Telmisartan

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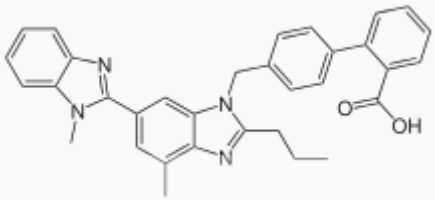

Systematic (IUPAC) name	
2-(4-{[4-Methyl-6-(1-methyl-1*H*-1,3-benzodiazol-2-yl)-2-propyl-1*H*-1,3-benzodiazol-1-yl]methyl}phenyl)benzoic acid	
Clinical data	
Trade names	Micardis
AHFS/Drugs.com	monograph
MedlinePlus	a601249
Pregnancy cat.	D (Au), D (U.S.)
Legal status	S4 (Au), POM (UK), ℞-only (U.S.)
Routes	Oral
Pharmacokinetic data	
Bioavailability	42–100%
Protein binding	≥99.5%
Metabolism	Minimal hepatic
Half-life	24 hours
Excretion	Faecal 97%
Identifiers	
CAS number	144701-48-4
ATC code	C09CA07
PubChem	CID 65999
IUPHAR ligand	592
DrugBank	DB00966
ChemSpider	59391
UNII	U5SYW473RQ

KEGG	D00627
ChEBI	CHEBI:9434
ChEMBL	CHEMBL1017
Chemical data	
Formula	$C_{33}H_{30}N_4O_2$
Mol. mass	514.617 g/mol
SMILES	• O=C(O)c1ccccc1c2ccc(cc2)Cn3c4cc(cc(c4nc3CCC)C)c5nc6ccccc6n5C
InChI	InChI=1S/C33H30N4O2/c1-4-9-30-35-31-21(2)18-24(32-34-27-12-7-8-13-28(27)36(32)3)19-29(31)37(30)20-22-14-16-23(17-15-22)25-10-5-6-11-26(25)33(38)39/h5-8,10-19H,4,9,20H2,1-3H3,(H,38,39) Key:RMMXLENWKUUMAY-UHFFFAOYSA-N

Telmisartan (INN) /tɛlmɪˈsɑrtən/ is an angiotensin II receptor antagonist (angiotensin receptor blocker, ARB) used in the management of hypertension. It is marketed under the trade name **Micardis** (by Boehringer Ingelheim), among others.

Indication

Telmisartan is indicated in the treatment of essential hypertension.[1][2]

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.[1]

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 is not

known whether the drug passes into the breast milk.[3] Also it is contraindicated in bilateral renal artery stenosis in which it can cause renal failure.

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.[3]

Mode of action

Telmisartan is an angiotensin II receptor blocker that shows high affinity for the angiotensin II receptor type 1 (AT_1), with a binding affinity 3000 times greater for AT_1 than AT_2. It has the longest half-life of any ARB (24 hours)[1][4] and the largest volume of distribution among ARBs (500 liters).[5][6]

In addition to blocking the RAs, telmisartan acts as a selective modulator of peroxisome proliferator-activated receptor gamma (PPAR-γ), a central regulator of insulin and glucose metabolism. It is believed that telmisartan's dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD).[4]

Telmisartan's activity at the PPAR-γ receptor has prompted speculation around its potential as a sport doping agent as an alternative to GW 501516.[7] Telmisartan activates PPARδ receptors in several tissues.[8][9][10][11]

Clinical trials

ONTARGET

The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) was one of the largest ARB clinical studies ever undertaken;[12] 25,620 patients from 733 centres in 41 countries were randomised for 5.5 years of treatment of either telmisartan, the ACE inhibitor ramipril or a combination of the two. The study aimed to investigate the role of telmisartan in cardiovascular (CV) protection through the primary composite outcome of death from CV causes, myocardial infarction, stroke or hospilization for heart failure, in high CV risk patients.

The study showed telmisartan was as effective as ramipril but with lower rates of cough and angioedema, which led to fewer discontinuations. The combination group experienced similar efficacy, but with increased risk of hypotensivesymptoms. Moreover, in a patient population selected to tolerate ACE inhibitors, telmisartan was shown to be better tolerated and associated with higher treatment compliance than ramipril.[13]

TRANSCEND

As part of the ONTARGET study, patients who could not tolerate ACE inhibitors were randomly assigned to receive either telmisartan or placebo as part of the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) study. An accompanying editorial comments: "Overall, data supporting use of angiotensin-receptor blockers to prevent vascular events in various cardiovascular groups, other than heart failure, are incomplete. TRANSCEND's results challenge the non-inferiority shown in ONTARGET and suggest no more than a modest effect, if any at all."[14]

PRoFESS

The Prevention Regimen For Effectively Avoiding Second Strokes (PRoFESS) study investigated therapy with telmisartan initiated soon after an ischemic stroke and continued for 2.5 years. This treatment did not significantly lower the rate of recurrent stroke, major cardiovascular events, or diabetes.[15]

See also

- Discovery and development of angiotensin receptor blockers
- GW 501516

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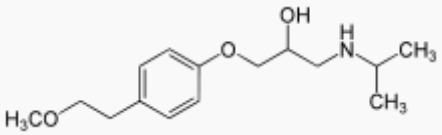
Metoprolol

Metoprolol



Systematic (IUPAC) name	
(*RS*)-1-(Isopropylamino)-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol	
Clinical data	
Trade names	Lopressor, Toprol-xl
AHFS/Drugs.com	monograph
MedlinePlus	a682864
Licence data	US FDA:link
Pregnancy cat.	C (AU) C (US)
Legal status	℞ Prescription only
Routes	Oral, IV
Pharmacokinetic data	
Bioavailability	12%
Metabolism	Hepatic via CYP2D6, CYP3A4
Half-life	3-7 hours
Excretion	Renal
Identifiers	
CAS number	51384-51-1
ATC code	C07AB02
PubChem	CID 4171
IUPHAR ligand	553
DrugBank	DB00264
ChemSpider	4027
UNII	GEB06NHM23
KEGG	D02358
ChEBI	CHEBI:6904

ChEMBL	CHEMBL13
Chemical data	
Formula	$C_{15}H_{25}NO_3$
Mol. mass	267.364 g/mol
SMILES	• O(c1ccc(cc1)CCOC)CC(O)CNC(C)C
InChI	InChI=1S/C15H25NO3/c1-12(2)16-10-14(17)11-19-15-6-4-13(5-7-15)8-9-18-3/h4-7,12,14,16-17H,8-11H2,1-3H3 Key:IUBSYMUCCVWXPE-UHFFFAOYSA-N
Physical data	
Melt. point	120 °C (248 °F)

Metoprolol (/mɛˈtoʊproʊlɑːl/, /mɛtoʊˈproʊlɑːl/) is a selective β_1 receptor blocker used in treatment of several diseases of the cardiovascular system, especially hypertension. The active substance metoprolol is employed either as *metoprolol succinate* or as *metoprolol tartrate* (where 100 mg metoprolol tartrate corresponds to 95 mg metoprolol succinate). The tartrate is an immediate-release and the succinate is an extended-release formulation.[1]

Medical uses

Metoprolol is used for a number of conditions including: hypertension, angina, acute myocardial infarction, supraventricular tachycardia, ventricular tachycardia, congestive heart failure, and prevention of migraine headaches.[2]

- Treatment of heart failure.[3]
- Vasovagal syncope[4][5]
- Adjunct in treatment of hyperthyroidism
- Long QT syndrome, especially for patients with asthma, as metoprolol's β1 selectivity tends to interfere less with asthma drugs, which are often β2-adrenergic receptor-agonist drugs[*citation needed*]
- Prevention of relapse into atrial fibrillation (controlled-release/extended-release form)[6]

Due to its selectivity in blocking the $beta_1$ receptors in the heart, metoprolol is also prescribed for off-label use in performance anxiety, social anxiety disorder, and other anxiety disorders.

Adverse effects

Side-effects, especially with higher dosages, include the following: dizziness, drowsiness, fatigue, diarrhea, unusual dreams, ataxia, trouble sleeping, depression, and vision problems. It may also reduce blood flow to the hands and feet, causing them to feel numb and cold; smoking may worsen this effect.[7] Due to the high penetration across the blood brain barrier, lipophilic betablockers such as propranolol and metoprolol are more likely than other less lipophilic beta blockers to cause sleep disturbances such as insomnia and vivid dreams and nightmares.[8]

Serious side-effects that are advised to be reported immediately include, but are not limited to, symptoms of bradycardia (resting heart rate slower than 60 beats per minute), persistent symptoms of dizziness, fainting and unusual fatigue, bluish discoloration of the fingers and toes, numbness/tingling/swelling of the hands or feet, sexual dysfunction, erectile dysfunction(impotence), hair loss, mental/mood changes, depression, trouble breathing, cough, dyslipidemia, and increased thirst. Other highly unlikely symptoms include easy bruising or bleeding, persistent sore throat or fever, yellowing skin or eyes, stomach pain, dark urine, and persistent nausea. Symptoms of an allergic reaction include: rash, itching, swelling, and severe dizziness. Taking it with alcohol might cause mild body rashes and therefore is not recommended.[7]

Precautions

Metoprolol may worsen the symptoms of heart failure in some patients, who may experience chest pain or discomfort; dilated neck veins; extreme fatigue; irregular breathing; an irregular heartbeat; shortness of breath; swelling of the face, fingers, feet, or lower legs; weight gain; or wheezing.[9]

This medicine may cause changes in blood sugar levels or cover up signs of low blood sugar, such as a rapid pulse rate.[9]

This medicine may cause some people to become less alert than they are normally, making it dangerous for them to drive, use machines, or do other things.[9]

Overdosage

Excessive doses of Metoprolol can cause severe hypotension, bradycardia, metabolic acidosis, seizures and cardiorespiratory arrest. Blood or plasma concentrations may be measured to confirm a diagnosis of poisoning in hospitalized patients or to assist in a medicolegal death investigation. Plasma levels are usually less than 200 µg/L during therapeutic administration, but can range from 1–20 mg/L in overdose victims.[10][11][12]1212 ĊČİ þ฿¢↔

Physical properties

Metoprolol has a very low melting point, tartrate around 120°C, succinate around 136°C. Because of this, metoprolol is always manufactured in a salt-based solution, as drugs with low melting points are difficult to work with in a manufacturing environment. The free base exists as a waxy white solid, and the tartrate salt is finer crystalline material.(Metox-Wockhardt)

Metabolism[edit]

Metoprolol undergoes a-hydroxylation and O-demethylation as a substrate of the cytochrome liver enzymes CYP2D6 [13][14] and a small percentage by CYP3A4.

Pharmacology

- Selective
- Moderately lipophilic
- Without intrinsic sympathomimetic activity (ISA)
- With weak membrane stabilizing activity
- Short half-life, therefore must be taken at least twice daily or as a slow-release preparation
- Decreases heart rate, contractility and cardiac output, therefore decreasing blood pressure
- Metabolized in the liver to inactive metabolite

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