



## A REVIEW ON COMPARATIVE STUDY OF ADVERSE DRUG REACTIONS BETWEEN AMLODIPINE AND LOSARTAN IN OUT-PATIENTS OF PRIMARY HEALTHCARE CENTRE

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### ABSTRACT

Hypertension (HTN or HT), also known as high blood pressure (HBP), is a long term medical condition in which the blood pressure in the arteries is persistently elevated. High blood pressure usually does not cause symptoms. Long term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease. Amlodipine is a calcium channel blocker that dilates (widens) blood vessels and improves blood flow. Amlodipine is used to treat chest pain (angina) and other conditions caused by coronary artery disease. Amlodipine is also used to treat high blood pressure (hypertension). Lowering blood pressure may lower your risk of a stroke or heart attack. Amlodipine is for use in adults and children who are at least 6 years old. Losartan was first angiotensin II blocker. Food and Drug Administration (FDA) approved it in 1995 as an antihypertensive. There has been great progress in understanding the effects of angiotensin II (All) in the kidney and the benefits of blockade of All at the AT1 receptor. Although losartan is now one of many angiotensin receptor blockers (ARBs), it was the first clinically used and has significantly contributed to both the physiologic understanding of All and the clinical benefit of All blockade.

**KEY WORDS:** Hypertension, Amlodipine, Losartan, calcium channel blocker

### INTRODUCTION

According to the World Health Statistics 2012 report, India has low rates of hypertension compared to world figures. Here, 23.10% men and 22.60% women above 25 years suffer from hypertension. India also fares better than the global average of 29.20 in men and 24.80 in women respectively.

Because of the aging of the population and rising rates of obesity, hypertension is increasing in prevalence worldwide. Approximately 10% of patients with diagnosed hypertension have resistant hypertension, defined as a systolic blood pressure of 140 mm Hg or higher despite adherence to at least three maximally tolerated doses of antihypertensive medications from complementary classes, including a diuretic at an appropriate dose.<sup>1-4</sup> Patients with resistant hypertension who are receiving appropriate medical therapy have high rates of cardiovascular complications, with few treatment options.

#### 1.1 What is hypertension?

Hypertension (HTN), defined as systolic blood pressure (SBP) > 140 mmHg or diastolic blood pressure (DBP) > 90

mmHg, is a major growing health problem across the globe. It is the most common risk factor for cardiovascular disease and affects nearly two-thirds of adults aged 60 years or older.

#### Diagnosis and patient evaluation

Measurement of blood pressures can be done either manually using a sphygmomanometer or an automated electronic device (both office and home) or when feasible ambulatory blood pressure monitoring is utilized. The latter two are preferred since they are reproducible and rule out observer bias

#### Treatment of Hypertension

To prevent high blood pressure, everyone should be encouraged to make lifestyle modifications, such as eating a healthier diet, quitting smoking and getting more exercise.

#### Antihypertensive

Antihypertensives are a class of drugs that are used to treat hypertension (high blood pressure).

Antihypertensive therapy seeks to prevent the complications of high blood pressure, such as stroke and myocardial infarction. Evidence suggests that reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease.

## Types of Antihypertensives

### i.) Diuretics

Hydrochlorothiazide, a popular thiazide diuretic, Diuretics help the kidneys eliminate excess salt and water from the body's tissues and blood. A diuretic is any substance that promotes diuresis, that is, the increased production of urine. This includes forced diuresis. There are several categories of diuretics. All diuretics increase the excretion of water from bodies, although each class does so in a distinct way.

### Calcium channel blockers

Calcium channel blockers block the entry of calcium into muscle cells in artery walls. Calcium channel blockers (CCB), calcium channel antagonists or calcium antagonists are several medications that disrupt the movement of calcium (Ca<sup>2+</sup>) through calcium channels. Calcium channel blockers are used as antihypertensive drugs, i.e., as medications to decrease blood pressure in patients with hypertension

### ACE inhibitors drugs

Captopril, the prototypical ACE inhibitor. ACE inhibitors inhibit the activity of angiotensin-converting enzyme (ACE), an enzyme responsible for the conversion of angiotensin I into angiotensin II, a potent vasoconstrictor. ACE also breaks down bradykinin (a vasodilator substance).

### Angiotensin II receptor antagonists

Valsartan, an angiotensin II receptor antagonist

Angiotensin II receptor antagonists work by antagonizing the activation of angiotensin receptors. These drugs have very similar effects to angiotensin converting enzyme (ACE) inhibitors and are used for the same indications (hypertension, heart failure, post-myocardial infarction).

### Adrenergic receptor antagonists

Propranolol, the first beta-blocker to be successfully developed.

Beta blocker, also written  $\beta$ -blocker, is a class of medications that are particularly used to manage cardiac

arrhythmias, and to protect the heart from a second heart attack (myocardial infarction) after a first heart attack (secondary prevention). They are also widely used to treat hypertension, although they are no longer the first choice for initial treatment of most patients.

### Benzodiazepines

Although controversial over this off-label purpose, benzodiazepines may play a role in lowering blood pressure. They work as an agonist of the GABA-a receptors in the brain, thus slowing down neurotransmission and dilating blood vessels. GABA is an abbreviation for gamma-aminobutyric acid.

### Renin Inhibitors

Renin comes one level higher than angiotensin converting enzyme (ACE) in the renin-angiotensin system. Inhibitors of renin can therefore effectively reduce hypertension. Aliskiren (developed by Novartis) is a renin inhibitor which has been approved by the U.S. FDA for the treatment of hypertension.

### 1.6 Drug Profiling

As you can see there are lots of drugs for hypertension drug therapy, but the most common drugs which are used are

1. Amlodipine
2. Losartan
3. Atenolol

**i.) Amlodipine:** Amlodipine is a calcium channel blocker that dilates (widens) blood vessels and improves blood flow. Amlodipine is used to treat chest pain (angina) and other conditions caused by coronary artery disease. Amlodipine is also used to treat high blood pressure (hypertension). Lowering blood pressure may lower your risk of a stroke or heart attack. Amlodipine is for use in adults and children who are at least 6 years old.

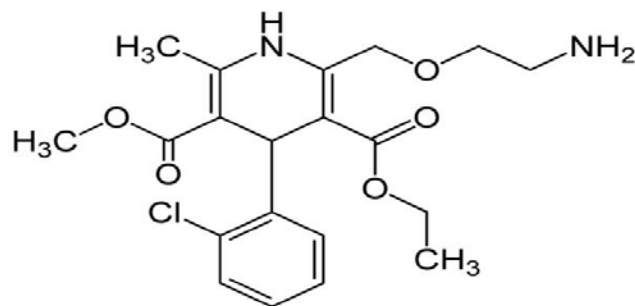


Fig.1: Chemical structure of Amlodipine

**Losartan:** Losartan was first angiotensin II blocker. Food and Drug Administration (FDA) approved it in 1995 as an antihypertensive. There has been great progress in

understanding the effects of angiotensin II (All) in the kidney and the benefits of blockade of All at the AT1 receptor. Although losartan is now one of many angiotensin receptor blockers (ARBs), it was the first clinically used and has significantly contributed to both the physiologic understanding of All and the clinical benefit of All blockade.

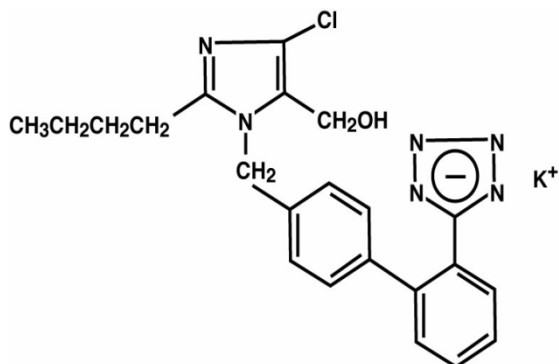


Fig. 2: Chemical structure of Losartan

#### a.) Mechanism of action

Losartan, also known as DuP 753, is a selective non-peptide antagonist blocking the AT1 receptors. Its chemical structure is 2-Butyl-4-chloro-1-[(2'-(1H-*etrazol*-5-yl) (1, 1'-biphenyl-4-yl) methyl]-1H-imidazole-5-methanol with the molecular formula of C<sub>22</sub>H<sub>22</sub>N<sub>6</sub>O and molecular weight of 461.01. The chemical part of the imidazole-5-acetic acid derivatives is for the drug effect on cardiovascular systems.

#### b.) Pharmacokinetics

Losartan, the first orally available angiotensin II receptor antagonist, is an active nonpeptide, selective, and competitive angiotensin II receptor, type 1 (AGTR1) antagonist without agonist properties<sup>[14]</sup>

Losartan is rapidly and almost completely absorbed, and reaches maximum concentrations 1-2 hours after oral administration<sup>[15]</sup>. The reported bioavailability of losartan is around 35%, probably due to variable first-pass metabolism. Losartan and its pharmacologically active metabolite E 3174 have a relatively low volume of distribution, consistent with the high protein binding of these acidic compounds, primarily to albumin.

#### c.) Adverse Drug Reactions.

All of the physiological effects of angiotensin II, including release of aldosterone, are antagonized in the presence of losartan. Reduction in blood pressure occurs independently of the status of the renin-angiotensin system. As a result of losartan dosing, plasma renin activity increases due to removal of the angiotensin II feedback. There are other adverse effects like headache, dizziness, backache, muscle pain, hypotension, chest

pain. Major adverse effects of CCBs are Dizziness, lightheadedness, swelling ankles/feet, or flushing may occur.

An adverse drug reaction (ADR) is an injury caused by taking a medication. ADRs may occur following a single dose or prolonged administration of a drug or result from the combination of two or more drugs. The meaning of this expression differs from the meaning of "side effect", as this last expression might also imply that the effects can be beneficial. The study of ADRs is the concern of the field known as pharmacovigilance. An adverse drug event (ADE) refers to any injury occurring at the time a drug is used, whether or not it is identified as a cause of the injury. An ADR is a special type of ADE in which a causative relationship can be shown.

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