REVIEW OF DRUGS
DILTIAZEM HYDROCHLORIDE

Chemical name: \((2S\text{-cis})-3-(\text{acetyloxy})-5-[2-(\text{dimethylamino}) \text{ethyl}]-2,3\text{-dihydro}-2-(4\text{-methoxy-Phenyl})-1,5\text{benzothia-zepin4 (5H)-one monohydrochloride.}

Structural formula:

![Structural formula of Diltiazem Hydrochloride](image)

Figure 7. Structural formula of Diltiazem Hydrochloride

Molecular formula: \(C_{22}H_{26}N_{2}O_{4}S\).

Category: Calcium channel blocker or Calcium antagonist.

Description: Diltiazem hydrochloride is white to off-white crystalline powder. It is odorless and has bitter taste.

Melting point: \(210^\circ\text{C}\)

Solubility:

| Solvent             | Solubility
|---------------------|--------------
| Chloroform          | Freely soluble
| Formic acid         | Freely soluble
| Methanol            | Freely soluble
| Water               | Freely soluble
| Dehydrated alcohol  | Sparingly soluble
| Benzene             | Practically insoluble
| Ether               | Insoluble

Dissociation constant: 7.7

Pharmacology:
Diltiazem is a member of the group of drugs known as benzothiazepines, which are a class of calcium channel blockers, used in the treatment of hypertension, angina pectoris, and some types of arrhythmia. It is a class 3 anti-anginal drug, and a class IV antidysrhythmic. It incites very minimal reflex sympathetic changes. Diltiazem is a potent vasodilator, increasing blood flow and variably decreasing the heart rate via strong depression of A-V node conduction. Its pharmacological activity is somewhat similar to verapamil.

Pharmacokinetic properties:

i) Oral absorption: 90%
ii) Bioavailability: absolute bioavailability is 36-50%.
iii) Metabolism: hepatic.
iv) Plasma half life range: 2-11h
   Mean (single dose): 4.5 h
v) Volume of distribution: 5 l/kg
vi) Plasma protein binding: 80-90%
Adverse effects:
Reflex sympathetic response. Caused by the peripheral dilatation of vessels and the resulting drop in blood pressure; the response works to counteract the ionotropic, chronotropic and dromotropic effects of diltiazem are Hypotension, Bradycardia, Dizziness, Flushing and acute hepatic injury and paralytic ileus have also been reported.

Drug interaction:
Diltiazem should never be used concurrently with a i.v. beta-blocker; it can result in AV block. Quinidine should not be used concurrently with calcium channel blockers because of reduced clearance of both drugs and potential pharmacodynamic effects at the SA and AV nodes. Diltiazem and verapamil inhibit hepatic drug metabolizing enzymes, promoting possible drug interactions.

Uses and administration:
Stable angina pectoris, unstable angina pectoris, myocardial infarction coronary artery spasm, hypertension, arrhythmias, raynaud’s phenomenon, esophageal motility disorder, migraine, primary pulmonary hypertension.

Administrations: Oral

Precautions and contraindication:
Patients with reduced ventricular function may not be able to counteract the ionotropic and chronotropic effects of diltiazem, the result being an even higher compromise function of SA node or AV conduction disturbances. Use of diltiazem should be avoided in patients with SA or AV nodal abnormalities, because of its negative chronotropic and dromotropic effects and low blood pressure. Patients with systolic blood pressures below 90 mm Hg should not be treated with diltiazem. Diltiazem may paradoxically increase ventricular rate in patients with WPW syndrome because of accessory conduction pathways.
LOVASTATIN [6-10]

Chemical name: [1S-[1α(R*),3α,7β,8β(2S*,4S*),8α]-2-methylbutanoic acid 1,2,3,7,8,8α-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo2H-pyran-2-yl)ethyl]-1-naphthalenylester

Structural formula:

![Figure 8. Structural formula of Lovastatin](image)

Molecular formula: C_{24}H_{36}O_{5}
Molecular weight: 404.543
Category: Cholesterol (hypolipidemic agent) in those with hypercholesterolemia and so preventing cardiovascular disease

Description: Lovastatin is a white crystalline powder.

Melting point: 175°C
Solubility: Sparingly soluble in alcohol and insoluble in water

Dissociation constant: Consistent with structure, Lovastatin exhibits no acid/base dissociation constant.

Pharmacology:
The mode of action of statins is HMG-CoA reductase enzyme inhibition. This enzyme is needed by the body to make cholesterol. Lovastatin not only causes cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL (low density lipoprotein) particles. Apolipoprotein B concentration falls substantially during treatment with Lovastatin. Lovastatin's ability to lower LDL is thought to be due to a reduction in VLDL, which is a precursor to LDL. Also, Lovastatin may increase the number of LDL receptors on the surface of cell membranes, and thus increase the breakdown of LDL. Lovastatin can also produce slight to moderate increases in HDL, and slight to moderate decreases in triglycerides. Both of these effects are typically beneficial to a patient with a poor lipid profile. Both Lovastatin and its b-hydroxyacid metabolite are highly bound (>95%) to human plasma proteins. Animal studies demonstrated that Lovastatin crosses the blood-brain and placental barriers. Elderly patients or those with renal insufficiency may have higher plasma concentrations of Lovastatin after administration and may require a lower dose. The usual recommended starting dose is 20 mg once a day given with the evening meal and the dose range is 10-80 mg a day in a single dose, or divided into two doses.

Pharmacokinetic properties:

i) Oral absorption -- Incomplete
ii) Presystemic metabolism -- Extensive
iii) Plasma half life range -- 1.1 - 1.7 h
iv) Plasma protein binding -- > 95%

Adverse effects:

Lovastatin is usually well tolerated. Lovastatin and all statin drugs can rarely cause
myopathy or rhabdomyolysis. This can be life-threatening if not recognised and treated in time, and so any unexplained muscle pain or weakness whilst on lovastatin should be promptly mentioned to the prescribing doctors.

**Drug interaction:**

As with all the statin drugs, drinking grapefruit juice during therapy increases the risk of serious side effects. Grapefruit juice inhibits CYP3A4, and thus decreases the metabolism of statins, increasing their plasma concentrations. Lovastatin at doses higher than 20 mg per day should not be used in conjunction with gemfibrozil or other fibrates, niacin, or cyclosporin. This is because of the significantly increased risk of rhabdomyolysis.

**Dosage:**

Hypercholesterolemia
Dosage 20 mg p.o., tablet
Type IIb hyperlipidemia
Dosage 20 mg p.o., tablet

**Uses and administration:**

1) Reduction of total and LDL cholesterol level in patients with primary hypercholesterolemia when the response to diet and other non-pharmacological measure has been inadequate.

2) Reduction of elevated cholesterol level in patients with combined hypercholesterolemia and hypertriglyceridemia, when the hypercholesterolemia is the abnormality of more concern.

3) Reduction of VLDL levels in type III hyperlipidemia with correction of characteristic compositional abnormality in this fraction.

4) Reduction of elevated cholesterol level in secondary hyperlipidemia caused by non-insulin dependent diabetes mellitus or the nephritic syndrome.

**Precautions and contraindication**

i) Hypersensitivity to any component of the preparation.

ii) Active liver disease or unexplained persistent elevation of serum transaminases.
PROPRANOLOL HYDROCHLORIDE

Chemical name: (RS)-1-isopropylamino-3-naphthoxy) propan-2-ol hydrochloride

Structural formula:

![Structural formula of Propranolol Hydrochloride](image)

Figure 9. Structural formula of Propranolol Hydrochloride

Molecular formula: C\textsubscript{16}H\textsubscript{21}NO\textsubscript{2}HCl

Category: β-adrenoceptor blocking agent, antianginal, and antihypertensive

Description: Propranolol hydrochloride is a white or off-white odorless powder with bitter taste.

Melting point: 163 - 166 °C

Solubility:
- In alcohol --- 1 in 20.
- Soluble in water and ethanol 95%, slightly soluble in chloroform, practically, insoluble in ether.

Dissociation constant: 9.5

Pharmacology:
Propranolol is a blocker of epinephrine on both β\textsubscript{1}- and β\textsubscript{2}-adrenergic receptors. It has little intrinsic sympathomimetic activity (ISA) but has strong membrane stabilizing activity (only at high blood concentrations, e.g. overdosage). Only L-propranolol is a powerful adrenoceptor antagonist, whereas D-propranolol is not. However, both have local anesthetic effect.

Pharmacokinetic properties:
- Oral absorption -> 95%
- Presystemic metabolism - 50-95%
- Plasma half life range - 3 - 6 hrs
  - Mean - 3.9 hrs
- Volume of distribution - 2.3 - 5.5 l/kg
- Plasma protein binding - 80 - 95%

Adverse effects:
Hypotension, severe Bronchospasm, Hypoglycemia, and Bradyarrhythmias usually in patients with pre-existing organic heart disease. Cardiogenic shock, convulsions and seizures.

Drug interaction:
Beta blockers, including propranolol, have an additive effect with other drugs which decrease blood pressure, or which decrease cardiac contractility or conductivity. Clinically-significant interactions particularly occur with:

- Verapamil
• Epinephrine
• β2-adrenergic receptor agonists
• Clonidine
• Ergot alkaloids
• Isoprinosine
• Non-steroidal anti-inflammatory drugs
• Quinidine
• Cimetidine
• Lidocaine
• Phenobarbital
• Rifampicin

Uses and administration:

Propranolol is indicated for the management of various conditions including:

• Hypertension
• Angina pectoris
• Tachyarrhythmia
• Myocardial infarction
• Control of tachycardia/tremor associated with anxiety and hyperthyroidism
• Essential tremor
• Migraine prophylaxis
• Tetralogy of Fallot
• Phaeochromocytoma (along with α blocker)
• Post Traumatic Stress Disorder (experimental)

Precautions and contraindication:

Propranolol should be used with caution in patients with:

• Diabetes mellitus or hyperthyroidism, since signs and symptoms of hypoglycemia may be masked
• Peripheral vascular disease and Reynaud's syndrome, which may be exacerbated
• Phaeochromocytoma, as hypertension may be aggravated without prior alpha blocker therapy
• Myasthenia gravis, may be worsened
• Other drugs with bradycardiac effects
ATENOLOL (15-19)

Chemical name: 2-[4-[2-hydroxy-3-(1-methylethylamino) propoxy] phenyl] ethanami

Structural formula:

![Figure 10. Structural formula of Atenolol](image)

Molecular formula: C\textsubscript{14}H\textsubscript{22}N\textsubscript{2}O\textsubscript{3}

Category: β-adrenoceptor antagonist

Description: It is white powder. It is odorless and has slightly bitter taste.

Melting point: 150 - 152 °C

Solubility:
- In alcohol --- > 1 in 50
- In water --- > 1 in 100

Soluble in water and 95% ethanol, slightly soluble in chloroform, practically
Insoluble in ether.

Dissociation constant: 9.6

Pharmacology:
Atenolol antagonize the chronotopic response to stimulation of the cardiac accelerator nerve in the cat over the dose range 5-100 μg·kg\textsuperscript{-1} in dogs, Atenolol in dose of 100 μg kg\textsuperscript{-1} displaced the heart rate response to isoproterenol infusion to the right in parallel fashion. When bronchospasm was induced by acetylcholine or histamine, no effect of this dose of atenolol on the bronchodilating effect of isoproterenol could be demonstrated. Atenolol has no effect upon other receptors such as the 5-HT receptor.

Pharmacokinetic properties:
- i) Oral absorption − 44%
- ii) Presystemic metabolism − Nil
- iii) Plasma half life range − 6-8 hrs
- iv) Volume of distribution − 0.5-1.5 l/kg
- v) Plasma protein binding − > 5%

Adverse effects:

Atenolol causes significantly fewer central nervous system side effects (depressions, nightmares) and fewer bronchospastic reactions, both due to its particular pharmacologic profile. It was the main β-blocker identified as carrying a higher risk of provoking type 2 diabetes, leading to its downgrading in the United Kingdom in June 2006 to fourth-line agent in the management of hypertension. In addition, β-blockers blunt the usual sympathetic nervous system response to hypoglycemia (i.e. sweating, agitation, tachycardia). These drugs therefore have an ability to mask a dangerously low blood sugar, which further decreases their safety and utility in diabetic patients.
Drug interaction:

Beta blockers, including propranolol, have an additive effect with other drugs which decrease blood pressure, or which decrease cardiac contractility or conductivity. Clinically-significant interactions particularly occur with:

- Verapamil
- Epinephrine
- \( \beta_2 \)-adrenergic receptor agonists
- Clonidine
- Ergot alkaloids
- Isoprinosine
- Non-steroidal anti-inflammatory drugs
- Quinidine
- Cimetidine
- Lidocaine
- Phenobarbital
- Rifampicin

Uses and administration:
The indication for atenolol is broadly similar to those for propranolol and other beta blockers, when the therapeutic target is the heart itself. It is used in the treatment of:

- Hypertension
- Angina pectoris
- Cardiac arrhythmias
- Myocardial infarction.

It is administered orally as well as parenterally.

Precautions and contraindication:
1) Second and third degree heart block
2) Untreated heart failure
3) Cardiogenic shock.

Symptoms of overdose are due to excessive pharmacodynamic actions on \( \beta_1 \) and also \( \beta_2 \) receptors. These include bradycardia, severe hypotension with shock, acute heart failure, hypoglycemia (= low blood sugar) and bronchospastic reactions. Treatment is largely symptomatic. Hospitalization and intensive monitoring is indicated. In early cases emesis can be induced. Activated charcoal is useful to absorb the drug. Atropine will counteract bradycardia, glucagon helps with hypoglycemia, dobutamine can be given against hypotension and the inhalation of a \( \beta_2 \)-mimetic as hexoprenaline or salbutamol will terminate bronchospasm.
REFERENCES:

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