Drug Profile

2.1 Atenolol

2.2 Metoprolol tartrate

References
THE THERAPEUTIC efficacy of a drug to be maximum with minimum side effects; an optimal concentration of the drug in blood plasma must be maintained. The conventional dosage forms such as tablets and capsules demonstrate great fluctuations in the plasma level of the drug. The need for certain drugs to be delivered at a preprogrammed rate over a period led to the development of the transdermal therapeutic systems. The advantages, reliability, formulation design and the potential of the transdermal therapeutic systems as a vehicle for potential cardiovascular drugs have aroused interest and revolutionized the art of therapy.

2.1 ATENOLOL

Atenolol, first introduced in 1973, is a mild beta-blocker, a group of drugs belonging to the adrenergic antagonistic-acting family used primarily in the treatment of hypertension and cardiovascular disease, than its predecessor propranolol. The adrenergic antagonists are a class of drugs that work in the messaging systems of the body, the central nervous system (CNS) and the peripheral nervous system. They alter the neuronal pathways by binding directly to receptors and blocking messenger chemicals from sending the proper messages. The beta blockers, a subset of this class of drugs, direct their blocking action against two specific receptors in the pathway, the beta-1 receptor and the beta-2 receptor, which play central role in the control of blood flow and muscle action throughout the body (Johansson, 2001).

Atenolol is very hydrophilic and appears to penetrate the brain only to a limited extent. Its biological half-life is somewhat longer than that of Metoprolol. Atenolol is incompletely absorbed (about 50%), but most of the absorbed dose reaches the systemic circulation. The drug is excreted largely unchanged in the urine and the elimination half-life is about 5 to 8 hours. The transdermal route is capable of avoiding the hepatic first pass effect, thus achieving higher systemic bioavailability of Atenolol (Tripathi, 2001).
2.1.1 Description (Budvari, 1996 and Johansson, 2001)

Structural formula

![Chemical Structure](image)

**Chemical Name**: 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]benzeneacetamide.

**Registry Number**: ICI-66082

**Molecular Formula**: $\text{C}_{14}\text{H}_{22}\text{N}_{2}\text{O}_{3}$

**Molecular Weight**: 266.34

**Composition**

- C = 63.13%
- H = 8.33%
- N = 10.52%
- O = 18.02%

**Physical nature**

It is a white or almost white powder. It is odorless or almost odorless.

**Solubility**

Freely soluble in methanol; soluble in acetic acid, DMSO; sparingly soluble in 96 % ethanol; slightly soluble in acetone, dioxane, practically insoluble in acetonitrile, ethylacetate, chloroform.

**Therapeutic Category**

Beta-adrenoceptor antagonist.
2.1.2 Pharmacology (Hardman et al., 2001)

Atenolol is a beta-adrenoreceptor antagonist, or a more commonly known as a beta-blocker. Beta-blockers are competitive inhibitors and interfere with the action of stimulating hormones on beta-adrenergic receptors in the nervous system. Beta-blockers can be subdivided into two distinct groups known as beta-1 and beta-2. Beta-1 blockers mainly affect the heart; beta-2 blockers mainly affect receptors in bronchial tissue.

Most beta-blockers are non-specific i.e. they have both beta-1 and beta-2 effects eg. labetolol, nadolol, oxprenolol, pindolol, propanolol, sotalol and timolol. Some of the beta-blockers are specific i.e. cardioselective eg. acebutolol, atenolol, betaxolol, esmolol and metoprolol.

Atenolol is a beta-1 blocker. Atenolol works by competing for receptor sites on cardiac muscle. This slows down the strength of the heart’s contractions and reduces its oxygen requirements and the volume of blood it has to pump. Hypertension (high blood pressure) may be treated with these drugs because of their ability to increase the diameter of the blood vessels thus allowing blood to flow under less pressure. Some of these medicines include a diuretic drug to help reduce blood pressure by increasing the excretion of excess fluid. Beta-blockers are also used to treat myocardial infarction (heart attack) and arrhythmias (rhythm disorders), angina (chest pains), and disorders arising from decreased circulation and vascular constriction, including migraine.

2.1.3 Pharmacokinetic Properties (Hardman et al., 1996)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral bioavailability</td>
<td>56 ± 30%</td>
</tr>
<tr>
<td>Distribution</td>
<td>0.95 ± 0.15 (L/kg)</td>
</tr>
<tr>
<td>Bound in plasma</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Peak plasma level (Cmax)</td>
<td>1.0 µg / ML</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td>94 ± 8%</td>
</tr>
<tr>
<td>Elimination rate constant (Ke)</td>
<td>0.1136 hr⁻¹</td>
</tr>
<tr>
<td>Terminal elimination (t1/2)</td>
<td>6.1 ± 2.0 hrs</td>
</tr>
<tr>
<td>Clearance</td>
<td>2.0 ± 0.2 (mL / min / kg)</td>
</tr>
</tbody>
</table>
2.1.4 Administration and Dosage (St. Louis, 1998)

- Hypertension (oral)

*Initial dosage* - The 50 mg dosage once daily, used alone or added to a diuretic. The full effect of the dose will usually be seen within 1 to 2 weeks. If an optimal response is not achieved, increase to 100 mg / day. Dosage if greater than 100 mg / day is unlikely to produce any further benefit.

- Angina pectoris (oral)

*Initial dosage* - The oral initial dosage is of 50 mg / day for angina pectoris. If an optimal response is not achieved within 1 week, the dose is increased to 100 mg / day. Some patients may require 200 mg / day for optimal effect. With once daily dosing, 24-hour control is achieved by giving doses larger than necessary to achieve an immediate maximum effect.

- Acute myocardial infarction

*Intra venous* - Treatment is initiated as soon as possible after the arrival of the patient in the hospital and after eligibility is established. Treatment is started with 5 mg over 5 minutes followed by another 5 mg i.v. injection 10 minutes later. Dilutions in dextrose injection, sodium chloride injection or sodium chloride may be used. These admixtures are stable for 48 hours if not used immediately.

*Oral* - In patients who tolerate the full 10 mg i.v. dose, the dose of 50 mg tablet is initiated after 10 minutes of the last i.v. dose followed by another 50 mg dose 12 hours later. Thereafter, 100 mg once daily or 50 mg twice daily for a further 6 to 9 days or until discharge from the hospital is administered.

2.1.5 *Uses* (Johansson, 2001)

Atenolol can be used as an antihypertensive to treat raised blood pressure, as an anti-anginal to relieve anginal symptoms and to improve tolerance and as an anti-arrhythmic to regulate heartbeat and to treat myocardial infarctions. It is also used in the management of alcohol withdrawal, in anxiety states, migraine prophylaxis, hyperthyroidism, and tremor.
Administration can be oral as tablets, capsules or syrup, or by injection. It is also available with diuretics for the treatment of antihypertensive patients. In alcohol withdrawal, Atenolol can be used in conjunction with standard alcohol withdrawal treatments and may be useful in the treatment of some patients with alcohol withdrawal Syndrome.

- **Anxiety disorders** - Atenolol is normally used in acute stress reactions, generalized anxiety and panic disorder. It is considered most effective in patients with somatic anxiety, and especially helps in the reduction of tremor and/or palpitations. The patient normally improves within 1-2 hours with relatively low doses.

- **Cardiac disorders, angina pectoris** - The basis of angina therapy is to reduce the frequency and severity of the attack and to improve functional capacity and to prevent myocardial infarction or sudden death. At present, there are three groups of anti-anginal drugs: nitrates, beta-blockers and calcium channel blockers. They can either be used alone or in combination with each other. Beta-blockers are particularly effective in patients with exertional angina, normally young to middle aged people and is especially helpful to those with hypertension, hyperdynamic left ventricular systolic function, or an excessive heart rate or large blood pressure increases due to exercise.

- **Cardiac arrhythmias** - Atenolol is used to combat cardiac arrhythmias primarily due to beta blockade, and is a class II anti-arrhythmic agent. It is also used to control the ventricular response rate in chronic atrial fibrillation, supraventricular tachycardia and in symptomatic premature ventricular complexes.

- **Congestive heart failure** - Atenolol should not be given if congestive heart failure is not under control. It must be given with great care. A low initial dose is given, increasing gradually and continuing for several months.

- **Myocardial infarction** - The intravenous infusion of Atenolol in the early period following myocardial infarction has been associated with a reduction in mortality. Analysis also suggests that beta-blockers improve early survival by reducing the incidence of cardiac rupture. Studies demonstrate that in patients who survive acute myocardial infarction
long-term treatment reduce mortality and rate of re-infarction. Patients are normally started on the treatment whilst in hospital and continue taking medication for at least a year after the infarction.

- **Hyperthyroidism**- Atenolol is effective in controlling sympathetic over activity associated with hyperthyroidism including tremor, anxiety, and muscle weakness. Beta-blockers in general have been used in the pre-operative management of hyperthyroidism.

- **Migraine**- Atenolol can be used for the prophylaxis of migraine but propanolol is more effective and is considered to be the treatment of choice. Long-term treatment may be necessary but is controversial.

- **Tremor**- Beta-blockers in general including Atenolol have become drugs of first choice in patients with essential tremor, needing regular medication. Propanolol is by far the best predominantly due to blockade of beta-2 receptors on extrafusal muscle fibers and muscle spindles, although there may be some CNS effect.

- **Hypertension**- Atenolol causes a fall in blood pressure but is not without risks. The fall usually occurs 1-2 weeks after oral administration. Atenolol is not necessarily appropriate for all hypertensive patients.

### 2.1.6 Adverse Effects And Treatments

The most frequent and serious adverse effects of beta-blockers are directly related to its ability to block beta-receptors. The most serious adverse effects are heart failure, heart block and bronchospasm. Other more minor side effects include fatigue and coldness of extremities. Reactions tend to be more severe after intravenous injection as compared to oral administration.

- **Cardiovascular effects**- These include bradycardia and hypotension. Congestive heart failure or heart block, this can be a precipitated in-patient with previously underlying cardiac disorder. Abrupt withdrawal of beta-blockers may exacerbate angina and may lead to sudden death.
• Bronchospasm- This may be precipitated in some susceptible patients due to blockade of beta-2 receptors in the bronchial smooth muscle. Pneumonitis, pulmonary fibrosis, and pleurisy have also been reported.

• CNS effects- These include depression, hallucinations, confusion and sleep disturbances. Convulsions and coma have been reported following beta-blocker overdose. Beta-blockers with high lipid solubility are more likely to cause these effects.

• Fatigue- Besides fatigue paraesthesia, peripheral neuropathy and myopathies have been reported.

• Gastro-intestinal effects- Nausea and vomiting, diarrhea, constipation, and abdominal cramping have been observed.

• Integumentary system effects- Skin rash, pruritus, and reversible alopecia are noted.

• Ocular effects- Decreased tear production, blurred vision and soreness have been noticed.

• Hematological effects- Nonthrombocytopenic purpura, thrombocytopenia, and rarely agranulocytosis, transient eosinophilia can also occur.

2.1.7 Overdose

Many overdose cases concerning beta-blockers are uneventful, but some patients do develop severe and occasionally fatal cardiovascular depression. Effects can include bradycardia, cardiac conduction block, hypotension, cardiac failure, cardiogenic shock, convulsions, coma and respiratory depression.

In some cases bronchoconstriction can also occur, although infrequently. Most reports of serious toxic reactions following beta-blocker overdose concern beta-blockers with significant membrane-stabilizing activity, such as propanolol or oxprenolol. Overdose of beta-blockers with intrinsic sympathomimetic activity may give tachycardia and hypertension. Overdose of sotalol, a beta-blocker with class II and class III anti-arrhythmic properties usually give rise to ventricular tachyarrhythmia.
2.1.8 Treatment

The overdosing of beta-blockers can be treated with gastric lavage with charcoal for patients who have recently ingested the beta-blocker. When indicated additional measures can be instituted to counter hypotension. Mild hypotension may respond to fluid administration; if hypotension continues glucagon or sympathomimetic agents may be required. Bradycardia may be treated with atropine, sympathomimetic agents or a pacemaker. If anti-arrhythmic agents are required, lignocaine or phenytoin is preferred.

2.1.9 Precautions

Beta-blockers should not be given to patients with bronchospasm or asthma or to those with a history of obstructive airway disease. This applies even if it is a cardioselective (beta-1 blocker). Other contra-indications include metabolic acidosis, sinus bradycardia, or partial heart block. They should not be given to patients with congestive heart failure unless their heart failure is controlled and even then great care is still necessary. Patients with pheochromocytoma should not receive beta-blockers without concomitant alpha-adrenoceptor blocking therapy. Beta-blockers may mask the symptoms of hyperthyroidism and hypoglycemia. They may unmask myasthenia gravis. Psoriasis may be aggravated. Some elderly patients with hypertension may not respond well to a beta-blocker as well as a younger patient. Dosage will need to be reduced in patients with renal or hepatic dysfunction. A abrupt withdrawal of beta-blockers has sometimes resulted in angina, myocardial infarction, ventricular arrhythmias, and death. Patients who are on beta-blockers long-term should have their medication discontinued slowly over a period of 1-2 weeks. Patients with hypersensitivity to stings and antigens may find that their reaction to stings etc is increased. Therefore causing a greater incidence of anaphylactic shock.

2.1.10 Interactions

- Adrenaline-Blood pressure becomes elevated due to alpha mediated vasoconstriction. His is followed by reflex bradycardia and occasionally arrhythmias. The bronchodilator effects of adrenaline are inhibited.
• Alcohol - Atenolol is not affected by alcohol intake.
• Antacids - Concurrent use of Atenolol and antacids shows a drop in the bioavailability of Atenolol. The results are variable for other beta-blockers.
• Amiodarone - Bradycardia, cardiac arrest, and ventricular fibrillation have been reported.
• Ampicillin - Serum Atenolol concentrations are reduced by concurrent administration of ampicillin given in doses of 1g orally in 6 healthy subjects.
• Calcium channel blockers - Concurrent use has resulted in hypotension, bradycardia, conduction defect, and cardiac failure.
• NSAIDS - The anti-hypertensive effects of beta-blockers may become impaired when taken with NSAIDS.

2.1.11 Rare Adverse Effects

Skin rash, pain in the joints and muscles, unusual dreams, itching, headache, dizziness, nausea, diarrhea, indigestion, chest pains, shortness of breath, most often associated with a heart attack (angina pectoris), congestive heart failure, respiratory arrest, suffocation due to bronchial muscle spasms, psychosis are rarely observed side effects. With beta-blockers the medication should not be stopped suddenly. Severe life-threatening adverse reactions may occur. The physician is notified promptly if medication is discontinued.

2.1.12 Special Conditions To Observe

• Children - Atenolol is normally not prescribed to children under 12 years old. Physician is consulted for the best treatment course. If a child is given this medication, he or she is monitored closely and any adverse effect, an especially low sugar level in the blood is reported immediately to the physician.
• Pregnancy - Women who are pregnant are under direct care of a physician.
• Elderly - The minimum doses needed is used and physician is notified immediately in case of any adverse reactions. Geriatric patients have been determined to be at greater risk for heart complications while using this medication.
2.2 Mетопролол тартарате

The drug Metoprolol tartrate a selective adrenergic blocking agent, has become well established as a first choice drug in the treatment of mild to moderate hypertension and stable angina and is beneficial in post-infarction patients. However, Metoprolol tartrate is reported to be subjected to extensive hepatic first-pass metabolism following oral administration and has a short biological half-life.

On the basis of above fact it is therefore, thought appropriate to incorporate Metoprolol tartrate in the polymer matrices and design a transdermal therapeutic system in order to achieve the objective like patient compliance, convenience of application, removal, reduced frequency of drug dosing, avoidance of first pass effect and incompatibility of orally co-administered drugs (Tripathi, 2001).

2.2.1 Description (Budavari, 1996)

Structural Formula:

\[
\text{Chemical Name} : \quad (\pm)-1\text{-}(\text{isopropyl amino})-3 - [p - \text{-(\beta - methoxy ethyl) phenoxy}] -2\text{-propanol.}
\]

\text{Drug code Number} : \quad \text{CGP 2175 : H93 / 26}

\text{Molecular Formula} : \quad \text{Metoprolol (C}_{15}\text{H}_{25}\text{NO}_{3}) \quad \text{Metoprolol tartrate (C}_{15}\text{H}_{25}\text{NO}_{3})_{2} \text{C}_{6}\text{H}_{12}\text{O}_{6}

\text{Molecular Weight} : \quad 267.37

\text{Composition} : \quad \text{C} = 67.38 \%
\quad \text{H} = 9.43 \%
\quad \text{N} = 5.24 \%
\quad \text{O} = 17.95 \%
Physical nature

Metoprolol tartarate is a white odorless crystalline powder with a bitter taste having melting point 120°.

Solubility

Very soluble in water; soluble in alcohol and chloroform; Practically insoluble in acetone and ether. Protect from light

Therapeutic Category

Beta-1 adrenergic blocker.

2.2.2 Pharmacology

It is selective beta-1 receptor blocker devoid of ISA (Intrinsic sympathomimetic activity). It effectively inhibits the inotropic and chronotropic responses of isoprenaline, and its potency in this regard is equal to propranolol. It reduces plasma renin activity in hypertensives. The antianginal effect is also comparable to that of propranolol. Because of its relative cardio selectivity, metoprolol tartarate may be preferred to a nonselective agent in asthmatics, patients prone to develop hypoglycemia, and in those with peripheral vasospastic diseases. It also reduces mortality in post infarct patients.

2.2.3 Pharmacokinetics Parameter (Hardman et al., 2001)

<table>
<thead>
<tr>
<th>Parameter</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral bioavailability</td>
<td>38 ± 14%</td>
</tr>
<tr>
<td>Distribution</td>
<td>4.2 ± 0.7 (Lts / kg)</td>
</tr>
<tr>
<td>Bound in plasma</td>
<td>11 ± 1%</td>
</tr>
<tr>
<td>Peak plasma level (C_max)</td>
<td>25 ± 18 ng / mL</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td>10 ± 3%</td>
</tr>
<tr>
<td>Elimination rate constant (K_ε)</td>
<td>0.198 hr^{-1}</td>
</tr>
<tr>
<td>Terminal elimination (t_{1/2})_el</td>
<td>3.3 ± 0.2 hrs</td>
</tr>
<tr>
<td>Clearance</td>
<td>15 ± 3 (mL / min / kg)</td>
</tr>
</tbody>
</table>
2.2.4 Administration and Dosage (St. Louis, 1998)

- Hypertension

*Initial dosage*- The dosage of 100 mg / day in single or divided doses, used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved.

*Maintenance dose*- The dose 100 mg to 450 mg / day is required. Dosage > 450 mg / day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of 24-hour period; larger or more frequent daily doses may be required.

- Angina pectoris

*Initial dosage*- The dose 100 mg / day in two divided doses, dosage may be gradually increased at weekly intervals until optimum clinical response is obtained or a pronounced slowing of heart rate occurs. Effective dosage range is 100 mg to 400 mg / day. Dosages above 400 mg / day have not been reported. If treatment is to be discontinued, reduce dosage gradually over 1 to 2 weeks.

- Myocardial infarction (MI)

*Early treatment*- During the early phase of definite or suspected acute MI, treatment initiated as soon as possible after the patient’s arrival in a coronary care or similar unit immediately after the patient is hemodynamically stable. The patient is administered 3 IV bolus injections of 5 mg each, at approximately 2 minutes intervals. During IV administration, carefully monitoring of blood pressure, heart rate and ECG is done. In patients who can tolerate the full IV dose, the treatment is started with 25 mg or 50 mg orally every 6 hours (depending on tolerance) 15 minutes after the last IV dose or as soon as the clinical condition allows. In patients with severe intolerance, the treatment is discontinued.
Late treatment - Patients with contraindications to early treatment, patients who do not tolerate the full early treatment and patients in whom therapy is delayed for any other reason the treatment is initiated with 100 mg orally, twice daily, as soon as the clinical permits. The treatment continued for at least 3 months. Although the efficacy beyond 3 months has not been conclusively established, data suggest treatment should continue or 1 to 3 years.

2.2.5 Unwanted Effects (Rang et al., 2000)

- Effects on CNS - Highly lipid soluble compounds produce sedation, lethargy, lack of drive, forgetfulness, disturbed sleep, nightmare, depression and psychotic symptoms. These are less with lipid soluble compounds. (Nadolol, Atenolol).

- Effect on CVS-
  A) Overdosage may precipitate severe bradycardia leading to partial and complete heart blocks.
  B) Withdrawal of cardiac sympathetic drive may precipitate or aggravate congestive cardiac failure.
  C) Variant angina may become worse due to unopposed effect following β-blockade.
  D) Exacerbation of peripheral vasospastic diseases (e.g. Raynaud's phenomenon) due to unopposed vasoconstriction by α-receptor.

- Bronchial muscle - It may precipitate an acute attack of bronchial asthma in susceptible patients.

- Metabolic effects - It is unadvisable to use beta - blockers in insulin dependent diabetic patients since, (a) by blocking glycogenolysis they potentiate hypoglycaemic action of Insulin & oral hypoglycaemic agents and (b) they mask the system of hypoglycemic like palpitation and tremor, which are the warning signs for the patients to take food. It increases serum LDL levels and decreases serum HDL levels.
2.2.6 Contraindications

- Hypertension and angina: Metoprolol tartarate is contraindicated in sinus bradycardia, heart block greater than first degree, cardio shock and cardiac failure.

- Myocardial infarction: Metoprolol tartarate is contraindicated in patients with a heart rate less than 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure less than 100 mm Hg or moderate-to-severe cardiac failure.

2.2.7 Interaction (McEvoy, 2001)

- Drug-drug cardiac glycosides: Enhanced bradycardia and patient to be monitored closely.

- Diuretics or other antihypertensive agents: Antihypertensive effects are potentiated and patient is monitored closely.

- Sympathomimetic agents: Beta-adrenergic effects of sympathomimetic agents antagonized and drug effect monitored.

- Verapamil: The bioavailability of metoprolol may be decreased when given with antiarrhythmic agents and patients monitored for drug effect.
REFERENCES


