ANGIOTENSIN II RECEPTOR ANTAGONISTS

SUMMARY

- Angiotensin II receptor antagonists (AIIRAs) selectively antagonise the actions of the potent vasoconstrictor angiotensin II at its receptor site.
- AIIRAs show similar efficacy to other major classes of antihypertensive agents and are well tolerated.
- There is currently no outcome data on the efficacy of AIIRAs in reducing long-term morbidity precluding their use as first choice agents.
- AIIRAs are likely to find initial use in patients who are not well managed with or are intolerant of established alternatives.

INTRODUCTION

The angiotensin II receptor antagonists (AIIRAs) are the first new class of antihypertensive agents to be introduced since the angiotensin converting enzyme (ACE) inhibitors. They have similarities to, but also important differences from, the ACE inhibitors. It is logical that the two classes will be compared. There are currently six AIIRAs licensed in Ireland and more under development. Losartan was the first to be approved for the treatment of hypertension in 1995. This has since been followed by valsartan, eprosartan, irbesartan, candesartan and telmisartan. AIIRAs are now being investigated for use in congestive heart failure. A niche for AIIRAs is evolving.

PHARMACOLOGY

The renin-angiotensin system (RAS) has been implicated in both the initiation and maintenance of essential hypertension. This has generated interest in developing new pharmacologic approaches to block the RAS.[1]

	Renin		ACE		AIIRAs
			ACE inhibitors		
Angiotensinogen		Angiotensin I		Angiotensin II	AT1 receptor

ACE converts angiotensin I to angiotensin II which is the primary mediator of the RAS. ACE is also involved in the degradation of bradykinin. ACE inhibitors reduce the production of angiotensin II thus inhibiting the RAS. However, they also result in increases in bradykinin which is postulated to cause adverse effects such as cough and angioedema.
Because angiotensin II may also be formed by non-ACE pathways, ACE inhibitors do not completely block the RAS. The effect of angiotensin II on blood pressure is mediated via angiotensin type 1 receptors and the new AIIRAs act at this level. This may allow more complete inhibition of the RAS and does not interfere with the degradation of bradykinin. Their selectivity may provide a more favourable adverse effect profile.

CLINICAL INDICATIONS

Hypertension

Published data has shown the antihypertensive efficacy of this group of drugs to be similar to that of ACE inhibitors.[1-8] Comparative studies with losartan, candesartan, valsartan, irbesartan and telmisartan have been conducted with thiazide diuretics, calcium antagonists and beta-blockers again showing equivalent blood pressure reductions. There is very little comparative data on eprosartan.[6]
Additive effects with other antihypertensives such as diuretics have been confirmed in clinical studies.[9-12] It appears in some studies that the lower dose of AIIRA combined with a thiazide, produced a greater reduction in blood pressure than the maximum dose of the AIIRA alone.[12] A combined preparation of losartan and hydrochlorothiazide became available in 1997 and may improve compliance.
According to the first head-to-head comparison of two AIIRAs in which both drugs were studied at their maximum dose, irbesartan appears to be more effective than losartan in lowering blood pressure in patients with mild to moderate hypertension.[13,14] There is however insufficient evidence to date that any one of these agents is superior to another. Overall the individual agents are quite comparable.

Heart Failure

None of the AIIRAs are currently marketed in Ireland for heart failure although losartan has been granted a licence. A recent consensus report notes that there is no conclusive evidence that AIIRAs are equivalent or superior to ACE inhibitors for heart failure.[15,16] It recommends that these drugs are only considered in patients intolerant of ACE-inhibitors.

ADVERSE EFFECTS

Clinical trials to date have shown AIIRAs to be well tolerated in the majority of patients with essential hypertension. Adverse events are usually mild and transient and those most often considered to be drug related are headache, dizziness and fatigue.[3-8]

First-dose hypotension does not appear to be a problem with AIIRAs provided the patient is not severely sodium and/or volume depleted as a result of, for example, high dose diuretic treatment.[9,17]

Although one of the advantages of AIIRAs is the reduced incidence of cough and angioedema compared with ACE-inhibitors, sporadic cases have been reported.[18-24]

Most evidence indicates that ACE inhibitors are 'metabolically neutral'.[3-8,17] The same may be expected for the AIIRAs but as yet there are few data. Losartan has a uricosuric effect that has not been reported with the other agents.[25,26]

Whether these agents will have the same renoprotective potential as ACE inhibitors remains to be seen.[9] They are likely to have an adverse effect in patients with renal artery stenosis as seen with ACE inhibitors.[9] AIIRAs are contraindicated in pregnancy and lactation.[11]

DRUG INTERACTIONS

No clinically significant drug interactions have been observed between most of the available AIIRAs and digoxin, warfarin, glibenclamide, cimetidine and ranitidine.[10]

Concurrent administration of potassium supplements or potassium-sparing diuretics is not recommended because of the danger of hyperkalaemia.[27]

Fluconazole but not itraconazole interacts with losartan by inhibiting its metabolism to its active metabolite.[28] The implication is that coadministration of losartan with fluconazole could lead to reduced antihypertensive action of losartan.

Whether non-steroidal anti-inflammatory drugs (NSAIDs) interact with AIIRAs is not yet known.[9,26] NSAIDs are known to blunt the hypotensive effect of several classes of antihypertensives in particular ACE inhibitors.

Reversible increases in serum lithium concentrations have been reported when ACE inhibitors are coadministered and there may be a similar effect with AIIRAs.

WHICH ANTIHYPERTENSIVE?

There is no longer uncertainty about whether hypertension should be treated. The two main issues that clinicians face are first, how low a blood pressure to aim for and second, which drug regimen to choose.

The World Health Organisation/International Society of Hypertension (WHO/ISH) have issued new guidelines on the management of hypertension, the first update since 1993.[12] The new guidelines do not specify particular drug classes that should be used to start therapy in general. They say instead, that all available drug classes are

suitable for the initiation and maintenance of antihypertensive therapy. This is a broader recommendation than that in the previous guidelines which graded the drugs in order of benefit shown from mortality and morbidity trials. Diuretics headed this list followed by beta-blockers, ACE-inhibitors, calcium channel blockers and alpha blockers in that order. AIIRAs have been added to the list of possible drug treatments. These drugs were not widely available when the last guidelines were issued. The new guidelines put more emphasis on choosing the right class of drug for each patient depending on their individual risk factor profile. These guidelines also put stronger emphasis than before on combination drug therapy at submaximal doses to achieve maximal blood pressure lowering with minimal side-effects. This is not uncommon as monotherapy fails to control blood pressure in about 50 per cent of all hypertensive patients on one drug of any class and with revised targets as low as 130/85mmHg a substantial minority require a regimen involving three or more agents.[11,12]

Hypertension guidelines seem to be a particularly sensitive area, probably because of the enormous market for antihypertensive drugs. The main question to ask regarding AIIRAs is whether they offer any advantages over ACE inhibitors other than a reduced frequency of cough. To date, there is insufficient evidence to support benefits of AIIRAs over ACE inhibitors. This issue will probably be settled over the next few years upon completion of large-scale clinical trials, currently underway, comparing AIIRAs with ACE inhibitors. These trials span many different conditions including hypertension, heart failure and renal disease.

Thiazide diuretics and beta-blockers are the only classes of antihypertensive agents that have been shown to reduce morbidity and mortality in long-term clinical trials and should, in the absence of contra-indications to their use, remain drugs of first choice for the majority of hypertensives.[11] Their tolerability is further enhanced if lower doses e.g. bendrofluazide 1.25mg-2.5mg or atenolol 50mg are used.[11]

During the next 2-3 years there is likely to be a flurry of revised guidelines for the treatment of hypertension as the new outcome trials are reported and digested. The long-term safety issue in relation to nifedipine will be resolved. If one class out-performs the others in prevention of complications, then clearly this class will become the preferred treatment for hypertension. Despite the good efficacy / tolerability data available for AIIRAs, their cost-benefit analysis means that they should be restricted to patients who have failed to respond to or are intolerant to more established drug regimens

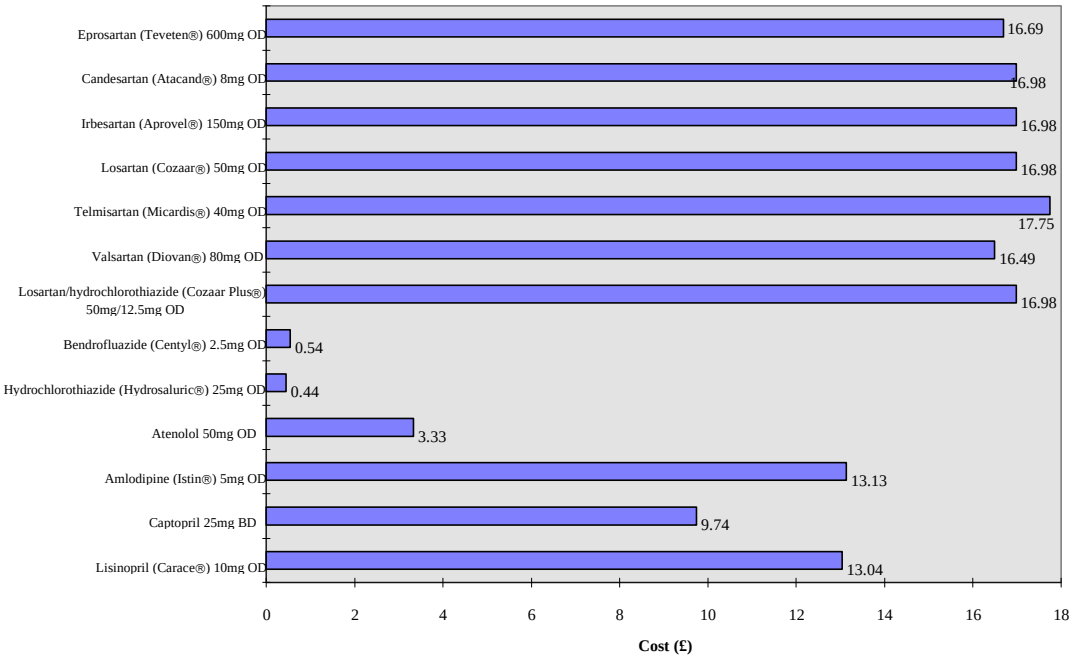
COSTS

- Almost 6,000 prescriptions for AIIRAs were dispensed at a cost of almost £120,000 under the General Medical Services (GMS) Scheme in 1997.

- This expenditure is expected to have increased to almost £400,000 when 1998 data becomes available.

Comparative Costs for 28 Days Therapy

Drug costs are based on data from GMS 1999.



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