ISSN 2582 – 6050

Available Online at www.ijpba.info
International Journal of Pharmaceutical & Biological Archives 2020; 11(2):65-70

REVIEW ARTICLE

Novel Antihypertensive Drug Used in Clinical Practice: A Review

Sanjay Bais[1]*, Sarfaraz Kazi[2], Sajid Shaikh[3]

[1]Department of Quality Assurance, Fabtech College of Pharmacy, Sangola, Solapur, Maharashtra, India, [2]Department of Pharmacy, Shri Jagdishprasad Jhabarmal Tibrewala University, Jhunjhunu, Rajasthan, India, [3]Department of Pharmacology, Vedprakash Patil College of Pharmacy, Georai Tanda, Aurangabad, Maharashtra, India

Received: 01 February 2020; Revised: 01 March 2020; Accepted: 01 April 2020

ABSTRACT

Introduction: Blood pressure (BP) control continues to be important in reducing cardiovascular risk, along with the modification of other cardiovascular risk factors, especially cholesterol level. Lifestyle modification to reduce BP may control Stage 1 hypertension. Drug treatment should be based on evidence of improved outcomes and individualized account for the patient age, race, and quality of life. BP varies from minute to minute and is influenced by measurement technique, time of day, emotion, pain, discomfort, hydration, temperature, exercise, posture, and drugs. **Purpose of Review:** In this review, we examine how synthetic novel drugs involved in the management of hypertension not only in the wider population but also within special population groups such as the elderly, pregnant women, and those with a trial fibrillation. **Conclusion:** The extensive synthetic work carried out shows that some molecules are very effectively managing the hypertension in all ages of patients. **Summary:** We have made an attempt in reviewing the literature on 1,2 pyrazoline derivatives for their medicinal uses with the help of chemical abstract, journals, and internet surfing.

Keywords: Blood pressure, clinical management, hypertension, synthetics drugs

INTRODUCTION

Blood pressure (BP) control continues to be important in reducing cardiovascular risk, along with the modification of other cardiovascular risk factors, especially cholesterol level. Lifestyle modification to reduce BP may control Stage 1 hypertension. Drug treatment should be based on evidence of improved outcomes and individualized account for patient age, race, and quality of life. Although the number of cardiovascular deaths has decreased over the past 25 years, achieving long-term control of hypertension in millions of patients remains an important objective. BP varies from minute to minute and is influenced by measurement technique, time of day, emotion, pain, discomfort, hydration, temperature, exercise, posture, and drugs. The dividing line between normal BP and hypertension is arbitrary.[1,2] According to the Joint National Committee VI, hypertension is when the diastolic BPs measurement is 90 mm Hg or higher, and systolic BPs measurement is consistently >140 mm Hg.[3] Hypertension remains one of the largest unmet medical needs in the 21st century, especially when one considers that hypertension is the potent of future debilitating cardiovascular disease.[1] The interrelation of a number of regulatory factors to control BP and tissue perfusion was first described by page in 1949. According to this concept, tissue perfusion/pressure/resistance are interdependent on factors designated chemical, reactivity, volume, vascular caliber, viscosity, cardiac output, elasticity, and multifactorial derangement of normal equilibrium.[4] The baroreceptors, mainly in the walls of the aorta and the internal carotid arteries, act on rapidly adjust to changes in pressure (stretch) response time in seconds. This is accomplished by activation of afferent nerves from the baroreceptors

***Corresponding Author:**
Dr. Sanjay Bais
E-mail: sanjaybais1968@gmail.com

© 2020, IJPBA. All Rights Reserved

to the brain stem centers and modulation of efferent sympathetic nerve activity of peripheral blood vessels (norepinephrine release), to kidney(remain release) to the heart (acetylcholine release).

SYMPTOMS OF HYPERTENSION[5,6]

Hypertension often has no symptoms. The only way to detect it is to check it regularly, such as headache, nosebleeds, blurred vision, palpitation, dizziness, and tinnitus (ringing in the ear).

CAUSES OF HYPERTENSION[3,7-9]

The most common of them are as follows: Obesity, alcohol intake, cigarette smoking, high sodium intake, anxiety, diabetes, endocrine disorders such as adrenal disorders, thyroid disorders, and Cushing syndrome, and medications such as appetite suppressants, corticosteroids, and birth control pills.

DIFFERENT TYPES OF HYPERTENSION

(1) Primary hypertension:[10] Individuals typically suffer primary hypertension as a result of poor lifestyle habits, while this type of hypertension accounts for most of the cases diagnosed by doctors. While medication may be required, dietary changes, stress management, and physical activity are essential elements of treatment. (2) Secondary hypertension:[11] Secondary hypertension is the symptom of an underlying medical condition such as kidney disease, problems with the liver, congestive heart failure, stress, sleep apnea, or endocrine disorders such as hyperthyroidism or Cushing's syndrome, which produces elevated levels of hormones. Renal artery stenosis is a frequent cause of secondary hypertension. Treatment of secondary hypertension involves controlling the underlying medical condition or disease in addition to prescribing antihypertensive drugs. (3) Alcohol-induced hypertension:[12] Heavy drinking of alcohol may be one of the most common causes of secondary hypertension. (4) Isolated systolic hypertension:[13] Isolated systolic hypertension occurs in people as they grow older. The build-up of plaque in the arteries makes it more difficult for blood to flow through. Treating the elderly with diuretics not only decreases the risk of developing the cardiovascular disease but may also reduce the risk of dementia and related depression. (5) Pregnancy-induced hypertension:[14] It begins to suffer from hypertension after the 20th week of pregnancy. In the majority of cases, these women are overweight or obese. Women who are diagnosed with pregnancy-induced hypertension are at greater risk of preeclampsia during pregnancy. Symptoms may include headache, dizziness, swelling of the hands and face, nausea, vomiting, and pain in the abdomen. (6) Medication-induced hypertension:[15] Non-steroidal anti-inflammatory drugs, decongestants, and weight loss supplements are common OTC drugs that can cause an increase in BP. Corticosteroids, immunosuppressive, and cancer drugs are among the prescription medications, for which high BP can be a side effect. These drugs constrict blood vessels and can cause kidney problems. (7) Malignant hypertension:[16] Malignant hypertension is considered to be a medical emergency as the BP can suddenly rise to a dangerous level.[17-21]

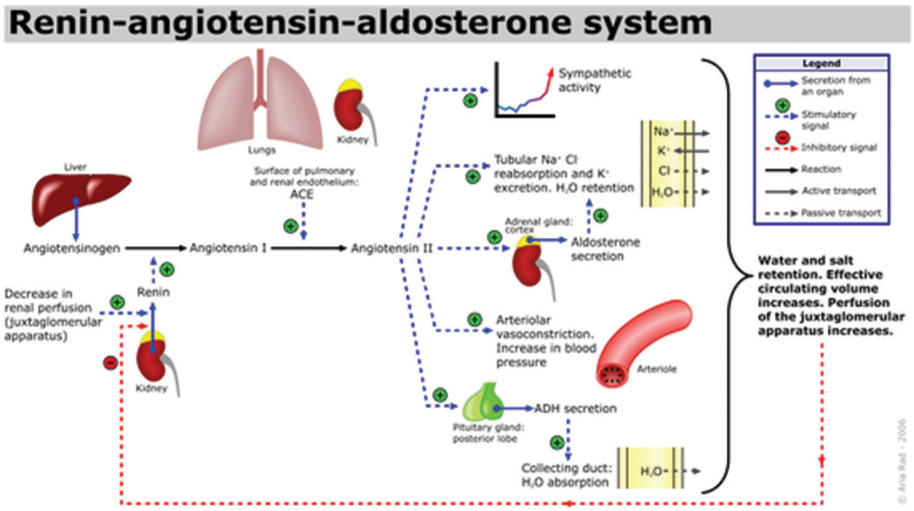
MECHANISM OF HYPERTENSION

Three theories have been proposed to explain this:[22]

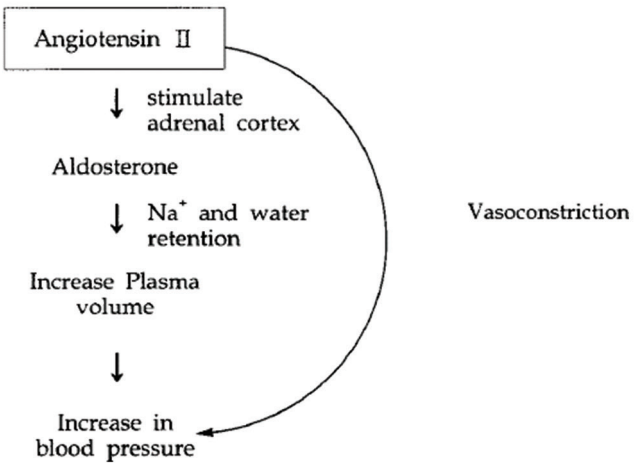
- The inability of the kidneys to excrete sodium, resulting in natriuretic factors such as atrial natriuretic factor being secreted to promote salt excretion with the side effect of raising total peripheral resistance
- An overactive renin–angiotensin system (RAS) leads to vasoconstriction and retention of sodium and water. The increase in blood volume plus vasoconstriction leads to hypertension
- An overactive sympathetic nervous system, leading to increased stress responses.

RAS

The RAS or the renin-angiotensin-aldosterone system (RAAS) is a hormone system that regulates



Major Effector organ	Angiotensins	Enzyme involved in the transformation
Liver	Angiotensinogen	
Kidney	↓	Renin
	Angiotensin I	
Lung Kidney	↓	Angiotensin Converting Enzyme (ACE)
	Angiotensin II	
	↓	
	Receptors	



the tubules of the kidneys to increase the reabsorption of sodium and water into the blood. This increases the volume of fluid in the body, which also increases BP.[23,24] These drugs are one of the main ways to control high BP (hypertension), heart failure, kidney failure, and the harmful effects of diabetes.[25]

ANTIHYPERTENSIVE DRUGS

History of treatment of hypertension[26] hypertension and its drug therapy has been remarkably improved in the past 50 years. Different classes of drugs have received prominence with the passage of time in this period. Before 1950, hardly any effective and tolerated antihypertensive agent was available. Veratrum and sodium thiocyanate could lower BP but were toxic and difficult to use. The ganglionic blockers developed in the 1950s were effective but inconvenient. The therapeutic potential of hydralazine could not be tapped fully because of marked side effects when it was used alone. Guanethidine introduced in 1961, was an improvement in ganglionic blockers. The antihypertensives of the 1960–70s were methyldopa, β blockers and diuretics were consolidated in the 1970s and selective α-blocker prazosin broke new grounds. The antihypertensives of the 1980–1990s are angiotensin-II converting enzyme inhibitors (ACE) and calcium channel blockers. Angiotensin II antagonists are the latest antihypertensives.[27,28] Diuretics help the kidneys eliminate excess salt and water from the body's tissues and blood.[27] For example, loop diuretics such as bumetanide, ethacrynic acid, furosemide, torsemide, and thiazide diuretics are epitizide, hydrochlorothiazide, and chlorothiazide bendroflumethiazide. Thiazide-like diuretics are indapamide and chlorthalidone metolazone, potassium-sparing diuretics are amiloride, triamterene, and spironolactone. Despite lowering

BP, alpha-blockers have a significantly poorer endpoint and are no longer recommended as a first-line choice in the treatment of hypertension.[27] Calcium channel blockers: Calcium channel blockers block the entry of calcium into muscle cells in artery walls like dihydropyridine are amlodipine, felodipine, isradipine, lercanidipine, nicardipine, nifedipine, nimodipine, nitrendipine and non-dihydropyridines: diltiazem, and verapamil. ACE inhibitors inhibit the activity of ACE, an enzyme responsible for the conversion of angiotensin I into angiotensin II, a potent vasoconstrictor,[28] for example, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril, and benazepril. Angiotensin II receptor antagonists work by antagonizing the activation of angiotensin receptors are candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan. Vasodilators act directly on the smooth muscle of arteries to relax their walls, so blood can move more easily through them; they are only used in hypertensive emergencies or when other drugs have failed and even so are rarely given alone.[28] Sodium nitroprusside, a very potent, short-acting vasodilator, is most commonly used for the quick, temporary reduction of BP in emergencies (such as malignant hypertension or aortic dissection).[27] Hydralazine and its derivatives are also used in the treatment of severe hypertension, although they should be avoided in emergencies.[27,28] Central alpha agonists lower BP by stimulating alpha-receptors in the brain which open peripheral arteries easing blood flow,[28] for example, clonidine, guanabenz, methyldopa, moxonidine. Some adrenergic neuron blockers are used for the most resistant forms of hypertension, such as guanethidine and reserpine. Angiotensin II receptor antagonists, also known as angiotensin receptor blockers, AT_1-receptor antagonists, or sartans, are a group of pharmaceuticals which modulate the RAAS. Their main use is in hypertension (high BP), diabetic nephropathy (kidney damage due to diabetes), and congestive heart failure [Figure 1].[28,29]

DRUG COMPARISON AND PHARMACOKINETICS[30]

The mean BP reduction achieved with losartan in a dosage of 50–150 mg once daily is 5.5–10.5 mm Hg for systolic pressure and 3.5–7.5 mm Hg for diastolic pressure.[31] A hydrochlorothiazide-losartan combination (Hyzaar) is also available. This combination contains 12.5 mg of hydrochlorothiazide and 50 mg of losartan.[32] Candesartan cilexetil has been shown to be effective for the treatment of hypertension [Table 1]. The affinity of candesartan for the AT_1 receptor is more than 10,000 times greater than its affinity for the AT_2 receptor. With Valsartan taken in a dosage of 80–320 mg once daily, the mean reduction in diastolic BP is 6–9 mm Hg. Studies have shown that valsartan is as effective as enalapril, lisinopril, and amlodipine in the treatment of mild-to-moderate hypertension.[33,34]

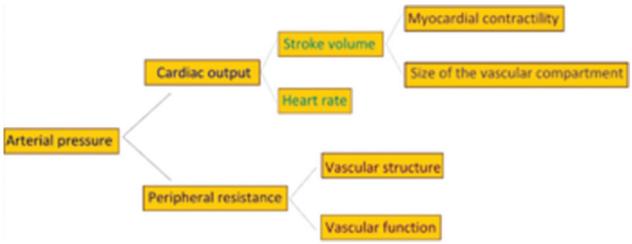


Figure 1: Factors affecting arterial pressure[22]

Table 1: Drug comparison and pharmacokinetics of angiotensin II blocking agent[30]

Drug	Trade name	Biological half-life (h)	Protein binding (%)	Bioavailability (%)	Renal/hepatic clearance (%)	Food effect	Daily dosage (mg)
Losartan	Cozaar	2 h	98.7	33	10/90	Minimal	50–100 mg
EXP 3174		6–9 h	99.8	–	50/50	–	–
Candesartan	Atacand	9h	>99	15	60/40	No	4–32 mg
Valsartan	Diovan	6 h	95	25	30/70	No	80–320 mg
Irbesartan	Avapro	11–15 h	90–95	70	1/99	No	150–300 mg
Telmisartan	Micardis	24 h	>99	42–58	1/99	No	40–80 mg
Eprosartan	Teveten	5 h	98	13	30/70	No	400–800 mg
Olmesartan	Benicar	14–16 h	>99	29	40/60	No	10–40 mg

The affinity of the valsartan for the AT1 receptor is about 20,000 times greater than its affinity for AT2 receptor. In comparison, the affinity of losartan for AT1 receptor is about 1000 times greater than its affinity for AT2 receptors.[31] Irbesartan is a safe and effective angiotensin II receptor antagonist with an affinity for the AT1 receptor that is more than 8500 times greater than its affinity for AT2 receptor.[35] Non-linear pharmacokinetics yield a greater than proportional increase in plasma telmisartan concentration with increasing dosage. It is a newly synthesized molecule which requires a very high daily dose as compared to other drugs of this class of around 400–500 mg.[36] It is orally administered in the form of olmesartan medoxomil in combination with hydrochlorothiazide. Twenty milligram or 40 mg olmesartan medoxomil is combined with 12.5 mg hydrochlorothiazide and 40 mg with 25 mg hydrochlorothiazide.[33-40] Adverse effects:[41,42] Orthostatic hypotension, dyspepsia, decreased hemoglobin level, insomnia, renal impairment, pharyngitis or nasal congestion, and hyperkalemia.

CONCLUSION

The present work which was undertaken is novel work on the synthesis of various medicinal derivatives. We have made an attempt in reviewing the literature on drug for their medicinal uses with the help of chemical abstract, Journals and internet surfing. The drugs were found to be non-toxic and could be synthesized in good yield. The active drugs were taken as lead for the treatment of hypertension. The present work is an attempt in this direction and the efforts have proved to be fruitful and promising.

REFERENCES

1. Shankie S. Hypertension in Focus. 6th ed. London, UK: Pharmaceutical Press; 2002.
2. Carretero OA, Oparil S. Essential hypertension: Part I: Definition and etiology. Circulation 2000;101:329-35.
3. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., *et al*. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 2003;42:1206-52.
4. The sixth report of the joint national committee on detection, evaluation and treatment of high blood pressure, (JNC VI). Arch Intern Med 1997;157:2413-46.
5. Braunwald E. Heart Disease: A Textbook of CNS Medicine. Philadelphia, PA: Saunders;1997. p. 780-875.
6. Barst RJ, McGoon M, Torbicki A, Sitbon O, Krowka MJ, Olschewski H, *et al*. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2004;43:40S-7.
7. Yu PN, Goodwin JF. Progress in Cardiology. Vol. 8. Philadelphia, PA: Lea and Febiger; 1979. p. 325-30.
8. Holt K. Hypertension Causes, Prevention and Treatment. Amsterdam, Netherlands: Elsevier; 2006.
9. Fuster V, Alexander RW, O'Rourke RA. Hurst's: The Heart. 11th ed., Vol. 1. New York: The McGraw-Hill; 2004. p. 1531-70.
10. Victor R. Arterial Hypertension. 23rd ed., Ch. 66. Philadelphia, PA: Saunders Elsevier; 2008.
11. Onusko E. Diagnosing secondary hypertension. Am Fam Physician 2003;67:67-74.
12. Clark LT. Alcohol induced hypertension: Mechanisms complications, and clinia implications. J Natl Med Assoc 1985;77:385-9.
13. Zwieten PA. Drug treatment of isolated systolic hypertension. Nephrol Dial Transplant 2001;16:1095-7.
14. Sabour S, Franx A, Rutten A, Grobbee DE, Prokop M, Bartelink ML, *et al*. High blood pressure in pregnancy and coronary calcification. Hypertension 2007;49:813-7.
15. Handler J. Drug-induced hypertension. J Clin Hypertens 2003;5:83-5.
16. Scarpelli PT, Gallo M, De Cesaris F, Chiari G, Dedola G, Cappeli S, *et al*. Continuing follow up of malignant hypertension. J Nephrol 2002;15:431-7.
17. Milne F, Redman C, Walker J, Baker P, Bradley J, Cooper C, *et al*. The pre-eclampsia community guideline (PRECOG): How to screen for and detect onset of pre-eclampsia in the community. BMJ 2005;330:576-80.
18. Yadav S, Boddula R, Genitta G, Bhatia V, Bansal B, Kongara S, *et al*. Prevalence and risk factors of pre-hypertension and hypertension in an affluent north Indian population. Indian J Med Res 2008;128:712-20.
19. Juliu S, Nesbitt SD, Egan BM, Weber MA, Michelson EL, Kaciroti N, *et al*. Feasibility of treating prehypertension with an angiotensin-receptor blocker. N Engl J Med 2006;354:1685-97.
20. August P. Overview: Mechanisms of hypertension: Cells, hormones, and the kidney. J Am Soc Nephrol 2004;15:1971-73.
21. Merck Manual Home. High Blood Pressure: Heart and Blood Vessel Disorders. New Jersey, USA: Merck Manual Home; 1899.
22. Gilbert S. Pathophysiology of Hypertension. m J Physiol Heart Circ Physiol. 2008 Feb;294(2):H541-50.
23. Laragh JH, Brenner BM. Hypertension: Pathophysiology, Diagnosis and Management. 2nd ed., Vol. 1. New York: Raven Press; 1995. p. 3-37.
24. Brunton LL, Lazo JS, Parker KL. Goodman and Gilman's

the Pharmacological Basis of Therapeutics. 11th ed. New York: The McGraw-Hill; 2006. p. 789-865.
25. Contreras F, Parte MA, Cabrera J, Ospino N, Hernández R, Lezama E, *et al*. Functional aspects of the renin angiotensi aldosterone system and angiotensin II receptor AT1 blockers in arterial hypertnsion. Int Congr Ser 2002;1237:87-98.
26. Page IH, Taylor RD, Corcoran AC. Pyrogens in the Treatment of Malignant Hypertension: Hypertension, Minneapolis. Minneapolis, Minnesota: Minnesota Press; 1950. p. 524-33.
27. Tripathi KD. Essentials of Pharmacology. 6th ed. New Delhi: Jaypee Brothers Medical Publishers; 2007. p. 539-55.
28. Williams DA, Lemke TL. Foye's Principles of Medicinal Chemistry. 5th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2002. p. 533-60.
29. Hoeper MM, Barberà JA, Channick RN, Hassoun PM, Lang IM, Manes A, *et al*. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol 2009;54:S85-96.
30. Nelson M. Drug treatment of elevated blood pressure. Aust Prescr 2010;33:108-12.
31. Gradman AH, Arcuri KE, Goldberg AL, Ikeda LS, Nelson EB, Snavely DB, *et al*. A randomized placebo-controlled, double-blind, parallel study of various doses of Losartan potassium compared with enalapril maleate in patients with essential hypertension. Hypertension 1995;25:1345-50.
32. Rhodes CJ, Davidson A, Gibbs JS, Wharton J, Wilkins MR. Therapeutic targets in pulmonary arterial hypertension. Pharmacol Ther 2009;121:69-88.
33. Oparil S, Dyke S, Harris F, Kief J, James D, Hester A, *et al*. The efficacy and safety of Valsartan compared with placebo in the treatment of patients with essential hypertension. Clin Ther 1996;18:797-809.
34. Holwerda NJ, Fogari R, Angeli P, Porcellati C, Hereng C, *et al*. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: Efficacy and safety compared with placebo and enalapril. J Hypertems 1996;14:1147-51.
35. Weir MR, Elkins M, Liss C, Vreenak AJ, Barr E, Edelman JM. Efficacy, tolerability and quality of life of Losartan, alone or with hydrochlorothiazide, versus Nifedipine GITS in patients with essential hypertension. Clin Ther 1996;18:411-28.
36. Severe P. Candesartan citexitil: A new, long acting, effective angiotensin II Type 1 receptor blocker. J Hum Hypertens 1997;11:S91-5.
37. Kassler-Taub K, John TL, Elliott W, Ruddy T, Alder E. Comparative efficacy of two angiotensin II receptor antagonists Irbesartan and Losartan in mild-to-moderate hypertension. Am J Hypertens 1998;11:445-53.
38. Micardis. Psckage Insert Ridgefielld Conn. Ingelheim am Rhein: Boehringer Ingelhim Pharmaceuticals, Inc.; 1998.
39. Bottorff MB, Tenero DM. Pharmacokinetics of eprosartan in healthy subjects, patients with hypertension, and special populations. Pharmacotherapy 1999; 19:73S-8S.
40. Gardner SF, Franks AM. Olmesartan medoximil: The seventh angiotensin receptor antagonist. Ann Pharmacother 2003;37:99-105.
41. Wexler RR, Greenlee WJ, Irvin JD, Goldberg MR, Prendergast K, Smith RD, *et al*. Nonpeptide angiotensin II receptor antagonists: The next generation in antihypertensive therapy. J Med Chem 1996;39:625-56.
42. Müller-Nordhorn J, Willich SN. Angiotensin II antagonists in the treatment of hypertension effective and efficient? Herz 2003;28:733-7.