Angiotensin II type 1 receptor antagonists and their combinations in the treatment of hypertension

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Keywords: angiotensin II type 1 receptor antagonists, hypertension

 S Afr Fam Pract 2012;54(3):210-211

Introduction

The pathophysiology of hypertension is not multifactorial in nature, and there is a complex interplay of mechanisms of control and counter-regulatory responses activated by drugs. The problem for clinicians is that it is not really possible to recognise the various clinical phenotypes of hypertension. In other words, the heterogeneity of hypertension remains a clinical problem.[1] Current overwhelming evidence is that the most important treatment concept in the management of hypertension is that treatment should reduce blood pressure to goal levels.[2] The majority of hypertensive patients will need two or more antihypertensive drugs to control their blood pressure at goal. Conceptually, a strong case can be made for the early use of combination therapy in the treatment of hypertension.[3]

Choosing a combination: What is the problem?

The essential problem is that there are very little data from prospective randomised controlled clinical trials that test specific combinations against one another, to guide clinicians in choosing the "superior" combination. Most of the trials that have been carried out tested one drug against another, and then other drugs were added to both treatment arms. Also, in most trials, the second added drug (to both the treatment arms) was the same.

However, there are recommendations in the literature on combinations.[3] These are depicted in the Table I as preferred, acceptable, and unacceptable combinations.

The best evidence from which claims can be made from outcomes in favour of a particular combination regimen, derives from four trials:[3]

- LIFE (Losartan Intervention For Endpoint reduction in hypertension) study: angiotensin- receptor blocker (ARB) trial
- ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial): angiotensin-converting enzyme (ACE) inhibitors trial
- ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients living with Systolic Hypertension) trial: ACE inhibitor trial
- VALUE (Valsartan Antihypertension Long-term use Evaluation) trial: ARB trial.

Table I: Drug combinations in hypertension[3]

Preferred combinations
ACE[a] inhibitor plus diuretic
ARB[b] plus diuretic
ACE inhibitor plus calcium-channel blocker
ARB plus calcium-channel blocker
Acceptable combinations
Beta blocker or diuretic (not a high dose)
Calcium-channel blocker (dihydropyridine) or beta blocker
Calcium-channel blocker or diuretic
Renin inhibitor or diuretic
Renin inhibitor or calcium-channel blocker
Dihydropyridine or non-dihydropiridine calcium-channel blocker
Unacceptable combinations
ACE inhibitor or ARB
Renin inhibitor or ARB
Renin inhibitor or ACE inhibitor
Calcium-channel blocker (non-dihydropyridine) or beta blocker
Centrally-acting agent or beta blocker

What evidence is there for angiotensin-receptor blocker combinations?

Currently, dual renin-angiotensin aldosterone system (RAAS) blockade, specifically an ACE inhibitor plus an ARB, should not be used for the treatment of hypertension, as there are no real benefits. Moreover, the risks may outweigh the benefits.[4] This was demonstrated in the well-known ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial).

In the LIFE trial, 9 193 hypertensives were treated either with an ARB (losartan) or beta blocker (atenolol), but in both groups, hydrochlorothiazine (HCTZ) was added in

the majority of patients.[5] The combination of losartan plus HCTZ, as compared to the combination of atenolol plus HCTZ, reduced the composite primary cardiovascular end-point by 13%. The major benefit of losartan plus HCTZ was in the secondary end-point of stroke (a component of the primary end-point), which was reduced by 25%. This achieved result occurred against the background of an equally reduced level of blood pressure.

In the VALUE trial, 15 245 hypertensives received either an ARB (valsartan) or amlodipine (calcium-channel blocker), and to each arm, HCTZ could be added to control blood pressure over 4.2 years.[6] The primary composite end-point of cardiac morbidity and mortality was similar in the two arms, comparing valsartan plus HCTZ vs. amlodipine plus HCTZ, but early, better control of blood pressure in the amlodipine arm led to less myocardial infarctions. This trial also linked to the cardiovascular benefit of early blood pressure control in high-risk hypertensives.

The cumulative evidence from these trials supports the view that an ARB plus calcium-channel blocker combination is likely to be associated with better cardiovascular outcomes, than combinations containing beta blockers and thiazide diuretics.[3] Numerous factorial design studies have shown that the combination of a thiazide diuretic plus an ARB (many ARBs) results in fully additive blood pressure reduction. Diuretics activate the RAAS by depleting intravascular volume and addition of ARB, then attenuates this counter-regulatory response, and mitigates the hypokalemia induced by the diuretic.

Numerous efficacy and tolerability studies on the combination of an ARB plus a calcium-channel blocker have been carried out, and demonstrated greater blood pressure reductions with the combinations, and significantly more patients achieving goal blood pressure.[7] The combinations tested were amlodipine and valsartan, and amlodipine plus telmisartan, in varying fixed combinations. The combination of amlodipine plus candesartan, as compared to amlodipine alone, also showed increased efficacy for the combination.[8] It is foreseen that all ARBs on the market will be combined with a calcium-channel blocker. In a recent trial, 350 hypertensives were treated with a calcium-channel blocker plus an ARB, or a calcium-channel plus a beta blocker, or a calcium-channel blocker plus a thiazide diuretic,[9] and the clinical effects tested in these three arms. After 3.61 years of treatment, two thirds of the patients achieved target blood pressure, and the three combinations were equally effective in achieving goal blood pressure. Equally, all three combinations had the same reduction of the primary composite outcome of cardiovascular events.

In an efficacy and safety trial, an ARB plus calcium-channel blocker plus HCTZ (triple combination) resulted in significantly more patients reaching goal blood pressure, than the combinations of the ARB plus HCTZ, or ARB plus calcium-channel blocker, or calcium-channel blocker plus HCTZ combinations.[10] This study demonstrates that triple therapy (ARB plus calcium-channel blocker plus HCTZ) can be given safely, can achieve goal blood pressure more often, and can do so promptly.

In summary, there appears to be enough data to support the combination of an ARB plus a diuretic and/or a calcium-channel blocker, either as two separate drugs, or in a fixed combination, with the aim of improving the percentage of hypertensive patients who can reach goal blood pressure.

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