Introduciton

Angiotensin-converting enzyme (ACE) inhibitors are commonly used in the management of hypertension, cerebrovascular disease, diabetes-associated nephropathy, heart failure and stable coronary heart disease.\(^1\) ACE inhibitors have been shown to improve the vascular endothelial function.\(^1,2\) They are often used in combination with diuretics and calcium-channel blockers. However, this class of drugs has side-effects, which, at times, can result in patients being non-compliant. Therefore, it is important for clinicians to be aware of these side-effects, so as to educate patients, and improve compliance. In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial, perindopril (an ACE inhibitor) was combined with indapamide (a diuretic), a combination which demonstrated better blood pressure control and reduced risk of stroke and vascular events when compared to perindopril alone.\(^3\) Withdrawal from this study was due to side-effects.\(^3\) In another study, the side-effects of ACE inhibitors, calcium-channel blockers, diuretics and beta blockers were compared. Results showed side-effects of 7% for ACE inhibitors, 5% for beta blockers, 4% for calcium-channel blockers, and 3% for diuretic treatment.\(^4\)

In this paper, we discuss ACE inhibitors with reference to mechanism of action, indications, precautions, and side-effects. Major side-effects will be discussed in detail.

Mechanism of action

ACE inhibitors inhibit the conversion of angiotensin I to angiotensin II, and the degradation of bradykinin.\(^4\) This inhibition reduces the level of angiotensin II, and increases the level of bradykinin in tissues (Figures 1 and 2). Angiotensin II is a vasoconstrictor, and increases intracellular adhesion molecule-1, vascular cell adhesion molecule-1, growth factors, oxyradical formation, plasminogen activator inhibitor-1, smooth muscle cell proliferation and matrix degradation. All of these result in endothelial dysfunction, inflammation, coagulation and atherogenesis (Figure 2).

Angiotensin II also stimulates the adrenal cortex to release aldosterone, a hormone which causes salt and water retention and potassium excretion. Bradykinin causes vasodilation and increases nitric oxide, tissue plasminogen activator and prostacyclin, thus protecting the endothelium against the effects of angiotensin II.

Indications

ACE inhibitors are indicated in the management of patients with hypertension, heart failure, cerebrovascular disease, diabetes-associated nephropathy, coronary heart disease, and reduced left ventricular function, with ejection fraction of ≤ 35% without heart failure.\(^1,5,6,7\)

Precautions

Clinicians should take precautionary measures when prescribing ACE inhibitors to patients with hypotension, heart failure, cardiac outflow obstruction, and impaired renal function, as well as to patients taking multiple antihypertensive medication.\(^8\) In such situations, patients should start taking a low dose of an ACE inhibitor. If they are on a diuretic, it may be necessary to stop taking it before starting to take an ACE inhibitor.\(^8\)
**Side-effects**

The side-effects of ACE inhibitors include the following: dry cough, angioedema, hypotension, acute renal failure, hyperkalaemia, glycosuria, foetopatric potential, hepatotoxicity, dysgeusia, vomiting, neutropenia, and skin rashes, such as maculopapular rash and erythema multiforme.5,7,8

**Hypotension**

The patient with ACE inhibitor-induced hypotension will present with a history of being on ACE inhibitors, and may experience dizziness, fatiguability, weakness, syncope, and/or low blood pressure. Hypotension is common in patients whose renin-angiotensin system has been activated. These are patients with heart failure and those who are volume depleted, including patients on diuretic therapy. Black patients have low plasma renin activity, and respond poorly to ACE inhibitor monotherapy. When an ACE inhibitor is combined with a diuretic, the effect is the same as the response in those with increased plasma renin activity. Low-dose initial therapy is recommended for patients to whom an ACE inhibitor has to be given.2,8 If the patient is on diuretic therapy, it may be advisable to stop the diuretic therapy for about three to five days before initiating an ACE inhibitor-containing regimen.5,8
Acute renal failure

Angiotensin II causes efferent (postglomerular) arteriolar constriction. This effect maintains intraglomerular pressure and the glomerular filtration rate. Blocking this effect with an ACE inhibitor reduces intraglomerular pressure, and decreases the glomerular filtration rate, resulting in acute renal failure. Patients at high risk of developing acute renal failure include those with bilateral renal artery stenosis, congestive cardiac failure, hypertensive nephrosclerosis, polycystic kidney disease, and chronic renal failure. In patients at risk of developing renal failure, renal function needs to be checked three to five days after starting an ACE inhibitor.8

Hyperkalaemia

Angiotensin II and the increase in plasma potassium concentration stimulate the release of aldosterone from the adrenal zona glomerulosa. Aldosterone is a hormone that increases the urinary excretion of potassium. Locally generated angiotensin II in the zona glomerulosa mediates potassium-induced aldosterone release. Blocking angiotensin II formation with an ACE inhibitor will reduce aldosterone release, and this will reduce potassium excretion, and therefore cause hyperkalaemia. As a side-effect of an ACE inhibitor, hyperkalaemia is more common in patients with renal dysfunction, diabetes mellitus, concurrent use of an ACE inhibitor with potassium-sparing diuretics, and nonsteroidal anti-inflammatory drugs. In these patients, a low dose of an ACE inhibitor may lessen the development of hyperkalaemia.8

Dry cough

A dry cough is noted in 5-20% of patients on an ACE inhibitor.6,8 Patients may present with bronchospasm, and may be misdiagnosed with asthma. A cough may occur within one to two weeks of starting an ACE inhibitor. An ACE inhibitor-induced cough is more common in women than in men, and it usually resolves within one to four days of stopping therapy, but it can take up to four weeks to cease, or even longer.6,8 The cough recurs when the patient is rechallenged with the same, or a different, ACE inhibitor. In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), 4.2% of patients on ramipril stopped therapy permanently due to a dry cough.9 The mechanism of cough is not clear in these patients, but it is thought to be related to a high concentration of kinins, prostaglandins, thromboxane and substance P.9 The presence of a cough in some patients, and not in others, suggests that genetic factors may play a role. Treatment may involve cessation of the drug, or reduction of the dose.8 If the drug is stopped, and it is still necessary to use a renin-angiotensin system blockade, an angiotensin receptor blocker would be the drug of choice. Alternatively, depending on the clinical indication, a different class of drugs could be prescribed.8

Angioedema

This is a rare, but potentially fatal, side-effect of ACE inhibitors. In the ONTARGET trial, 0.3% of patients on ramipril stopped the drug permanently due to angioedema.8 The risk factors for the development of ACE inhibitor-induced angioedema may be genetic, e.g. black race and female gender, or may be environmental, e.g. smoking.8 Angioedema can occur after the first dose, or as late as two years after beginning treatment. The pathophysiology of angioedema in patients taking an ACE inhibitor is due to a decrease in bradykinin degradation. Aminopeptidase P and dipeptidyl peptidase P are important in the degradation of substance P, and when they are reduced, angioedema may occur.4,10 Clinical features of angioedema include swelling and oedema of the face (common), tongue, oropharynx, larynx and intestines. The oedema is mostly localised, non-pruritic and non-pitting. Management strategies depend on the severity of angioedema at presentation. Drug therapies include glucocorticoids, antihistamines, and epinephrine. In severe cases, the patient may need intubation and mechanical ventilation.4,10,11

Conclusion

The side-effects of ACE inhibitors can cause non-compliance in some patients. Sometimes, they can be life-threatening, as in severe angioedema. Therefore, it is important for clinicians to be aware of these side-effects, and to warn patients about them. This is important for patients’ safety and improvement of compliance.

References