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ANGIOTENSIN-CONVERTING ENZYME INHIBITOR DRUGS AND SOME OF THEIR ADVERSE EFFECTS

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Annotation. ACE inhibitors can reduce the activity of an enzyme called angiotensin-converting enzyme, or ACE for short. The enzyme is responsible for hormones that help control your blood pressure. It has a powerful narrowing effect on your blood vessels, which increases your blood pressure. ACE inhibitors inhibit or limit this enzyme, making your blood vessels relax and widen. This, in turn, lowers your blood pressure and improves blood flow to your heart muscle.

Keywords: Angiotensin-converting enzyme inhibitors (ACEIs), cardiovascular and renal diseases, heart failure, acute coronary syndrome, nephrotic syndrome, diabetes, hypertension.

Hypertension

Angiotensin-converting enzyme inhibitors effectively lower the mean arterial blood pressure as well as systolic and diastolic blood pressure both in hypertensive and normotensive subjects. Angiotensin-converting enzyme inhibitors have been evaluated as antihypertensive drugs in multiple randomized controlled trials. In 2014, the Eighth Joint National Commission (JNC8) published evidence-based guidelines for treating high blood pressure in adults, which recommended that ACE inhibitors are one of four drug classes recommended for initial therapy for adults with elevated blood pressure. The other three classes of drugs are calcium channel blockers, thiazide diuretics, and angiotensin receptor blockers, which are useful as initial therapy for the general nonblack population. Only thiazide and calcium channel blockers are recommended as initial therapy for the general black population with elevated blood pressure. Recent guidelines released by the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC) also recommend ACE inhibitors as first-line antihypertensive therapy, especially in patients with diabetes mellitus and cardiovascular diseases. Although ACE inhibitors are generally very effective antihypertensive drugs, they have been proven to be less effective in hypertensive Black race individuals than in whites in clinical practice.

Heart Failure

Angiotensin-converting enzyme inhibitors (ACEIs) improve heart failure by decreasing afterload, preload, and systolic wall stress, which results in increased cardiac output without any increase in heart rate. ACE inhibitors play an important role in promoting salt excretion by augmenting the renal blood flow and reducing aldosterone and antidiuretic hormone production. Apart from decreasing the afterload, ACEIs also reduce cardiac myocyte hypertrophy. Since the 1980s, several large, prospective, randomized, placebo-controlled trials have proved that treatment with ACE inhibitors reduces overall mortality, especially in patients with heart failure with reduced ejection fraction (0HFrEF). These trials demonstrated that ACE inhibitors reduce mortality even in asymptomatic patients with left ventricular dysfunction. Based on the above-mentioned evidence, ACE inhibitors are strongly recommended as first-choice therapy in patients with heart failure.

Post Myocardial Infarction

Over the last few decades, several prospective, randomized trials have studied the effect of ACE inhibitors on mortality after myocardial infarction (MI). The vast majority of these trials have shown a significant decrease in mortality and a slowing of the progression to congestive heart failure after MI in patients treated with ACE inhibitors. The clinical practice guidelines in the contemporary era recommend that patients with left ventricular dysfunction or heart failure be treated with ACE inhibitors without delay after infarction. It is also recommended that all patients should be treated with ACE inhibitors initially, with a review of the need for continuation later based on left ventricular function assessment.

Diabetes

The Renin-Angiotensin-Aldosterone system and increased glomerular capillary pressure have been reported to increase the progression of renal dysfunction due to diabetes mellitus related nephropathy. A large, prospective, randomized, placebo-controlled has demonstrated that ACE inhibitors slow down the progression of nephropathy in patients with insulin-dependent diabetes mellitus and significantly reduce the combined endpoints of dialysis, transplantation, and death. Current recommendations are using ACEi or ARB as first-line therapy for hypertension in patients with a history of diabetes. Also, the use of ACEi in diabetic hypertensive patients with no history of coronary heart disease has been shown to decrease the incidence of myocardial infarction and improve heart function.

Nephrotic Syndrome or Proteinuria

Angiotensin-converting enzyme inhibitors have been reported to decrease glomerular capillary pressure by decreasing arterial pressure and selectively dilating efferent arterioles. It has been shown that the use of ACE inhibitors prevents the progression of microalbuminuria to overt proteinuria. Angiotensin-converting enzyme inhibition provides long-term protection against the development and progression of proteinuria and stabilizes renal function in previously untreated patients with impaired renal function.

Chronic Kidney Disease

ACE inhibitors or ARBs are the first-line drugs in managing chronic kidney disease (CKD) patients. The use of ACEI or ARB has been proven to have a superior effect compared to placebo treatment on decreasing proteinuria and slowing kidney disease progression. The efficacy of ACEI and ARB is comparable.

Glomerular Disease and Post-transplant Glomerulonephritis

The use of ACE inhibitors or ARB is the mainstay of treatment in patients with glomerular diseases. It slows down the decline in glomerular filtration rate (GFR) and proteinuria. The use of renin-angiotensin-aldosterone inhibitors prolongs graft survival in patients with post-transplant glomerulonephritis.

Mechanism of Action

The exact mechanism of ACE inhibitors is not fully known. They interfere with the renin-angiotensin-aldosterone system, but their effect is not directly related to renin levels in the blood. As the name implies, ACE inhibitors block an angiotensin-converting enzyme that converts angiotensin I to angiotensin II. Decreased production of angiotensin II enhances natriuresis, lowers blood pressure, and prevents remodeling of smooth muscle and cardiac myocytes. Lowered arterial and venous pressure reduces preload and afterload. Also, the hypothesis is that ACE inhibitors interfere with the degradation of bradykinin, a peptide that causes vasodilation. Angiotensin-converting enzyme regulates the balance between the vasodilatory and natriuretic properties of bradykinin and the vasoconstrictive and salt-retentive properties of Angiotensin II. ACE inhibitors alter this balance by decreasing the formation of Angiotensin II and the degradation of bradykinin. ACE inhibitors also alter the formation and degradation of several other vasoactive substances, such as substance P, but the contribution of these compounds to the therapeutic or adverse effects of ACE inhibitors is uncertain.

ACE inhibitors differ in their chemical structure, potency, bioavailability, plasma half-life, route of elimination, as well as their distribution and affinity for tissue-bound angiotensin-converting-enzyme. Depending on the chemical structure, ACE inhibitors are classified into three groups:

Sulfhydryl-containing ACE inhibitors

Captopril – Hypertension therapy is 25 mg, either BID or TID, with a maximum of 450 mg. Heart failure therapy is 6.25 mg TID, with a maximum of 450 mg.

Dicarboxylic.

Phosphorus.

Fosinopril – Hypertension therapy dosing is 10 mg, increasing to a maximum dose of 80 mg. May split into two equal doses during the day to control blood pressure. Heart failure therapy is 5 to 10 mg daily to a maximum dose of 40 mg.

All of the ACE inhibitors are prescribed orally, except for enalapril, which can be given intravenously. Enalapril's IV dosage is initially 0.625 to 1.25 mg every 6 hours. Dosage titration up can be to 5 mg IV every 6 hours. Geriatric dosing should definitely initiate at the lower end of the adult dosing regimen. There should be a dosage decrease in patients with heart failure, salt-depleted patients, and/or renal impairment. Lisinopril and captopril are the only ACE inhibitors that do not have to be activated in the body to be effective. All the other ACE inhibitors are prodrugs and require activation. Most reach peak serum levels within 1 hour after ingestion. Since most of the activation occurs in the liver, a non-prodrug form is preferable in patients with underlying liver issues.

Even though ACE inhibitors help many people, they have potential risks to be aware of. Below, we'll discuss seven ACE inhibitor side effects and how to manage them.

1. ACE inhibitor cough

An ACE inhibitor-induced cough is one of the most well-known side effects of these medications. It's typically a dry, persistent cough with a tickling or scratching sensation in the throat. Although it's not dangerous, it can be bothersome. ACE inhibitors raise levels of two proteins called bradykinin and substance P. This can cause your airways to tighten (constrict), leading to a cough. The cough can occur immediately after your first dose or months later.

2. Low blood pressure

ACE inhibitors lower blood pressure — which is often why they're prescribed. But they can lower blood pressure too much, leading to hypotension. This is more likely if you have certain health conditions, like aortic valve stenosis, or if you take other medications that lower blood pressure, like diuretics ("water pills"). Symptoms of hypotension include dizziness, tiredness, and weakness.

3. Dizziness

Medications that lower your blood pressure, including ACE inhibitors, can also cause dizziness. When you first start taking an ACE inhibitor, your body has to get used to its effects. This can take a little time, and dizziness may happen in the meantime. In most cases, dizziness is mild and improves as your body gets used to the medication. But it can also be severe or continue to worsen. In these cases, your healthcare provider may recommend a lower dose of your ACE inhibitor. Or they may recommend switching to another blood pressure medication.

4. Kidney problems

ACE inhibitors usually help protect your kidneys and improve blood flow to them. This makes them a first-choice medication for people with high blood pressure and chronic kidney disease. But in rare cases, ACE inhibitors can cause kidney damage. This can occur at any time while you're taking the medication. It's more likely in people with heart failure or existing kidney disease and in people who take diuretics or medications that constrict your blood vessels. Examples include nonsteroidal anti-inflammatory medications (NSAIDs) like ibuprofen (Advil, Motrin). Usually, any changes to your kidney function will be mild and temporary.

5. High potassium levels

ACE inhibitors can cause high potassium levels in the blood (hyperkalemia). Hyperkalemia from ACE inhibitors is usually mild. But it can be severe and lead to abnormal heart rhythms, which can be life-

threatening. ACE inhibitors are more likely to increase your potassium levels if you have other risk factors for hyperkalemia. These include having diabetes or existing kidney problems, or taking certain medications like beta blockers or potassium supplements.

6. Angioedema

Angioedema refers to the swelling of deep tissues. It most often occurs in the face, neck, and mouth. It can occur at any time during ACE inhibitor treatment, even after you've been taking it for a while. But it's rare — less than 1% of people taking an ACE inhibitor will experience angioedema. Angioedema from ACE inhibitors may occur due to a buildup of bradykinin in the body, which can cause swelling. In severe cases, this swelling can block your airways and lead to trouble breathing.

All in all, Angiotensin-converting enzyme (ACE) inhibitors treat hypertension and other heart-related conditions. These medications have possible side effects, like ACE inhibitor-induced coughing, very low blood pressure, and high potassium levels. ACE inhibitors also have rare but serious side effects like kidney damage and angioedema.

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