α Blockers in Resistant Hypertension: 
A Cardiology Perspective

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Introduction

Development of resistance to antihypertensive therapy may occur more frequently than expected, and is clearly associated with increased risk of cardiovascular events. Considering the diversity of possible influences on blood pressure, management of resistant hypertension involves a thorough evaluation of the possible causes. If the secondary causes of resistance are ruled out, the approach to pharmacotherapy assumes vital importance.1,2 Resistance is implied by an insufficient control of blood pressure, despite the use of 3 antihypertensive drugs in optimal doses, including a diuretic.1,2 To meet the goal of blood pressure, addition of antihypertensives from different classes may become essential. Such multi-drug approach requires important pharmacological considerations to maximise the efficacy, minimise adverse effects and maintain adherence with the prescribed regimens. α blockers are an important class of hypertensives relevant to this group of patients, and may have clinical utility in various comorbidities. This review focuses on the clinical utility of α blockers, in the management of resistant hypertension.

α Blockers: Current Position in Antihypertensive Ladder

ALLHAT study results, published in the year 2000, were suggestive of a higher incidence of congestive cardiac failure with doxazosin, relative to chlorthalidone.3 Although these observations have been a subject of much controversy and debate,4,5 post these observations, α blockers have not been preferred as first-line antihypertensive agents. Subsequently, several small and large studies have evaluated the profile of α blockers, as add-on drugs in various multidrug regimens. Including a block in antihypertensive regimens is an attractive proposition, owing to their favourable metabolic profile, fewer safety risks, good tolerability particularly observed with improved formulations, apart from their consistent efficacy across various groups of patients. Addition of α blockers may be particularly preferred in presence of comorbidities like diabetes, dyslipidaemia, gout, prostatic hyperplasia (males) or lower urinary tract dysfunction (females), or in presence of dialysis, vigorous work, sports, or exercise. Sympathetic activity may significantly influence the development of hypertension, particularly in conditions like renal disease, stress-associated disorders, habitual smoking, increased morning blood-pressure surge, lead poisoning and phaeochromocytoma. Inclusion of α-blockers in the antihypertensive regimens implies a rational approach for such patients. Apart from these specific benefits, combining α blockers with other antihypertensive agents may demonstrate additional therapeutic advantages. Considering these aspects, α blockers are reasonably considered in combination with the first line antihypertensive agents, across various groups of patients, to improve the control of blood pressure.

α Blockers: Favourable Profile in Combination Regimens

After the ALLHAT study, many investigations have attempted to highlight various perspectives of the use of α blockers, as add-on therapy in uncontrolled hypertension. These studies describe the therapeutic profile of α blockers, in terms of antihypertensive efficacy, safety, metabolic effects, cardiovascular or renal outcomes.

The ASOCIA study group evaluated the efficacy and safety of doxazosin GITS, in patients with uncontrolled hypertension.6 Over 3,500 patients of uncontrolled hypertension were included, of which 7.3% were not receiving any drug, 19.7% were receiving 2 or more drugs, and the remaining were on monotherapy.
at baseline. Addition of doxazosin GITS lead to achievement of goal blood pressure in 39% of these patients at 4 weeks, and in 61% patients at 16 weeks. Interestingly, the efficacy of add-on doxazosin GITS was equally good in patients receiving 2 or more drugs, monotherapy or no therapy at baseline. Also, systolic or diastolic blood pressure reductions did not differ significantly between the groups receiving different initial drugs (ACE inhibitors, ARBs, calcium channel blockers, diuretics or β blockers). 1.57% of patients observed drug-related adverse events, with dizziness and headache being the most common. Only 1 drug-related serious adverse event was observed, in the form of urinary incontinence in a 71-year old woman. < 1% of patients discontinued treatment due to drug-related adverse events.6 Similar findings were observed in the GATES study, indicating a significantly improved blood pressure control on addition of doxazosin Gits, to the antihypertensive regimen in uncontrolled cases.7

A large observational analysis of the Anglo-Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm (ASCOT-BPLA), evaluated the efficacy and safety of doxazosin GITS as a third line therapy, in uncontrolled hypertension.8 In over 10,000 patients observed in this analysis, addition of doxazosin GITS demonstrated significant Blood pressure reductions by approximately 12/7 mmHg, in all subgroups of patients. Within different subgroups, more prominent systolic blood pressure reductions were observed in the elderly, those receiving atenolol and those without diabetes, while diastolic blood pressure reductions were more prominent in the elderly, females, those receiving amlodipine, and patients with diabetes. Similar blood pressure reductions were observed in patients with or without metabolic syndrome. Antihypertensive efficacy increased in proportion to increase in the age, baseline body weight, or baseline body-mass index. Significant improvements were observed in terms of lipid profile, including reductions in the total cholesterol, LDL cholesterol, and triglyceride levels. A small increase was observed in the fasting blood glucose levels, which possibly reflected a natural increase in the elderly participants. Importantly, the risk of heart failure was not increased, with the addition of doxazosin GITS in the antihypertensive regimen. This observational analysis suggested that α blockers can be used safely and effectively in various patient groups, as third line antihypertensive agents, without an increase in the risk of heart failure.8 Similar results were also observed in a smaller Japanese study, evaluating doxazosin as a third line antihypertensive agent.9 According to a large retrospective analysis, doxazosin and other α blockers appear to be safe in the vast majority of patients with a lesser degree of cardiac ischaemia. However, in patients with significant cardiac ischaemia, the use of α blockers, particularly doxazosin, may be associated with adverse cardiac outcomes.10

Stress related sympathetic hyperactivity is an essential mechanism responsible for stress-induced hypertension. It may manifest as masked hypertension, white-coat hypertension, morning surge in blood pressure, or workplace hypertension.11,12 Addressing stress-induced hypertension, by control of sympathetic activity with α-blockade, is a rational clinical approach. Evidence clearly indicates that these manifestations of stress-related hypertension are associated with increased cardiovascular disease independently of the average 24-hour blood pressure control.11-13 α-adrenergic blockade has demonstrated beneficial effects on masked hypertension, when used in combination regimen.14 α blockers have a particular advantage in controlling the morning surge in blood pressure. α blockers generally achieve a great pharmacodynamic effect in the morning, when the α-adrenergic tone is at its peak. Also, they do not cause a significant reduction in night time blood pressure, as sympathetic activity is suppressed during the night and activated rapidly after waking up. Greater fall in night time blood pressure is possible with other agents, including diuretics and short acting calcium channel blockers.15,16 The Japan Morning Surge-1 (JMS-1) study evaluated the influence of the addition of α-blocker doxazosin to antihypertensive regimen, in 611 patients with increased morning blood pressure surge.15 Additional α-blockade resulted in significant reductions in blood pressure and urinary albumin excretion. This is an important observation, as diuretic antihypertensives may negatively influence morning hypertension. In about half of the patients, combination of α and β blockade was required to achieve the target morning blood pressure of 135 mmHg. Equivalent reductions were observed in blood pressure and microalbuminuria, when doxazosin was combined with RAS inhibitor, calcium channel blocker, combination of RAS inhibitor and calcium channel blocker, or diuretics. Significantly more adverse events were observed in patients receiving doxazosin, but the rate of major events was comparable to the control group. Out of the 308 patients in doxazosin group, 6 patients suffered from heart failure, 5 of whom were receiving concomitant β blocker.15 Another study evaluated the effect of addition of doxazosin to amlodipine therapy, on morning blood pressure and left ventricular hypertrophy, in 49 patients over 1 year.17 A significant reduction in morning blood pressure was observed with doxazosin and amlodipine regimen, along with regression of left ventricular hypertrophy, reduction in insulin resistance, total cholesterol and triglycerides. Regression in left ventricular hypertrophy was a clinically significant observation, and was correlated to the control of morning blood pressure and insulin resistance. No case of heart failure was reported. 4 of the 49 patients were withdrawn from the study, due to adverse events including urinary incontinence and vasodilatory oedema.12 For the α-blocker formulations that may not provide sustained 24 hour efficacy, bedtime dosing
mild to moderate heart failure.

**Synergistic Effects with Other Antihypertensive Classes**

α blockers have a particularly suitable profile as add-on drugs in antihypertensive regimens, owing to multiple favourable characteristics. They demonstrate additive or synergistic effect with most of the antihypertensive drug classes, a notable exception being the centrally acting α agonists. They play a vital role in controlling the influence of sympathetic activity on hypertension. The other important influences include renin angiotensin activity and volume excess, which can be countered appropriately by RAS blockers, calcium channel blockers or diuretics. Simultaneous management of these influences lead to more effective and complete control of hypertension.

α blockers do not worsen the disorders, which frequently coexist with hypertension, including gout, chronic obstructive lung disease, peripheral ischaemia, diabetes, or dyslipidaemia. α blockers may counteract the adverse effects associated with diuretics or β blockers, in terms of the changes in lipid, glucose or uric acid profiles.

Favourable haemodynamic alterations observed with α blockers, combined with the cardioprotective action of β blockers, forms an excellent combination for patients with renal disease. In combination regimens, the haemodynamic influences of α-blockers may also be beneficial in cardiovascular disease, including heart failure and stroke, as discussed previously. Diuretics may negatively influence blood pressure control, particularly the morning surge and nocturnal dipping. α blockers may play an important role to address the morning blood pressure surge.

The use of α-blockers in resistant hypertension is supported by evidence based recommendations. Effective diuresis may be essential in addressing the resistance to hypertension. Hence, short-term use of aldosterone antagonists may be an important intervention in resistant hypertension, apart from optimising the use of thiazides or thiazide like diuretics. However, the use of aldosterone antagonists is associated with a serious risk of hyperkalaemia, which may be compounded with the simultaneous use of RAS inhibitors. Strict monitoring of serum potassium levels becomes essential for such patients. Apart from this, the hormonal side effects associated with spironolactone use, may negatively impact patient compliance. The efficacy, safety, minimal pharmacological interactions and pleiotropic benefits are essential considerations, favouring the choice of α blockers in long-term management of resistant hypertension.

**Conclusion**

α blockers are useful add on drugs in most clinical...
conditions, but not an ideal monotherapy. α blockers have a suitable pharmacological profile for use in combination regimens. In combination regimens, the consistent antihypertensive efficacy across various patient groups, reduced risk of adverse effects, improved tolerability observed particularly with slow sustained release formulations, pleiotropic metabolic and haemodynamic benefits, and minimal drug interactions, favour the clinical use of α blockers. In conditions associated with increased sympathetic activity, α receptor blockade is a particularly relevant approach. Effective blood pressure control is achievable, with the addition of α blockers to the therapeutic regimen, across diverse spectrum of resistant hypertension.

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