CHAPTER

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Management of Hypertension – Role of Combination Therapy

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Introduction

The aggressive use of combination therapy early in the management of hypertension may be the most important change clinicians can make in their attempt to achieve adequate blood pressure control in hypertensive patients. Hypertension has been identified as the most powerful modifiable risk factor for the development of cardiovascular disease,[1] and its control has been shown to significantly decrease cardiovascular morbidity and mortality.[2-3] Despite this knowledge less than one third of the hypertensive patients in India achieve conservative goals of 140/90 mmHg.[5] Because inadequate blood pressure control remains an important risk factor for coronary artery disease, it is not surprising that the reductions in coronary artery disease among hypertensive patients have been disappointing. Achieving optimal blood pressure control is the most important issue in the management of hypertension, and in 60% of hypertensive patients, it is difficult or impossible to control blood pressure with one drug.[6,9] The use of combination therapy as first line treatment, or early in the management of hypertension, will substantially enhance blood pressure control rates[5] and ultimately have a significant impact on coronary artery disease among hypertensive patients. JNC VII recommended combination in stage 2 hypertension.

With this in mind, the concept of combination therapy is to combine complementary agents to provide maximal efficacy and at the same time minimize side effects

Why we should use combination therapy ?

The two qualities most important to physicians in their selection of antihypertensive agents are efficacy and safety. Use of combination therapy potentially optimizes these qualities.

Efficacy

The most important reason for use of combination therapy in clinical practice is that combining two complementary antihypertensive agents produces significantly greater efficacy than either of the components as monotherapy.[10,12] When two physiologic systems are interrupted, counter-regulatory mechanisms are frequently neutralized, enabling greater reductions in blood pressure.

For example, diuretics, which stimulate the renin angiotensin system, are ideally combined with angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Alternatively, diuretics may be combined with beta blockers, which inhibit the release of renin. Dihydropyridine calcium channel blockers (CCBs) increase circulating catecholamines,

which also tend to activate the renin-angiotensin system. Thus, dihydropyridine. CCBs may be logically combined with ACE inhibitors. On the other hand, nondihydropyridine CCBs decrease circulating catecholamines, so combination with betablockers is not logical. Similarly, ACE inhibitors and beta blockers both seem to interrupt the renin-angiotensin system and so are not a logical combination.

The combination of two complementary antihypertensive agents often results in blood pressure reductions that are additive and may be synergistic.

Safety

Safety and efficacy tend to move in opposite directions as we increase the dose of antihypertensive agents. This frequently results in physicians accepting less effective blood pressure control to minimize adverse effects. Most of the adverse effects of antihypertensive drugs are dose dependent, with the exception of ACE I induced cough and angioedema. Thus, combinations that use smaller drug dose in hypertensive patients will cause fewer adverse effects. Combination therapy provides adequate blood pressure control with smaller doses of each of the components, thereby reducing dose-dependent adverse effects.

In the management of hypertension it is better to reduce blood pressure in a physiologic manner, thus reducing adverse events. For example, dihydropyridine CCBs are powerful arterial vasodilators. Although useful in the management of hypertension, these drugs reduce blood pressure by affecting only the arterial side of the circulation, leading to frequent adverse events–for example, peripheral edema and increased proteinuria in diabetic patients with renal disease. Adding an ACE Inhibitor to a dihydropyridine CCB now provides venous dilation, and the combination produces a more physiologic reduction in bloodpressure involving the entire vascular tree. This combination not only reduces CCB induced edema[12] but also proteinuria in diabetic patients with renal disease, often to a greater extent than that of an ACEI given as monotherapy.[14]

Effective combinations of two different antihypertensive drugs

Over the years, several combinations of antihypertensive drugs have been studied and shown to be effective in lowering elevated blood pressure. In this chapter we will discuss a series of combinations which are assumed to be effective and probably beneficial in certain groups of patients. Although not all are based upon large intervention studies required for evidence-based decisions, we have chosen these combinations on the basis of hemodynamic and pathophysiological considerations, mostly supported by studies as well as by our own experience.

Thiazide-diuretics + beta-blockers

This combination has long been favored by guidelines for patients with uncomplicated hypertension without target organ damage. This combination has been included in several large-scale intervention studies (e.g. STOP[4]; MRC[5], ALLHAT[12]) and can be considered as firmly established.

Thiazide-diuretics + ACE-inhibitors

Useful in patients with hypertension and congestive heart failure (CHF), ISH, as well as hypertension in the elderly (which is frequently ISH). This combination is considered to be a very potent antihypertensive medication, and the addition of an ACE-inhibitor to a diuretic (or vice versa) should be performed cautiously, in order to prevent a too rapid decrease in BP. Furthermore, both, ACE-inhibitors and diuretics are considered as standard therapy in CHF.

Diuretics + AT 1-blockers (ARB)

This is proved to be a more effective combination for the treatment of hypertension with left ventricular hypertrophy, than beta-blocker + diuretics.[10] ISH is also a condition where this combination could successfully be applied.[11] It may also be beneficial for those with hypertension and CHF.

Diuretics + imidazoline (I 1) receptor agonists

This combination, which has not been studied on any larger scale, can be thought of if a beta-blocker cannot be added to a diuretic agent because of contra-indications.

Diuretics + calcium antagonist (dihydropyridines)

Dihydropyridine calcium antagonists, known to be potent vasodilators, can concomitantly be administered with diuretics in ISH- patients, who are usually elderly. There exists evidence both for diuretics[4,5] and for dihydropyridine calcium antagonists[6] (although not so clearly for their combination) that they are effective in lowering BP in ISH, as well as for protective activity towards the complications of hypertensive disease.

Alpha-blockers + beta-blockers

This combination may be used in accelerated hypertension. There is little evidence for the efficacy of this combination. Accelerated hypertension is probably based on sympathetic hyperactivity and its sequelae. For this reason sympatholytic activity, as caused by both drugs of the combination, appears to be a logical therapeutic approach. For sympathetic overactivity centrally acting antihypertensives (clonidine, imidazoline I1 receptor stimulants) and nondihydropyridine calcium antagonists may also be thought of.

Beta-blockers + ACE-inhibitors

Although the antihypertensive effect of this combination is less than that of diuretics +beta-blockers,[12] it could be used in hypertensive patients after myocardial infarction (MI), in those with coronary heart disease (CHD) or with CHF.[8]

Calcium antagonists (dihydropyridine-type!) + beta-blockers

Patients with hypertension and CHD can be treated by this combination. Both types of drugs, apart from being efficacious antihypertensives, are known to display beneficial activity in CHD patients. The fixed combination of the two types of drugs can help improve patients' therapeutic compliance.[17]

Calcium antagonists + ACE-inhibitors

This combination can be suggested for the treatment of hypertensive patients with nephropathy, CHD or established atherosclerosis. The combination displays pronounced antihypertensive activity. Ca-antagonists are known to have anti-ischemic activity in CHD. ACE-inhibitors are proved to be renoprotective, particularly in patients with diabetic nephropathy. Calcium antagonists, as shown for lacidipine in the ELSA study[9], amlodipine in PREVENT study[13] and nifedipine GITS in the INSIGHT study[14] are proved to display anti atherogenic activity. For ACE-inhibitors this effect has also been revealed (SECURE study)[15].

Calcium antagonists (dihydropyridines) + AT-blockers

Presumed beneficial effects of this combination are globally the same as for the combination calcium-antagonists + ACE-inhibitors.[16] The renoprotective activity in diabetic (type 2) nephropathy appears to be well established.[9] Dihydropyridine-type calcium antagonists and the AT1- blocker losartan are known to display uricosuric activity, which may be advantageous also in patients with gout.

ACE-inhibitors + AT1-blockers

This combination can be thought of in hypertensive patients with diabetic nephropathy as well as with glomerulonephritis, since both types of drugs have been shown to decrease proteinuria more than the individual components, so they may display renoprotective activity.

ACE-inhibitors + imidazoline receptor agonists

Theoretically this combination could be thought of if it would be desirable to simultaneously suppress the activities of both the renin angiotensin aldosterone system (RAAS) and the sympathetic nervous system (SNS). The metabolic syndrome has been proposed as a target for SNS-suppressant drugs such as moxonidine or rilmenidine, since this syndrome is believed to be partly the result of SNS-hyperactivity.

Drugs	Potential use
Beta-blockers + diuretics	Uncomplicated hypertension without target organ damage
Diuretics + ACE-inhibitors	Hypertension + congestive heart failure (CHF)
Diuretics + AT1-blockers	Isolated systolic hypertension (ISH) + CHF Possibly: ISH
Diuretics + imidazoline (I1)-receptor agonists to a diuretic	To be used when a ^{2}-blocker (contra-indications) cannot be added
Diuretics + calcium-antagonists (dihydropyridines)	ISH (usually elderly patients)
Beta-blockers + alpha-blockers	Accelerated hypertension
Beta-blockers + ACE-inhibitors	Hypertensives: post MI (sec. prevention) CHD, CHF
Ca-antagonist + Beta-blockers	Hypertension + CHD
Ca-antagonist + ACE-inhibitors	Hypertension + nephropathy, CHD or atherosclerosis
Ca-antagonists + AT1-blockers	Hypertension+ nephropathy, CHD or atherosclerosis (?)
ACE-inhibitors + AT1-blockers	Hypertension + nephropathy
ACE-inhibitors + imidazoline (I1)-receptor agonists	Patients with activated RAAS and SNS
Diuretics + Beta-blockers + calcium antagonists	Accelerated hypertension
Diuretics + calcium antagonists + ACE-inhibitors	Accelerated hypertension ISH, hypertension + diabetes mellitus
Diuretics + calcium antagonists + AT1-antagonists	Ibid.
ACE-inhibitors + alpha1-blockers + imidazoline (I1)-receptor agonists	Hypertension + diabetes mellitus. Metabolic syndrome
ACE-inhibitors + Ca-antagonists + Beta-blockers	Hypertension + CHD

Triple combinations

A few suggestions have been put forward for triple combinations involving different antihypertensive drugs. These combinations are put together on merely theoretical grounds, virtually without formal clinical evidence. Arguments in favour of the use of 1 particular category of drugs are the same as those discussed above for the components of combinations of 2 different drugs. The following drug combinations are conceivable:

Diuretics + beta-blockers + calcium antagonists

A very potent combination which could be used in treatment of accelerated hypertension.

Diuretics + calcium antagonists + ACE-inhibitors

Diuretics + calcium antagonists + ACE-inhibitors, Potentially beneficial in the treatment of diabetic hypertensive patients, of those with accelerated hypertension or ISH.

AT1-antagonists + calcium antagonists + diuretics

This triple combination may help reaching the target BP (< 130/85 mm Hg) in hypertensive patients with type-2 diabetes mellitus, or with ISH.

ACE-inhibitors + alpha1-adrenoreceptor antagonists + imidazoline agonists

Potentially beneficial in the treatment of diabetic hypertensive patients or for those with metabolic syndrome, in particular when beta-blockers are contra-indicated or not well tolerated.

ACE-inhibitors + Ca-antagonists + beta-blockers

Potentially beneficial in hypertensive patients with coronary heart disease.

Conclusions

Combination therapy has become widely accepted for the management of hypertensive disease and a substantial fraction of patients is best treated by

2, or frequently 3 antihyper tensive drugs. Tablets with fixed combination of 2 drugs will facilitate the therapeutic schedule and thus improve patient compliance. The choice of drug combinations is mainly based upon hemodynamic and metabolic criteria, and for most combination formal evidence has not (yet) been put forward.

References

1. Smolensky MH, Haus E.Circadian rhythms in clinical medicine with applications to hypertension, *AM J Hypertens* (Part 2); 280S-290S , 2001
2. Harter JG, Reddy WJ, Thorn GW, studies on an intermittent corticosteroid dosage regimen. *N Engl J Med* 296:591-595,1963.
3. Reinberg AE, The chronopharmacology of corticosteroids and ACTH. In Lemmer B (ed) . Chronopharmacology. Cellular and Biochemical interactions. Dekker, *New YOURK* 1989;PP 137-167.
4. Dahlöf B, Lindholm LH et al. Morbidity and mortality in the Swedish Trial in old patients with hypertension (STOP-Hypertension). *Lancet* 1991; 338, 1281 - 5.
5. Medical Research Council Working Party. MRC Trial of treatment of mild hyperten- sion. *BMJ* 1985; 291, 47 - 104.
6. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. *JAMA* 1991; 265, 3255 - 64
7. Staessen JA, Fagard R et al. Randomised double blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; 350, 757 - 64.
8. Menezes Falcão L, van Zwieten PA. Current diagnosis and treatment in heart failure. Publ Lidel, Lisbon 2001, pp. 207 - 22.
9. Burnier M, Brunner HR. Angiotensin II-receptor antagonists. *Lancet* 200; 355, 637 - 45.
10. Dahlöf B, Devereux RB, Kjeldsen SE et al. for the Losartan Intervention for Endpoint reduction (LIFE) study group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359:995 - 1003.
11. Kjeldsen SE, Dahlöf B, Devereux RB et al. for the Losartan\ Intervention for Endpoint reduction (LIFE) study group. Benefits of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hyperthrophy: a LIFE substudy. *JAMA* 2002; 288: 1491 - 8.
12. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALL- HAT). *JAMA* 2002; 288: 2988 - 97.
13. Pitt B et al. Effect of amlodipine on the progression of atherosclerosis and the occur- rence of clinical events. Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT). *Circulation* 2000; 102: 1503 - 10.
14. Brown MJ, Palmer C et al. Morbidity and mortality in patients randomised to double- blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a goal in hypertension treatment (INSIGHT). *Lancet* 2000; 356: 366 - 72.
15. Lohn EM, Yusuf S et al. for the SECURE Investigators. Effects of ramipril and vita- mine E on atherscleros is. The Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamine E (SECURE). *Circulation* 2001; 103: 919 - 25.
16. Farsang C, Kaweczka-Jaszcz K et al. for the Multicentre Study Group. Antihypertensive effects and tolerability of candesartan cilexetil alone and in combination with amlodipine. *Clin Drug Invest* 2001; 21: 17 - 23.
17. Dahlöf B, Hosie J on behalf of the Swedish/UK study group. Antihypertensive efficacy and tolerability of a new once-daily felodipine-metoprolol combination compared with each component alone. *Blood Pressure* 1993; 2(Suppl. 1): 22 - 9.