

A Review of Telmisartan in the Treatment of Hypertension

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ABSTRACT

Telmisartan is a potent, long-lasting, nonpeptide antagonist of the angiotensin II type-1 (AT1) receptor that is indicated for the treatment of essential hypertension. It selectively inhibits stimulation of the AT1 receptor by angiotensin II without affecting other receptor systems involved in cardiovascular regulation. Very high lipophilicity a unique feature of telmisartan coupled with a high volume of distribution indicate that the compound offers the clinically important advantage of good tissue penetration. It also activates peroxisome proliferator-activated receptor c (PPAR-c) and increase adiponectin protein content in adipocytes. By this means they may improve insulin sensitivity. It belongs to a class II drug in BCS classification i.e. low solubility and high permeability. One of the major problems with this drug is its low solubility in biological fluids which results into poor bioavailability after oral administration to improve the aqueous solubility and dissolution rate of the telmisartan solid dispersions of drug using different methods were prepared and investigated. Enhancement of solubility of Telmisartan was observed with solid dispersion of drug using carriers such as Poly vinyl pyrrolidonek30, Poly ethylene glycol-4000 and β -Cyclodextrin, poly ethylene glycol 6000, alkalizers, Gelucire 43/01, Poloxamer 407, PVP K30 and HPMC E4, PEG 6000 and NaHCO₃. The observed results showed the solid dispersion of drug greater than the pure drug.

I. INTRODUCTION

The renin-angiotensin system plays an important role in the development and maintenance of hypertension and hypertensive heart disease. Blockade of angiotensin II (AII) receptors represent a logical approach to the selective inhibition of the pressor response of the renin-angiotensin system and therefore to the reduction of blood pressure. 1 Angiotensin receptor blockers (ARBs), which antagonize angiotensin II type 1

(AT1) receptors, are among the most popular classes of drugs used in the treatment of hypertension. Moreover, ARBs are also increasingly prescribed for other indications, such as heart failure and diabetic nephropathy. The use of angiotensin converting enzyme inhibitors and, because of their better tolerability angiotensin II type 1 antagonists (Angiotensin receptor blockers [ARBs]) has largely increased. 2, 3 Telmisartan was identified as a direct receptor antagonist. On this basis telmisartan was expected to possess therapeutic potential in the pharmacotherapy of hypertension. The results presented here established that telmisartan is a potent and selective antagonist for the AT1 receptor subtype. Telmisartan exerts potent and sustained antagonism of AII-mediated pressor responses in vivo and effectively lowers blood pressure in animal models of hypertension as well as in humans. The hypotensive effects are of long duration. The compound exhibits favorable effects on renal function in laboratory animals and is not associated with significant ancillary pharmacological effects and limited clinical suggest the potential superiority of telmisartan over losartan 50 mg once daily. 1, 4 Angiotensin can promote insulin resistance; thus, any approach leading to a decreased concentration (angiotensin-converting enzyme inhibitors) or effect (ARB) of angiotensin may result in improved insulin sensitivity. Furthermore, it has been proposed that some ARBs act as partial activators of peroxisome proliferator-activated receptor c (PPARc) at concentrations that are achieved with the recommended oral doses for antihypertensive treatment.

Predicted Properties Of Telmisartan:

Chemical Formula: C₃₃H₃₀N₄O₂

Water solubility 3.50e-03 g/l

LogP6.66

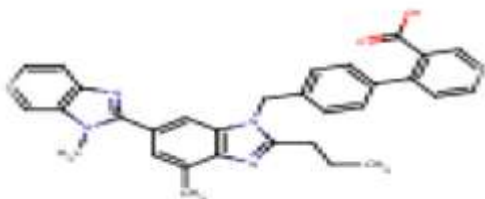
LogP6.04

Logs -5.2

PKa 0

Hydrogen acceptor count 4

Hydrogen donor count1
Polar surface area72.94
Rotatable bond count 7
Refractivity164.49
Polarizability58.61



Structure of TELMISARTAN

Pharmacodynamics:

Telmisartan is an orally active nonpeptide angiotensin II antagonist that acts on the AT1 receptor subtype. It has the highest affinity for the AT1 receptor among commercially available ARBS and has a minimal affinity for the AT2 receptor. New studies suggest that telmisartan may also have PPAR γ agonistic properties that could potentially confer beneficial metabolic effects, as PPAR γ is a nuclear receptor that regulates specific gene transcription, and whose target genes are involved in the regulation of glucose and lipid metabolism, as well as anti-inflammatory responses. 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.

Pharmacokinetics and Metabolism:

Approximately 50% is absorbed following an oral dose with peak plasma concentrations measured at 0.5 – 1 h⁹. Trough plasma telmisartan concentrations are 10 – 25% of the peak levels with once-daily dosing. Bioavailability increases in a dose-dependent fashion from 42 to 58% for doses between 40 – 160 mg. More than 99% of telmisartan are plasma protein-bound to albumin and α -1 glycoprotein. Of this, more than 80% reflects the parent compound, with the remainder being the glucuronide conjugate of Telmisartan⁹,

10 Following an oral dose, nearly all (> 98%) is excreted unchanged in faeces via the biliary system, with urinary excretion accounting for < 1% of the dose.⁹ Clearance of an oral dose is related to age, dose, alcohol consumption and hepatic impairment, but not to serum creatinine or smoking history.¹¹ Telmisartan is not metabolized by the cytochrome P450 system, and hence interactions with other drugs are uncommon. This is an advantage in the elderly, who are often receiving multiple medications, which increases the risk for adverse drug interactions. Dose adjustments are not usually required in the elderly unless there is plasma volume depletion.¹² In mild to moderate hypertensive patients, the terminal half-life is 24 h, which is longer than all other ARBs on the market currently.

Mechanism of Action:

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. Studies also suggest that telmisartan is a partial agonist of PPAR γ , which is an established target for antidiabetic drugs. This suggests that telmisartan can improve carbohydrate and lipid metabolism, as well as control insulin resistance without causing the side effects that are associated with full PPAR γ activators.

Telmisartan clinical trials:

1). Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPAR- γ -modulating activity:

Telmisartan was the only ARB that caused substantial activation of PPAR- γ . Telmisartan functioned as a moderately potent, selective PPAR- γ partial agonist, activating the receptor to 25–30% of the maximum level achieved by the full agonists rosiglitazone and pioglitazone. Telmisartan also increased the expression of known PPAR- γ target genes and induced adipogenesis in pre-adipocyte fibroblasts. Administration of telmisartan to rats caused a significant attenuation of weight gain compared with losartan and controls (~10%). This could not be attributed to reduced energy intake as food intake was nearly identical in all treatment groups. Serum glucose levels significantly decreased after 5 weeks of treatment with telmisartan compared with both losartan ($p < 0.01$) and controls ($p < 0.001$). Serum insulin levels also tended to be lower in telmisartan-treated rats (0.05

< $p < 0.10$). Serum triglycerides were significantly decreased in the telmisartan treated group compared with both the losartan group ($p < 0.05$) and controls ($p < 0.01$). During the oral glucose tolerance test, serum glucose levels were similar between all three treatment groups. However, serum insulin levels were significantly lower in the telmisartan group compared with the losartan and control groups. Losartan did not have any significant effects on any of the parameters measured when compared with controls.¹³ PPAR- γ activation reduces oxidative stress and inflammatory response in the vasculature and adipose tissue therefore, telmisartan has been expected to have a dual action for preventing atherosclerosis and metabolic disorders.

2). Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor activity:

Telmisartan and irbesartan potently enhanced lipid accumulation, and increased PPAR- γ -dependent 3T3-L1 adipocyte differentiation, as shown by a significant increase in mRNA expression of the adipogenic marker gene adipose protein 2 (aP2) (irbesartan 10 $\mu\text{mol/L}$, 3.3-fold induction; telmisartan 10 $\mu\text{mol/L}$, 3.1-fold induction; both $p < 0.01$). There was a more pronounced induction of aP2 expression at lower, pharmacologically relevant concentrations with telmisartan, compared with the other ARBs. In contrast, losartan enhanced aP2 expression only at high concentrations (losartan 100 $\mu\text{mol/L}$: 3.6-fold induction; $p < 0.01$). Eprosartan at concentrations $\leq 100 \mu\text{mol/L}$ had no significant effects. Irbesartan and telmisartan (10 $\mu\text{mol/L}$) markedly induced PPAR- γ transcriptional activity, by 3.4-fold and 2.6-fold ($p < 0.05$), respectively, compared with 5.2-fold stimulation by the PPAR- γ ligand pioglitazone 10 $\mu\text{mol/L}$.

3 An angiotensin II AT1 receptor antagonist, telmisartan augments glucose uptake and GLUT4 protein expression in 3T3-L1 adipocytes:

Higher concentrations (1 and 10 $\mu\text{mol/L}$), but not 0.1 $\mu\text{mol/L}$, of telmisartan facilitated differentiation of 3T3-L1 cells. However, Valsartan had no effect on adipogenesis, even at a concentration of 10 $\mu\text{mol/L}$. As expected, pioglitazone 1 $\mu\text{mol/L}$ facilitated pre-adipocyte differentiation. Treatment of both differentiating adipocytes and fully differentiated adipocytes with telmisartan 10 $\mu\text{mol/L}$ caused an increase in mRNA levels for PPAR- γ target genes such as aP2 and adiponectin. Valsartan did not augment expression of PPAR- γ target genes in either

differentiating or mature adipocytes. Gene expression of 11 γ -HSD1 was not changed by the compounds during differentiation of 3T3-L1 cells, but was significantly decreased by telmisartan 10 $\mu\text{mol/L}$, but not Valsartan, in differentiated adipocytes. Telmisartan 1 or 10 $\mu\text{mol/L}$ significantly increased glucose uptake in differentiated 3T3-L1 adipocytes in the presence or absence of insulin. Valsartan did not affect glucose uptake.

Furthermore, Western blot analyses showed that GLUT4 protein expression was significantly enhanced (compared with vehicle) when cells were differentiated with telmisartan 1 or 10 $\mu\text{mol/L}$.

4). Telmisartan is a dual ARB and PPAR gamma activator that limits weight gain, body fat accumulation, and adipocyte size in rats fed a high fat, high carbohydrate diets:

Preclinical studies have suggested that the acetyl-CoA carboxylase 2 (ACC2) gene plays an essential role in controlling fatty acid oxidation. ACC2-deficient mice fed a high-fat, high-carbohydrate diet has a higher fatty acid oxidation rate, accumulate less fat and live a normal lifespan compared to wild-type mice which develop diabetes when given the same diet. It is hypothesized that telmisartan may suppress the ACC2 gene and that this may explain its effects on weight gain. This study investigated the mechanism by which telmisartan attenuates weight gain in rats fed a high-fat, high carbohydrate. The current findings suggest that telmisartan attenuates diet induced weight gain by limiting fat accumulation, possibly by increasing fatty acid oxidation through suppression of ACC2.

5). Insulin-sensitizing effects of telmisartan: Implications for treating insulin-resistant hypertension and cardiovascular disease:

The patient's insulin resistance and triglyceride levels improved on telmisartan, but deteriorated when switched to Valsartan, an angiotensin II type 1 receptor blocker that does not activate peroxisome proliferator-activated receptor- γ (PPAR- γ). Body weight, total cholesterol, HDL cholesterol and LDL cholesterol remained unchanged throughout the observation period.

6). Safety of telmisartan in patients with arterial hypertension: an open-label observational study:

Seventy-six percent of patients achieved a full response to treatment (diastolic BP $\leq 90\text{mm Hg}$ or $\geq 10\text{mm Hg}$ reduction) and 22% had an inadequate response to telmisartan therapy

(diastolic BP > 90mm Hg or < 7mm Hg reduction). Overall, heart rate was reduced from 78.0 to 73.8 beats/min after 6 months of treatment. The dosage was increased in 24% of patients because of the insufficient BP reduction with the lower dosage. Global tolerability was rated as very good, good, moderate or poor in 75%, 22%, 1% and 1% of patients, respectively. There were no significant differences in global tolerability ratings between the patient groups. Telmisartan had only a minor or no effect on serum creatine levels across all patient groups. Serious adverse events were reported in 0.06% of patients and included death in 6 patients. None of the deaths were considered drug-related.

7). Effects of telmisartan compared with eprosartan on blood pressure control, glucose metabolism and lipid profile in hypertensive, type 2 diabetic patients: a randomized, double-blind, placebo-controlled 12-month study:

End of treatment trough diastolic BP was significantly lower with telmisartan compared with eprosartan ($p < 0.05$). Systolic BP was significantly reduced from baseline after 6 months of treatment with telmisartan or eprosartan ($p < 0.05$). In addition, systolic BP after 6 months was significantly lower in both groups compared with placebo ($P < 0.05$). Total cholesterol, triglycerides and LDL cholesterol were significantly reduced from baseline after 6 months treatment with telmisartan ($p < 0.05$). There were no significant changes in body mass index, the proportion of glycosylated hemoglobin, fasting plasma glucose, fasting plasma insulin or insulin sensitivity compared with baseline in any of the treatment groups at 6 or 12 months, and no significant differences in values between treatment groups.

8) Comparison of the effects of telmisartan and nifedipine gastrointestinal therapeutic system on blood pressure control, glucose metabolism, and the lipid profile in patients with type 2 diabetes mellitus and mild hypertension:

A 12-month, randomized, double-blind study: In this selected sample of patients with type 2 diabetes and mild hypertension, 12 months of treatment with telmisartan conferred a slight but statistically significant advantage in terms of plasma lipid control compared with nifedipine GITS.

9) Comparative effect of telmisartan and losartan on glucose metabolism in hypertensive patients with the metabolic syndrome:

Telmisartan, unlike losartan, improves

glucose metabolism in patients with metabolic syndrome and hypertension. Telmisartan administration for 3 months improves fasting FPG [fasting plasma glucose], post-prandial FPG, insulin sensitivity and HbA1c. The insulin-sensitizing actions of telmisartan may be due to its partial PPAR γ agonism. Telmisartan produces significantly greater 24-h means ambulatory blood pressure reductions than lisin. Telmisartan, therefore, offers a useful treatment option for patients with hypertension and glucose intolerance²¹ and patients with IGT telmisartan compared to losartan improved endothelial function and insulin resistance independently, supporting the hypothesis that glucometabolic and vascular insulin resistance are differentially regulated.

10) Replacement of Valsartan and condensation by telmisartan in hypertensive patients with type 2 diabetes:

Metabolic and antiatherogenic consequences: Telmisartan has additional effects on insulin sensitivity and antiatherosclerosis, probably via its effects on PPAR- γ . These findings offer a new idea for the drug targeted to defend against type-2 diabetes with accompanying metabolic disorder.

11) Telmisartan: an angiotensin II receptor antagonist with selective PPAR- γ activity:

A cell-based transactivation assay showed that telmisartan was a moderately potent, selective PPAR- γ agonist, activating the receptor to 25–30% of the maximum level achieved with pioglitazone and rosiglitazone. Irbesartan caused slight PPAR- γ activation, while candesartan Cilexetil, Valsartan, olmesartanmedoxomil, aprelintin and losartan had minimal PPAR- γ agonist activity. In addition, only telmisartan induced adipogenesis and influenced the expression of a number of genes involved in adipocyte differentiation. Telmisartan also attenuated weight gain and modestly improved glucose, insulin and triglyceride levels compared with losartan and placebo in rats fed a high-fat, high-carbohydrate diet.

12) Telmisartan – killing two birds with one stone: ARBs and PPAR-agonism:

In one study, both telmisartan and irbesartan increased lipid accumulation in mouse 3T3-L1 preadipocytes. The expression of the adipose protein 2 gene, an adipogenic marker, was also increased with telmisartan, and high concentrations of irbesartan and losartan. The effects of telmisartan and irbesartan on PPAR- γ were not mediated by AT1, as these agents were

shown to increase PPAR- γ activity in cells lacking AT1 receptors. Another study demonstrated that telmisartan at concentrations of 1 and 5 $\mu\text{mol/L}$ and irbesartan $\geq 10 \mu\text{mol/L}$, but not candesartan Cilexetil, Valsartan, olmesartanmedoxomil or eprosartan, induced differentiation in 3T3-L1 pre-adipocytes. In addition, telmisartan increased the expression of the adipogenic marker gene, adipose protein 2, in mouse pre-adipocytes.

13) Effects of telmisartan on proteinuria or albuminuria: A meta-analysis of randomized trials:

Based on a meta-analysis of 20 randomized controlled trials including >25,000 patients, telmisartan therapy is likely effective in the improvement of proteinuria/albuminuria or in the prevention of progression in proteinuria/albuminuria.

14) Telmisartan reduced abdominal circumference and body weight to decreasing triglyceride level in patients with type 2 diabetes and Metabolic syndrome:

Telmisartan is expected to provide beneficial effects for glucose and lipid metabolism without causing obesity. In the present study, we examined the effects of Telmisartan in patients with type-2 diabetes and metabolic syndrome. Thirty-two patients enrolled in this study were administered 40 mg per day of Telmisartan for 6 months. Telmisartan treatment significantly reduced systolic and diastolic blood pressure accompanied by induction of plasma renin activity (PRA) and reduction of serum aldosterone concentration and significantly decreased waist circumference, body mass index (BMI), and triglycerides (TG). In the 16 patients who did not take sulfonylurea, fasting plasma glucose (FPG) decreased and HbA1c significantly decreased from 3 months to 6 months. The results provide evidence that Telmisartan may improve glucose and lipid metabolism with the reduction in visceral fat mass in patients with type-2 diabetes and metabolic syndrome.

Solubility Enhancement of Telmisartan

Telmisartan belongs to class II drug in BCS classification i.e. low solubility and high permeability. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. The solubility of Telmisartan in aqueous medium was very low i.e. 0.078 mg/ml in water. Absolute bioavailability of the Telmisartan was 42-58% and biological half-life is only 24

hours that results into poor bioavailability after oral administration. Poor solubility of Telmisartan leads to poor dissolution and hence variation in bioavailability. Thus increasing aqueous solubility and dissolution of Telmisartan is of therapeutic importance. The solid dispersion is a technique to achieve this goal particularly the poor aqueous soluble drugs in which the drug is incorporated into the water soluble polymeric matrix.

A. Solid dispersion with different carriers and different methods:

1. B-cyclodextrin
2. Pvp k30
3. PEG 4000

Preparation of physical mixtures:

Accurately weighed quantities of the drug and the carrier were weighed taken in a glass mortar were mixed thoroughly. The resultant mixture was passed through sieve number 100 # and was stored in desiccators for the complete removal of moisture and was tested for the content uniformity. Drug: polymerratios of 1:1, 1:2 and 1:4 were prepared.

Preparation of inclusion complexes with carriers:

a. Solvent evaporation technique –

In this method the drug and carriers are used in different ratios [1:1, 1:2, 1:4]. The respective amount of carrier was dissolved in methanol (20ml) and Telmisartan was added in parts with continuous stirring. The solvent was then removed by evaporation. The prepared dispersions were pulverized and sifted through 100 # and stored in desiccators for further studies.

b. B Kneading Method-

In this method the drug and carriers are used in different ratios [1:1, 1:2, 1:4] Both drug and carrier was triturated by using a small volume of ethanol and water(1:1) to give a thick paste, which was kneaded upto 60 minutes and then kept for air dry. Then the dried mass was scratched and pulverized and sifted through 100# and stored in desiccators for further studies.

B. Solid dispersion of Telmisartan using NaHCO₃ by Hot Melt method:

SDs containing equalizer could be a useful method to increase the dissolution rate of an ionizable drug like TEL in a pH-dependent manner. It was evident that the alkalizer in PEG 6000 based SDs synergistically enhanced dissolution of TEL not only by modulating pH but also by changing

drug crystallinity to an amorphous form via molecular interactions. The alkaliser used to modify the pH of TEL was NaHCO₃, in the solid dispersion (SD) system significantly increased the drug dissolution rate in gastric fluid (pH 1.2). A significant enhancement in solubility and dissolution rate was seen when polymers were used in the ratio of 1:400 (NaHCO₃: PEG6000).

C. Solid dispersion of Telmisartan by Fusion method with polymers like Gelucire 43/01, Poloxamer 407, PVP K-30 and HPMC E4 and PEG 6000:

Accurately weighed amounts of carrier were placed in an aluminum pan on a hot plate and melted, with constant stirring, at a temperature of about 60°C. An accurately weighed amount of Telmisartan was incorporated into the melted carrier(s) with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained. The pan was then removed from the hot plate and allowed to cool at room temperature. It was then scrapped, dried and was passed through sieve no. 60 and stored in a desiccator until further evaluation. The increase in dissolution rate is in the order of: PXM 407 >Gelucire 43/01> HPMC E4 >PVP K30 >PEG 6000. The dissolution rate of Telmisartan in solid dispersion was strongly dependent on the relative concentrations of the carrier. As the concentration of the carrier in the solid dispersion increased, the dissolution rate also increased. This may be attributed to the increase in the wettability, conversion to amorphous form and solubilisation of the drug due to hydrophilic carrier and solubilizing effect of surfactants.

D. Solid dispersion of Telmisartan by Hot melts method with KOH and peg 6000:

Solid dispersion of telmisartan on peg was obtained by the hot melt method. Telmisartan: equalizer: pug mix containing 10:1:200, 10:1:400, 10:1:600 were heated to 100°C with constant stirring. The telmisartan was miscible in the peg melt in all proportions with equalizer. The melt was allowed to cool and solidify at room temperature and then stored at 4°C. The solid product was grounded in a motar at room temperature and then sieved (105- 250#) A significant enhancement in solubility and dissolution rate was seen when polymers were used in the ratio of 1:400 (KOH: PEG 6000).

II. SUMMARY

Telmisartan is a potent, insurmountable AII receptor antagonist that shows high specificity for the AT1 receptor subtype. Among the AII receptor antagonists, telmisartan exhibits the highest partition coefficient, reflecting high lipophilicity and extensive penetration into target tissues and organs. In clinical studies in hypertensive patients, telmisartan was shown to reduce blood pressure more effectively than the AII-receptor antagonist, losartan, and lowered blood pressure to the same extent as members of other major antihypertensive drug classes, such as ACE inhibitors, receptor blocking agents and calcium antagonists. In common with other sartans, telmisartan offers placebo-like Safety and tolerability in hypertensive patients. Telmisartan's pharmacological profile, including a long elimination half-life, results in an excellent trough: peak ratio and sustained control of blood pressure throughout the once-daily dosing interval.

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