EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 1
137-140
Year: 2016

ROLE OF COMBINATION THERAPY (VALSARTAN PLUS HYDROCHLOROTHIAZIDE) IN HYPERTENSION: A REVIEW

Shubhangi Bhilla* and Gaurav Agarwal

Faculty of Pharmacy, R.P. Educational Trust Group of Institutions, Bastara, Karnal-132001, India.

***Author for Correspondence: Shubhangi Bhilla**
Faculty of Pharmacy, R.P. Educational Trust Group of Institutions, Bastara, Karnal-132001, India.

Article Received on 06/11/2015 **Article Revised on 27/11/2015** **Article Accepted on 17/12/2015**

ABSTRACT
Hypertension is one of the most prevailing disease in adults. The estimated prevalence of hypertension in the United States is 66% in men and women aged 60 years and older, which is the highest among all age groups. This figure is higher in certain regions of the world. Hypertension, in general involve multiple factors, hence treatment of hypertension with combination therapy has several advantage over monotherapy. In combination therapy, two or three drugs act through different mechanism and simultaneously lower dose of the individual drug is required hence reduce side effects and increase patient compliance. Combination therapy generally involve Angiotensin Receptor Blockers (ARBs) and Thiazide diuretics. Choice of combination depends on the presence of comorbidities like diabetes mellitus, chronic renal failure and thyroid disorders.

KEYWORDS: Valsartan/Hydrochlorothiazide, combination therapy, hypertension.

INTRODUCTION
Hypertension is defined as a systolic blood pressure (SBP) of > 140 mmHg and/or diastolic blood pressure (DBP) of > 90 mmHg. It is one of the most common cardiovascular risk factor in adult population.[1-3] The most common is essential hypertension with no known cause. Secondary hypertension is usually due to a renal disorder. Often, no symptoms develop unless hypertension is severe or long-standing. The duration of hypertension and values of blood pressure influence the risk of stroke, heart failure, atherosclerosis and kidney disease.[4-7] In the United States (US), about 65 million people have hypertension, 59% are being treated and only 34% have adequately controlled BP.[1] Lack of diagnosis, inadequate treatment and poor compliance to pharmacologic therapies are the main reasons for poor control of BP.[8] Inadequate compliance of some patients may be due to unpleasant side effects of prescribed drugs.[9]

Table 1. Classification of Blood Pressure.

Classification	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	>160	or >100

When blood pressure is higher (e.g. >180/110 mm Hg), treatment & evaluation should be done immediately.

- The presence of hypertension should be confirmed in the clinical evaluation
- The severity of hypertension and its harmful effects on other organs should be determined
- Effect of cardiovascular risk factors and other existing diseases on the treatment of hypertension should be identified.[10-13]

CONCEPT OF COMBINATION THERAPY
The aim of antihypertensive therapy is to lower the elevated blood pressure to an acceptable level. Treatment of hypertension with a single drug or monotherapy does not produce the desired result hence when monotherapy fails to produce the desired effect, concept of combination therapy (addition of second or third drug) is the treatment of choice. In most of the cases or in patients suffering from diabetes, treatment of hypertension require two or more drugs. Two or more drugs (with different mechanism of action) when

combined, produce greater anti hypertensive effect than the individual drug (synergistic effect) with the increase in tolerability and patient compliance.

Combination therapy: when to initiate?

The decision to initiate monotherapy or combination therapy depends on the severity of the disease or on the presence of other risk factors like diabetes, renal and cardiovascular disease.[14] In general, when the initial blood pressure is more than 20 mm Hg systolic and 10 mm Hg diastolic above the target Blood Pressure, then combination therapy should be recommended as first line therapy.

Combination Therapy: Theoretical Considerations

Efficacy

In combination therapy two or more selected anti hypertensive drugs are co administered. Two or more drugs are selected in such a way that lowers blood pressure to a greater degree compared with monotherapy. This comparatively lower blood pressure can be achieved by combining drugs which act through different mechanism of action or effectively block counter regulatory responses. The result of combination therapy in reducing blood pressure depends on the pharmacological properties of the drugs. In general combination therapy is approximately five times more effective in blood pressure reduction than increasing the dose of one drug.[15] The critical parameter in combination therapy is the pharmacokinetic compatibility of the added drugs. Combination therapy should result in effective blood pressure reduction throughout the dosing interval.[16]

Tolerability

Most of the antihypertensive agents produce dose dependent side effects. In combination therapy side effect of one drug can be neutralized by the pharmacologic properties of an added drug.[16] In combination therapy dose dependent side effects can be minimized by giving lower dose of the drug. Thus, combination therapy results in reduction in side effects with the additional reduction in blood pressure.

Adherence

For the effective control of blood pressure, adherence to treatment is very important. Increase in the dosing frequency and number of medication per day may adversely affect medication adherence. Combination therapy can reduce both the above factors and result in long term adherence to the treatment. One drawback of combination therapy is that some branded combinations are often more expensive and can affect the medication adherence.

Specific Drug Combinations

Angiotensin Receptor Blocker (ARB) + Diuretic

The combination of Valsartan, an orally active, specific angiotensin II receptor blocker with a low dose thiazide diuretic results in significant reduction in blood pressure.[17-21] Valsartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by blocking the binding of angiotensin II to the AT1 receptor thereby relaxing blood vessels, causing them to widen. Hydrochlorothiazide (HCTZ) is a thiazide diuretic. The diuretic action of HCTZ reduces plasma volume with consequent increase in plasma rennin activity, increase in aldosterone secretion, increase in urinary potassium loss and decrease in serum potassium. Co administration of angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.[22] Combination of Angiotensin Receptor Blocker (ARB) with a diuretic results in high blood pressure reduction with the increase in safety and efficacy profile.

One study suggested that although a goal blood pressure of <140/90 mm Hg can be reached in the majority of patients with SBP<160 mm Hg with valsartan monotherapy, most patients with moderate to severe (stage 27 or grade 2 or 3) hypertension (baseline SBP> 160 mm Hg) require combination therapy for blood pressure goal to be reached.[23-26]

SOME IMPORTANT SPECIAL SITUATIONS

Metabolic syndrome and Hypertension

A) **Diabetes and Proteinuria**

Hypertension may act synergistically in increasing complications of diabetes and blood pressure in diabetic patients.[27] Various trials some of which have been randomized have shown decrease in these complications when blood pressure was lowered to safer limits (<130/80 mm of Hg). This blood pressure control has been found to be difficult to achieve with monotherapy.[28]

Angiotensin Receptor Blockers (ARBs) and Diuretics have different indications in diabetes. Combination therapy should be the first line antihypertensive treatment in patient with diabetes. The combined therapy with an ARBs has a potentially useful anti-proteinuric effect in patients with type 2 diabetic nephropathy, even when their renal function is reduced. This was also shown in Fogari et al study also.[29]

B) **Dyslipidemia and Hypertension**

Patients with hypertension have a increased risk of hypercholesterolemia, reverse also holds true. National Health and Nutrition Examination Survey (NHANES III) has shown that 64% of patients with hypertension also have dyslipidemia and conversely approximately 47% of patients with dyslipidemia have hypertension. Increase in blood pressure and increase in cholesterol level, increase the risk of coronary heart disease.[30] Valsartan, an angiotensin II receptor blocker, also has a unique property that activates Peroxisome Proliferator Activated Receptor γ (PPAR-γ) hence improve insulin sensitivity and reduce triglyceride levels. Reduction in triglycerides level reduce the risk of atherosclerosis in patients with hypertension.

Heart failure with Hypertension

Treatment of hypertension in patients with heart failure must taken into account the type of heart failure, systolic dysfunction or diastolic dysfunction, in which there is a limitation to diastolic filling and therefore in forward out-put due to increased ventricular stiffness. The choice of agents in the treatment of hypertension with heart failure depends on the severity of heart failure. Combination of Angiotensin Receptor Blockers (ARBs) with Diuretics are useful in the management of heart failure and have been shown to reduce morbidity and mortality in selected patients with heart failure.

Chronic renal failure with Hypertension

Patients with Chronic Kidney Disease (CKD) may have hypertension. Hypertension can worsen the renal failure. Treatment of hypertension in patients suffering from chronic kidney disease should primarily reduce blood pressure and simultaneously reduce protein excretion. There is a direct relationship between the degree of proteinuria and progression to end stage renal disease hence the choice of agent will primarily depend on the presence of proteinuria. First line agents in the treatment of hypertension with Chronic Kidney Disease (CKD) include an ARB and often requires the addition of a diuretic.

Hypertension in thyroid disorders

Among hypothyroidism and hyperthyroidism, prevalence of hypertension is approximately 3% in hypothyroidism and 20-30% in hyperthyroidism. Age related increase in blood pressure occurs more frequently in hypothyroid state. A significant correlation between Diastolic Blood Pressure and either T4 or T3 suggesting that thyroid hormone deficiency contributes to increase in blood pressure when it is slight to moderate. The exact mechanism of increased blood pressure in hypothyroidism is not known but suggested mechanism is that thyroid hormone deficiency may accelerate the structural change of vascular tissue and deficiency of thyroid hormone may alter the autonomic nervous function which leads to hemodynamic changes. In patients suffering from hyperthyroidism, systolic pressures are increased and diastolic pressures are often low, which results in a widened pulse pressure. All these may increase cardiac output, stroke volume, heart rate and cardiac contractility. In patients suffering from hyperthyroidism, activity of RAAS is increased but the role of the RAAS in hypertension associated with hyperthyroidism is not defined as angiotensin II receptor blocker do not always reduce blood pressure.

Hypertension in elderly population

The estimated prevalence of hypertension in the United States is 66% in men and women aged 60 years and older, which is the highest among all age groups.[31] A meta analysis showed that treating hypertension in the elderly yields the greatest benefits in relation to stroke and coronary heart disease. Importantly, total mortality and coronary heart disease mortality were found to be significantly reduced.[32] Treatment of hypertension in this particular population generally require combination of two or more drugs.

Table 2. Usual dose and frequency of Antihypertensive medications.

Class	Drug	Usual dose range, mg/day	Usual daily frequency
Diuretics	Hydrochlorothiazide	12.5-50	1
ARBs	Valsartan	80-320	1

CONCLUSION

Hypertension may increase the complication of diabetes, hypercholesterolemia, chronic kidney disease, and thyrotoxicosis. Treatment of hypertension with combination therapy reduce blood pressure to the normal range and simultaneously reduce other risk factors hence combination therapy should be recommended as first line therapy in the treatment of hypertension. Fixed dose combination of Valsartan and Hydrochlorothiazide was used due to low side effects. It may be concluded that Valsartan Hydrochlorothiazide is a potent antihypertensive medication. It is indicated both in non diabetic and diabetic patient due to its potency and metabolic neutral action.

REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet., 2005; 365: 217-223.
2. Ong KL, Cheung BM, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. Hypertension, 2007; 49: 69-75.
3. Fields LE, Burt VL, Cutler JA, Hughes J, Roccella EJ, Sorlie P. The burden of adult hypertension in the United States 1999 to 2000: a rising tide. Hypertension, 2004; 44(4): 398-404.
4. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. J. Am. Med. Assoc., 1996; 275(20): 1571-1576.
5. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. N. Engl. J. Med., 2001; 345(18): 1291-1297.
6. Lindeman RD, Tobin J, Shock NW. Association between blood pressure and the rate of decline in renal function with age. Kidney Int., 1984; 26(6): 861-868.
7. Wollom GL, Gifford RW. The kidney as a target organ in hypertension. Geriatrics, 1976; 31(8): 71-79.
8. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed dose combinations improve medication compliance: a meta-analysis. Am. J. Med., 2007; 120(8): 713-719.

9. Beto JA, Bansal VK. Quality of life in treatment of hypertension: a meta analysis of clinical trials. Am. J. Hypert, 1992; 5(3): 125-133.
10. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. Seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure. Hypertension, 2003; 42(6): 1206-1252.
11. Petrac D i sur. Interna medicina, 2009; 110-115.
12. Gifford RW Jr, Kirkendall W, O'Connor DT, Weidman W. Office evaluation of hypertension: a statement for health professionals by a writing group of the council for high blood pressure research, American heart association. Circulation, 1989; 79(3): 721-731.
13. Lifton RP, Jeunemaitre X. Finding genes that cause human hypertension. J. Hvpertens, 1993; 11(3): 231-236.
14. Mancia G, De Backer G, Dominiczak A. Guidelines for the management of arterial hypertension. J. Hypertens, 2007; 25(6): 1105–1187.
15. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am. J. Med., 2009; 122(3): 290–300.
16. Sica DA. Rationale for fixed dose combinations in the treatment of hypertension: the cycle repeats. Drugs., 2002; 62(3): 443–462.
17. Chrysant SG. Antihypertensive effectiveness of low-dose lisinopril hydrochlorothiazide combination. A large multicenter study. lisinopril-hydrochlorothiazide group. Arch. Intern. Med., 1994; 154(7): 737–743.
18. Chrysant SG, Fagan T, Glazer R, Kriegman A. Effects of benazepril and hydrochlorothiazide, given alone and in low- and high-dose combinations, on blood pressure in patients with hypertension. Arch. Fam. Med., 1996; 5(1): 17–24.
19. Pool JL, Cushman WC, Saini RK, Nwachuku CE, Battikha JP. Use of the factorial design and quadratic response surface models to evaluate the fosinopril and hydrochlorothiazide combination therapy in hypertension. Am. J. Hypertens, 1997; 10(1): 117–123.
20. Gradman AH, Kad R. Renin inhibition in hypertension. J. Am. Coll. Cardiol., 2008; 51(5): 519–528.
21. Mackay JH, Arcuri KE, Goldberg AI, Shapinn SM, Sweet CS. Losartan and low-dose hydrochlorothiazide in patients with essential hypertension. A double-blind, placebo-controlled trial of concomitant administration compared with individual components. Arch. Intern. Med., 1996; 156(3): 278–285.
22. Ambrosioni E, Borghi C, Costa FV. Captopril and hydrochlorothiazide: rationale for their combination. Br. J. Clin. Pharmacol, 1987; 23(Suppl 1): 43–50.
23. Frishman WH, Ram CVS, McMahon FG, Chrysant SG, Graff A, Kupiec JW, Hsu H. Comparison of amlodipine and benazepril monotherapy to amlodipine plus benazepril in patients with systemic hypertension: a randomized, double-blind, placebo-controlled, parallel-group study. J. Clin. Pharmacol, 1995; 35(11): 1060–1066.
24. Philipp T, Smith TR, Glazer R, Wernsing M, Yen J, Jin J, Schneider H, Pospiech R. Two multi-center, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Clin. Ther., 2007; 29(4): 563–580.
25. Chrysant SG, Melino M, Karki S, Lee J, Heyrman R. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, controlled, 8-week factorial efficacy and safety study. Clin. Ther., 2008; 30(4): 587–604.
26. Gradman AH, Cutler NR, Davis PJ, Robbins JA, Weiss RJ, Wood BC. Combined enalapril and felodipine extended release (ER) for systemic hypertension. Enalapril-felodipine ER factorial study group. Am. J. Cardiol., 1997; 79(4): 431–435.
27. Davis TM, Millns H, Stratton IM, Holman RR, Turner RC. Risk factors for stroke in type 2 diabetes mellitus: United Kingdom prospective diabetes study (UKPDS) 29. Arch. Intern. Med., 1999; 159(10): 1097-1103.
28. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz, I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N. Engl. J. Med., 2001; 345(12): 851-860.
29. Fogari R, Derosa G, Zoppi A, Preti P, Lazzari P, Destro M, Fogari E, Rinaldi A, Mugellini A. Effect of telmisartan amlodipine combination at different doses on urinary albumin excretion in hypertensive diabetic patients with microalbuminuria. Am. J. Hypertens, 2007; 20(4): 417-422.
30. Devabhaktuni M, Bangalore S. Fixed combination of amlodipine and atorvastatin in cardiovascular risk management: patient perspectives. Vasc. Health Risk Manag., 2009; 5(1): 377-387.
31. Ong KL, Cheung BM, Man YB, Lam KS, Lau CP. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. Hypertension, 2007; 49(1): 69-75.
32. Rouleau JL, Roecker EB, Tendera M, Mohacsi P, Krum H, Katus HA, Fowler MB, Coats AJ, Castaigne A, Scherhag A, Holcslaw TL, Packer M. Carvedilol prospective randomized cumulative survival study group. Influence of pretreatment systolic blood pressure on the effect of carvedilol in patients with severe chronic heart failure: the carvedilol prospective randomized cumulative survival (COPERNICUS) study. J. Am. Coll. Cardiol., 2004; 43(8): 1423-1429.