British Heart Foundation

Factfile 07/2002

ACE-INHIBITORS: AN UPDATE

The Renin-Angiotensin System (RAS)

The major product of this system is angiotensin II, a potent vasoconstrictor which also stimulates salt and water retention through aldosterone release from the adrenal glands. Angiotensin II is synthesised by the action of angiotensin converting enzyme (ACE) on angiotensin I (which derives from a precursor, angiotensinogen, under the influence of renin, a protease enzyme secreted by the kidneys). The major stimulus for renin release is renal hypoperfusion, caused by volume depletion or low cardiac output. It is activated therefore in response to dehydration, haemorrhage and heart failure when vasoconstriction, mediated by angiotensin II, helps maintain blood pressure while salt and water retention restore plasma volume.

It is now recognised that >80% of the angiotensin II produced within the body, derives not from the circulating RAS but from a tissue-bound autocrine/paracrine RAS found throughout the body, including the vasculature and the myocardium. Like the circulating RAS, this tissue-bound system depends upon ACE for the synthesis of angiotensin II. Its physiological role, however, is different and involves long-term modulation of vascular function, wall thickness and myocardial mass. These effects are almost certainly involved in the pathophysiology of hypertension, vascular disease (including atherosclerosis) and heart failure.

ACE-Inhibitors (ACE-Is)

These drugs were developed in the 1970s for the treatment of hypertension. By inhibition of ACE, they reduce angiotensin II synthesis in the circulation and the tissues. Because ACE is also involved in the breakdown of bradykinin, ACE-Is cause activity of this vascular peptide to increase, no doubt contributing to their vasodilator effects. ACE-Is can produce profound hypotension in susceptible patients (mainly those on diuretics or who are already hypotensive). In such patients careful monitoring of blood pressure and serum biochemistry is important early in the course of treatment to guard against pre-renal failure. Treatment is contraindicated in patients with aortic stenosis and those known to have renal artery stenosis although renal dysfunction is not a contraindication to treatment. In patients taking diuretics, dosage reduction may be required when ACE-Is are introduced, but because these drugs conserve potassium, supplements (or potassium-sparing diuretics) are not usually necessary. ACE-Is are usually well tolerated, the most siginificant side-effect being a dry cough that affects up to 10% of patients. This effect is unrelated to dose and if the cough is intolerable, the only remedy is drug withdrawal and substitution with an angiotensin AII receptor blocker (See Factfile 6/2001 - Angiotensin Receptor Antagonists).

Hypertension

ACE-Is are highly effective antihypertensive drugs that lower blood pressure and help reverse left ventricular hypertrophy. They are particularly useful in young patients because of the low incidence of impotence and have a special role when hypertension is associated with co-morbidity such as heart failure, diabetes or coronary artery disease. Patients of African origin appear relatively less responsive to treatment and high doses may be necessary. The efficacy of ACE-Is is enhanced by their co-prescription with diuretics.

Heart failure

ACE-Is, together with diuretic, are first-line drugs in symptomatic heart failure and alone in asymptomatic left ventricular dysfunction. In symptomatic heart failure, inhibition of angiotensin II synthesis not only causes vasodilatation, which increases cardiac output by afterload reduction, but also removes the major stimulus for aldosterone secretion, thereby enhancing the renal excretion of salt and water. Of particular importance, however, is the finding that these drugs improve long-term prognosis in heart failure [1]. This prognostic benefit applies also to patients with asymptomatic left ventricular dysfunction [2]. The mechanism almost certainly relates to inhibition of the tissue-bound RAS with potential benefits that include protection against left ventricular remodelling

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(hypertrophy and dilatation), and against progressive atherosclerosis and myocardial infarction.

Secondary Prevention of Coronary Artery Disease

Acute Myocardial Infarction (AMI)

ACE-Is should be prescribed for all patients with an anterior AMI [3,4]. These drugs protect against left ventricular remodelling (see above) thereby reducing the incidence of heart failure and death. They may also have a direct effect on the atherosclerotic process and susceptibility to plaque events, thereby reducing the risk of recurrent infarction. ACE-Is are also indicated in those patients with an inferior AMI who show evidence of heart failure.

Stable Coronary Artery Disease

ACE-Is should be considered for high risk patients with coronary artery disease, including the elderly and those with multiple risk factors or diabetes. Treatment helps stabilise the coronary endothelium [5] and reduces the risk of cardiovascular events [6].

Diabetes

ACE-Is have an established role in diabetes to protect against microvascular problems, particularly nephropathy and retinopathy. In addition, there is evidence that they may be protective against macrovascular complications, making them an important part of the armamentarium for treatment of diabetic coronary artery disease [7].

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