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A Review of Telmisartan Angiotensin II Receptor Blocker: Treatment of Hypertension

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ABSTRACT

Telmisartan, a long-acting antihypertensive agent is essential to achieve blood pressure control in the early morning due to its terminal elimination half-life of 24hrs and has a large volume of distribution. According to CBS classification it belongs to class II i.e. low solubility and high permeability. High volume of distribution coupled with high lipophilicity is the unique feature of angiotensin II receptor blocker, it offers the clinical advantage of good tissue penetration. It particularly blocks the angiotensin II receptor without blocking other receptors which are involved in cardiovascular regulation. According to recent data telmisartan 80mg controls early morning blood pressure more effectively than ramipril 5-10mg and has greater effect over cardiovascular risk. It is also more effective than losartan and in addition, angiotensin II blocker provides superior blood pressure control after a missed dose compared with valsartan 80mg.

KEYWORDS: *Angiotensin II Blocker, Antihypertensive, Telmisartan, Cardiovascular Disease, Blood Pressure*

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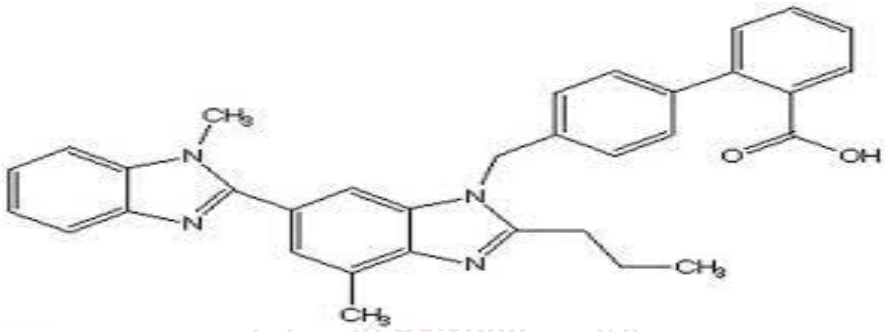
INTRODUCTION

Telmisartan is a direct acting angiotensin II antagonist, it plays an important role in development and maintenance of hypertensive cardiovascular diseases. Moreover, they are also prescribed and highly indicated to heart failure and diabetic nephropathy. The hypotensive effect of telmisartan is for longer duration. The compounds exhibit favorable effects on renal function in laboratory animals. Angiotensin II receptor blocker telmisartan has the longest half-life of about 24hrs so are highly effective antihypertensive agents and are widely regarded as having tolerability profiles similar to that of placebo. It has high tissue penetration, intracellular absorption and bioavailability due to its unique feature of its high lipophilicity property. The high volume of distribution of approximately 500L. Other features that differentiate telmisartan from other angiotensin II receptor blockers candesartan cilexetil, losartan, and Olmesartan is that it is not prodrug; thus, antihypertensive potency is related to activity of the parent compound. The efficacy of telmisartan monotherapy is studied whether the blood pressure control at the end of the once daily dosing interval. In a study comparing telmisartan 40-120mg with the long-acting calcium channel blockers, both treatments produced comparable reductions in clinical blood pressure after 12 weeks in patients with mild moderate hypertension. Telmisartan 80mg displayed superior reduction in last 6hrs mean systolic blood pressure and diastolic blood pressure compared with ramipril 10mg after 14 weeks. 40mg or 80mg Telmisartan when compared with losartan 50mg demonstrated superior control of both SBP and DBP during last 6hrs of the dosing interval.

Telmisartan is a non-peptide molecule, chemically described as 4'-[(1, 4'-dimethyl-2'-propyl [2, 6'-bi-1H-benzimidazol]-1'-yl) methyl]-[1, 1'-biphenyl]-2-carboxylic acid.

Some patients may 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. Telmisartan is a white to slightly yellowish solid. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base. Literature survey revealed that there were many methods like Spectrophotometry using first order derivative Simultaneous equation, RP-HPLC and LC–MS/MS and HPTLC for determination of Telmisartan with alone and with other drugs in combination have been reported. As the analysis is an important component in the formulation development of any drug molecule. Hence there is a need to develop a simple, sensitive, accurate, precise, reproducible method for the estimation of drug samples. Our main concern is development and validation of UV spectrophotometric method as per ICH guidelines

Chemical Structure:-



CHEMISTRY:-

Chemical formula for telmisartan is (C33 H30 N4 O2)

Hydrogen acceptor count = 4

Hydrogen donor count = 1

Water solubility = 3.50e-03g/L

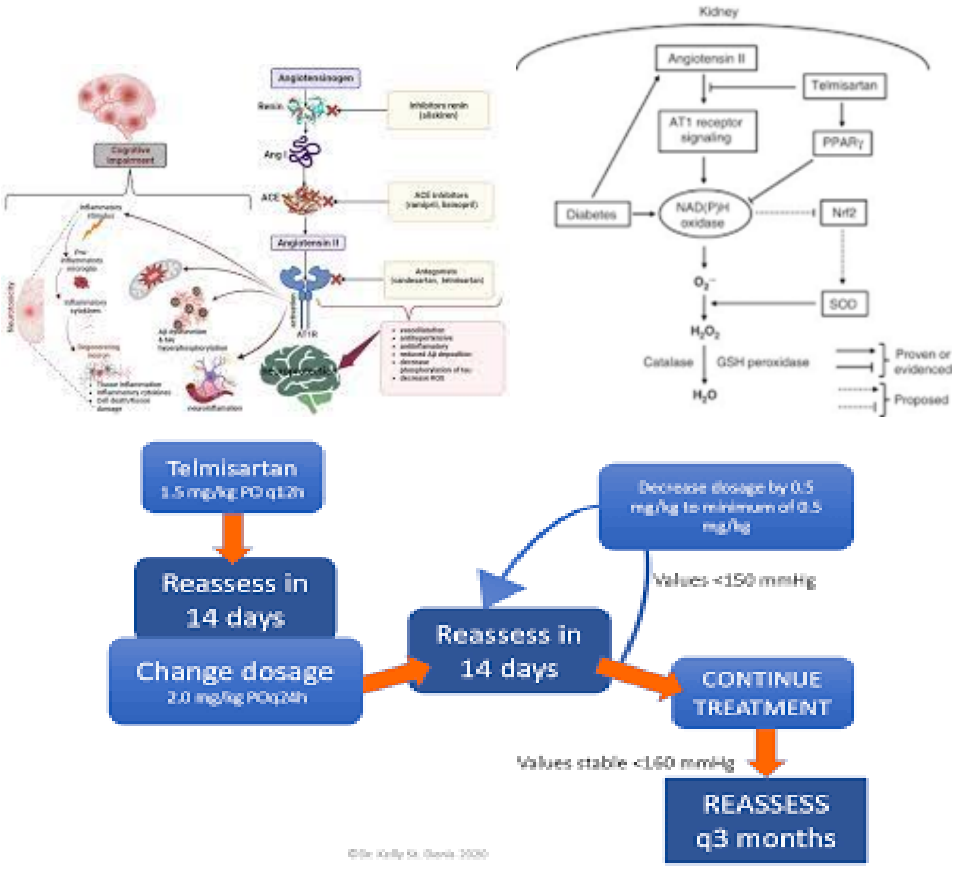
Telmisartan is a white crystalline powder with a molecular weight of 514.6 and a melting point of about 261-to-263-degree Celsius. Telmisartan is acting, as such it is not a prodrug, and it shows excellent oral absorption and tissue penetration Due to its physiochemical properties. Telmisartan is the most lipophilic compound with a partition coefficient log P = 3.2(n-octanol buffer at PH 7.4). Telmisartan is chemically described as 4'- [(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl) methyl]- [1,1' -biphenyl]-2-carboxyclic acid (Micardis) does not appear to bear any structural relationship to this class, but there is actually an agent. The acidic tetrazole system is replaced by carboxylic acid. This acid plays an important role in receptor binding. telmisartan in aqueous solution is strongly PH- dependent, with maximum solubility observed at high and low. Telmisartan is an orally active peptide angiotensin II antagonist that acts on the angiotensin receptor subtype

Stability

characterized telmisartan 1-O-acylglucuronide as the principal metabolite of telmisartan in humans, in terms of chemical stability and the structure of its isomerization products was elucidated. In addition, pharmacokinetics of telmisartan 1-O-acylglucuronide was assessed in rats after i.v. dosing. Similar to other acylglucuronides, telmisartan 1-O-acylglucuronide and diclofenac 1-O-acylglucuronide, which was used for comparison, showed the formation of different isomeric forms.

MECHANISM OF ACTION

Telmisartan interferes with the binding of angiotensin II to the angiotensin II AT1 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 effect results in decreases in systemic vascular resistance. Study also suggests that telmisartan is partial agonist of PPAR gamma, 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 activators. Telmisartan does not inhibit the angiotensin converting enzyme other hormone receptors, or ion channels.



Telmisartan is a vasodilator that functions as an angiotensin II receptor blocker (ARB). Angiotensin II acts primarily on the type 1 and type 2 receptors, but telmisartan has high affinity and selectivity for the angiotensin II subtype 1 (AT-1) receptor and preserves the beneficial effects from the AT-2 subtype (angiotensin II, subtype 2 receptor). Compared with angiotensin-converting enzyme (ACE) inhibitors, it directly blocks the receptor, rather than inhibits synthesis of angiotensin II. Angiotensin II is produced in animals with heart disease and kidney disease and in response to an activated renin–angiotensin–aldosterone system (RAAS). Telmisartan has a long binding affinity for the angiotensin II receptor, producing long-lasting effects and is capable of blocking the AT-1 receptor, regardless of the source of angiotensin; therefore it is effective in states of angiotensin breakthrough. Telmisartan and other ARBs have been used in people who cannot tolerate ACE inhibitors. ARBs have the advantage of being less likely to induce hyperkalemia and are more easily tolerated in people.

In cats, telmisartan has an approved indication for treating hypertension in cats and has been shown to be superior to ACE inhibitors for this use. It was approved for use in cats by the FDA in May 2018. Hypertension in cats is a common problem that often occurs with chronic kidney disease (CKD) and hyperthyroidism. Proteinuria has been associated with renal hypertension, and telmisartan can be helpful to decrease proteinuria.

In dogs, telmisartan does not have an FDA-approved indication but is used to treat hypertension when other agents have been ineffective. It may produce a more complete blockade of aldosterone production than ACE inhibitors.

Telmisartan may have some anticancer properties through activation of a receptor that can induce apoptosis of cancer cells The application of this property in animals has so far been unexplored.

Pharmacokinetics: Telmisartan has a longer half-life and is more lipophilic than other ARBs. In dogs, the half-life is approximately 5 hours. In cats, the oral bioavailability is approximately 33%. Oral absorption is lower with feeding, but it may be administered with a small amount of food if necessary, without decrease in efficacy. Peak concentration occurs in 15–30 minutes after administration. The half-life in cats is approximately 8–8.5 hours. By comparison, the half-life in people is 20–24 hours.

PHARMACOKINETICS

Over 50% of telmisartan is absorbed orally with the plasma concentration measured at 0.5 - 1hrs 9. in mild to moderate hypertensive patients, the terminal half-life is 24 hrs. which is longer than all other ARDs on the

market currently. Clearance of oral dose is related to age, dose, alcohol consumption and hepatic history. Food slightly decreases the bioavailability of telmisartan. For instance, when administered with food, a decrease of about 6% is seen and with the 160mg dose, there is a decrease of about 20%. With once daily dosing, telmisartan has trough plasma concentration of about 10% to 25% of peak plasma concentrations. Telmisartan is not metabolized with cytochrome P450 system, and hence interactions with the other drugs are uncommon. Bioavailability was 42 and 58% at 40-160mg. with uncommon interaction of telmisartan with other drugs it is of advantage in the elderly patient who are receiving multiple drug therapy by decreasing the risk of adverse drug interactions. More than 90% of telmisartan is plasma protein bound to albumin and alpha-1 glycoprotein. Of this more than 80% reflects the parent compound, with the remainder being the glucuronide conjugated of telmisartan following an oral dose, nearly all (>98%) is excreted unchanged in faeces via the biliary system with urinary excretion according for (<1 %).

PHARMACODYNAMICS

Telmisartan has the highest affinity for the AT1 receptor and has minimal affinity for the AT2 receptor. Telmisartan is an orally active nonpeptide angiotensin II antagonist that acts on the AT1 receptor subtype. Studies also says that telmisartan also have PPAR gamma agonistic properties that could potentially confer beneficial metabolic effects, as PPAR gamma is a nuclear receptor that regulates the specific gene transcription, and whose target genes are involved in the regulation of glucose and lipid metabolism, as well as anti-inflammatory responses. Telmisartan blocks the vasoconstrictor and aldosterone secretary effects of angiotensin II, angiotensin II is formed by Coverting it into angiotensin I with the help of enzyme called angiotensin converting enzyme and by blocking this angiotensin converting enzyme, telmisartan gives effect of vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium.

TOXICITY

Acute oral toxicity is low. No deaths and no changes occurred in rats or dogs at 2000 mg/kg, the highest dose tested. And limited data is collected with the toxicity in humans. Overdosage may cause hypotension, dizziness, and tachycardia, bradycardia could occur from parasympathetic stimulation (vagal) stimulation.

More common side effects:-

The more common side effects that occur with telmisartan include:

1. Sinus Pain And Congestion
2. Back Pain
3. Diarrhea
4. Sore Throat
5. Flu-Like Symptoms, Such As Fever And Body Aches
6. Upset Stomach
7. Muscle Pain
8. Headache
9. Dizziness
10. Fatigue
11. Nausea

If these effects are mild, they may go away within a few days or a couple of weeks. If they're more severe or don't go away, talk with your doctor or pharmacist.

Serious side effects

Call your doctor right away if you have any of these serious side effects. Call 911 if your symptoms feel life threatening or if you think you're having a medical emergency.

Low blood pressure. Symptoms include:

1. faintness
2. dizziness
3. Kidney disease. If you already have kidney disease, this drug may make it worse.
4. Symptoms include:
5. swelling in your feet, ankles, or hands
6. unexplained weight gain
7. Allergic reaction. Symptoms include:
8. swelling of your face, tongue, or throat

9. trouble breathing
10. skin rash

Telmisartan may interact with other medications

Telmisartan oral tablet can interact with other medications, herbs, or vitamins you might be taking. An interaction is when a substance changes the way a drug works. This can be harmful or cause the drugs that you take to not work as well. To help prevent interactions, your doctor should manage all of your medications carefully. To find out how this drug might interact with something else you're taking, talk with your doctor or pharmacist

Highlights for telmisartan

Telmisartan oral tablet is available as both a generic and brand-name drug. Brand name: Micardis.

Telmisartan only comes as a tablet you take by mouth.

Telmisartan oral tablet is used to treat high blood pressure. It may also be used to lower your risk for heart attack, stroke, or death from heart disease if you're 55 years or older and at high risk of major heart disease events and can't take angiotensin-converting enzyme (ACE) inhibitors.

MATERIALS AND METHODS

Reagents :-

Telmisartan was obtained as free gift sample from Ranbaxy Laboratories Limited, Gurgaon, India. The pharmaceutical preparation i.e. Telmisartan tablet is procured from local market. Remaining all the reagents and solvents of spectroscopy grade were purchased from Thomas baker, India while double distilled water was used for whole experiment.

Instrumentation :-

A Jasco double beam UV–visible spectrophotometer, Model: V-630, with a fixed band width (2 nm) and a pair of 1-cm quartz cell was used for Spectral and absorbance measurements

Preliminary solubility studies of drugs :-

25mg of Telmisartan was weighed and solubility was checked in water, methanol, ethanol, 0.1N NaOH. The drug was found to be soluble in 0.1N NaOH.

Calibration curve for Telmisartan *:-*

For the standard stock solutions appropriate stock solutions were made to obtain concentration in the range of 2,4,6,8,10 and 12 Ug/ml. The sperctra were recorded absorbance were measured at 295 nm and calliberation curve was plotted.

METHOD A: ABSORPTION MAXIMA METHOD

For the selection of analytical wavelength, standard solution of Telmisartan was scanned in the spectrum mode from 200 nm to 400 nm separately. From the spectra of drug, 295 nm was selected as λmax of TEM for the analysis (Figure No.1). Aliq were validated by the high value of the correlation coefficient and the intercept value .uots of standard stock solution were made and calibration curve was plotted.

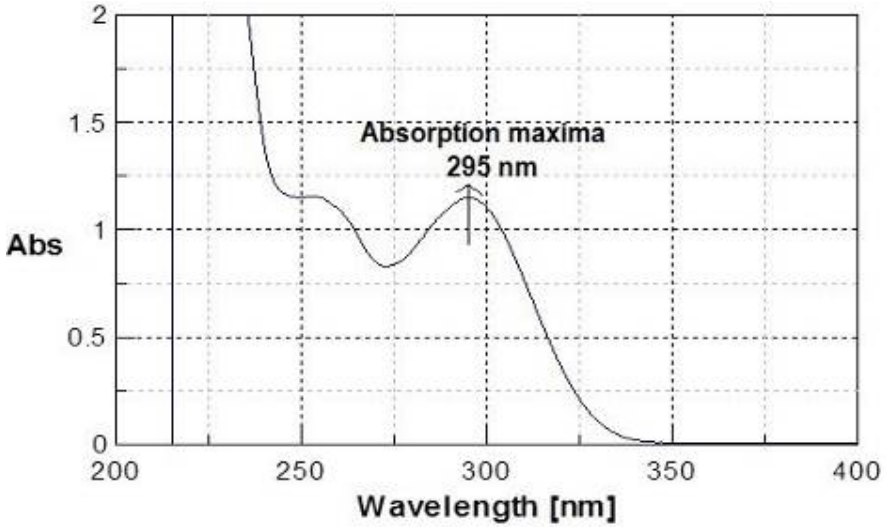


Fig.no.1:It shows Absorption Maxima of Telmisartan

Method B:Area under Curve

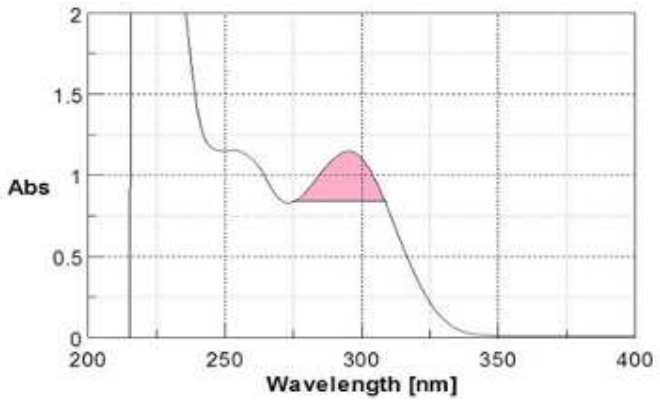


Fig.no.2:It shows area under the curve method

For the determination of Telmisartan using the area under curve (AUC) method, suitable dilutions of the working stock solutions (100 µg/mL) of Telmisartan were prepared in 0.1 N NaOH and scanned in the range of 200 - 400 nm. For Area under curve method, the sampling wavelength ranges from 275-310 nm (Figure No. 2) selected for estimation of Telmisartan and area were integrated between these selected wavelength range, which showed linear response with increasing concentration hence the same wavelength range were used for estimation of tablet formulations.

METHOD VALIDATION :-

Various method of analysis of TEM in bulk and pharmaceutical formulations (marketed and developed) was carried out as ICH

Parameters λmax (nm)	Method A 295 nm	Method B Area range 275 nm- 310 nm
Beer's range (µg/ml)	2-12 µg/ml	2-12 ug/ml
Regression equation	0.999	0.999
Intercept (a)	Y = 0.12009x + (-0.02858)	Y = 1.423319x + (-0.137431)
Slope (b)	0.120096	1.423319

THERAPEUTIC EVALUATION OF TELMISARTAN

Patients undergoing monotherapy were on telmisartan 80mg (20.1%) and telmisartan 20mg (14.4%). In combination therapy, the majority of the patients were prescribed telmisartan and amlodipine (39.1%). Other combinations were also followed such as telmisartan and chlorthalidone (25%), telmisartan and hydrochlorothiazide (18.7%), and telmisartan and metoprolol succinate (17.2%) The monotherapy and combination therapy of telmisartan were received by 32.5% and 67.5% of the patients, respectively. In combination therapy, dual therapy was the most prescribed for 14.5% of the patients only. 65.5% of patients having monotherapy were prescribed telmisartan 40mg dose. The most commonly prescribed triple drug combination therapy was telmisartan 40mg, amlodipine 5mg, and hydrochlorothiazide 12.5 mg (79.3%)

TREATMENT DURATION, DOSE TITRATION, AND PRIOR THERAPY

The majority of patients (81.3%) had dosage up-titration and 18.1% of the patients had dosage down-titration during the treatment. Before the telmisartan-based therapy, a total of 22.4% of the patiwents were treated with the other antihypertensive. The dose titration was done only for 1479 patients (17.2%). The median duration of the treatment was 12.0 months.

TELMISARTAN THERAPY OUTCOME

Analysis of the patient compliance suggested that a total of 98.4% of the patients were compliant, and 97.6% of the patients achieved the target bp goal with telmisartan-based therapy. and a total of 157 patients reported adverse events. The result suggested that the mean systolic blood pressure significantly decreased after the monotherapy, dual therapy, and triple therapy of telmisartan. The mean diastolic blood pressure also changes. Further analysis shows that median SBP and DBP increased significantly with the growing age. Stage I hypertension was seen in adults and young patient, In the elderly patient population (>60years), stage II hypertension was common.

INTERACTIONS

DRUG INTERACTION:-

Abaloparatide : the risk or severity of adverse effects can be increased when telmisartan is combined with abaloparatide.

Abemacicib : telmisartan may decrease the excretion rate of abemacicib which could result in higher serum level.

Abrocitinib : the metsbolism of abrocitinib can be decresedn combined with temisartan.

Acebutolo : telmisartan may increase the hypotensive activities of acebutolol.

Aceclofenac : the risk or severity of renal failure, hyperkalemia, and hypertension can be increased when telmisartan is combined with aceclofenac.

Acemetacin: the risk of severity of renal failure, hypertension can be increased when telmisartan is combined with acemetacin.

Acenocoumarol : the metabolism of acenocoumarol can be decreased when combined with telmisartan.

Acetyldigitoxin: the serum concentration of acetyldigitoxin can be increased when it is combined with telmisartan.

Acetylsalicyclic acid: the risk of severity of renal failure, hyperkalemia, and hypertension can be increased when telmisartan is combined with acetyl cyclic acid.

Afatinib: telmisartan may decrease the excretion of afatinib which could result in a higher serum level.

FOOD INTERACTION: -

Telmisartan when taken with or without food, its bioavailability may vary. It may decrease the bioavailability of telmisartan when taken with food.

TELMISARTAN CLINICAL TRIALS

Identification of telmisartan as unique angiotensin II receptor antagonist with selective PPAR gamma modulating activity.

Angiotensin type I receptor blockers induce peroxisome proliferator activated receptor activity.

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

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

Insulin –sensitizing effects of telmisartan implications for testing insulin-resistant hypertension and cardiovascular disease.

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

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.

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.

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

Replacement of valsartan and condensation by telmisartan in hypertensive patients with type 2 diabetes; metabolic and antiatherogenic consequences.

Telmisartan; an angiotensin II receptor antagonist with selective PPAR gamma activity.

Telmisartan-killing two birds with one stone; ARBs and PPAR agonism.

Antifibrotic effect of telmisartan in silymarin treated HCV. Egyptian patients.

Telmisartan is a potent target for prevention and treatment of human prostate cancer.

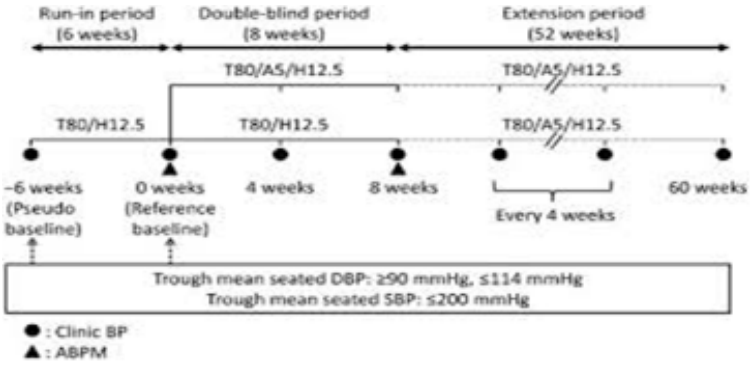
Cerebro protective action of telmisartan by inhibition of macrophages/microglia expressing HMGB1 via a peroxisome proliferator- activated receptor-depended mechanism.

Effect of telmisartan on proteinuria or albuminuria: a meta-analysis of randomized trails.

Protective effect of telmisartan against cadmium-induced nephrotoxicity in mice.

Myocardial savaging effect of telmisartan in experimental models of myocardial infractions.

Telmisartan reduced abdominal circumference and body weight to decrease triglyceride levels in patients with type 2 diabetes and metabolic syndrome.



Treatment of hypertension with an angiotensin II receptor antagonist compared with an angiotensin converting enzyme inhibitor; review of clinical studies of telmisartan and enalapril.

Telmisartan improves lipid metabolism and Adi protein production but does not affect glycemic control in hypertensive patients with type 2 diabetes.

Telmisartan improves nonalcoholic steatohepatitis in medaka (oryzias latipes) by reducing macrophage infiltration and fat accumulation.

Reno protective effects of telmisartan on renal injury in obese Zucker rats.

Telmisartan protects against insulin resistance by attenuating inflammatory response in rats.

Comparative effects of telmisartan in the treatment of hypertension.

Telmisartan lowers home blood pressure and improves insulin resistance without correlation between their changes.

SUMMARY

Telmisartan is selective AT2 receptor antagonist. it is the potent drug used in treatment of hypertension as well as other cardiovascular dieseases. the compound also have some favourable effects on renal, heart failure, and diabetic nephropathy. telmisartan is a type of small molecule with molecular weight of 514.6 and melting point of 261 to 263 degree celsius.it has excellent oral absorption and greater tissue penetration property. studies suggeste that telmisartan is partial PPAR gamma agonist. telmisartan is indicated alone or in combination with other classes of antihypertensive for the treatment of congestive heart failure and in diabetic nephropathy in hypertensive patients weith type 2 diabetes mellitus. volume of distribution of telmisartan is 500 literes with highly protein bounding capacity mainly to albumin and alpha 1-acid glycoprotein. cytochrome P450 isoenzyme is not involved in metabolism of telmisartan but is excreted in urine. terminal half-life is approximately 24hrs. telmisartan has total plasma clearance of >800 ml/min. route of elminiation is oral or intravaneous route, oral toxicity is low. averse effects are mostly hypotension, dizziness, tachycaria. drug interaction may cause risk if renal failure, hyperkalemia, and hypertension.

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