

Atenolol Drug Profile



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Atenolol is a β -1 selective (Cardioselective) β adrenergic receptor blocking agent. It does not have membrane stabilizing and intrinsic sympathomimetic (partial agonist) activities.

Besides being one of the most widely used β -blockers clinically, it has often been used as a reference drug in randomized controlled trials of hypertension.¹⁻⁴ The present review focuses on pharmacological profile of atenolol discussing its; structure, pharmacokinetics and metabolism, pharmacodynamics, dosage, administration, adverse effects and contraindications.

Structure

Atenolol may be chemically described as a benzene acetamide, 4-[2¹ - hydroxy - 3¹ -[(1- methyl ethyl) amino] propoxy]. The molecular and structural formula is as shown Figure 1.

Atenolol (free base) has a molecular weight of 266.34. It is a relatively polar hydrophilic compound with water solubility of 26.5 mg/ml at 37°C and a log partition coefficient (octanol / water) of 0.23. Lipid insoluble hydrophilic compounds (atenolol, sotalol, nadolol) are excreted only by the kidneys and have low brain penetration. Metoprolol and propranolol are more lipophilic compounds and so are more often used in migraine and have more cerebral side effects of β -blockers.

Pharmacokinetics and Metabolism

Atenolol is incompletely absorbed (about 50%), but most of the absorbed dose reaches the systemic circulation. Peak blood levels are reached between two and four hours after ingestion. Unlike propranolol or metoprolol, atenolol undergoes little or no metabolism by the liver and the absorbed portion is eliminated by renal excretion. Over 85% of intravenous dose is excreted in urine within 24 hours compared with 50% for an oral dose. Only a small amount (6-16%) is protein-bound resulting in relatively consistent plasma drug levels with about a four-fold inter-patient variation.

The elimination half-life of atenolol is 6 to 7 hours and there is no alteration of kinetic profile of drug by chronic administration.

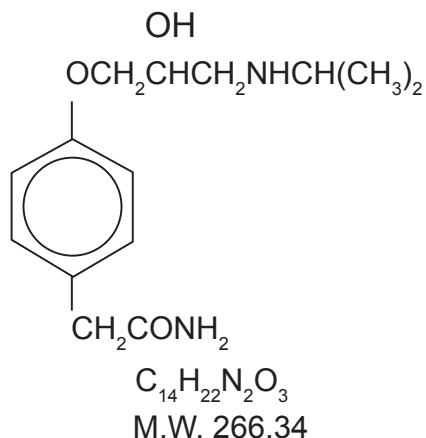


Fig. 1 : Molecular and structural formula of atenolol

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Following intravenous administration peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid (5 to 10 fold) during the first 7 hours. Following oral doses of 50 mg or 100 mg both β -blocking and anti-hypertensive effects persist for at least 24 hours. The drug accumulates in patients with renal failure and dosage should be adjusted for patients whose creatinine clearance is less than 35 mL/min/1.73m².

Pharmacodynamics

β -blockers are classified into three generations⁵ Table 1.

Atenolol (2nd generation β -blocker) is a β_1 selective antagonist (cardio selective); however this selectivity is not absolute and at higher doses atenolol inhibits β -2 Adrenoceptors chiefly located in bronchial and vascular musculature. It has no partial agonist and intrinsic sympathomimetic activity and so results in disturbances in lipid profile (unlike acebutolol).

CVS: The major therapeutic effects are on cardiovascular system (Table 2). It is important to distinguish these effects in normal subjects from those in subjects with cardiovascular disease (CVD) such as hypertension or myocardial ischemia. The negative inotropic and chronotropic effects are modest when stimulation of β -receptors is low. However, in presence of activated sympathetic nervous system as during exercise or stress; atenolol attenuates the expected rise in heart rate (HR) and myocardial contractility. The exercise-induced increase in cardiac output (CO) is less affected because of an increase in stroke volume. It decreases the effects of catecholamine on determinants of myocardial oxygen consumption (heart rate; contractility and systolic pressure), hence improving the relationship between cardiac oxygen supply and demand; exercise tolerance is improved in patients with angina.

The duration of action is dose-related and also bears a linear relationship to the logarithm of plasma atenolol concentration. Besides reducing HR, cardiac index and blood pressure; effects on total peripheral resistance have been documented; though less uniformly. Acute intravenous administration is usually followed by increase in total peripheral resistance of 20-30%.⁶ Studies during chronic oral administration of atenolol have found either no change in vascular resistance⁷⁻⁸ or an increase in about 5%.⁹ In long term studies, Lund Johansen¹⁰ has demonstrated that haemodynamic effects of atenolol are unchanged after 1 and 5 years of therapy.

Atenolol blunts the reflex mediated increase in heart rate that usually follows the Valsalva maneuver or abrupt tilting to the upright position.⁹ It also prolongs the sinus node recovery time and lengthens the RR interval. An increase in atrial refractory period follows administration of atenolol and atrioventricular (A-V) conduction is prolonged. Besides prolonging AV nodal refractoriness, decrease in intracellular calcium overload and after-depolarization mediated automaticity is seen. The anti-arrhythmic actions of atenolol are less than of sotalol and propranolol (due to less membrane stabilizing action).

Others

Atenolol has no effect on plasma volume, exchangeable sodium or potassium or total body potassium.^{9,11} However, because it does not block peripheral β_2 receptors, it does not

Table 1 : Important pharmacological properties of various β -blockers.

| Drug | Membrane stabilizing activity | Intrinsic agonist activity | Lipid solubility | Extent of absorption (%) | Oral Bioavailability (%) | Plasma $t_{1/2}$ (hours) | Protein binding (%) |
|--|-------------------------------|----------------------------|------------------|--------------------------|--------------------------|--------------------------|---------------------|
| Classical non-selective β -blockers (1st Generation) | | | | | | | |
| Nadolol | 0 | 0 | Low | 30 | 30–50 | 20–24 | 30 |
| Propranolol | ++ | 0 | High | <90 | 30 | 3–5 | 90 |
| Timolol | 0 | 0 | Low to moderate | 90 | 75 | 4 | <10 |
| β -1 selective β -blockers (2 nd Generation) | | | | | | | |
| Acebutolol | + | + | Low | 90 | 20–60 | 3–4 | 26 |
| Atenolol | 0 | 0 | Low | 90 | 50–60 | 6–7 | 6–16 |
| Bisoprolol | 0 | 0 | Low | \leq 90 | 80 | 9–12 | ~ 30 |
| Esmolol | 0 | 0 | Low | NA | NA | 0.15 | 55 |
| Metoprolol | + | 0 | Moderate | ~ 100 | 40–50 | 3–7 | 12 |
| Nonselective & β -1 selective β -blockers with additional actions (3 rd Generation) | | | | | | | |
| Carvedilol | ++ | 0 | Moderate | >90 | ~ 30 | 7–10 | 98 |
| Labetalol | + | + | Low | >90 | ~ 33 | 3–4 | ~ 50 |
| Celiprolol | 0 | + | Low | ~74 | 30–70 | 5 | 4–5 |

Table 2 : Cardiac effects of Atenolol

1. Negative Chronotropic (decreased heart rate)
2. Negative dromotropic (decreased conduction)
3. Negative inotropic (decreased contractility)
4. Anti arrhythmic
5. Anti ischemic

prevent fall in serum potassium levels that can occur when plasma catecholamine rises.¹²

Like other β -blocking agents, atenolol inhibits the release of renin,⁹ inhibits lipolysis¹³⁻¹⁴ and causes increased plasma triglyceride levels and a fall in HDL concentration. When administered in large doses enough to block β -2 receptors, the resulting reduction of glucose production in response to catecholamine release can prolong hypoglycemia induced by insulin.

Atenolol reduces renal vascular resistance in hypertensive patients⁹. No effect on creatinine clearance, glomerular filtration rate or renal blood flow has been observed in contrast to non-selective β -blockers.

Although atenolol does not pass the blood brain barrier fully, some of the compound reaches the central nervous system.¹⁵ The following symptoms, possibly related to CNS effect have been reported, dizziness, vertigo, lightheadedness, tiredness, fatigue, lethargy, drowsiness, depression and vivid dreams.

Dosage and Administration

Hypertension

The initial dose of atenolol for the treatment of hypertension usually is 50 mg per day given once daily. If an adequate therapeutic response is not evident within several weeks, the daily dose may be increased to 100 mg. Higher doses are unlikely to provide any greater anti-hypertensive effect. Young hypertensives have high renin hypertension and increased sympathetic activity. So β -blockers are used in younger ages only now. In elderly hypertensives β -blockers specially atenolol is no longer a preferred drug.

In hypertensive patients with arrhythmias owing to excess sympathetic stimulation like in pheochromocytoma or clonidine withdrawal, β -blockers can result in unopposed α adrenergic stimulation, with resulting severe hypertension and /or α adrenergic mediated arrhythmias. In such patients we should use α and β adrenergic antagonists such as labetalol.

Sudden discontinuation of some β adrenergic blockers can produce a withdrawal syndrome that is likely due to up regulation of β receptors during blockade, causing enhanced tissue sensitivity to endogenous catecholamines; this can exacerbate the symptoms of coronary artery disease. The result, especially in active patients, can be rebound hypertension. Thus, β adrenergic blockers should not be discontinued abruptly except under close observation. The dosage should be tapered over 5 - 10 days prior to discontinuation.

Ischaemic Heart Disease

In angina pectoris the initial dose is 50 mg once daily. If an optimal response is not achieved within one week, the dosage should be increased to 100 mg. Some patients may require a dose of 200 mg.

In some patients with acute MI (within 6 hours) specially those with anterior infarction and sinus tachycardia but not in failure and no history of asthma or left bundle branch block intravenous atenolol may be given. 5 mg atenolol over 5 minutes followed by another 5 mg intravenous injection 10 minutes later can be given. It should be administered under carefully controlled conditions including monitoring of blood pressure, HR and electrocardiogram. In most patients atenolol 50 mg should be initiated on the first day. Thereafter, it can be given orally either 50 mg once or twice a day.

The BHAT¹⁶ and ISIS-I¹⁷ trials have documented the role of propranolol and atenolol in post MI patients respectively. In ISIS-I (n=16072) patients with suspected or definite MI presenting within 12 hours of symptom onset were randomized to atenolol 5-10 mg i/v followed by 100 mg daily or to usual care. The seven day mortality rate in atenolol group was 3.9% as compared to 4.6% in control group, a significant 15% mortality reduction (P< 0.04). Almost all of mortality benefit occurred on day one (25% reduction in risk of death p < 0.003), possibly owing to favourable effect with atenolol on incidence of cardiac rupture¹⁸. The mortality benefits of early atenolol treatment persisted at one year (10.7% in atenolol group vs 12% in control p< 0.01).

In most patients of myocardial infarction, β -blockers are used for secondary prophylaxis and a treadmill test (TMT) is required for risk stratification. However, false negative TMT can occur in patients on β -blockers. Conversion of negative or mildly positive TMT into strongly positive result after withdrawal of β -blockers has been reported¹⁹. It is suggested that β -blockers can and should be withdrawn in post-MI patients before doing TMT.

Table 3 : Atenolol and other β -blockers - contraindications and cautions

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| <p>Atenolol and other β-blockers - contraindications and cautions</p> <p>Cardiac Absolute: Severe bradycardia, high-degree heart block, overt left ventricular failure Relative: Treated heart failure, Prinzmetal's angina, high doses of other agents depressing SA or AV nodes (verapamil, diltiazem, digitalis, anti-arrhythmic agents); avoid sudden withdrawal.</p> <p>Pulmonary Absolute: Severe asthma or bronchospasm. Relative: Mild asthma or bronchospasm or chronic airways disease.</p> <p>Central Nervous Absolute: Severe depression (avoid propranolol). Relative: Vivid dreams: Visual hallucinations: avoid highly lipid soluble agents (propranolol) and pindolol. Fatigue (all agents; try change of agent).</p> <p>Peripheral Vascular Absolute: Active disease: gangrene, skin necrosis, severe or worsening claudication, rest pain. Relative: Cold extremities, Raynaud's phenomenon.</p> <p>Diabetes Mellitus Relative: Insulin requiring diabetes: nonselective agents decrease reaction to hypoglycemia; use selective agents – atenolol, metoprolol.</p> <p>Liver Disease Relative: Avoid agents with high hepatic clearance (propranolol, oxprenolol, timolol, acebutolol, metoprolol). Use agents with low clearance (atenolol, nadolol, sotalol or pindolol).</p> |
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Its effect on conduction tissue are utilized to control HR in patients of mitral stenosis in sinus rhythm. In atrial fibrillation atenolol is useful to control ventricular rate (as is digitals and verapamil). Besides above common uses, atenolol has been used in hypertrophic cardiomyopathy and for prevention of migraine, familial tremors and also controlling symptoms of hyperthyroidism.

Precaution, Adverse Effects and Contraindications

In patients with congestive heart failure some β -blockers like carvedilol, metoprolol succinate and bisoprolol are standard forms of therapy. However, there is no data on use of atenolol and hence it should be avoided in such patients specially in those with class IV symptoms.

Because β -blockers slow A-V conduction, they should not be used in patients with advanced grades of heart block such as 2nd and 3rd degree AV block because of risk of producing complete heart block.

When used in low doses it may not lower the limb blood flow in patients with peripheral vascular disease, as occurs with use of non selective β -blockers²⁰. Similarly, the incidence of cold extremities, acrocyanosis or aggravation of Raynaud's phenomenon occurs to a lesser extent with low dose of atenolol.

The occurrence of bronchospastic disease, masking of tachycardia associated with hypoglycemia in diabetes, similarly is lesser with low dose atenolol as compared to non-selective agents²¹. Atenolol unlike ACE inhibitors tends to diminish insulin sensitivity, as proposed by Santucci & Ferris.²²

The β -receptors mediate activation of hormone-sensitive lipase in fat cells, leading to release of free fatty acids into the circulation. This increased flux of fatty acids is an important source of energy for exercising muscle. β -receptor antagonists can attenuate the release of free fatty acids from adipose tissue. Nonselective β -receptor antagonists like propranolol

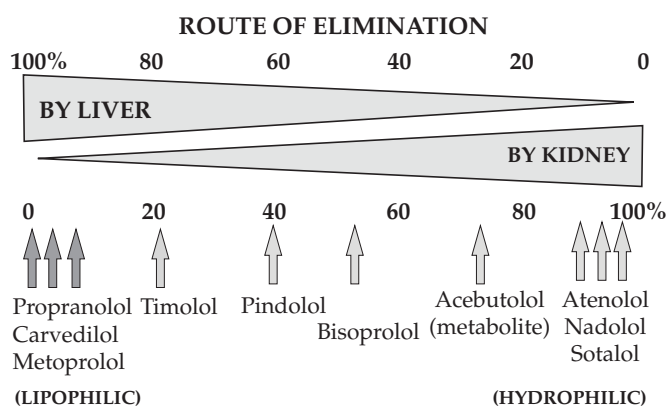


Fig. 2 : Comparative routes of elimination of β -blockers.

consistently reduce HDL cholesterol, increase LDL cholesterol and increase triglycerides. While drugs such as propranolol and atenolol increase triglycerides, plasma triglycerides are reduced with chronic carvedilol therapy. Nebivolol and carvedilol, reportedly improve the serum lipid profile of dyslipidemic patients.

Small doses of atenolol may lead to decrease in serum potassium levels.²³ This effect could be a problem in patients on chronic diuretic therapy who are potassium depleted.

The CNS adverse effects like chronic fatigue, sleep disturbance, insomnia, nightmares, depression, loss of energy again occur to lesser extent with atenolol due to its water solubility and non penetration of blood brain barrier. It may lead to exacerbation of psoriasis, hence should be used with caution.²⁴

Atenolol has been reported to cause sexual dysfunction and impotence. Impotence is a side effect quite frequently complained of by middle aged men, who in any case may be prone to this problem. The Treatment of Mild Hypertension Study (TOMHS)²⁵, at 4 years, did not find a higher rate of erectile dysfunction with atenolol compared with a diuretic, calcium channel blocker, ACE-inhibitor, or an α_1 blocker. In the trial of anti-hypertensive interventions and management (TIAM), the β -blocker atenolol did not worsen sexual function over 6 months. Problems with erection were seen in 1% of patients given a β -blocker, compared with 26% with diuretics and 3% with placebo²⁶. Speculatively, a change of β -blocker to a vasodilatory compound might be beneficial, coupled with reassurance. Alternatively, the use of very low dose combination therapy as in bisoprolol- hydrochlorothiazide (6.25 mg) may be better. Results show that the knowledge and prejudice about side effects of β -blockers can produce anxiety, that may cause erectile function²⁷.

Atenolol, when administered in pregnant patients crosses placental barrier and appears in cord blood. Administration starting in 2nd trimester has been associated with birth of infants that are small for gestational age. Neonates born to mothers who are receiving atenolol at parturition or breastfeeding may be at risk for hypoglycemia and bradycardia.

Atenolol is excreted unchanged by kidney (Figure 2) hence, serum levels are increased in patients with impaired renal function. It does not accumulate significantly unless creatinine clearance falls to less than 35 ml/min/1.73m² at which point the maximum daily dose of atenolol should be limited to 50 mg. When a clearance is less than 15ml/min/1.73m² dosage should be limited to 25 mg daily. Patients who require haemodialysis should receive 25 or 50 mg after each period of dialysis²⁸.

Thus caution is to be exercised with use of atenolol during

: known hypersensitivity to atenolol, pregnant and lactating mothers, elderly patients with impaired renal functions, renal disorders, bradycardia (sinus bradycardia, AV block greater than 1st degree), congestive heart failure – NYHA class IV, asthma, bronchitis, COPD, emphysema, insulin receiving diabetics, pheochromocytoma, psoriasis, Raynaud's phenomenon and peripheral arterial disease

Drug Interactions

Atenolol should be used with caution when used concomitantly with drugs like reserpine (Catecholamine-depleting drugs); other β -blockers (increased risk of cardiac depressant effects like enhanced bradycardia), calcium channel blockers (negative inotropic and chronotropic effects); disopyramide and amiodarone (negative chronotropic effects), clonidine withdrawal (rebound hypertension); digitalis (bradycardia).

Overdose of β -Blockers

Bradycardia may be countered by intravenous atropine. If serious, temporary transvenous pacing may be required. When an infusion is required, glucagon (2.5 to 7.5 mg/h) is the drug of choice, because it stimulates formation of cyclic AMP by bypassing the occupied β -receptor. Logically an infusion of a phosphodiesterase inhibitor, such as amrinone or milrinone, should help cyclic AMP to accumulate. Alternatively, dobutamine is given in doses high enough to overcome the competitive β -blockade (15 μ g/kg/min). In patients without ischemic heart disease, an infusion (up to 0.10 μ g/kg/min) of isoproterenol may be used.

Atenolol a cardioselective agent is more potent and has an increased safety profile as compared to other non-selective agents. Its role as a reference drug and first choice in treatment of hypertension has now declined especially after 2 large mega trials LIFE & the ASCOT BPLA study²⁹⁻³⁰. However, it continues to be an important add on anti-hypertensive and its role in patients with angina pectoris & post MI angina is well documented.

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