Overview of Alpha-blockers in Hypertension: Reappraisal of Perspectives

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Introduction

Hypertension is the biggest public health problem of the world. It is far bigger in prevalence than coronary heart disease, diabetes mellitus, cancer and HIV. The field of “Hypertension” is increasingly being recognised as a major cause of stroke, renal and cardiovascular disease. It has not seen the emergence of any new molecules for the management of this silent killer. It has received less public health initiative compared to the Big 4 due to the perceived ease of diagnosis and management by the medical community. Also it does not involve any of the “shock and awe” impact of the Big 4 on the common man. It underscores the fact that hypertension remains the most under diagnosed, most under treated and most modifiable risk factor in the public health domain.

The key focus of policy makers, clinicians and researchers in hypertension has been to find newer, safer and effective drugs to manage hypertension. Relatively the effort to ensure definite diagnosis, prompt treatment and ensure treatment adherence has been at best lackadaisical. To put it in a religious perspective, we have been obsessed by the choice of path to God that we miss Him eventually.

Alpha blockers have been in our armamentarium since 1976 when prazosin was introduced in the market. Subsequently doxazosin and terazosin have appeared and long acting formulations of all of them have been available to ensure once a day administration. The much hyped “First dose phenomenon” is done away with by developing newer technology like GITS and administering the drug at bed time. Many studies have demonstrated their equivalence in safety and efficacy at equipotent doses. Hence it is rational to assume that in alpha blockers the benefits and demerits are a class effect and not a molecule effect. Increasing understanding of the positive metabolic effects and ideal hemodynamic effects of “alpha-blockers” developed over 45 years ago has prompted us to review this drug which went into hibernation over the decades.

As is well known, management of hypertension require more than two drugs for effective long term good blood pressure control. The metabolically effective “alpha adrenergic receptor blocker” is a preferred drug of choice as add on drug. The drug is associated with a relatively low incidence of serious side effects and can be combined with almost all the antihypertensive agents used as first line agents recommended for management of hypertension.

Are Alpha Blockers an Effective Antihypertensive Therapy?

As a first line agent

In the TOMHS study1,2 the average doxazosin related BP reduction was up to 20 mm Hg in systolic and 10 mm Hg in diastolic blood pressure. Like all agents the BP fall is directly proportional to the starting BP. Higher the BP more dramatic the fall.

ALLHAT study3 made us squirm about its use as a first line agent and hence it is abandoned worldwide for this indication.

As a second line agent

GATES study4 done in 195 patients for role of doxazosin as a second line agent on top of preexisting antihypertensive therapy(usually monotherapy) showed 37.3%/10.7% efficacy in SBP/DBP lowering.
ASOCIA study\(^5\) was a short (16 wk) but big trial (3631 patients) which showed target BP achievement in 39% at 4 weeks and 61% in 16 weeks with doxazosin as add on therapy vs placebo. It also showed a 15% fall in pulse pressure and rate pressure product by 19% and thus reduce resting myocardial oxygen demand.

**As a third line agent**

ASCOT-BPLA study\(^6\) compared an amlodipine based regimen(± perindopril) vs atenolol based regimens (± thiazide) in 19,257 patients. Doxazosin was added as a third line agent to non responders and intolerant patients. Eventually almost half (9799 patients) received doxazosin and it helped 31% achieve targets. It vindicates safety and efficacy as a third line agent.

A small Japanese study\(^7\) of 41 patients looked at usefulness of doxazosin on top of CCB + ACE/ARB as a third line agent for hypertension control and established its role as add on choice. It also had an interesting observation that they were equally effective in obesity associate hypertension endorsing Toyonaga’s earlier findings.\(^8\)

**Are Alpha Blockers Safe?**

Safety and tolerability are used interchangeably when describing drug effects. However alpha blockers demonstrate the paradox between the two in an interesting fashion. When tolerability is considered, Itskovitz et al\(^9\) showed in 16,000 patients with a variety of concomitant disease including CHF, peripheral vascular disease, COPD, diabetes and obesity, that drop out due to adverse events was only 2%. Side effect profile was very favourable; e.g. comparable to placebo\(^10\) and better than other anti hypertensives especially chlorothalidone with respect to impotence (\(↓\) 6% vs \(↓\) 10%).\(^11\)

**Safety**

The concept that treatment for one condition may precipitate another underlying masked predisposed condition has gained momentum and public attention with the glitazone family. In fact Alpha blockers were pioneers in this field. ALLHAT randomised 42424 patients for HT treatment with 9067 receiving doxazosin and was prematurely terminated at 2 years raising safety concerns about alpha blockers (25% increase in secondary endpoint, combined cardiovascular disease).\(^12\)

**ALLHAT FINDINGS**

- The primary endpoint of fatal CHD or non-fatal CHD, nor total mortality differed between the two groups.
- Chlorothalidone provided superior BP lowering efficacy at the doses used by 3 mm Hg systolic.
- The increase in HF incidence occurred in all subgroups except chlorothalidone. The RR risk of HF with lisinopril, amlodipine and doxazosin was 1.19, 1.38, 1.80 respectively.
- The increase in HF incidence did not increase the mortality in any of the subgroups.
- The divergence in HF occurred very early in the trial and the separation was noticed very early on, within the first few months of therapy and all the difference occurred only in the first year and the separation disappeared significantly at one year for lisinopril and reduced dramatically for amlodipine and to a significant extent for doxazosin in the second year.
- The diagnosis of HF was made on the basis of SHEP criteria by site physician (1 symptom and 1 sign of HF)\(^13\) (e.g. pedal oedema was one criteria used). The protocol did not include a measurement of EF or BNP either before or at the time of HF diagnosis. The clinical trials centre was informed of HF only if patient was hospitalised or died.
- ACE inhibitors have been shown to reduce the HF incidence by 20-25% across all agents and all trials\(^14\).
- Doxazosin has been shown to be effective therapy in the treatment of CHF.\(^15\)

**Unanswered questions**

Would it have made a difference in results if the following changes had been made in ALLHAT Protocol?

1. Inclusion of EF/BNP assessment prior to enrolment
2. More comprehensive HF assessment by a cardiologist
3. Allowing up-titration of doxazosin beyond 8 mg
4. Use of long acting preparation of doxazosin or other long acting alpha blocker preparations
5. Having HF as a primary endpoint
6. The confounding effect of prior treatment drug on the outcomes (i.e. diuretic being replaced by study drug)
7. Discrimination between systolic and diastolic heart failure (since diuretics have a clear edge in the latter)
8. The equivalent results beyond year 1 of follow up with interim MIs contributing to a larger number of individuals with impaired LVEF could have tilted the results eventually\(^16\)
9. Lack of mortality difference occurring because of the increased mortality in diuretic group due to malignancy (renal\(^17\) and colonic\(^18\))

**OTHER TRIAL EVIDENCES**

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There is a pertinent need to critically analyse the findings to form an independent opinion on this safety debate.

**Alpha blockers - is there Anything New?**

Long acting preparations appear to have a better pharmacokinetic profile with obvious pharmacodynamic benefits.

1. Lower incidence of postural hypotension and its associated symptoms.\(^1\)
2. More consistent BP lowering with night dose with preserved nocturnal dip.\(^2\,\(^3\)
3. Average of 3 bpm reduction in heart rate.\(^4\)
4. No increased incidence of heart failure in 40,000 patient years exposure\(^5\)
5. Pleiotropic effects
   a. Decrease total and LDL cholesterol and increase HDL.\(^6\)
   b. Reduce or neutral effect on plasma glucose and improve insulin sensitivity.\(^7\)
   c. Improves endothelial function and reduces arterial stiffness.\(^8\)
   d. Recovery of spontaneous baroreflex sensitivity and short-term heart rate variability.\(^9\)

**Guidelines**

European Society of Cardiology, European Society of Hypertension,\(^10\) NICE guidelines\(^11\) all are non-committal about alpha blockers in hypertension. They mention it as add-on option (in case of failure of preferred combinations) or step 4 combination. None endorse or boycott alpha blockers. JNC 8\(^12\) is equivocal about the indications of alpha blockers.

**Take Home Message**

Alpha blockers have been superseded by ACE/ARB, CCBs and Diuretics as a first choice anti hypertensive drug. However to achieve target BP goals, combination therapy is an inevitable scenario in more than 2/3 patients. Add on therapy is usually indicated in most patients in natural history of hypertension. Alpha blockers provide a definite choice in this setting.

**Special Scenarios**

**Obese/black populations**\(^13,\(^14\)

Alpha blockers have shown no racial or weight based efficacy difference making it a good choice in this subsets.

**Chronic Kidney Disease**

Alpha blockers have been effective across all stages of Chronic Kidney disease irrespective of GFR status and degree of proteinuria.\(^15,\(^16\) It is especially useful in patients with borderline renal status, non compliant patient behaviour with irregular follow up.

**Benign Prostatic Hyperplasia**

It is often touted as a compelling indication for alpha blockers.\(^17\) The positive effect on impotence is also cited as an indication in young and uncomplicated hypertensive.

**Pregnancy and lactation**

Given the wealth of evidence with labetalol (combined alpha and beta blocker) in pregnancy, it seems rational to consider it as an option for pregnancy (class C drug).

**Phaeochromocytoma/chronic lead poisoning**\(^18\)

Both are uncommon in incidence but commonly sought out in differential diagnosis workup. Alpha blockers in combination with beta blockers work effectively in this subset of patients.

**Should we Start?**

Yes always as add on and in combination with diuretics.

**Should we Stop?**

Hypertensive patients well controlled on alpha blockers should continue to take them for life unless they develop heart failure or other such complications.

Since all alpha blockers are off patent at present, further trials supported by pharmaceutical industry are unlikely in the future. Hence physician based initiative or regulatory authority funded trials can only throw light on the unanswered questions posed herewith and enlighten the exact role of alpha blockers in present day hypertension management.

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**References**


