenon was initially reported in patients with renal artery stenosis and a solitary kidney or in the presence of bilateral tight renal artery stenosis. Predisposing conditions to this process include dehydration, congestive heart failure, non-steroidal anti-inflammatory drug use, and/or either micro- or microvascular renal disease.[13,15] The underlying cause in each of these conditions (in the untreated state) is a fall in afferent arteriolar flow. When this occurs, glomerular filtration temporarily declines. In response to this reduction in glomerular filtration, local renal production of angiotensin-II rises. In conjunction with this increase in angiotensin-II, the efferent or post-glomerular circulation constricts, which re-establishes hydrostatic pressures within the more proximal glomerular capillary bed.[2,3]

The abrupt removal of angiotensin-II, as occurs with an ACE inhibitor (or an ARB), will abruptly dilate the post-glomerular circulation in tandem with a reduction in systemic BP. In combination, these hemodynamic changes can drop glomerular hydrostatic pressure to such a degree that the GFR will plummet.[13] This type of functional renal insufficiency is best treated by discontinuation of the responsible agent, careful volume expansion (if intravascular volume contraction is a contributing factor), and, if warranted on clinical grounds, evaluation for the presence of renal artery stenosis (Figure).[13]

Pregnancy

A situation comparable to that of functional renal insufficiency is exposure to ACE inhibitors or ARBs after the first trimester of pregnancy. The fetal kidney is formed after the first trimester and thereafter becomes susceptible to hemodynamic insults. When ACE inhibitors are given, the fetal renin-angiotensin system is interrupted and fetal ischemia occurs from maternal hypotension and/or decreases in fetal-placental blood flow. These events lead to in utero acute renal failure with oligohydramnios and specific abnormalities thought to be secondary to reduced amniotic fluid volume (limb deformities, cranial ossification deficits, lung hypoplasia).[16–18]

This sequence of events is the basis for the ACE inhibitor contraindication in the second and third trimester of pregnancy.[19] This "black-box" warning applies to all ACE inhibitors as well as the ARB class of drugs. The level of female patient exposure to ACE inhibitors or ARBs in the second and third trimester of pregnancy remains unknown.[19] The possibility of ACE inhibitor-related fetopathy should remain an important consideration in the selection of an antihypertensive agent in a female of child-bearing potential, particularly if the intention is there to become pregnant in the near future.[19] If ACE inhibitors or ARBs are required

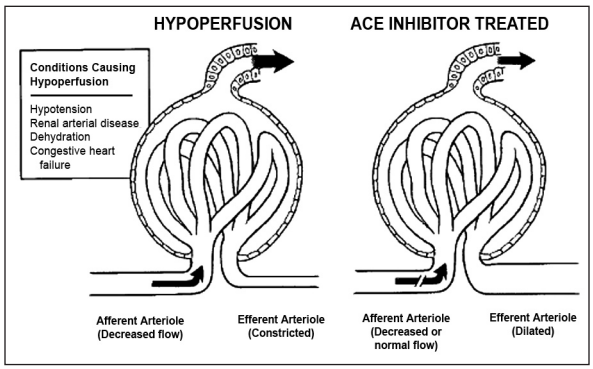

Figure. Schematic illustration of settings wherein angiotensin-converting enzyme (ACE) inhibitor therapy may worsen renal function. Conditions causing renal hypoperfusion include systemic hypotension, high-grade renal artery stenosis, extracellular fluid volume contraction (simplified as "dehydration" in the Figure), and administration of vasoconstrictor agents (non-steroidal anti-inflammatory drugs or cyclosporine, not shown), and congestive heart failure. These conditions typically increase renin secretion and angiotensin-II production. Angiotensin-II constricts the efferent arteriole to a greater extent than the afferent arteriole, such that glomerular hydrostatic pressure and glomerular filtration rate (GFR) can be maintained despite hypoperfusion. When these conditions occur in ACE-inhibitor treated patients, angiotensin-II formation and effect are diminished, and GFR may decrease. Adapted with permission from Circulation. *2001;104:1985–1991.*[13]

or are being incidentally used when a women is nursing, there will be minimal entry of these compounds into breast milk. Although not all ACE inhibitors or ARBs have been submitted to formal study, in most cases breast milk selectively restricts the passage of these drugs.[20]

Hyperkalemia

Hyperkalemia is an additional ACE inhibitor-associated side effect that has a strong physiologic basis.[21–25] ACE inhibitor-related hyperkalemia, like all forms of hyperkalemia, is highly definitional in nature. Once a specific definitional threshold value has been reached during ACE inhibitor therapy, a specific criterion for hyperkalemia will be satisfied and the patient then counts as an affected case. In reality, ACE inhibitors will increase the serum potassium value in virtually all treated subjects but to a degree (0.1–0.2 mEq/L) that is clinically undetectable and never reaches (or even approaches) an assignment criterion for the diagnosis of hyperkalemia.

Thus, it is axiomatic in the use of an ACE inhibitor to always anticipate an increase in serum potassium values. The frequency with which serum potassium values should be monitored in an ACE inhibitor-treated patient should be based on pretherapy serum potassium value and level of renal function, as well as the presence of diabetes and whether concomitant medications are being given that might also influence systemic potassium balance.[1,2,24] Potassium supplements or potassium-sparing diuretics, when given with ACE inhibitors, not suprisingly increase the probability of developing hyperkalemia.[24] To this end, two other common drug causes of hyperkalemia (when given together with an ACE inhibitor) exist: first, salt substitutes (≈60 mEq/tsp of potassium chloride) and second, non-steroidal anti-inflammatory drugs and cyclooxygenase inhibitor therapy. These latter two drug classes decrease potassium excretion by reducing aldosterone concentrations, and through this mechanism interact with ACE inhibitors in the development of hyperkalemia.

It is uncommon even under the most extreme circumstances to see more than a 2.0-mEq/L increase in serum potassium values with an ACE inhibitor. When such extreme changes occur, it is generally in conjunction with a sudden fall in GFR—either prompted by the ACE inhibitor (as is the case with renal artery stenosis) or as a consequence of intercurrent illness having lead to volume contraction. Conversely, ACE inhibitors will cut the potassium loss ordinarily occurring with diuretic therapy. ACE inhibitor hyperkalemia appears to be class-specific with very little experimental evidence supporting one ACE inhibitor over another in lessening the risk of hyperkalemia. If differences between ACE inhibitors in the incidence of hyperkalemia do exist—as has been suggested for fosinopril—they are probably coupled to the pattern of drug accumulation for these drugs in chronic kidney disease.[12,26] A final consideration on this topic is whether ARB therapy is associated with a lesser rate of hyperkalemia development than is the case for ACE inhibition. Although there are few data to support this notion relative to hyperkalemia per se, the degree of change in serum potassium with an ARB (in an absolute sense) can be somewhat less than what is observed with an ACE inhibitor.[25]

NON-PHYSIOLOGIC SIDE EFFECTS

Cough

A dry, irritating, nonproductive cough is a common complication with ACE inhibitors, with an incidence between 0% and 44%.[27] The wide variability in cough relates to the differing representation in surveyed populations for variables associated with an increased cough incidence, which include: age, gender, ethnicity, and geographic location of the studies. Cough is a class phenomenon with ACE inhibitors and has been attributed to an increase in bradykinin and/or other vasoactive peptides, such

as Substance P, which may play a second messenger role in setting off the cough reflex. Although numerous therapies have been tried, few have had any lasting success in eliminating ACE inhibitor-induced cough.[28,29] The sensible clinical approach for suspected ACE inhibitor-related cough is to re-assess the patient several weeks after drug discontinuation. Disappearance of the cough can then be taken as proof of an ACE inhibitor etiology. In most cases it is not necessary to re-challenge a patient with an ACE inhibitor to obtain absolute proof of a cause-and-effect relationship for cough.

Angioedema

Angioneurotic edema is a potentially life-threatening complication of ACE inhibitors that is more common in blacks.[30] Angioedema can be quite subtle in its early presentation with non-specific oral, lingual, and lip symptoms. In its early presentation it is often attributed to food or other concurrent medication; however, early non–life-threatening episodes of angioedema presage episodes with a more extreme presentation. Angioedema can be effectively managed in the long-term with simple discontinuation of the offending ACE inhibitor.[31] Angioedema can occasionally recur with ARB therapy in a patient having previously experienced it with an ACE inhibitor, but it is generally mild and not life-threatening.[32] Angioedema of the intestine (more common in women) can also occur with ACE inhibitor therapy with a typical presentation being one of abdominal pain/diarrhea with or without facial and/or oropharyngeal swelling.[33] This process can be intermittent in nature developing even several years after ACE inhibitor therapy has been initiated.[34] However, the use of ACE inhibitors is not associated with a significantly increased risk of acute pancreatitis.[35]

Anemia

Another side effect consideration with ACE inhibitors is that of anemia. ACE inhibitors suppress the production of erythropoietin in a dose-dependent manner, which presents a particular problem when ACE inhibitors are administered in the presence of renal failure.[36] ACE inhibitor-related anemia is at least, in part, related to N-acetyl-seryl-aspartyl-lysyl-proline accumulation. This substance is a potent natural inhibitor of hematopoietic stem cell proliferation as well as an antifibrotic moiety, which is degraded mainly by ACE.[37] Because of the increase in N-acetyl-seryl-aspartyl-lysyl-proline concentrations with ACE inhibitor therapy, these compounds may possibly be better suited for suppression of red blood cell production when it is a desired clinical goal. Such settings include post-transplant erythrocytosis[38,39] and high-altitude polycythemia with as much as a 4.5-g/dL fall in hemoglobin concentration being observed with ACE inhibitor therapy.[40]

NON-SPECIFIC SIDE EFFECTS

Non-specific side effects with ACE inhibitors are generally uncommon with the exception of taste disturbances, leucopenia, and dysgeusia, which are largely seen in captopril-treated patients. Although skin rashes are seen with captopril, cutaneous reactions including life-threatening angioedema, pruritus, bullous eruptions, urticaria, other generalized rashes, photosensitivity, and hair loss can occur with any of the ACE inhibitors. ACE inhibitor skin reactions thus mimic a broad variety of skin diseases, and these drugs should be considered when sudden, unexplainable skin eruptions occur.[41] Whereas a number of antihypertensives have headache as an accompanying side effect with their use, this is not so with ACE inhibitors. In fact, ACE inhibitors have been used for migraine prophylaxis[42]; moreover; they have been proven effective in reducing the risk of headache with nitrate therapy.[43]

CANCER AND ACE INHIBITORS

It went largely unnoticed in the prospective Studies of Left Ventricular Dysfunction (SOLVD)[44] study that enalapril-treated patients with left ventricular dysfunction showed a slightly higher incidence of malignancy than those receiving placebo (odds ratio, 1.59; confidence interval, 0.90–2.82). Since the SOLVD study, several case reports have linked ACE inhibitors to the development of malignancies. For example, pemphigus vulgaris, which can be seen in association with internal malignancies, is found in association with the use of captopril. One case report has linked enalapril to pemphigus vegetans with a simultaneously occurring internal malignancy.[45] In another case report, Kaposi's sarcoma appeared in a 70 year-old female 8 months after starting captopril. Upon stopping the captopril there was a marked reduction in both the cutaneous and gastric lesions of this disease, suggesting a cause-and-effect relationship between the captopril and the malignancy.[46] A subsequent study disputed these findings in that it was shown that captopril inhibited angiogenesis in Kaposi's sarcoma.[47]

These limited data contrast with a greater body of evidence supporting the absence of a cancer

risk with ACE inhibitors. In the Heart Outcomes Protection Study (HOPE) trial, a total of 9297 high-risk patients treated either with ramipril or placebo for a mean of 5 years had similar numbers of deaths from noncardiovascular causes in both groups. In addition, several other retrospective studies investigating the possible association between various antihypertensives and cancer risk have been unable to detect such a relationship with the use of ACE inhibitors.[48–50] Finally, the Scottish retrospective cohort study (between January 1, 1980, and December 31, 1995) by Lever et al.,[51] who compared 1599 patients taking ACE inhibitors and 3648 on other antihypertensive drugs, demonstrated a risk reduction for female sex-specific malignancies and lung cancers. In this cohort study, the reduced relative risk of cancer in patients on ACE inhibitors was greatest with follow-up of longer than 3 years. Thus, the evidence available to date suggests that ACE inhibitors have a neutral cancer risk in hypertension[52] and might conceivably decrease the risk.[53]

CLASS AND AGENT-SPECIFIC DRUG INTERACTIONS

Several class-specific drug interactions occur with ACE inhibitors. For example, the concurrent administration of lithium with an ACE inhibitor increases the likelihood of lithium toxicity.[54] This seems to relate to two renal processes associated with ACE inhibitor therapy: first, a reduction in GFR and second, an increase in proximal reabsorption, both of which can decrease lithium renal clearance. This appears to be a class-specific phenomenon and one that is more apt to occur when an ACE inhibitor is combined with a diuretic and some degree of volume contraction has occurred. Finally, combining an ACE inhibitor with allopurinol is associated with a higher risk of hypersensitivity reactions with several reports of the Stevens-Johnson syndrome described with the combination of captopril and allopurinol.[55] Quinapril reduces the absorption of tetracycline by ≈35%, which may be due to the high magnesium content of quinapril tablets.

CONCLUSIONS

ACE inhibitor therapy is now a mainstay of clinical practice. The ease with which these compounds can be used in most subjects is reassuring; however, numerous considerations arise when these drugs are used in certain patient types, including the elderly and/or volume contracted patient and/or those with comorbid conditions of a renal or cardiac nature. ACE inhibitor side effects are either physiologic or non-physiologic. Physiologic side effects with an ACE inhibitor are to a degree correctable and often allow a restart of the medication under more strictly controlled circumstances (liberalized intake of sodium or a decrease in diuretic dose). Non-physiologic side effects are unpredictable in their occurrence and can go unrecognized; however, when recognized, the decision to discontinue an ACE inhibitor (other than for angioedema) is one of some subjectivity. Alternatively, certain ACE inhibitor properties (such as suppressing red blood cell production) can be taken advantage of as in the case of erythrocytosis.

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