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Review

Combining Other Antihypertensive Drugs With β-Blockers in Hypertension: A Focus on Safety and Tolerability

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ABSTRACT

Combining multiple classes of antihypertensive drugs together is one of the most important factors for achieving blood pressure control in most hypertensive patients. The benefits of combination therapy in comparison with monotherapy include: a synergistic enhancement of each drug's hypertensive effects and a potential reduction of side effects if each drug is used at a lower dose. Although long-acting dihydropyridine calcium channel blockers and β-blockers are a good fit for combination therapy, because of the risk of atrioventricular block and bradycardia, the combination of verapamil and β-blockers is not advised. In addition, the combination of higher-dose diltiazem and β-blockers is also not advised. β-blockers and diuretic agents as initial lone combination therapy are not the preferred combination to be used in uncomplicated hypertension. Using an angiotensin-converting enzyme inhibitor as initial combination therapy with most β-blockers is not recommended because of a lack of antihypertensive efficacy. Nebivolol, however, appears different in this regard and might provide an opportunity for combining these 2 classes of agents with proven cardiovascular benefits for better blood pressure control. Adding an α-blocker to a β-blocker is an effective combination.

RÉSUMÉ

La combinaison de multiples classes d'antihypertenseurs est l'un des plus importants facteurs pour atteindre la régulation de la pression artérielle chez la plupart des patients hypertendus. Les avantages d'un traitement combiné comparativement à la monothérapie incluent : une amélioration de la synergie de chacun des effets hypertenseurs des médicaments et une réduction potentielle des effets secondaires si chaque médicament est utilisé à plus faible dose. Bien que les bloqueurs du canal calcique de la classe des dihydropyridines à action prolongée et les β-bloquants conviennent au traitement combiné, en raison du risque de bloc auriculoventriculaire et de bradychardie, la combinaison de vérapamil et de β-bloquants n'est pas conseillée. De plus, la combinaison de diltiazem à dose plus élevée et de β-bloquants n'est également pas conseillée. Les β-bloquants et les diurétiques comme seul traitement combiné initial ne sont pas la combinaison à privilégier lors d'hypertension non compliquée. L'utilisation d'un inhibiteur de l'enzyme de conversion de l'angiotensine associé à la plupart des β-bloquants comme multithérapie initiale n'est pas recommandée en raison du manque d'efficacité contre l'hypertension. Cependant, le nébivolol semble différent à cet égard et pourrait offrir la possibilité de combiner ces 2 classes d'agents qui démontrent des avantages cardiovasculaires conduisant à une meilleure régulation de la pression artérielle. L'association d'un α-bloquant et d'un β-bloquant est une combinaison efficace.

Combining multiple classes of antihypertensive drugs together is one of the most important factors for achieving blood pressure (BP) control in most hypertensive patients. Individual drugs have unique profiles with differing sets of interactions and side effects; therefore, knowledge in the use of safe and effective drug combinations ensures that health care providers are proficient at managing hypertension. As an example, two-thirds of the patients from the **H**ypertension **O**ptimal **T**reatment (HOT) trial with diastolic BPs of 100 mm Hg or greater as an entry criteria required 2 or more hypertensive agents to achieve optimal BP control.[1] Similarly, in the **A**ntihypertensive **L**ipid-**L**owering Treatment to Prevent **H**eart **A**ttack **T**rial (ALLHAT) study, the largest hypertension study ever with more than 40,000 patients enrolled, more than two-thirds of patients required 2 or more agents. Over time, as the number of antihypertensive agents per person increased, so did the fraction of patients achieving BP control. After 5 years, BP control reached 80%.[2] The benefits of combination therapy compared with monotherapy include: a synergistic enhancement of each drug's hypertensive effects and a potential reduction of side effects if each drug is used at a lower dose. The benefits of achieving targets with combination therapy were demonstrated in an analysis of patients after an acute coronary syndrome, in whom combining therapies for risk factor reduction was associated with greatly improved mortality.[3] The 5 classes of medications

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recommended for the initial treatment of hypertension include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers (CCBs), and diuretic agents. For each of these classes there is sufficient evidence, in people with hypertension, demonstrating benefit in hard outcomes such as a reduction of mortality, stroke, or heart attack, to be included in the Canadian Hypertension Education Program clinical practice guidelines.[4] In this article, the benefits and cautions in prescribing β-blockers in combination with other antihypertensive agents with a focus on the most useful combinations will be described (Table 1).

β-Blockers and CCBs

Dihydropyridine CCBs

The 3 dihydropyridine (DHP) CCBs widely in use today in Canada include: amlodipine, nifedipine, and felodipine. Presently, the most commonly prescribed CCB is amlodipine; it is available as a single generic drug and also in multiple combinations, usually with an angiotensin receptor blocker. These agents work by reducing peripheral vascular resistance by blocking transmembrane movement of calcium, reducing vascular smooth muscle tone. In the past, β-blockers have been used in combination with short-acting CCBs to reduce the tachycardia induced by these agents. With the development of long-acting nifedipine and felodipine, the issue of increased heart rate was markedly reduced; a faster heart rate does not occur with the use of amlodipine.[5] In addition to improvements in heart rate, β-blockers and DHP CCBs combine to produce reductions in BP that are greater than when either agent is used alone. CCBs are metabolically neutral, making them favourites for the initial management of hypertension in severely hypertensive patients who have or are at risk for metabolic complications. Even though CCBs have a linear dose-response curve, there is much greater synergy for BP control when adding another antihypertensive agent such as a β-blocker to a CCB than is achieved by simply doubling its dose.[6]

In summary, long-acting DHP CCBs and β-blockers are a good fit for combination therapy.

Table 1. Summary of benefits and risks for β-blocker combination therapy

Drug	Benefits of combination therapy	Risks/concerns of combination therapy
Calcium channel blockers		
Dihydropyridine	Additive blood pressure-lowering effect Improved heart rate control	
Nondihydropyridine		Risk of bradycardia and atrioventricular block
Diuretic agents		Risk of negative metabolic effects and increased risk of diabetes
ACEi and ARBs	Third-generation β-blockers might produce an additive blood pressure-lowering effect	Lack of antihypertensive efficacy in combination with first- and second-generation β-blockers
α-Blockers	Additive blood pressure-lowering effect Safe for use in patients younger than the age of 70 years	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Non-DHP CCBs

Whereas DHP CCBs combine well with β-blockers, non-DHP CCBs do not. Verapamil, in particular, but also diltiazem at higher doses, should be avoided as concomitant therapy with β-blockers, because of the risk of bradycardia and atrioventricular block. A disproportionality analysis of adverse events caused by drug interactions received by the US Food and Drug Administration between the years 1968 and 2001 indicated that the rate of reporting β-blocker and verapamil conduction-related interactions leading to bradycardias was approximately 10%; double the rate reported for either agent taken alone.[7] Evidence for an interaction between β-blockers and diltiazem comes from a 2009 study investigating the reinfarction rates in non-Q-wave myocardial infarction patients.[8] Participants were randomly assigned to receive diltiazem or placebo. Patients in the diltiazem arm received 360 mg of this agent daily for 14 days after a myocardial infarction and 61% of the 287 patients in this group were already treated with a β-blocker at baseline. In the placebo treatment arm, 64% of the 289 patients were taking a β-blocker at baseline. At the end of the study, 3.4% of patients in the treatment group developed a second-degree heart block compared with 0.5% of patients taking placebo.[8]

In summary, because of the risk of atrioventricular block and bradycardia, the combination of verapamil and β-blockers is not advised. In addition, the combination of higher-dose diltiazem and β-blockers is also not advised.

β-Blockers and Diuretic Agents

The use of β-blockers with diuretic agents was one of the earliest forms of combined hypertension therapy and was used widely in the 1980s. Earlier evidence for the efficacy of a stepped-care combination approach to therapy came from the **H**ypertension **D**etection **F**ollow-up **P**rogram (HDFP)[9] and the **M**ultiple **R**isk **F**actor **I**ntervention **T**rial (MRFIT)[10] which both combined diuretic agents with reserpine. In the **M**edical **R**esearch **C**ouncil Trial of Mild Hypertension (MRC), β-blockers and diuretic agents were combined to treat hypertension in older adults when a single agent failed to produce a sufficient change in BP.[11] In this study, the diuretic arm was found to be effective at preventing cardiovascular outcomes whereas the β-blocker arm was not, possibly because of earlier and greater BP control in the diuretic arm. In the MRC trial, the β-blocker propranolol raised potassium slightly and a thiazide diuretic reduced it slightly. Therefore, initially the combination of β-blockers and diuretic agents appeared advisable and was widely recommended for its effectiveness at BP-lowering at a reasonable cost.

Further evidence for this combination came from the **S**wedish **T**rial in **O**ld **P**atients with Hypertension-2 (STOP-2) study, designed to compare the cardiovascular and mortality effects of conventional agents (β-blockers and diuretic agents)

vs the newer agents at that time (ACE inhibitors and CCBs) in the treatment of older patients with hypertension.[12] Participants in the β-blocker arm were treated with atenolol, metoprolol, or pindolol, and given hydrochlorothiazide and amiloride as second-line treatment if needed to achieve BP target. Patients in the CCB arm were treated with felodipine or isradipine; second-line treatment was atenolol, metoprolol, or pindolol. At the end of the study, 46.0% of all patients were receiving combination therapy. There was no significant difference in BP control between the groups nor was there a difference in frequency of fatal and nonfatal stroke or in frequency of myocardial infarctions between the 2 treatment groups. This is a reminder that diuretic agents and β-blockers have demonstrated efficacy in reducing mortality and reducing cardiovascular morbidity.[13] In the STOP-2 study there was also no difference in new-onset diabetes between the 2 groups.[12]

Over time it was recognized that the combination of β-blockers and diuretic agents did lead to metabolic changes, in particular a predisposition to diabetes. The **S**ystolic **H**ypertension in the **E**lderly **P**rogram (SHEP) compared chlorthalidone with placebo with the later addition of atenolol. Initially a nonsignificant trend to more diabetes in the treatment arm was noted (7.5% vs 6.4%).[14] When the data were reanalyzed using a fasting glucose of 7.0% as the definition of diabetes, a significant difference in diabetes rates emerged. The treatment group experienced significantly more diabetes compared with the control group (13.0% vs 8.7%). Further, results of a subanalysis were that significantly more patients taking chlorthalidone plus atenolol (16.4%) had developed diabetes compared with those taking chlorthalidone alone (11.8%).[15] This indicates that adding atenolol to diuretic agents increased the time-related trend to new diabetes. In a review, Mancia et al. concluded that diuretic agents and β-blockers together might amplify the natural time-dependent tendency toward the development of diabetes.[16]

In the **A**nglo-**S**candinavian **C**ardiac **O**utcomes **T**rial (ASCOT) - BP lowering arm, male and female hypertensive patients were randomly assigned to treatment with amlodipine-based combination therapy vs atenolol-based combination therapy. Most patients in the ASCOT trial received a second agent to reduce BP to target. In the amlodipine arm, patients were treated with amlodipine and perindopril and the second agent in the atenolol group was a thiazide diuretic. The study found significantly fewer cardiovascular events in patients with diabetes treated with amlodipine/perindopril compared with β-blocker/diuretic therapy.[17] Metabolic markers including blood glucose, creatinine, and triglycerides were all significantly higher, and high-density lipoprotein cholesterol lower in patients treated with β-blocker and diuretic-based therapy. There was a corresponding increase in new-onset diabetes in the β-blocker/diuretic treatment arm.[18]

In summary, β-blockers and diuretic agents as initial lone combination therapy are not the preferred combination of agents to be used in uncomplicated hypertension.

β-Blockers and ACE Inhibitors

The ALLHAT study was designed to determine whether treatment with ACE inhibitors and CCBs would lower the incidence of coronary heart disease and cardiovascular disease compared with diuretic agents. A total of 33,357 hypertensive patients 55 years of age and older and with at least 1 other coronary heart disease risk factor were randomized to receive treatment with lisinopril, amlodipine, or chlorthalidone, excluding the doxazosin arm. Atenolol, reserpine, and clonidine were added as second-line therapy to achieve BP reduction targets. Compared with patients in the chlorthalidone group, patients randomized to the lisinopril group experienced a 10% higher incidence of cardiovascular disease, 15% higher incidence of stroke, and 19% higher incidence of heart failure. Whereas atenolol and chlorthalidone combine to produce an additive effect on lowering BP, the combination of lisinopril and atenolol resulted in a 2 mm Hg higher systolic BP.

In a 2000 report, the Diabetes Executive Working Group branch of the National Kidney Foundation reviewed a series of randomized, prospective long-term studies that investigated BP control in people with diabetes.[19] The end points for this review were cardiovascular events and progression of diabetic nephropathy. The consensus from this report was to add β-blockers to ACE inhibitors only in patients with heart rates greater than 84 beats per minute because of a lack of efficacy in patients with lower heart rates.

In contrast to these findings, recent data using a smaller population and a later generation β-blocker, suggest that there might be additive effects between an ACE inhibitor and nebivolol. In this study, combination therapy using nebivolol and lisinopril was compared with monotherapy using each of these agents separately, and placebo.[20] The study involved 664 patients aged 18 to 64 with stage 2 diastolic hypertension. The primary end point for this study was the change in diastolic BP at the end of 6 weeks. The combination therapy group achieved a response rate of 33.9% which was significantly greater compared with placebo (7.5%), nebivolol alone (21.6%), and lisinopril alone (21.7%). The combination group experienced a significantly greater mean reduction in diastolic BP of 17.2 mm Hg vs 8.0 mm Hg in the placebo group, 13.3 mm Hg in the nebivolol group, and 12.0 mm Hg in the lisinopril group. Although this short-term study cannot be compared with the ALLHAT study, the results suggest that third-generation β-blocker agents might potentially provide a new combination for the management of certain cases of hypertension.

In summary, using an ACE inhibitor as initial combination therapy with most β-blockers is not recommended because of a lack of antihypertensive efficacy. There is however, some data that suggest that nebivolol, unlike older-generation β-blockers, might produce an additive effect in combination with ACE inhibitors, but further study is required.

β-Blockers and α-Blockers

α-Blockers work by blocking peripheral α receptors, decreasing peripheral vascular resistance, and reducing BP. α-Blockers were studied in the ALLHAT study in which 9061 patients received doxazosin as initial therapy for their hypertension and were followed for a mean of 3.2 years.[21] That group was withdrawn early because of higher BP and an increase in stroke and cardiovascular disease compared with the diuretic arm, but there was no report of additional side effects. These agents are therefore not recommended as first-line use in hypertension, but make sense when multiple

antihypertensive agents are required, as in resistant hypertension. In the ALLHAT study, patients aged 55 and older were studied and there were 591 patients age 80 and older.[21]

In the ASCOT trial, the α-blocker, doxazosin, was used as a third-line therapy for patients when BP was not lowered to 140/90 with the use of 2 additional agents. The treatment groups were amlodipine with perindopril as second-line therapy and atenolol with bendroflumethiazide as second-line therapy. Of the 19,257 participants in this trial 11,768 were treated with doxazosin at a median time point of 8 months after randomization.[22] The addition of doxazosin led to significant reductions in systolic BP and diastolic BP in all subgroups of this study. The addition of doxazosin in the atenolol group led to a mean reduction in systolic BP of 13.4 mm Hg vs a 9.4 mm Hg reduction in the amlodipine group. Furthermore, the addition of doxazosin in the atenolol group led to a 7.1 mm Hg diastolic BP reduction and in the amlodipine group, a 6.5 mm Hg diastolic BP reduction.

In a 1990 double-blind, multicentre controlled trial, the combination of doxazosin and atenolol was compared with atenolol and placebo in patients with mild to moderate hypertension.[23] One hundred and thirteen patients aged 18-70 years were enrolled in this study, 87 of which completed the double-blind portion of the study. At the end of 12 weeks, patients in the combination group experienced a significant reduction in standing BP of 17.0/12.3 mm Hg in contrast to the atenolol/placebo group which achieved a reduction of 6.2/6.7 mm Hg. Patients in the combination therapy group achieved a supine BP reduction of 13.2/9.8 mm Hg vs 9.2/6.0 mm Hg in the atenolol placebo group. The difference in supine BP was not significant.

In summary, adding an α-blocker to a β-blocker is an effective combination in patients aged 70 years and younger.

β-Blockers have been used for many years to effectively treat hypertension and reduce the incidence of cardiovascular disease.[24] β-Blockers combine well with DHP CCBs and α-blockers. Although efficacy is good with diuretic agents, there is an increased risk of metabolic disturbance. There is a risk of bradycardia and heart block with non-DHP CCBs particularly with the use of verapamil. In combination with an ACE inhibitor and by extension, angiotensin receptor blocker, most β-blockers do not lead to synergy in BP-lowering, however, there is a synergy in BP-lowering with the third-generation β-blocker, nebivolol. β-Blockers as a class are recommended in the Canadian Hypertension Education Program clinical practice recommendations for use in uncomplicated hypertension alone and in combination. Having the knowledge of how to combine them with other antihypertensive agents expands the armamentarium of the clinician managing hypertension.

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