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Telmisartan

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Abstract
Telmisartan (Micardis), is a highly selective angiotensin II type 1 receptor antagonist, which is approved for the treatment of high blood pressure i.e, hypertension, either as monotherapy or in combination with other antihypertensive agents such as example hydrochlorothiazide. The long elimination half-life of telmisartan ensures the drug provides effect decrease in blood BP across the entire 24-hour dosage interval. From the well-designed clinical trials and the clinical practice that indicates that telmisartan, either as monotherapy or in combination with other antihypertensive agents, provides long-term antihypertensive efficacy and is well tolerated in a broad spectrum of hypertensive patients, including the elderly and those with co-existing type 2 diabetes mellitus, metabolic syndrome and/or renal impairment. BP control is maintained throughout the 24-hour dosage interval, including during the last 6 hours of this period and it is recordable. Mainly in some conditions like pregnancy, renal impairment and in hepatic failure conditions it is not given.

Keywords: Telmisartan, angiotensin II, blood pressure, hypertension, pregnancy, renal impairment, hepatic failure

Introduction
Telmisartan tablets is a non-peptide angiotensin II receptor antagonist. Telmisartan is also known as Micardis.
Chemical name of Telmisartan is described as 4'-[(1, 4'-dimethyl-2'-propyl [2, 6'-bi-1H-benzimidazol]-1'yl) methyl]-[1,1'-biphenyl]-2-carboxylic acid.
Molecular formula - $C_{33}H_{30}N_4O_2$. Molecular weight - 514.63.
Structural Formula: - (fig 1)

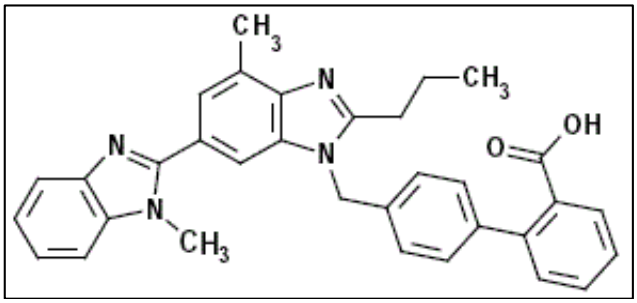

Fig 1: chemical structure of telmisartan

Physical Properties
Telmisartan is a white to slightly yellowish solid.
Solubility - practically insoluble in water, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base.
pH range - 3 to 9.
Telmisartan is available for oral administration, containing 20 mg, 40 mg, or 80 mg of telmisartan.
Sodium hydroxide, meglumine, povidone, sorbitol, and magnesium stearate are inactive ingredients present in tablets.
They are protected from moisture because they are hygroscopic in nature.

Mechanism of Action: - [Figure-1]
Angiotensin I is converted into angiotensin II by an enzyme called angiotensin-converting enzyme (ACE, kininase II). The main pressor agent of the renin-angiotensin system is Angiotensin II, with effects the vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium.
Telmisartan selectively blocks the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland in order to prevent the vasoconstrictor and aldosterone-secreting effects of angiotensin II. Therefore the action is independent of the pathways for angiotensin II synthesis.
The biosynthesis of angiotensin II from angiotensin is inhibited by blocking the renin-angiotensin system with ACE inhibitors which is widely used in the treatment of hypertension. Degradation of bradykinin is also inhibited by ACE inhibitors, a reaction also catalyzed by ACE, because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin.
Telmisartan does not bind to other hormone receptors or ion channels known to be important in cardiovascular regulation. The negative regulatory feedback of angiotensin II on renin secretion is inhibited by the Blockade of the angiotensin II receptor, but the resulting increased plasma renin activity and angiotensin II circulating levels don't overcome the effect of telmisartan on vital sign.

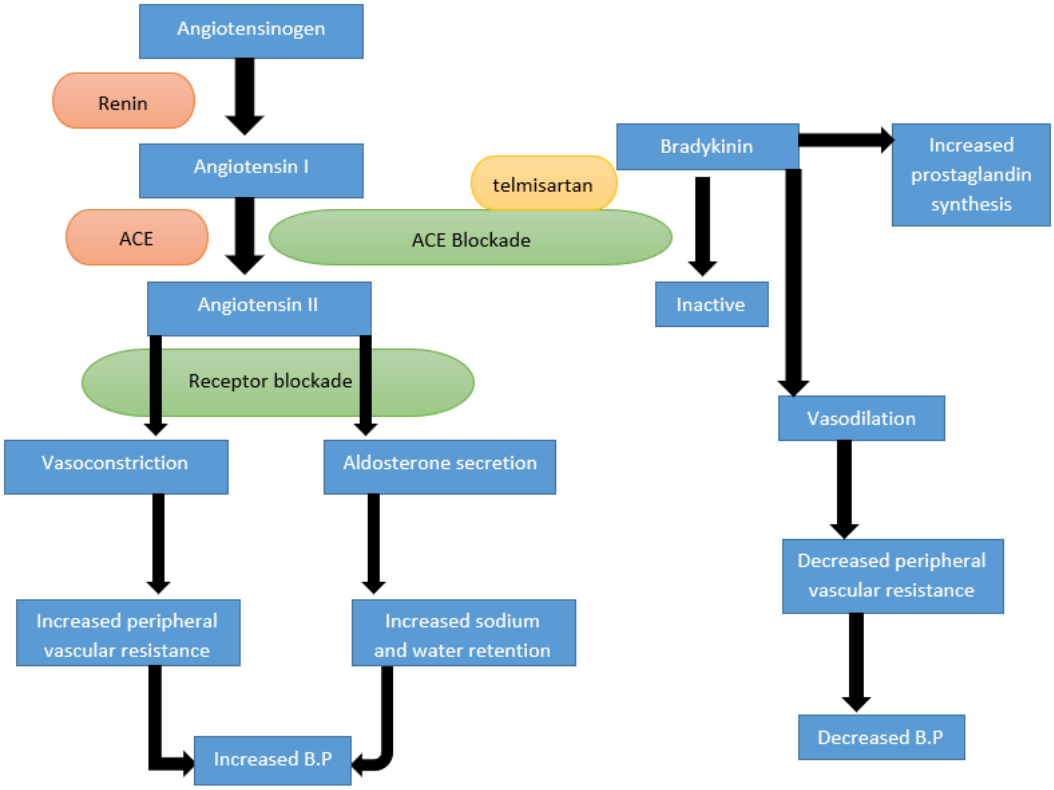

Fig 2: Mechanism of hypertension and blocking by taking telmisartan

Pharmacokinetics
General
Following oral administration, after dosing of telmisartan it reaches peak concentrations (Cmax) by 0.5-1 hour. There is a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose due to reduced bioavailability of telmisartan when food is consumed. Telmisartan is dose-dependent when it is in absolute bioavailability. The bioavailability was 42% and 58% at 40 and 160 mg, respectively. The pharmacokinetics of orally administered telmisartan with increasing doses are nonlinear over the dose range 20-160 mg, with greater than proportional increases of Cmax and AUC. Telmisartan shows a terminal elimination half-life of approximately 24 hours.
Telmisartan with once-daily dosing is having 10-25% of peak plasma concentrations. Telmisartan upon repeated once-daily dosing has an accumulation index in plasma of 1.5 to 2.0.

Distribution
Telmisartan is highly mainly bound to albumin and α1 - acid glycoprotein [plasma proteins (>99.5%)].
Volume of distribution for telmisartan - 500 liters indicating additional tissue binding.

Metabolism and Elimination
Telmisartan was eliminated unchanged in faeces through biliary excretion (>97%) and only very minute amounts were found in the urine.
Telmisartan - acylglucuronide which is pharmacologically inactive is metabolized by conjugation; to glucuronide of the parent compound is that the only metabolite that has been identified in human plasma and urine. After one dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma.
For the metabolism of telmisartan the cytochrome P450 isoenzymes are not involved.
Total plasma clearance of telmisartan is >800 mL/min.

Pharmacodynamics
The inhibition of the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for twenty-four hours is due to the dose of telmisartan 80 mg when it is given in normal volunteers. There is an increase in a dose dependent manner of plasma concentration of angiotensin II and plasma renin activity (PRA) when it is given after single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects didn't influence plasma aldosterone concentrations.
There are not any clinically remarkable changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid) when telmisartan is administered for multiple dose studies in hypertensive patients.
In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg together with hydrochlorothiazide 12.5 mg, there have been no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, reno-vascular resistance, or creatinine clearance.

Indication
Telmisartan tablets are used for the treatment of hypertension. It can be used in single or in combination with other antihypertensive agents eg: with hydrochlorothiazide.

Doseage
Usual Adult Dose for Hypertension - Initial dose: 40 mg orally once a day Maintenance dose: 40 to 80 mg orally dose daily one time

Usual Adult Dose for Cardiovascular Risk Reduction - 80 mg orally once a day

Special Populations
Paediatric: Telmisartan pharmacokinetics have not been investigated in patients <18 years of age.

Geriatric: The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years.

Gender: Plasma concentrations of telmisartan are generally 2-3 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

Renal Insufficiency: No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration.

Hepatic Insufficiency: In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%.

Warnings
The drug when is administered by pregnant woman (second and third trimester) and where the drug act directly on the renin-angiotensin system can cause foetal and neonatal morbidity and death (include hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death).
Depending upon the week of pregnancy so tests are done, Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP).
Mother and physicians should be aware, because oligohydramnios (refers to amniotic fluid volume that is less than expected for gestational age) may not appear until after the foetus has sustained irreversible injury.

Hypotension in Volume-Depleted Patients: In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with telmisartan tablets.
This condition can be corrected under the close medical supervision by administration of tablets with a reduced dose, or treatment. If the patient is in hypotension then he/she should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline.

Precautions:-Certain precautions should be taken in some conditions like Impaired Hepatic Function, Impaired Renal Function, Dual Blockade of the Renin-angiotensin-aldosterone System, and mainly in pregnancy women's.

Drug Interactions
Some drug interactions – **Contraindicated: -** Aliskiren < > Telmisartan

Severe interaction
- Benazepril < > Telmisartan
- Captopril < > Telmisartan
- Digoxin < > Telmisartan
- Lithium < > Telmisartan
- Ramipril < > Telmisartan
- Warfarin < > Telmisartan

Other Drugs: Acetaminophen, amlodipine, glibenclamide, simvastatin, hydrochlorothiazide or ibuprofen when co – administrated with telmisartan does not have a clinically significant interaction.

Adverse Drug Reaction: -Upper respiratory tract infection, Back pain, Sinusitis, Diarrhea, Pharyngitis, influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea and peripheral edema.

Autonomic Nervous System: incompetence, increased sweating, allergy, fever, leg pain, malaise

Cardiovascular: palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG

CNS: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoaesthesia

Gastrointestinal: flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders

Metabolic: gout, hypercholesterolemia, diabetes mellitus

Musculoskeletal: arthritis, arthralgia, leg cramps; Psychiatric: anxiety, depression, nervousness

Resistance Mechanism: infection, fungal infection, abscess, otitis media

Respiratory: asthma, bronchitis, rhinitis, dyspnea, epistaxis

Skin: dermatitis, rash, eczema, pruritus

Urinary: micturition frequency, cystitis

Vascular: cerebrovascular disorder

Special Senses: abnormal vision, conjunctivitis, tinnitus, earache.

Storage

Store at the temperature of 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Tablets should be removed from blisters when it is going to be administered immediately.

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