

Beta Blocker in Combination with Other Antihypertensives



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Introduction

It is estimated that presently there are one billion hypertensives worldwide; which is foreseen to explode to 1.5 billion by 2025.¹ Though the increasing tendency of aging and obesity in the developed as well as the developing population are seen as the root causes; the most important public health problem that it is going to emerge as cannot be neglected. Hypertension is a major cardiovascular risk factor but most patients remain asymptomatic for many years. Hypertension is a major contributor to cardiovascular disease and a leading cause of stroke, myocardial infarction, heart failure and kidney disease. The prevalence of hypertension increases with age and older patients are more likely to suffer from cardiovascular complications of hypertension. Although the benefits of hypertension treatment and control have been well documented, the majority of patients remain under treated and poorly controlled. In the USA, it has been estimated that less than 60% of patients receive any treatment and only 31% are adequately controlled. Although multiple factors contribute to poor patient compliance, medication cost and side effects have frequently been blamed.

Multiple medications have been approved for the treatment of hypertension, in general tabulated in one of six categories: diuretics, β -blockers, calcium channel blockers, blockers of the renin-angiotensin-aldosterone system, direct vasodilators and centrally acting agents. Each class of medication has a different mechanism of action and a potentially different side-effect profile.

Beta Blockers

Beta-blockers have been most popularly used to treat hypertension since 1980 and were recommended as first-line therapy in hypertension guidelines. Beta-adrenergic receptor blockers (beta-blockers) are effective and safe antihypertensive drugs, and have been recommended as first-line therapy for hypertension by all joint National Committees (JNCs) for the prevention, detection, evaluation, and treatment of high blood pressure (BP) from the first to the last (JNC-7) in 2003. However, recently questions have been raised by several investigators regarding the antihypertensive effectiveness and safety of these drugs. In primary hypertension, beta-blockers appear to offer no advantage for preventing first MI or death and less (by even 16%) advantage than other antihypertensive drugs for preventing stroke. Even the advantage over placebo or no treatment for preventing stroke found in this meta-analysis was half that found in an older meta-analysis (Lancet 1990; 335:827). The authors appropriately conclude that beta-blockers should not remain as first-line antihypertensive treatment in patients without coronary disease, but they caution against discontinuation in all patients.

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It is recently appreciated that beta blockers lower brachial blood pressure without lowering central aortic blood pressure as well which demerits it to offer no advantage for preventing first MI or stroke. This, however, is because they decrease the heart rate so much that the arterial wave reflection from the periphery returns during systole rather than during diastole.

Combinations : Rationale...

Randomised controlled trials of the treatment of hypertension performed over the past 30 years have shown that many patients will require more than one drug to reach the recommended level of blood pressure control. Only one-third of patients in the Hypertension Optimal Treatment (HOT)² study achieved their targets on one drug alone. The remainder needed up to five drugs. This trial confirms that more aggressive treatment targets are safe and effective in preventing cardiovascular events.

A judicious approach to prescribing would therefore suggest the use of low-dose combination products early in the treatment plan. The benefits of the combination selected and actual doses used over monotherapy must be proven. The two drugs in combination must be established to lower blood pressure by a greater amount than each alone. Lower doses in combination must be as effective as usual higher monotherapy doses but with fewer side effects.

- If these conditions can be met, the use of two drugs of different classes in low-dose combination has many potential advantages.
- Hypertension is heterogeneous in its response to treatment and a combination of two drugs will increase the likelihood of response in a given individual
- There may be enhancement of each drugs antihypertensive effect which in ideal combinations may even be synergistic rather than simply additive
- As the two drugs exert their antihypertensive effects by differing modes of action there is a potential for a smoother onset and longer duration of action
- By keeping both drugs at low dose the incidence of side effects from each may be minimised
- In many cases the combination of the two drugs can offset each others side-effect profile to some degree, eg palpitations caused by some CCB's may be reduced β -blocker therapy
- Different mechanisms may exert different beneficial effects beyond the benefits of blood pressure reduction on target organs. When a hypertensive patient develops cardiac, renal, or cerebral end-organ damage their prognosis worsens Combination treatments may reduce the rate of progression. Combination therapies, particularly in low dose, can usually be taken once daily with improvement in patient compliance with treatment
- Dose adjustments and titration will be simpler, blood pressure targets will be attained more quickly, and fewer clinic or physician visits will be required to achieve targets. This results in simpler and more effective strategies therapy

for induction of antihypertensive therapy in primary care

The overall cost of treatment can be reduced. Low-dose combination products may be less costly than the constituents prescribed separately and prescribing costs may be less in some countries for a single medication rather than for two separate drugs

Beta Blockers and CCB

Non-dihydropyridine CCB's, such as verapamil and diltiazem, should be avoided in combination with β -blockers due to the risk of symptomatic bradycardia and atrioventricular block. Dihydropyridine CCB's have however been shown to be effective with β -blockers and are another therapeutic option in low-dose combination β -blockers suppress renin secretion which potentiates the vasodilatory properties of CCB's and this theoretical advantage is supported by data combining felodipine plus metoprolol.³ This combination appears to have an additive effect on blood pressure.

An interesting study published in the Journal of the American College of Cardiology also showed "Ischemia during treadmill testing was more effectively suppressed by amlodipine, whereas ischemia during ambulatory monitoring was more effectively suppressed by atenolol. The combination was more effective than either single drug in both settings."

In the study by Dr Bisognano and colleagues,⁴ clinical effectiveness, defined as mean change in systolic blood pressure (SBP) or percentage of patients reaching JNC VI/JNC 7 blood pressure goals, was compared for CCBs, ACE inhibitors, and ARBs when added to a beta-blocker in a multicenter ambulatory practice setting. This study was a retrospective cohort study using a large, commercially available electronic medical record database. Approximately 370,000 patient records were available for analysis..

All the patients included in the analysis were adults aged ≥ 20 years who had visited a physician during 1998-2001 with a documented diagnosis of hypertension ($\geq 140/90$ mm Hg or $\geq 130/80$ mm Hg in patients with diabetes). Prior therapy consisted of a beta-blocker, and newly initiated treatment of a CCB, ACE inhibitor, or ARB.

Addition of a CCB, ACE inhibitor, or ARB to existing beta-blocker treatment resulted in significant reductions in blood pressure (mean decrease 12.2-17.2/7.5-9.1 mm Hg) compared with baseline during the study period. However, CCBs and ACE inhibitors were associated with significantly greater decreases in SBP, and a significantly higher number of patients receiving CCBs or ACE inhibitors reached blood pressure goals compared with those receiving ARBs (Table). The combination of a CCB with a beta-blocker resulted in a significantly greater decrease in diastolic blood pressure (DBP) compared with the reduction achieved with an ACE inhibitor plus a beta-blocker.

Adjusted Changes in SBP and DBP Calculated Using Multivariate Analysis

	Beta-blocker Plus:		
	CCB	ACEI	ARB
Adjusted SBP reduction (%)	-17.1*	-15.6†	-11.4
Adjusted DBP reduction (%)	-9.4¶	-7.1	-7.4
% reaching goal	46.1†	42.6†	30.7

Overall group defined as cohorts with either beta-blocker as first-line agents.

* P < .01

† β P < .05 vs ARB

¶ P < .05 vs ACE inhibitor

Another study⁵ assessed the effect of a fixed combination of nifedipine sustained release (SR) 20 mg + atenolol 50 mg on the blood pressure values of partial responders to treatment with a calcium channel blocker. Sixty hypertensive patients who had a diastolic blood pressure (DBP) >90 mm Hg throughout a period of monotherapy with a calcium channel blocker were included in the trial. After a 2-week run-in period with nifedipine SR 20 mg twice daily, 53 patients were randomly assigned to receive either the fixed combination nifedipine SR 20 mg + atenolol 50 mg once daily or nifedipine SR 20 mg twice daily. Mean systolic blood pressure was significantly lower (148 ± 13 mm Hg vs 156 ± 14 mm Hg) at 12 hours postdose in the combination group than in the nifedipine-only group. Responder patients (DBP <90 mm Hg) accounted for 65% in the combination group (15 of 23) and 43% in the nifedipine-only group (13 of 30), a nonsignificant difference. Two patients in the nifedipine-only group discontinued treatment because of side effects, compared with none in the combination group. We conclude that a single daily dose of a fixed combination of nifedipine SR 20 mg + atenolol 50 mg yields greater improvement in systolic blood pressure than nifedipine SR 20 mg alone, in patients who exhibited a partial response to treatment with a calcium channel blocker.

Beta Blockers and Diuretics

Diuretics activate renin release by volume contraction whereas beta blockers are known to reduce renin levels. So, their mechanisms are complimentary to each other. By the opposing homeostatic effects the beta blockers reduce the potassium sparing effect of the diuretics. The incidence of hypokalaemia is 6.5% for diuretic monotherapy reduces to 0.7% if combined with beta blockers.

JNC VI specifically states that in the treatment of hypertension in the elderly, "thiazide diuretics or beta-blockers in combination with thiazide diuretics are recommended because they are effective in reducing morbidity and mortality in older persons with hypertension as shown in multiple randomized controlled trials."

When combining a beta blocker with a diuretic in patients with hypertension, consideration should be given to the potential advantages of intrinsic sympathomimetic activity (ISA). During long-term administration of a beta blocker without ISA, total peripheral resistance stabilizes at or slightly above the pretreatment level. Since cardiac output is decreased, blood pressure falls. Thus, beta blockers without ISA may exacerbate the underlying haemodynamic abnormality of long-standing hypertension, increased systemic resistance. In contrast, the reduction in pressure which occurs with a beta blocker possessing a high degree of ISA, such as pindolol, is associated with a reduction in total peripheral resistance and little change in cardiac output.

The STOP-H trial⁶ was a double blinded study the active therapy was atenolol 50mg, hydrochlorothiazide 25mg, with amiloride 2.5mg, metoprolol 100mg or pindolol 5mg daily. Most patients completed study on a combination of a beta blocker and a diuretic. The trial was terminated early at 25 months as a clear benefit in the active treatment group was noted.

In a single blinded MRC trial⁷ of older adults (65 to 74yrs) with SBP greater than 160 mm of Hg and DBP less than 115mm of Hg were randomized to atenolol 50mg, hydrochlorothiazide 25mg, amiloride 2.5mg or placebo. There was a 25% reduction in the stroke group and 17% reduction in the cardiovascular death group.

Beta Blockers and ACEI/ARB

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC vii) suggested that fixed-dose combinations could be used in those with Stage 1 hypertension (BP between 140-159 mm Hg/90-99 mm Hg), it recommended fixed-dose combinations as initial therapy for patients who fit into the "20/10 rule" (for example, individuals with Stage 2 hypertension who have their initial BP [greater than or equal to] 160/100 mm Hg and need a 20/10 mm Hg reduction in BP to achieve BP control).⁸

- Thus the combination of ACEI/ARB and Beta blockers can be overviewed for having multifaceted advantages :
- Achieving target BP reduction in the range of 20/10 mm of Hg, a BP reduction of an additional 15% SBP and 7.4% DBP was shown by the study of Dr Bisognano and colleagues(4)
- For target organ protection in patients ischaemic heart disease, heart failure and cardiomyopathies
- Renin concentrations in individuals taking a β blocker with either an ACE inhibitor were significantly lower compared with renin concentrations in groups not receiving β blocker treatment— These data suggest that the upregulation of renin by treatment with ACE inhibitors, diuretics, or both can be largely prevented by concomitant β blocker treatment.⁹

ACEI and beta blockers resulted in a significantly reduced plasma Hcy levels in hypertensive patients.¹⁰

Conclusion

Beta-blockers have long been used to treat hypertension and are recommended as first-line therapy in hypertension guidelines. However, their benefits have been overshadowed by the side-effect profile, including sexual dysfunction, fatigue, depression and metabolic abnormalities such as impaired glucose tolerance and lipid abnormalities. Combination low dose drug treatment increases efficacy and reduces adverse effects. From the average blood pressure in people who have strokes (150/90 mm Hg) three drugs at half standard dose are estimated to lower blood pressure by 20 mm Hg systolic and 11 mm Hg diastolic and thereby reduce the risk of stroke by 63% and ischaemic heart disease events by 46% at age 60-69.¹¹

Fixed-dose combination regimens that target complementary pathophysiologic BP-lowering mechanisms provide an effective initial approach to control BP. In addition, when used as an initial therapy, fixed-dose combination agents combat what has been called "therapeutic inertia (TI)," which describes the physician's failure to either increase the dose of antihypertensive medication or add another medication to achieve BP control. This was first described by Berlowitz et al¹² who surveyed Veterans Affairs (VA) clinics and found that while 40% of hypertensive patients had BP [greater than or equal to] 160/90 mm Hg despite an average of 6 annual clinic visits, increases in medications were prescribed in only 7% of those same clinic visits. Fixed-dose combination agents should be considered in many patients with hypertension as initial therapy in an effort to reduce TI, reach BP goals sooner, and better tolerate what is often lifelong therapy.

References

1. Keamey P M, Whelton M,Reynold K.;Global burden of Hypertension:Lancet 2005;365;217-23
2. Hansson L et al. Effects of intensive blood-pressure lowering and low-dose aspirin inpatients with hypertension; principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998; 351: 1755-1762
3. Dahlof B et al. Improved antihypertensive efficacy of the felodipine-metoprolol extended-release tablet compared to each drug alone. Blood Press 1993; 2 (Suppl 1): 37-45.
4. From Medscape Cardiology AVALON -- Atorvastatin and Amlodipine, Plus Further Results With ACE Inhibitors and ARBs Linda Brookes, MSc : Published: 03/16/2004
5. Journal Title:Current therapeutic research ISSN 0011-393X CODEN CTCEA9 ; Source :1996, vol. 57, no10, pp. 723-734 (27 ref.)
6. Berlowitz DR, Ash AS, Hickey EC, et al. Inadequate management of blood pressure in a hypertensive population. N Engl J Med 1998;339:1957-1963.
7. MRC trial of treatment of mild hypertension;BMJ 1992: 304(68240):405-412.
8. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-1252.
9. Heart 1998;80:45-48; doi:10.1136/hrt.80.1.45
10. A Poduri, 2009 : Journal of Human Hypertension
11. BMJ 2003;326:1427 (28 June), doi:10.1136/bmj.326.7404.1427
12. Dahlof B,Lindholm LH et al. Stop-Hypertension Lancet 1991;338(8778):1281-1285.