Journal of Advanced Zoology
ISSN: 0253-7214
Volume 45 Issue 4 Year 2024 Page 09-14

A Review On Safety And Tolerability Of Telmisartan

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Abstract:
Essential hypertension can be treated with telmisartan, a strong, long-acting nonpeptide antagonist of angiotensin II type-1 (AT1) receptor. Without influencing other receptor systems involved in the regulation of the cardiovascular system, it specifically blocks the activation of the AT1 receptor by angiotensin II. When combined with high volume of distribution and telmisartan's distinctively high lipophilicity, the molecule provides the clinically significant benefit of strong tissue penetration. Additionally, it causes an increase in the protein level of adiponectin in adipocytes and activates peroxisome proliferator-activated receptor c (PPAR-c). They might increase insulin sensitivity in this way. According to the BCS classification, it is class II medication because of its high permeability and low solubility. To increase the telmisartan solid dispersion's aqueous solubility and dissolution rate, various techniques were prepared and studied. One of the main issues with this medication is its low solubility in biological fluids, which leads to poor bioavailability after oral administration. Telmisartan's solubility was shown to be enhanced when the medication was dispersed solidly utilizing carrier such poly vinyl pyrrolidonek30, poly ethylene glycol 6000, βeta-cyclodextrin, Gelucire 43/01, Poloxamer 407, PVP K30 and HPMC E4, PEG 6000, and NaHCO3.

Keywords: Telmisartan, Angiotensin, Solubility, Pharmacokinetic, Pharmacodynamic activity.

INTRODUCTION

The development and maintenance of hypertension and hypertensive heart disease are significantly influenced by the renin-angiotensin system. One reasonable strategy for reducing blood pressure and selectively inhibiting the renin-angiotensin system's pressor response is to block angiotensin II (AII) receptor. [3] One of the most widely used pharmacological classes for the treatment of hypertension is angiotensin receptor blockers (ARBs), which work by blocking the angiotensin II type 1 (ATI) receptor. Additionally, ARBs are being recommended

more frequently for other conditions such diabetic nephropathy and heart failure, Due to their superior tolerability, angiotensin II type 1 receptor antagonists (also known as angiotensin receptor blockers, or ARBs) and angiotensin converting enzyme inhibitors have seen a significant increase in use. [1,2] Since telmisartan was found to be a direct-acting antagonist of AII receptor, it was anticipated that it would have therapeutic value in the pharmacotherapy of hypertension. The findings presented here demonstrated that telmisartan is a strong and specific antagonist for the AT1 receptor subtype. It also effectively lowers blood pressure in both human and animal models of hypertension, with long-lasting hypotensive effects. Additionally, the compound has positive effects on renal function in laboratory animals and is not linked to any notable ancillary pharmacological effects. Finally, the limited clinical data suggests that telmisartan may be superior to losartan 50 mg once daily in hypertension.[3,4] Because angiotensin can exacerbate insulin resistance, any strategy that lowers the amount of angiotensin in the body (angiotensin-converting enzyme inhibitor) or its action (ARB) may enhance insulin sensitivity. Additionally, it has been suggested that at concentrations that correspond to the suggested oral dosages for the treatment of hypertension, some ARBs functions as partial activators of peroxisome proliferator-activated receptor c (PPARc).[5,6]

CHEMISTRY:

Telmisartan's chemical formula is [1,1_-biphenyl]-2-carboxylic acid, [2,6_-bi-1H-benimidazol] methyl [4,2_-propyl]. –(CAS) (Figure 1). With a molecular weight of 514.6 and a melting point between 261 and 263°C, it is a white, crystalline powder. Telmisartan's solubility in aqueous solutions is highly pH-dependent, reaching its maximal solubility at both high and low pH values. It is only somewhat soluble in the pH range of 3-9. As such, telmisartan is not functioning as a prodrug. The stability of the telmisartan molecule is atypical. There has been no observation of Phase I- type metabolism. The highest lipophilic AII antagonist is telmisartan, which has a partition coefficient of log P = 3.2 (n-octanol buffer at pH 7.4). Telmisartan exhibits superior tissue penetration and oral absorption as a result of its physiochemical characteristics.[3]

PREDICTED PROPERTIES OF TELMISARTAN:[8]
Chemical Formula: C33H30N4O2
Water solubility: 3.50e-03 g/l
LogP: 6.66
LogP:6.04
Logs: -5.2
PKa: 0
Hydrogen acceptor count: 4
Hydrogen donor count: 1 Polar surface area: 72.94
Rotatable bond count: 7
Refractivity: 164.49
Polarizability: 58.61

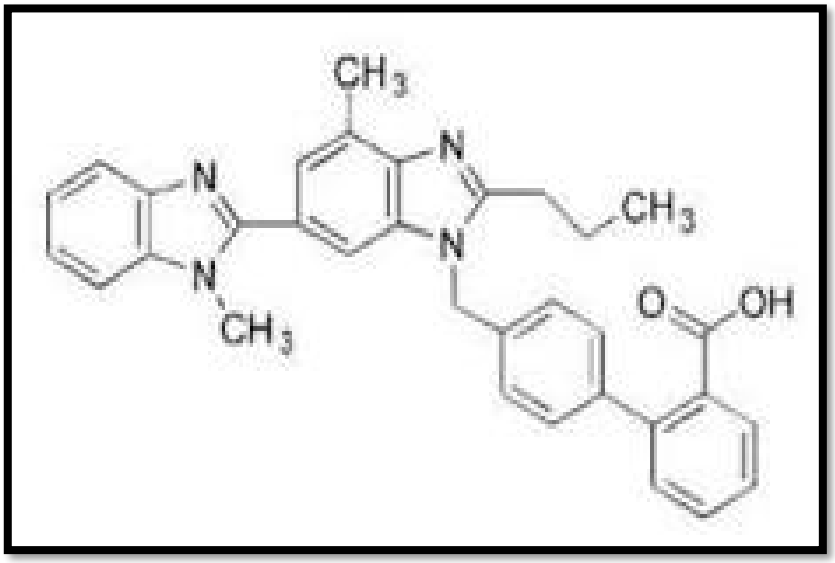

Fig 1: Structure of Telmisartan

PHARMACOKINETICS AND METABOLISM:

After an oral dosage, around half is absorbed, with peak plasma concentrations occurring between 0.5 and 1 hour 9. When telmisartan is taken once daily, the trough plasma concentration range from 10% to 25% of the peak levels. Between 40 and 160 mg, bioavailability rises in a dose-dependent manner from 42 to 58%. Over 99% of telmisartan is attached to albumin and α-1 glycoprotein via plasma proteins. Over 80% of this is the original chemical, and the remaining portion is Telmisartan's glucuronide conjugate.[9,10]
After an oral dose, almost all (>98%) is excreted through the biliary tract in unchanged form with feces and urine and lt;1% of dose[9] Oral dose elimination is related to age, dose, alcohol consumption, and liver impairment, but not to serum creatinine or smoking history[8] Telmisartan is not metabolized by the cytochrome P450 system, so interactions with other drugs are rare. This is an advantage for the elderly, who often take multiple medication, increasing the risk of drug side effects. In the elderly ,no dose adjustment is usually necessary unless plasma volume is reduced. 11 In patients with mild to moderate hypertension, the terminal half-life is 24 hours, which is longer than all ARBs currently on the market.[12]

PHARMACODYNAMICS:

Telmisartan is an oral non-peptide angiotensin II antagonist that acts on the AT1 receptor subtype. It has the highest affinity for the AT1 receptor and the lowest affinity for AT2 receptor of any commercially available ARBS. New studies indicate that telmisartan may also have agonistic properties of PPARγ, which can lead to beneficial metabolic effects, since PPARγ 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 against.-inflammatory responses. This finding is currently being investigated in clinical trials. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kinaseII). Angiotensin II is the main pressor agent of the renin-angiotensin system, whose actions include vasoconstriction, stimulation of aldosterone synthesis and release, cardiac stimulation and sodium reabsorption. Telmisartan works by blocking the vasoconstrictor and aldosterone-secreting effects of angiotensin II.[8,1] Telmisartan does not block angiotensin converting enzyme, other hormone receptor or ion channels. Studies also show that telmisartan is a partial agonist of PPARγ, an established target for antidiabetic drugs. This suggests that telmisartan can improve carbohydrate and lipid metabolism and control insulin resistance without the side effects associated with full PPARγ activators.[8,12]

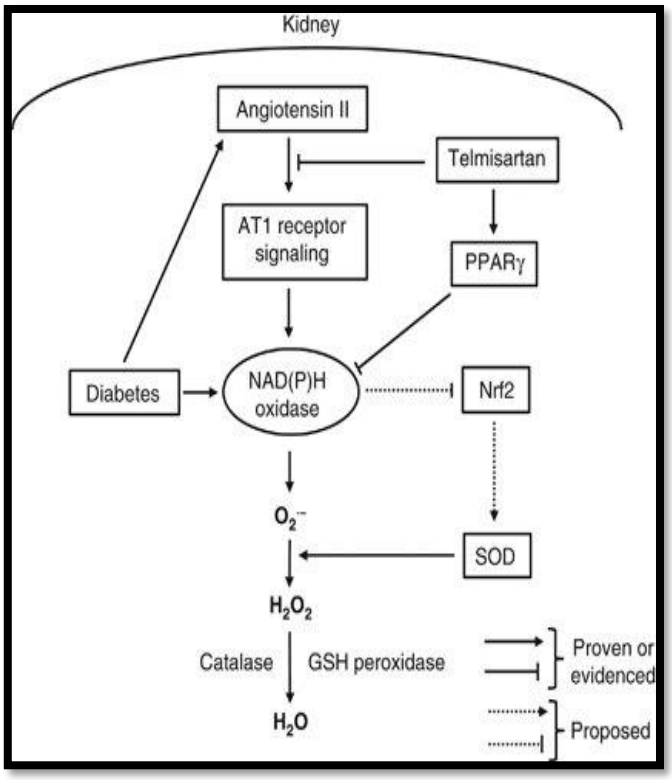

Fig 2: MOA of Telmisartan

TELMISARTAN AND DRUG INTERACTIONS

Drug interaction are an important issue to consider for the safe and appropriate use of drugs. Quantitative data obtained from clinical pharmacokinetic interaction studies provide valuable information for predicting therapeutic efficacy and possible side effects during concomitant therapy. Telmisartan is often used in combination regimens, but so far little is known about the interaction potential of this compound. As mentioned above, interaction of telmisartan with other drugs are unlikely to involve enzymes of phase I metabolism, such as CYP, because the affinity of telmisartan for most CYP isoforms known to be involved in drug metabolism is low.[13,14] However, we and others have found that telmisartan interacts with uptake and efflux transporters important for drugs pharmacokinetics, indicating that telmisartan may cause clinically important drug interactions despite its relatively low biotransformation.[15,16,17] We were able to demonstrate that telmisartan interacts with the dihydropyridine calcium channel blocker nisoldipine, increasing nisoldipine exposure in patients with essential hypertension.[18]

Since nisoldipine, a known substrate of CYP3A4, and telmisartan,which does not affect CYP3A4, do not appear to share phase I biotransformation pathways, the mechanism of this interaction remains unclear, but may involve ATP-binding cassette (ABC) transporters C2 and G2.[17] In contrast, co-administration of telmisartan and the dihydropyridine amlodipine did not show clinically relevant interactions between the two drugs, highlighting the need for clinical drug interaction studies. In addition, co-administration of temilsartan 80mg/day with ramipril 10mg/day resulted in an approximately twofold increase in ramipril bioavailability and peak plasma concentration in healthy subjects. Thus, when telmisartan and ramipril are co-administered, the response may be greater due to the potentially addictive pharmacodynamic effects of the combination drugs as well as the increased exposure of ramipril in the presense of telmisartan. It remains unclear whether this interaction contributed to the increase in renal failure in patients treated with telmisartan and ramipril in the ongoing Telmisartan Alone and Together with Ramipril Global Endpoint (ONTARGET) study.[20] In contrast, co administration of telmisartan with the anticoagulant warfarin, the analgesics ibuprofen and acetaminophen, the thiazide diuretic hydrochlorothiazide (HCTZ), the sulfonylurea derivative glibenclamide, or the HMG-CoA reductase inhibitor simvastatin did not produce a clinically significant pharmacokinetic parameter.

SAFETY AND TOLERABILITY OF TELMISARTAN

The excellent tolerability of telmisartan has been documented in several small and medium-sized clinical trails, large post-making follow-up studies and the recent large multicenter ONTARGET study programs.[21] For example, in a post marketing follow up study of nearly 20,000 hypertensive patients, treatment-related adverse events were reported in 1.9% of patients receiving telmisartan, the most common of which were headache, dizziness, and nausea. In addition, the number of patients with serious adverse events was remarkably low (0.06%).[22] Furthermore, in the ONTARGET trial, study drug discontinuation occurred more often in patients randomized to ramipril than in patients randomized to telmisartan, but more often in patients randomized to combination of both drugs. These data are consistent with results from other much smaller clinical trials where telmisartan is better tolerated than ramipril, lisinopril and enalapril. In addition, data from the ONTARGET trial suggest that the combination of telmisartan and ramipril is associated with an increased incidence of adverse events, but does not provide additional clinical benefits. The TRANSCEND trial demonstrated that telmisartan is tolerable to placebo in ACE-sensitive patients. Interestingly, telmisartan was tolerated even by patients with angioedema during ACE inhibitor therapy. However, approximately 11% of eligible patients were withdrawn from the efficacy phase of TRANSCEND, primarily due to poor compliance, elevated creatinine or potassium levels, symptomatic hypotension, or unspecified reasons. However, these data suggest that telmisartan may be an effective and well-tolerated alternative for patients intolerant to ACE inhibitors.

MARKETED FORMULATIONS OF TELMISARTAN:

Table 1: provides an overview of the marketed formulation of the Telmisartan drug

Brand Name	Dosage Form
Telmizem-40 AM Tablet	Tablet
Relmisart-40	Tablet
Telpride-40	Tablet
Telmisartan Tablet	Tablet
Micardis	Tablet

CONCLUSION

Telmisartan is a highly selective competitive AT1 receptor antagonist with a unique pharmacodynamic profile in the class of AT1 receptor antihypertensive drugs (ARBs) because it additionally activates PPAR-g and improves insulin resistance at clinically relevant concentrations in hypertensive patients. Pharmacokinetically, telmisartan is characterized by the longest half-life and largest volume of distribution of all ARBs and a low rate of biotransformation. However, telmisartan is the only ARB with a clinically significant ability to inhibit ABC transporters, which are important in drug pharmacokinetics and therefore may cause drug interactions through this pathway. Telmisartan has been shown to be as effective as other ARBs and first-line antihypertensive agents in controlling blood pressure. In addition, telmisartan has been shown to be well tolerated at normal doses in many high-risk cardiovascular patient and may lead to more widespread use of the drug to reduce cardiovascular risk in these individuals.

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