Alpha Adrenergic Blockers in the Treatment of Hypertension – A Nephrologist’s Perspective

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Introduction

We know by now that hypertension is associated with considerable cardiovascular morbidity. That control of blood pressure offers freedom from many such complications is also proven. But a lot more remains to be known about the enigma named hypertension.

We still do not know the exact pathogenesis of hypertension; every single author differs in defining hypertension. Little is known about the optimum goal of treatment. But maximum controversy centres on the choice of anti-hypertensive drug. With each new recommendation, some new group of drugs gets a nod while some drugs fall from the grace.

In nephrology practice, while selecting the appropriate anti-hypertensive agent, the clinician has to keep in mind two aspects in addition to achieving the target blood pressure (BP). Firstly, an agent should be chosen which is renoprotective. It will preserve renal function, thereby preventing or retarding the invariable downhill course of the disease. At the same time, it will not adversely affect the internal environment. Hence an agent which may aggravate or precipitate hyperkalaemia is not particularly welcomed by the nephrology community.

The group of drugs called alpha adrenergic blockers does not figure as the preferred agent in most of the recommendations of late.1

Mechanism of Action

Sympathetic nervous system plays a major role in the pathogenesis of hypertension. Blockade of alpha-1 receptors by appropriate agents provides a rational approach to the treatment of hypertension by inhibiting the binding of noradrenaline to the said receptors, thereby promoting smooth muscle cell relaxation, reduced vascular tone and decreased peripheral resistance.2 The net result is control of blood pressure.

Blood Pressure Control

The effects of alpha blockers have been extensively studied both as monotherapy and add on therapy. The results were encouraging. Both prazosin and doxazosin decreased blood pressure in approximately 70% patients following a 12 week treatment period.3 Alfuzosin was equally effective as propranolol when used as first line agent.4 Among patients who had not responded to monotherapy with diuretics, beta blockers, calcium channel blockers and ACE inhibitors, the addition of terazosin resulted in significant BP reduction.5

In the treatment of mild hypertension study (TOMHS) after four years of follow up, initial therapy with standard release doxazosin (1-2 mg per day) reduced systolic and diastolic BP by 13.4 and 11.2 mm Hg respectively, compared with mean reductions of 8.6 mm Hg for both systolic and diastolic BP among those who received placebo.6

Early Criticisms

The two important limitations encountered with alpha blockers earlier were postural hypotension and failure to achieve round the clock BP control. These were largely overcome by the development of controlled release formulations such as prazosin and doxazosin gastro intestinal therapeutic system (GITS). These formulations were successful in minimising the side effects by slowing absorption and reducing fluctuations in plasma concentration.7

Success Story of GITS

Prazosin GITS was shown to have similar BP lowering efficacy as enalapril in hypertensive patients with diabetes.
mellitus in an Indian population. In a sub-study of the HALT trial, evening dosing with doxazosin reduced both daytime and night time systolic and diastolic BP. Doxazosin GITS achieved more effective 24 hour BP control when administered at night (either alone or as add on therapy) in another study. In the randomised double blind doxazosin GITS as add on therapy in hypertension: an efficacy and safety (GATES) study doxazosin GITS (4 mg per day, titrated to 8 mg if required) or placebo was added to the existing anti-hypertensive therapy of patients with uncontrolled BP. After 6 weeks treatment, BP control (defined as < 140/90 mm Hg) was achieved in 37.3% in the doxazosin group, compared with 10.7% in those who received placebo.

In the ASOCIA study, when doxazosin GITS (4 mg per day, titrated to 8 mg if required) was added to the existing medications in a study population of 3631 Spanish patients, target BP (<140/90 mm Hg) was achieved in 39% at 4 weeks rising to 61% at 16 weeks.

Metabolic Effects

Alpha blockers have been shown to affect favourably various metabolic parameters, namely total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and plasma insulin levels, when used alone or in a combination. In 107 normotensive individuals with impaired glucose tolerance, doxazosin compared with placebo, from baseline to 6 months, resulted in a 6.5% reduction in total cholesterol, 9.8% reduction in LDL cholesterol, 8.3% increase in HDL cholesterol, 19% reduction in triglyceride, and 28% reduction in fasting plasma insulin. It is proposed that the increase in HDL cholesterol by doxazosin is mediated through gene transcription and is independent of its alpha blocking action.

Safety and Tolerability

The most common adverse events observed in patients receiving alpha blockers are dizziness, headache and asthenia. Patients may also encounter postural hypotension and syncope. Erectile dysfunction, though reported rarely, maybe the reason behind discontinuation of the drug. However, the GITS preparation is well tolerated and the reported incidence of discontinuation due to side effects is less.

The ALLHAT Outcome

The antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT) was designed to compare the effects of a thiazide diuretic (chlorthalidone) with an alpha blocker (doxazosin), a calcium channel blocker and an ACE inhibitor among hypertensive patients aged 55 years or more with at least one other cardiovascular risk factor. Though follow up was planned for 6-8 years, the doxazosin arm was discontinued prematurely based on a significantly higher incidence of combined cardiovascular disease events (a secondary end point) in the doxazosin arm. Major cardiovascular events were 25% more frequent among those who were assigned doxazosin, a result driven by higher rates of stroke and particularly congestive heart failure. Doxazosin was also associated with less effective BP control compared to chlorthalidone.

The results of ALLHAT generated much debate. The validity of heart failure diagnosis was questioned. It was also postulated that the early divergence of the event curves for heart failure represented the unmasking of symptoms of heart failure due to withdrawal of diuretics in the participants who were on antihypertensive therapy prior to randomisation.

Inspite of all the criticisms and questions about ALLHAT, in the seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure (JNC 7) guidelines, alpha blockers were not recommended for the routine treatment of hypertension.

The Anglo – Scandinavian Cardiac Outcomes Trial (ASCOT)

ASCOT was a multi centre international randomised trial conducted in 19,257 patients aged 40 to 79 years with hypertension and additional cardiovascular risk factors but no history of coronary heart disease. In an observational analysis, the effects of doxazosin GITS were evaluated in 10069 patients (32% having diabetes).

During a median of 12 months of uninterrupted therapy, mean BP fell by almost 12/7 mm Hg and target BP was achieved in 30% patients. During a median of 9 months of uninterrupted doxazosin treatment, there were significant reductions in total cholesterol (4.7%), LDL cholesterol (5.5%) and triglyceride (9.1%).

But the most significant observation was the crude heart failure rate, which was 1.5% among those who received doxazosin as against 1.54% among the remainder. This was despite the fact that recipients of doxazosin had more severe hypertensive disease (higher systolic BP and prevalence of left ventricular hypertrophy) at study entry compared to the rest of the study population.

Alpha Blockers in Renal Disease

Chronic kidney disease (CKD) has been reported to be accompanied by increased sympathetic activity, which partly explains the augmented cardiovascular risk in CKD. Microalbuminuria is now considered a surrogate marker for cardiovascular risk and is used
to screen for CKD. Sympathetic nerve activity is one of the mechanisms of morning hypertension. Alpha blockers when taken just before going to bed are reported to decrease morning BP surge. In the Japan Morning Surge – 1 (JMS-1) study, the effects of the alpha blocker doxazosin was tested in 611 patients with morning hypertension in terms of BP lowering and improvement in microalbuminuria. In the study conducted by 60 doctors at 16 institutions during a period from 1st August 2003 to 30th August 2005, there was a 10 mm Hg reduction of self measured systolic BP in the morning and 5 mm systolic BP reduction in the evening. The urinary albumin/creatinine ratio was more markedly reduced in the doxazosin group (-3.4 vs 0.0 mg/g) compared with the control group.19

When the effects of doxazosin were assessed in type 2 diabetic patients with macroalbuminuria, it was observed that doxazosin could reduce both waking and sleeping BP to the same extent over the 24 hour period. As a result, the sleeping/waking BP ratios did not alter.20

Six months continuous treatment with doxazosin treatment in a titrated dose not only reduced proteinuria (from 1.8 g/day to 1.3 g/day), the glomerular filtration rate (GFR) improved from 24.5 ml/min to 29.7 ml/min and mean serum creatinine dropped from 3.0 mg/dl to 2.5 mg/dl. It is proposed that the glomerular protective action of doxazosin is mediated through its inhibition of norepinephrine induced vasoconstrictive activity in both the afferent and efferent arteries of the kidney.21

That prazosin is an effective antihypertensive agent in all types of hypertensive dialysis patients, either alone or in combination, with minimal side effects, has been shown in more than one studies.22,23

The incidence of hypertension ranges from 60% to 80% in renal transplant recipients. Increased vascular resistance is a prominent feature of post transplant hypertension. Alpha blockers which act through peripheral vasodilatation, thereby reducing peripheral resistance, interfere with adrenergic vasoconstrictive mechanism, may be particularly beneficial in post transplant hypertension. The trough to peak (T/P) ratio is a single parameter that describes the consistency and duration of an anti-hypertensive drug’s action. In a population of cadaveric kidney transplant recipients, the T/P ratio of more than 50% in 24 hour BP monitoring was observed with doxazosin GITS.24 There were no metabolic adverse effects either. Beneficial effects in 6 renal transplant recipients could be observed with prazosin treatment in another study.25

In a 4 week prospective open multi centre study conducted in Indian population both peak urinary flow rate and IPSS (international prostate symptom score) improved in 75 male patients aged between 50 and 75 years having symptomatic benign prostatic hyperplasia, when treated with prazosin GITS 2.5 mg increased to 5 mg at bedtime if required.26

**Conclusion**

Alpha adrenergic blockers are a group of agents with time-tested efficacy in blood pressure control. They are effective in mild to moderate hypertension, can be used alone or in combination. The GITS formulation can be used as once daily formulation preferably at night. They have favourable effect on metabolic profile (e.g. lipids and insulin sensitivity) and are well tolerated. The most commonly encountered side effects are dizziness and postural hypotension which have been largely overcome by the night time administration of the GITS formulation.

From a nephrologist’s perspective, alpha blockers have been proved to be effective not only in controlling BP but also in reducing microalbuminuria, which is a surrogate marker of CKD progression. In that sense these agents are renoprotective. They have been tried successfully in dialysis and transplant population. The metabolic neutrality is an added advantage. Treatment with alpha blockers is not associated with serious side effects like hyperkalaemia.

In spite of all these advantages, these group of agents do not find a place in JNC recommendations. European Society of Hypertension, European Society of Cardiology, British Hypertension Society, National Institute of Health and Clinical Excellence, in short all the leading guidelines are either silent or have shown lack of interest in alpha blockers. The major driving force, in all likelihood, is the adverse outcome encountered in the ALLHAT. Though ASCOT tried to alleviate some of the apprehensions about the use of alpha blockers, questions continued to be raised about the outcome of ASCOT, namely inadequacies of observational data, possible sources of bias, the presence in each arm of ASCOT of a drug used to treat heart failure (e.g. diuretics, ACE inhibitors), differences between use of doxazosin as third or first line therapy and so on. That trials like ASCOT and ASOCIA failed to convince the medical fraternity about the potential benefits of alpha blockers is reflected in various recommendations.

Yet, to a nephrologist, they are a group of agents which demand a re-appraisal. Alpha blockers can be used in refractory cases as add on therapy, especially in the 50 plus age group with benign prostatic hyperplasia. They can also be considered in those with mild to moderate hypertension, who have repeated hyperkalaemia with ACE inhibitor or ARB use, and who develop worrisome peripheral oedema due to calcium channel blockers. The theoretical benefit of renoprotection will also tilt the balance in favour of alpha blockers.

Actually, though alpha blockers are in use for long,
they did not get the benefit of having a well controlled trial to counter the observations of ALLHAT. Indian data are also inadequate. Hence, a relook into the possible use of alpha blockers is only possible if multicentre randomised trials are conducted in the Indian population.

References


