British Heart Foundation

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ANGIOTENSIN RECEPTOR ANTAGONISTS

The first angiotensin receptor antagonist Losartan, was licensed for use in clinical medicine in the treatment of hypertension in 1994. Subsequently, five other members of this class of compound have been licensed in the United Kingdom, (Valsartan, irbesartan, candesartan, telmisartan and eprosartan).

Drugs which block the renin-angiotensin-aldosterone system have assumed increasing importance in the prevention and treatment of cardiovascular disease (hypertension, congestive cardiac failure, post myocardial infarction, diabetes). This evidence has accumulated from studies with angiotensin converting enzyme (ACE) inhibitors which block the conversion of angiotensin I to aniotensin II by inhibiting the enzyme (ACE). Angiotensin (AT) , receptor antagonists selectively block AT_1 receptors and differ from ACE inhibitors in the following respects:

1. They do not potentiate bradykinin, and thereby avoid bradykinin related side effects (cough and angioneurotic oedema)
2. They block actions of angiotensin II, irrespective of the synthetic pathway (in some tissues angiotensin is formed by non-ACE pathways)
3. Non AT_1 receptors remain unblocked (of uncertain benefit).

In hypertension they reduce blood pressure by peripheral vasodilatation without associated reflex sympathetic activation and thus there is no alteration in heart rate.

As a class of drugs they have equivalent blood pressure lowering efficacy to ACE inhibitors but in common with other classes of drugs, there are wide inter-individual variations in the magnitude of the blood pressure fall, reflecting the heterogeneity of the hypertensive population.

Their pharmacokinetic and dynamic profiles dictate that in general they can be administered once daily.

AT_1 receptor antagonists differ from other classes of ant-hypertensives in that no specific side effects have been identified in placebo controlled trials. In addition increasing dosage of the drug does not appear to increase the likelihood of side effects occurring. Nevertheless, they should be used with caution in patients at risk of hypovolaemia (dehydration diarrhoea) and they are contra-indicated in patients with renal artery stenosis.

Their use in pregnancy is contra-indicated because of potential risks to fetal growth and development.

Clinical Use

To achieve the desired blood pressure goals (British Hypertension Society Guidelines – BMJ 199;319: 630-5) the individual drug should be up titrated, if necessary to the maximum recommended dose. Failure to achieve target blood pressure requires the addition of a second drug, ideally a diuretic (low dose) or a calcium channel blocking agent.

Serum creatinine should be measured prior to and at three to six weeks following introduction of treatment with an AT_1 receptor antagonist.

Outcome Trials

To date no morbidity/mortality trials with an angiotensin receptor antagonist have reported in uncomplicated hypertensive patients but several are on-going and will complete within the next year or two. Until such time guidelines recommend their use when ACE inhibitors are poorly tolerated, or in patients intolerant of several other different classes of anti-hypertensive agent.

The preliminary results of the four trials of angiotensin II receptor antagonist in diabetes have recently been presented, but have yet to be published. In brief, they demonstrate that angiotensin receptor antagonists are superior to both placebo and to dihydropyridine calcium channel blockers in reducing microalbuminuria and proteinuria, and in slowing the progression of renal disease in patients with type 2 diabetes.

Similar recommendations apply in the treatment of patients with heart failure in which three recently reported trials have shown no clear advantage of AT_1 receptor antagonists over ACE inhibitors.

Additional studies are in progress in heart failure and post myocardial infarction.

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Factfile *is produced by the British Heart Foundation in association with the British Cardiac Society and is compiled with the advice of a wide spectrum of doctors, including general practitioners. It reflects a consensus of opinion.*

Further Reading

1. Goodfriend TL, Elliot ME, Catt KJ: Angiotensin receptors and their antagonists. N EnglJ Med 334:1654, 1996

2. Griendling KK, Lassegue B, Alexander RW: Angiotensin receptors and their therapeutic implications. Annu Rev Pharmacol Toxicol 36:281-306, 1996

3. Angiotensin II Receptor Antagonists. Eds Eppstein M and Brunner HR. Henley & Belfus, Inc, Philadelphia, 2000.