Lonet®

Tablet

Description

Lonet contains Atenolol, a synthetic β_1 selective (cardioselective) adrenoreceptor blocking agent without membrane stabilising or intrinsic sympathomimetic (partial agonist) activity. This preferential effect is not absolute, however, at higher doses, Atenolol inhibits β_2 adrenoreceptors, chiefly located in the bronchial and vascular musculature.

In standard animal or human pharmacological tests, β adrenoreceptor blocking activity of atenolol has been demonstrated by :

- Reduction in heart rate (both resting and during exercise) and cardiac output.
- Reduction of systolic and diastolic blood pressure at rest and on exercise.
- Inhibition of isoproterenol induced tachycardia.
- Reduction in reflex orthostatic tachycardia.

A significant β blocking effect of Atenolol, as measured by reduction of exercise induced tachycardia, is apparent within one hour following oral administration of a single dose. This effect is maximal at about 2 to 4 hours, and persists for at least 24 hours. The duration of action is dose related and also bears a linear relationship to the logarithm of plasma Atenolol concentration.

In controlled clinical trials, Atenolol, given as a single daily oral dose, was an effective antihypertensive agent providing 24 hour reduction of blood pressure. Atenolol has been studied in combination with Thiazide type diuretics, and the blood pressure reduction effects of the combination are approximately additive. Atenolol is also compatible with Methyldopa, Hydralazine, and Prazosin, each combination resulting in a larger fall in blood pressure than with the single agents above. The dose range of Atenolol is narrow and increasing the dose beyond 100 mg once daily is not associated with increased antihypertensive effect. The mechanisms of the antihypertensive effects of β blocking agents have not been established. Several possible mechanisms have been proposed :

- 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.

- Suppression of renin activity.

The results from long term studies have not shown any diminution of the antihypertensive efficacy of Atenolol with prolonged use.

By blocking the positive chronotropic and inotropic effects of catecholamines and by decreasing blood pressure, Atenolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long term management of angina pectoris. On the other hand, Atenolol can increase oxygen requirements by increasing left ventricular fiber length and end diastolic pressure, particularly in patients with heart failure.

The mechanism through which Atenolol improves survival in patients with definite or suspected acute myocardial infarction is unknown, as is the case for other β blockers in the postinfarction setting. Atenolol, in addition to its effects on survival, has shown other clinical benefits including reduced frequency of ventricular premature beats, reduced chest pain, and reduced enzyme elevation.

Indications

Hypertension : Atenolol is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide diuretic.

Acute myocardial infarction : Atenolol is indicated in the management of haemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows.

Angina pectoris due to coronary atherosclerosis : Atenolol is indicated for the long term management of patients with angina pectoris.

Dosage and Administration

Hypertension : The initial dose of Atenolol is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to Atenolol 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

Atenolol may be used alone or concomitantly with other antihypertensive agents including Thiazide type diuretics, Hydralazine, Prazosin, and α methyldopa.

Angina pectoris : The initial dose of Atenolol is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty four hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once a day oral doses of 200 mg.

Elderly patients or patients with renal impairmen : Atenolol is excreted by the kidneys; consequently dosage should be adjusted in cases of severe impairment of renal function. Some reduction in dosage may also be appropriate for the elderly, since decreased kidney function is a physiologic consequence of aging. Atenolol excretion would be expected to decrease with advancing age.

The following maximum oral dosages are recommended for elderly, and renally impaired patients due to other causes.

Creatinine Clearance ($ml/min/1.73m^2$)	**Elimination Half-life** (h)	**Maximum Dosage**
15 - 35	16 - 27	50 mg daily
< 15	> 27	25 mg daily

Some renally impaired or elderly patients being treated for hypertension may require a lower starting dose of Atenolol, 25 mg given as one tablet a day. If this 25 mg dose is used, assessment of efficacy must be made carefully. This should include measurement of blood pressure just prior to the next dose ("trough" blood pressure) to ensure that the treatment effect is present for a full 24 hours.

Although a similar dosage reduction may be considered for elderly and/or renally impaired patients being treated for indications other than hypertension, data are not available for these patient populations.

Cessation of Therapy in Patients with Angina Pectoris: If withdrawal of Atenolol therapy is planned, it should be achieved gradually and patients should be carefully observed and advised to limit physical activity to a minimum.

Contraindications

Atenolol is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and cardiac failure. It is contraindicated in patients with hypersensitivity to any of its components.

Precautions

General : Patients already on a β blocker must be evaluated carefully before Atenolol is administered. Initial and subsequent Atenolol dosages can be adjusted downward depending on clinical observations including pulse and blood pressure. Atenolol may aggravate peripheral arterial circulatory disorders.

Impaired renal function : The drug should be used with caution in patients with impaired renal function.

Cardiac failure : Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and β blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, Atenolol should be administered cautiously.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous Furosemide or equivalent therapy is a contraindication to β blocker treatment.

In patients without a history of cardiac failure : Continued depression of the myocardium with β blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalised and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalisation and diuresis, Atenolol should be withdrawn.

Concomitant use of calcium channel blockers : Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise when β blockers are administered with Verapamil or Diltiazem.

Bronchospastic diseases : Patients with bronchospastic disease should, in general, not receive β blockers. Because of its relative β_1 selectivity, however, Atenolol may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since β_1 selectivity is not absolute, the lowest possible dose of Atenolol should be used with therapy initiated at 50 mg, and a β_2 stimulating agent (bronchodilator) should be made available.

Anaesthesia and major surgery : It is not advisable to withdraw β adrenoreceptor blocking drugs prior to surgery in the majority of patients.

Diabetes and hypoglycaemia : Atenolol should be used with caution in diabetic patients if a β blocking agent is required. β blockers may mask tachycardia occurring with hypoglycaemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses Atenolol does not potentiate insulin induced hypoglycaemia and, unlike nonselective β blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis : β adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism.

Drug Interactions

Catecholamine depleting drugs (e.g., Reserpine) may have an additive effect when given with β blocking agents.

Calcium channel blockers may also have an additive effect when given with Atenolol.

β blockers may exacerbate the rebound hypertension which can follow the withdrawal of Clonidine. If the two drugs are coadministered, the β blocker should be withdrawal several days before the gradual withdraw of Clonidine.

Information on concurrent usage of Atenolol and Aspirin is limited.

Side Effects

Most adverse effects have been mild and transient. In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any β blocker, in Atenolol treated patients than in control patients. However, these usually responded to Atropine and/or to withholding further dosage of Atenolol. In addition, a variety of adverse effects have been reported with other β adrenergic blocking agents, and may be considered potential adverse effects of Atenolol.

Haematologic : Agranulocytosis

Allergic : Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central nervous system : Reversible mental depression progressing to catatonia; an acute reversible syndrome characterised by disorientation of time and place, short term memory loss, emotional lability with slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal : Mesenteric arterial thrombosis, ischaemic colitis.

Others : Erythaematous rash, Raynaud's Phenomenon.

Miscellaneous : There have been reports of skin rashes and/or dry eyes associated with the use of β adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable.

Use in Special Populations

Pregnancy : Pregnancy category D. Atenolol can cause foetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in cord blood. Administration of Atenolol, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age. No studies have been performed on the use of Atenolol in the first trimester, and the possibility of fetal injury cannot be excluded. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the foetus.

Lactation : Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when Atenolol is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Children : Safety and effectiveness in paediatric patients have not been established.

Commercial Packs

Lonet® 50 Tablet : Box containing 100 tablets in 10 x 10's blister strips. Each film coated tablet contains Atenolol BP 50 mg.

Lonet® 100 Tablet : Box containing 100 tablets in 10 x 10's blister strips. Each film coated tablet contains Atenolol BP 100 mg.