Review Article

A Novel Review on Anti-Hypertensive Drug Combination-Atenolol and Amlodipine

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ABSTRACT

Hypertension is a key independent risk factor for cardiovascular diseases (CVD), such as heart failure, stroke, coronary heart disease (CHD), and end-stage renal disease. The Sixth Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 6) recommended initiation of antihypertensive therapy using a diuretic or β-blocker for patients who have no specific indications for other drug classes (Joint National Committee 1997). Atenolol is a cardioselective beta blocker. Amlodipine is a dihydropyridine calcium-channel blocker that blocks the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Combination of the two drugs results in additive antihypertensive action.

Keywords: Amlodipine, Atenolol, Hypertension.

INTRODUCTION

Atenolol is a cardioselective beta blocker. Amlodipine is a dihydropyridine calcium-channel blocker that blocks the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Combination of the two drugs results in additive antihypertensive action.

Amolodipine

Physical Characteristics of Amolodipine

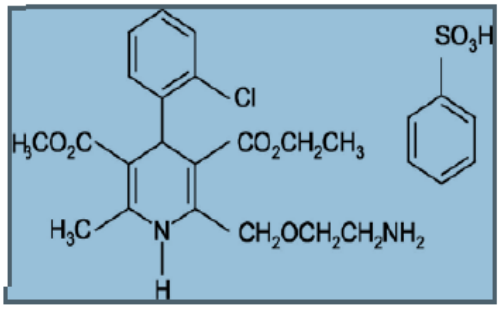
Amlodipine besylate found to exist in four solid forms: anhydrate, monohydrate, dihydrate, and amorphous The crystal structure of the dihydrate is at both 25 and −150 °C.The crystal lattices of both the dihydrate and the stable monohydrate collapse upon removal of water molecules will melt, from which the anhydrate subsequently crystallizes. Rapid cooling of the dehydration induced melt from any of the hydrates produces the amorphous form .The kinetic solubility rank order at 37 °C in water is found to be anhydrate > monohydrate > dihydrate., The dihydrate is found to be the most stable form, and other forms undergo solvent-mediated transformation (SMT) to yield the dehydrate.

Physical Properties

Molecular Weight	567.10
Ionisation constant	8.6
Melting point range	199-202°c
Loss on drying	Not more than 0.5%
Heavy metals ppm	0.002%
Total impurity	Not more than1.00%
solubility	Freely soluble in methanol, Sparingly soluble in ethanol,Slighthly soluble in water and in propanol.

Chemical Properties

Molecular formula: $C_{20}H_{25}ClN_2O_5 \bullet C_6H_6O_3S$
Chemical name: 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl]- 4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate.
Molecular structure:

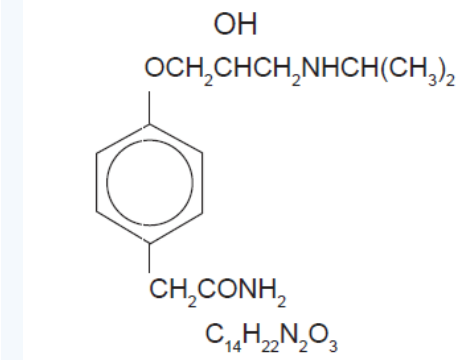


Appearance
White, crystalline powder; does not mix well with water.

Stability
Avoid reaction with oxidizing agents.

Pharmacodynamics
Amlodipine dilates peripheral arterioles and thus reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements. Amlodipine has been shown to block constriction in main coronary arteries and coronary arterioles induced by calcium, potassium, adrenaline, serotonin and thromboxane A2 analogue both in normal and in ischaemic regions. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Atenolol
Chemical properties
Molecular formulae**:** $C_{14}H_{22}N_2O_3$
Chemicalname**:**2-4-(2-Hydroxy-3-isopropylaminopropoxy)phenyl acetamide
Molecular structure



Physical Properties

Melting Point	152-154°C
Dissociation Constant Pka	9.6 @ 24°C
partition coefficient [log p(octanol)]	0.23
Appearance	Atenolol is an odourless white powder

Solvent	Relative Solubility
Water	0.3 mg/mL
Ethanol	3.4 mg/mL
Dmso	18 mg/mL
Ether	Practically Insoluble

Pharmacodynamics
It is a Beta blocker which effectively "block" the effects of adrenaline on the body's beta receptors. This reduces the nerve impulses that travel through the heart. In consequence, the heart does not have to work as hard because it needs less blood and oxygen. In addition, such drugs "block" the impulses that can cause an arrhythmia. competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output. A central effect leading to reduced sympathetic outflow to the periphery

Combination of Atenolol and Amolodipine
Used for treatment of Chronic stable angina, Hypertension.

Dosage administration oral .
1. Adult
   1. Per tablet contains atenolol 25 or 50 mg and amlodipine (as besylate) 5 mg.
   2. 1 tab once daily, may increase to 2 tablets daily if needed.

2. Elderly
   1. Per tablet contains atenolol 25 mg and amlodipine (besylate) 5 mg
   2. Initiate with 1 tablet daily.

3. Renal impairment
   1. Per tablet contains atenolol 25 mg and amlodipine (besylate) 5 mg
   2. Initiate with 1 tablet daily.

Pharmacokinetics
Absorption
Amlodipine: Plasma levels peak 6-12 hr after oral admin; absolute bioavailability is estimated to be 64-90%. Atenolol: Absorption

is rapid and consistent but incomplete; about 50% of an oral dose is absorbed in the GI tract; plasma levels peak 2-4 hr after oral admin.

Distribution
Amlodipine: 93% bound to plasma proteins. Atenolol: 6-16% bound to plasma proteins.

Metabolism
Amlodipine: About 90% converted to inactive metabolites hepatically. Atenolol: Little or no hepatic metabolism.

Excretion
Amlodipine: 10% of parent compound and 60% of the metabolites are removed in the urine; elimination from the plasma is biphasic with terminal half-life of about 30-50 hr. Atenolol: 50% of the oral dose is removed unchanged in the faeces; absorbed drug is removed mainly via renal elimination; half-life is about 6-7 hr.

Drug Interactions
Additive effect when used with catecholamine depleting drugs; monitor for hypotension and marked by bradycardia. If used with clonidine, clonidine withdrawal should occur a few days after withdrawal of the beta-blocker to prevent rebound hypertension; if replacing clonidine by beta-blocker, beta-blocker should be introduced only after clonidine administration has stopped for several days. Concurrent use with prostaglandin synthase inhibiting drugs (e.g. indomethacin) may reduce the hypotensive effects of beta-blockers**.**
ia, cold extremities. Drowsiness, chest pain & impotence rarely. Hypersensitivity reactions.

PRECAUTIONS

1. Excessive fall of BP may occur in elderly patients.
2. Caution in patients with COPD, thyrotoxicosis, congestive failure, vasospastic angina, hepatic & renal impairment
3. Caution in diabetic patients as beta-blockers may mask tachycardia occurring with hypoglycaemia. Withdrawal should be gradual.
4. Lactation.
5. Safety and efficacy have not been established in children.
6. Not to be used in untreated phaeochromocytoma.

Degradation of Combination
Amlodipine besylate, like all members of 1,4-dihydropyridine calcium channel blockers, is photosensitive and liable to degradation both in solution and in solid state. Light catalyses its oxidation to pyridine derivatives, such as amlox (2-┐(2-aminoethoxy) methyl└-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl pyridine), which lack therapeutic effects. Another pharmaceutical problem is the reported incompatibility in the solid formulation between amlodipine besylate and lactose in the presence of basic excipients (magnesium stearate) and water . Atenolol is said to be photo- reactive when exposed to UVA–UVB radiation with photo degradation increasing with a decrease in the pH value. The main photo degradation product at pH 7.4 was identified as 2-(4-hydroxyphenyl) acetamide.

Overdosage
Over dosage may cause hypotension and less commonly, congestive cardiac failure. Unabsorbed drug may be removed by gastric lavage or use of activated charcoal. Symptomatic treatment may be administered.

Poisoning of combination and treatment
The common feature of Atenolol toxicity is excessive blockade of the β-receptors resulting in bradycardia and hypotension. Poisoning by Amolodipine is characterized by cardiovascular toxicity with hypotension and conduction disturbances, including sinus bradycardia and varying degrees of atrioventricular block. Poisoning by Atenolol and Amolodipine usually produces hypotension and bradycardia, which may be refractory to standard resuscitation measures. For cases of Atenolol poisoning where symptomatic bradycardia and hypotension are present, high-dose glucagon is considered the first-line antidote. For cases of Amolodipine poisoning where cardio toxicity is evident, a combination of calcium and epinephrine should be used initiall**y**

CONCLUSION
The review is mainly on combined usage of atenolol and amlodipine .its dosage administration,drug interactions,overdosage,precautions,side effects,degradation of combinationand poisoining which mainly reduces the hypertension.

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