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A REVIEW ARTICLE OF TELMISARTAN IN THE TREATMENT OF HYPERTENSION

Ayasha Parveen* and Prof. (Dr) S.S Agarawal

Delhi Pharmaceutical Sciences and Research University, New Delhi 110017.
National Research Professor, Founder Vice Chancellor, Department of Clinical Research, Delhi Pharmaceutical Sciences and Research University New Delhi.

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***Corresponding Author**
Ayasha Parveen
Delhi Pharmaceutical Sciences and Research University, New Delhi 110017.

ABSTRACT

Measurement of blood pressure in the clinic may provide a false impression of blood pressure control. Ambulatory blood pressure monitoring (ABPM) allows the automatic recording of the circadian variation in blood pressure and evaluation of the efficacy of antihypertensive medication throughout the dosing interval. Ambulatory blood pressure provides more effective prediction of cardiovascular risk; blood pressure control at the time of heightened risk. Telmisartan, an angiotensin II receptor blocker, as well as having a terminal elimination half life of 24hrs, has a large volume of distribution due to its high lipophilicity. Telmisartan comes under the class of angiotensin receptor blockers (ARBs) and it is used for the treatment of high blood pressure, it reduces the risk of heart attack, stroke, or death from cardiovascular diseases, it is an angiotensin II receptor antagonist (ARB) that was used in the management of hypertension.

KEYWORDS: Angiotensin II receptor blocker, antihypertensive, cardiovascular disease, hypertension and telmisartan.

INTRODUCTION

High blood pressure is divided into two categories primary and secondary blood pressure. In primary there are 90-95% cases, because of nonspecific lifestyle like excess use of salt, regular smoking, alcohol consumption etc. The rest of 5-10% cases come under secondary blood pressure which is due to any causes like chronic kidney disease, and endocrine disorder etc.

Blood pressure is measured in two forms systolic and diastolic pressures which expressed the maximum and minimum pressures, respectively. For most people, normal blood pressure range is within the 100-130 millimeters mercury (mmHg) that is systolic and 60-80mmHg was diastolic. For most peoples, high blood pressure is expressed by the persistent at or increases 130/90 or 140/90mmHg. Ambulatory blood pressure monitoring found out more accurate than office-based blood pressure measurement after continuous measurement of 24-hours.

To minimize the risk factor and complications against health, it is important to change our lifestyle. Changing the lifestyle like: avoid junk foods, intake small amount of salt, regular exercise, no consumption of alcohol etc. If these changes are not sufficient to control or minimize blood pressure than used blood pressure controlling medications. the moderately high arterial blood pressure (defined as >160/100 mmHg) treats with medications is also associated with an improved life anticipation. The 16-37% of the population globally affects by High blood pressure. The 18% of all deaths (9.4 million globally) was due to hypertension in 2010.

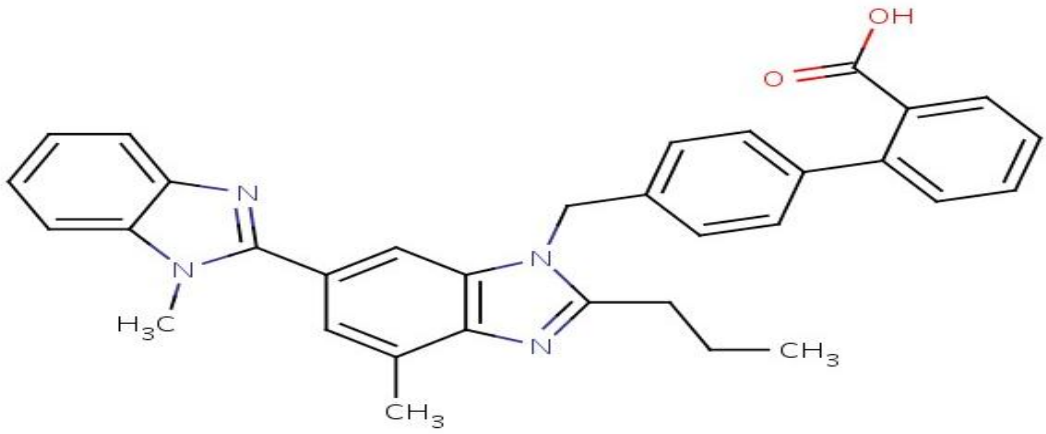
World Health Report 2002, describes that the largest cause of death and disability by 2020 in India will be cardiovascular diseases (CVD). In 2020 AD, set prediction was 2.6 million Indians die due to coronary heart disease that was constitutes 54.1% of all CVD deaths. Half percentages of the deaths are nearly to occur in middle and young aged peoples (30-69 years). Currently Indians experience CVD deaths at least a decade earlier than their counterparts in countries with established market economies (EME). 52% of CVD deaths occur below the age of 70 years in India as compared to 23% in EME as the study conducted by the GBD (Global Burden of Disease), resulting in a profound adverse impact on its economy. The contributing factors in cardiovascular disease especially hypertension, dyslipidemia, diabetes, overweight or obesity, physical inactivity and tobacco use. Through proper care of health, lifestyle and environment, it is an area where major health gains can be made.

Pharmacological properties of telmisartan

Telmisartan comes under the class of angiotensin receptor blockers (ARBs) and it is used for the treatment of high blood pressure, it reduces the risk of heart attack, stroke, or death from cardiovascular diseases, it is an angiotensin II receptor antagonist (ARB) that was used in the management of hypertension. It binds to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle,

ultimately leading to a reduction in arterial blood pressure. A recent study suggests that telmisartan may also have PPAR-gamma agonistic properties that could potentially confer beneficial metabolic effects.

Structure



[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl]methyl] 1,1 'biphenyl]– 2 carboxylic acid.

Molecular Formula:- $C_{33}H_{30}N_4O_2$

Molecular Weight:- 514.61

Description:- White to off-white crystalline powder.

Melting range:- Between 265.0^{o}C and 272.0^{o}C

Solubility:- Practically insoluble in water, slightly soluble in methanol, sparingly soluble in methylene chloride, it dissolves in 1M sodium hydroxide.

Partial coefficient:- The Octanol/buffer partial coefficient (log P) for Telmisartan is approximately 3.20

Storage & Stability:- Stored in well-closed, light-resistant containers at 5-30°C. When stored under these conditions, Telmisartan generally is stable for 24 months after the date of manufacture.

Indication: - For the treatment of hypertension.

Clinical pharmacology

Telmisartan is an orally active nonpeptide angiotensin II antagonist that acts on the AT_1 receptor subtype. New studies suggest that telmisartan may also have PPARγ agonistic properties that could potentially confer beneficial metabolic effects. This observation is currently being explored in clinical trials. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan works by blocking the vasoconstrictor and aldosterone secretory effects of angiotensin II.

Mechanism of Action

Telmisartan interferes with the binding of angiotensin II to the angiotensin II AT_1-receptor by binding reversibly and selectively to the receptors in vascular smooth muscle and the adrenal gland. As angiotensin II is a vasoconstrictor, which also stimulates the synthesis and release of aldosterone, blockage of its effects results in decreases in systemic vascular resistance. Telmisartan does not inhibit the angiotensin converting enzyme, other hormone receptors, or ion channels.

Pharmacokinetic properties

Absorption

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50%. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6% (40 mg dose) to approximately 19% (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

Linearity/non-linearity

The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. C_{max} and to a lesser extent AUC increase disproportionately at doses above 40 mg.

Distribution

Telmisartan is largely bound to plasma protein (>99.5%), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (Vdss) is approximately 500.

Biotransformation

Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Elimination

Telmisartan is characterized by biexponential decay pharmacokinetics with a terminal eliminate ion half-life of >20 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.

After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faces, mainly as unchanged compound. Cumulative urinary excretion is <1% of dose. Total plasma clearance (Cltot) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

Toxicity

Intravenous LD_{50} in rats is 150-200 mg/kg in males and 200 to 250 mg/kg in females. Acute oral toxicity is low: no deaths and no changes occurred in rats or dogs at 2000 mg/kg, the highest dose tested. Limited data are available with regard to over dosage in humans. The most likely manifestations of over dosage with telmisartan would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.

Protein Binding

Highly bound to plasma proteins (>99.5%), mainly albumin and a1-acid glycoprotein. Binding is not dose-dependent.

Biotransformation

Minimally metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Dosage and Administration

The usually effective dose telmisartan is 40–80 mg once daily. Some patients may already benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, telmisartan dose can be increased to a maximum of 80 mg once daily.

Contraindications

Telmisartan is contraindicated during pregnancy. Like other drugs affecting the renin angiotensin system (RAS), telmisartan can cause birth defects, stillbirths, and neonatal deaths. It should not be taken by breastfeeding women since it is not known whether the drug passes into the breast milk.

Side effects

Side effects are similar to other angiotensin II receptor antagonists and include tachycardia and bradycardia (fast or slow heartbeat), hypotension (low blood pressure), edema (swelling of arms, legs, lips, tongue, or throat, the latter leading to breathing problems), and allergic reactions.

CONCLUSION

Elevated blood pressure is associated with cardiovascular risk, it is crucial that antihypertensive medication controls blood pressure to minimize the risk. Unfortunately some antihypertensive gives once daily may not fulfill these requirements and may place the patient at increased risk. The ARB with the longest half life is telmisartan. It binds to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure.

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