2. Introduction to the Drugs...
2. INTRODUCTION TO THE DRUGS

2.1 HYPERCHOLESTEROLEMIA

Hyperlipidemia is a major cause of atherosclerosis and atherosclerosis-associated conditions, such as coronary heart disease (CHD), ischemic cerebrovascular disease, and peripheral vascular disease. Dyslipidemias, including hyperlipidemia (hypercholesterolemia) and low levels of high-density-lipoprotein cholesterol (HDL-C), are major causes of increased atherogenic risk; both genetic disorders and lifestyle contribute to the dyslipidemia seen in developed countries around the world. Recognition that dyslipidemia is a risk factor has led to the development of drugs that reduce cholesterol levels. These drugs provide benefit in patients across the entire spectrum of cholesterol levels, primarily by reducing levels of low-density lipoprotein cholesterol (LDL-C). Hyperlipidemia (elevated levels of triglycerides or cholesterol) and reduced HDL-C levels occur as a consequence of several interrelated factors that affect the concentrations of the various plasma lipoproteins. These factors may be lifestyle or behavioral (e.g., diet or exercise), genetic (e.g., mutations in a gene regulating lipoprotein levels), or metabolic.

Plasma lipoprotein

Lipids and cholesterol are transported through the blood stream as lipoproteins. Lipoproteins are macromolecular assemblies that contain lipids and proteins. The lipid constituents include free and esterified cholesterol, triglycerides, and phospholipids. The protein components, known as apolipoproteins or apoproteins, provide structural stability to the lipoproteins, and also may function as ligands in lipoprotein-receptor interactions or as cofactors in enzymatic processes that regulate lipoprotein metabolism. In all spherical lipoproteins, the most water-insoluble lipids (cholesteryl esters and triglycerides) are core components, and the more polar, water-soluble components (apoproteins, phospholipids, and unesterified cholesterol) are located on the surface. These apolipoproteins include apolipoprotein apoA-I, apoA-II, apoA-IV, apoA-V, apoB-100, apoB-48, apoC-I, apoC-II, apoC-III, apoE, and apo-a. Except for apo-a, the lipid-binding regions of all apoproteins contain structural features called amphipathic helices that interact with the polar, hydrophilic lipids (such as surface phospholipids) and with the aqueous plasma environment in which the lipoproteins circulate.
There are four main classes of lipoprotein differing in the relative proportion of the core lipoids and in the type of apoprotein. They are classified as

- High density lipoprotein (HDL)
- Low density lipoprotein (LDL)
- Very low density lipoprotein (VLDL)
- Chylomicrons

**Dyslipidaemia**

Dyslipidaemia may be primary or secondary. The primary form are genetically determined. They are classified according to which lipoprotein particle is raised. Secondary form of dyslipidemia are consequence of other conditions such as diabetes mellitus, alcoholism, nephrotic syndrome, chronic renal failure, hypothyroidism and administration of drugs.

Several drugs are used to decrease plasma LDL cholesterol. Drug therapy to lower plasma lipids is only one approach to treatment and is used in addition to dietary management and correction of other modifiable cardiovascular risk factors.

**Lipid lowering drugs**

- **HMG Co A reductase inhibitors**: Atorvastatin, simvastatin, lovastatin, pravastatin, cerivastatin, rosuvastatin.
- **Fibrates**: Benzafibrate, cipolfibrate, gemfibrozil, fenofibrate and clofibrate.
- **Bile acid binding resins**: Colestyramine and colestipol.
- **Nicotinic acid**
- **Ezetimibe**
- **Probucol**
- **Combination drug therapy**: Statins combined with drugs like ezetimibe, fibrates, bile acid binding resins and nicotinic acid.
2.1.1 ATORVASTATIN CALCIUM

NOMENCLATURE:

Chemical Name \(^{144}\): \([R-(R^*,R^*)]-2-(4-flurophenyl)-\beta,\delta\text{-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt trihydrate (2:1).}

Molecular weight \(^{144}\): 1209.42

CAS Number \(^{145}\): 134523-03-8

Formula:

Empirical formula \(^{145}\): \(C_{66}H_{68}CaF_{2}N_{4}O_{10}\)

Structural formula:

![Structural formula of Atorvastatin Calcium](image)

PHYSICAL PROPERTIES

Appearance \(^{145}\): It is a white off white crystalline powder.

Solubility \(^{144}\): It is slightly soluble in water, pH 7.4 phosphate buffer and acetonitrile; slightly soluble in ethanol and freely soluble in methanol.

Melting point: \(168-170^\circ C\)

UV spectrum: \(\lambda_{\text{max}}\) at 246 nm in methanol.

\(pK_a\) : 4.46

PHARMACOKINETICS \(^{144}\)

Atorvastatin is rapidly absorbed after oral administration. Maximum plasma concentration occurs within 1 to 2 hours. It is 98% plasma protein bound. It is extensively metabolized to ortho and para hydroxylated derivatives and various beta oxidation products. Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra hepatic metabolism. Mean plasma elimination half life of atorvastatin in humans is approximately 14 hours.
MODE OF ACTION
Atorvastatin is a selective, competitive inhibitor of HMG Co-A reductase, the rate limiting enzyme that converts 3-hydroxy-3 methyl glutaryl coenzyme A to mevalonate, a precursor of sterols including cholesterol. Atorvastatin reduced total cholesterol, LDL-C and apoB in patient with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia and mixed dyslipideamia.

INDICATION & USAGE
Atorvastatin is indicated in the prevention of cardiovascular diseases. It is indicted to reduce the risk of myocardial infarction, stroke, to reduce the risk for revascularization procedures and angina in a patient with multiple risk factors for coronary heart disease.

It is indicated as an adjunct to diet to reduce elevated total cholesterol, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipiemia. It is also indicated in a patient with elevated serum TG levels.

It is used in the treatment of primary dysbetalipoproteinaemia and homozygous familial hypercholesterolemia.

TOXIC EFFECTS
Atorvastatin is well tolerated. Adverse effects are usually mild and transient. The most frequent adverse effect observed are constipation, flatulence, dyspepsia and abdominal pain.

DOSE
For the treatment of hypercholesterolemia and mixed dyslipidemia the recommended dose is 10 – 20 mg once daily. For the treatment of heterozygous familial hypercholesterolemia in pediatric patients the recommended dose is 10 mg/day and maximum recommended dose is 20 mg/day.
2.1.2 EZETIMIBE

NOMENCLATURE:
Chemical Name \(^{146}\): (3R,4S)-1-(4-flurophenyl)-3-((3S)-3-(4-flurophenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)-2-azetidinone.
Molecular weight \(^{146}\): 409.42
CAS Number: 163222-33-1

Formula:
Empirical formula: C\(_{24}\)H\(_{21}\)F\(_2\)NO\(_3\)


![Structural formula of ezetimibe](image)

PHYSICAL PROPERTIES
Appearance \(^{146}\): It is a white crystalline powder.
Solubility \(^{146}\): It is freely soluble in ethanol, methanol and acetone and practically insoluble in water.
Melting point \(^{146}\): 164 - 166 °C
UV spectrum: \(\lambda_{\text{max}}\) at 232.8 nm in methanol
\(pK_a\) \(^{147}\): 9.75

PHARMACOKINETICS \(^{146}\)
After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide. Mean peak plasma concentration is achieved in 4-12 hours. Ezetimibe and ezetimibe-glucuronide are highly bound to plasma proteins. It is primarily metabolized in small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Both ezetimibe and ezetimibe glucuronide are slowly eliminated from plasma with a half-life of approximately 22 hours for both.
**MODE OF ACTION**

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by small intestine. The cholesterol content of liver is derived predominantly from three sources. The liver can synthesize cholesterol, take up cholesterol from the blood from circulating lipoproteins or take up cholesterol absorbed by the small intestines. Ezetimibe localizes and appears to act at the bush border of small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol stores and increase in clearance of cholesterol from blood.

**INDICATION & USAGE**

Ezetimibe is administered alone as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL-C and apo-B in patients with primary hypercholesterolemia. Ezetimibe in combination with HMG Co-A reductase inhibitor is used in the treatment of total cholesterol, LDL-C and apo-B in patient with primary hypercholesterolemia. It is administered in combination with fenofibrate for the treatment in patient with mixed hyperlipidaemia.

**TOXIC EFFECTS**

Ezetimibe is generally well tolerated. The adverse events reported are fatigue, abdominal pain, diarrhea, sinusitis, arthralgia, back pain and fatigue. It should not be used in pregnant women.

**DOSE**

The recommended dose of ezetimibe is 10 mg once daily.

### 2.1.3 SIMVASTATIN

**NOMENCLATURE:**

Chemical Name $^{148}$: (1S, 3R, 7S, 8S, 8aR)-1,2,3,7,8,8a hexahydro-3,7-dimethyl-8-{2-[(2R, 4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]-ethyl}-1-naphthyl 2,2-dimethyl butyrate.

Molecular weight $^{148}$: 418.6

CAS Number $^{148}$: 79902-63-9.

**Formula:**

Empirical formula $^{148}$: C$_{25}$H$_{38}$O$_{5}$

Structural formula:
PHYSICAL PROPERTIES

**Appearance**[^149]: It is a white to off white, non hygroscopic, crystalline powder.

**Solubility**[^149]: It is practically insoluble in water and freely soluble in chloroform, methanol and ethanol.

**Melting point**[^150]: 135-138 °C

**UV spectrum**: $\lambda_{\text{max}}$ at 231, 238 and 247 nm in methanol.

PHARMACOKINETICS[^148]

Simvastatin is absorbed from the gastro-intestinal tract and is hydrolyzed to its active beta hydroxyl acid form. Simvastatin undergoes extensive first pass metabolism in the liver. Less than 5% of the oral dose has been reported to reach the circulation as active metabolites. Both simvastain and its beta hydroxyl acid metabolite are about 95% plasma protein bound. It is mainly excreted in the faeces. About 10 to 15% is recovered in the urine mainly in inactive forms. The half life of active metabolite is 1.9 hours.

MODE OF ACTION[^149]

Simvastatin reduces cholesterol by inhibiting the conversion of HMG-CoA to mevalonate, an early step in the biosynthetic pathway for cholesterol. Simvastatin also reduces VLDL, TG and increases HDL-C.

INDICATION & USAGE[^148,149]

Simvastatin is used in conjunction with dietary modification in the treatment of hypercholesterolemia particularly type IIa and IIb hyperlipoproteinæmias. It may also be given prophylactically as an adjunct to diet in hypercholesterolaemic patients with ischemic heart disease. Simvastatin reduces risk of CHD mortality and cardiovascular events. Simvastatin is indicated to reduce the risk of total mortality by reducing CHD deaths. It reduces the risk of non-fatal myocardial infarction and stroke.

TOXIC EFFECTS[^148]

The common adverse effect of therapy with simvastatin is gastro-intestinal disturbances. Other adverse effects include headache, skin rashes, dizziness, blurred vision. Reversible increase in serum-aminotransferase concentration may occur and liver function should be monitored. Myopathy associated with increased creatine phosphokinase concentrations has been reported in patient taking simvastatin concurrently with immunosuppressive drugs or nicotinic acid.

[^149]:
[^150]:
[^148]:
[^148,149]:
[^13]:
DOSE

The usual recommended dose range is 5 - 80 mg/day. The recommended dose for patients with homozygous familial hypercholesterolemia is 40 mg/ day in the evening. For the treatment of adolescents heterozygous familial hypercholesterolemia the recommended dose is 10 mg/day in the evening.

2.1.4 NICOTINIC ACID

Synonym: Niacin

NOMENCLATURE:

Chemical Name: 3-Pyridinecarboxylic acid
Molecular weight: 123.1
CAS Number: 59-67-6.

Formula:
Empirical formula: C₆H₅NO₂
Structural formula:

PHYSICAL PROPERTY

Appearance: It is a white odourless crystalline powder.
Solubility: It is soluble in boiling water and boiling alcohol. It is sparingly soluble in water; very slightly soluble in chloroform; practically insoluble in ether and it dissolves in dilute solutions of alkali hydroxide and carbonates.
Melting point: 236.6 °C

UV spectrum: λmax at 263 nm in methanol.
pKₐ: 4.85

PHARMACOKINETICS

It is rapidly and extensively absorbed when given orally. After oral absorption nicotinic acid and its metabolites gets concentrated in liver, kidney and adipose tissue. Nicotinic acid undergo rapid and extensive first pass metabolism. It undergoes conjugation with glycine to form nicotinuric acid (NUA). NUA is then excreted in urine. The other pathway results in formation of nicotinamide adenine dinucleotide (NAD). Nicotinamide do not have any hypolipidaemic activity. Niacin and its metabolites are rapidly eliminated in urine. Following single and multiple doses
Introduction to the Drugs

approximately 60 – 76% of the niacin dose administered is recovered in urine as niacin and its metabolites.

MODE OF ACTION
The mechanism by which niacin alters lipid profiles has not been well defined. It may include several action including partial inhibition of release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity, which may increase the rate of chylomicron triglyceride removal from plasma. Niacin decreases rate of hepatic synthesis of VLDL and LDL and does not appear to affect fecal excretion of fats, sterols and bile acids.

INDICATION & USAGE
Nicotinic acid is indicated as an adjunct to diet for the reduction of elevated total cholesterol, LDL-C, apo-B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidaemia. Nicotinic acid in combination with HMG Co-A reductase is indicated for the treatment of primary hypercholesterolemia and mixed dyslipidaemia. Nicotinic acid in combination with a bile acid binding resin is indicated as an adjunct to diet for reduction of elevated total C and LDL-C levels in patients with primary hypercholesterolemia.

TOXIC EFFECTS
Adverse effects reported are flushing episodes (warmth, redness, itching), dizziness, tachycardia, palpitation, shortness of breath, sweating and chills.

DOSE
The recommended daily dose of nicotinic acid is 500 mg per day for a 4 week period. The maintenance dose is 1000 mg to 2000 mg once daily at bed time. The combination therapy with HMG Co-A reductase inhibitor should not exceed the dose of nicotinic acid 2000 mg daily.
2.2 HYPERTENSION

Hypertension is the most common cardiovascular disease. The diagnosis of hypertension is based on repeated, reproducible measurement of elevated blood pressure. Study indicates that the risk of damage to kidney, heart and brain are directly related to the extent of blood pressure elevation. Other positive risk factors include smoking, hyperlipidaemia, diabetes, manifestations of end organ damage at the time of diagnosis and a family history of cardiovascular disease.

A specific cause of hypertension is established in 10-15% of patients. Patients in whom no specific cause of hypertension can be found are said to have essential hypertension. In most of the cases, elevated blood pressure is associated with an overall increase in resistance to blood flow through arterioles while cardiac output is normal. Elevated blood pressure is usually caused by a combination of several abnormalities. Epidemiologic evidence points to genetic inheritance, psychological stress, environmental and dietary factors as perhaps contributing to the development of hypertension.

Physiologically, in both normal and hypertensive individuals, blood pressure is maintained by regulation of cardiac output and peripheral vascular resistance, exerted at three anatomic sites: arterioles, post capillary venules and heart. A fourth anatomic control site, the kidney, contributes to maintenance of blood pressure by regulating the volume of intravascular fluid. Baroreflexes mediated by autonomic nerves, acts in combination with humoral mechanisms, including the renin angiotensin-aldosterone system to coordinate function at these four control sites and to maintain normal blood pressure. Local release of hormones from vascular endothelium may also be involved in the regulation of vascular resistance. All hypertensive drugs acts by interfering with these normal mechanisms.

The drug used in the treatment of hypertension act by reducing the cardiac output and/or reducing total peripheral resistance without correcting the cause. The drugs are classified as bellows.
**Mechanism of action** | **Drugs**
--- | ---
Drugs acting centrally | Clonidine, methyl dopa, moxonidine
Ganglion blocking agents | Hexamethonium and trimethaphan
Drugs acting on postganglionic nerve endings | Guanethidine, bethanidine, debrisoquine, bretylum and reserpine
Drugs acting on adrenergic receptors | β blockers (Propranolol, atenolol, metoprolol, nebivolol, acebutolol, carvedilol), both α and β blocker (Labetalol), α adrenergic receptor antagonist (Prazosin, terazosin, phentolamine)
Drugs acting directly on vascular smooth muscle | Calcium channel blockers (nifedipine, amlodipine), hydralazine, minoxidil, Arteriolar venular vasodilator (Sodium nitroprusside)
Potassium channel activators | Diazoxide, minoxidil, nicorandil
Drugs acting reflexly by stimulating baroreceptors | Veratrum
Drugs which block rennin-angiotensin-aldosterone axis | β adrenergic blockers, drugs which block ACE (Captopril, enalapril, lisinopril, ramipril, benazepril, fosinopril), Drugs which block angiotensin II (Saralasin, losartan, irbesarten, valsartan), drugs which block action of aldosterone (Spironolactone)
Oral diuretics | Thiazide diuretics

An appropriate combination of antihypertensive drugs can produce beneficial effect on blood pressure, adverse reactions and hemodynamic effects. Drug combination not only help to get better blood pressure control but also reduces the incidence of adverse effects due to any one drug because of individual reduction of dosages.

### 2.2.1 NEBIVOLOL HYDROCHLORIDE

**NOMENCLATURE:**

**Chemical Name**[^16]: α, α’-[Imino bis (methylene)] bis [6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol], hydrochloride

**Molecular weight:** 441.9
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CAS Number\textsuperscript{156}; 99200-09-6.

Formula\textsuperscript{156}:

Empirical formula: C\textsubscript{22}H\textsubscript{25}F\textsubscript{2}N\textsubscript{0}4\cdot HCl

Structural formula: (rxlist)

\begin{center}
\includegraphics[width=\textwidth]{structural_formula.png}
\end{center}

PHYSICAL PROPERTIES

Appearance\textsuperscript{157}: It is a white powder.

Solubility\textsuperscript{157}: It is soluble in methanol, dimethylsulfoxide, and N,N-dimethylformamide, sparingly soluble in ethanol, propylene glycol, polyethylene glycol and very slightly soluble in hexane, dichloromethane, and methylbenzene.

Melting point: 140.7 °C

UV spectrum: $\lambda_{\text{max}}$ at 281.8 nm in methanol

pK\textsubscript{a} (base): 8.22

PHARMACOKINETICS\textsuperscript{158}

The absorption of nebivolol is rapid and not affected by food. The \textit{in vitro} human plasma protein binding of nebivolol is approximate\textsuperscript{y} 98\%, mostly to albumin, and is independent of nebivolol concentrations. It is extensively metabolized, partly to active hydroxy-metabolites. The metabolism by aromatic hydroxylation is subject to the CYP2D6 dependent genetic oxidative polymorphism. Urinary excretion of unchanged nebivolol is less than 0.5\% of the dose but increased plasma concentrations of the drug and the hydroxy metabolites have been found in hypertensive patients with moderate to severe renal disease.

MODE OF ACTION\textsuperscript{159,160}

Nebivolol is a cardioselective lipophilic beta-blocker devoid of intrinsic sympathomimetic and membrane-stabilizing actions. The pharmacological profile differs from that of conventional cardio selective beta3-blockers in that it displays nitric oxide- (NO) mediated vasodilator activity. The net hemodynamic effect of
nebivolol is the result of a balance between the depressant effects of beta3-blockade and an action that tends to maintain cardiac output, presumably connected with its after load, reducing vasodilator effect. The blood pressure lowering effect of nebivolol is linked to a reduction in peripheral resistance and an increase in stroke volume and preservation of cardiac output. Recent studies suggest that nebivolol may also restore endothelial dysfunction.

**INDICATION & USAGE**

Nebivolol is used in the treatment of mild to moderate essential hypertension. It is also used in the treatment of angina pectoris and in elderly patients with congestive heart failure.

**TOXIC EFFECTS**

The most frequent adverse events are headache, dizziness, tiredness and paraesthesia. Other adverse events reported are diarrhoea, constipation, nausea, dyspnoea and oedema.

**DOSE**

The recommended starting dose of nebivolol is 5 mg once daily, with or without food, as monotherapy or in combination with other agents. For patients requiring further reduction in blood pressure, the dose can be increased at 2-week intervals up to 40 mg.

2.2.2 **AMLODIPINE BESYLATE**

**NOMENCLATURE:**

**Chemical Name**

3- ethyl-5-methyl (4RS)-2-[(2-amino ethoxy) methyl]-4-(2-chlorophenyl)-6 methyl-1, 4-dihydropyridine-3,5-dicarboxylate, benzenesulphonate.

**Molecular weight**

567.06

**CAS Number**

11470-99-6.

**Formula:**

**Empirical formula**

\[ C_{20}H_{25}ClN_2O_5C_6H_6O_3S \]

**Structural formula:**

![Structural formula of Amodipine Besylate]
PHYSICAL PROPERTIES

**Appearance** 162: It is white crystalline powder.

**Solubility** 162: It is slightly soluble in water and sparingly soluble in ethanol.

**Melting point:** 199 - 201 °C

**UV spectrum:** $\lambda_{\text{max}}$ at 237.4 nm and 360 nm in methanol

**$pK_a$** 163: 8.6

PHARMACOKINETICS 156

Amlodipine is well absorbed following oral administration with peak plasma concentration in 6 - 12 hours. The bioavailability is about 60 - 65%. It has a prolonged elimination half life of 50 hours. It is extensively metabolized in liver. Metabolites are excreted in urine. Amlodipine is about 97% plasma protein bound.

MODE OF ACTION 162

Amlodipine is a dihydropyridine calcium antagonist that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium influx across cell membranes selectively, with a greater effect on vascular smooth muscle than on cardiac muscle cells.

Amlodipine is peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

INDICATION & USAGE

Amlodipine is indicated in the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. Amlodipine is indicated for the symptomatic treatment of chronic stable angina and vasospastic angina. It may be used as monotherapy or in combination with other antianginal drugs.

TOXIC EFFECTS

Amlodipine is well tolerated up to 10 mg doses. The adverse effects reported are arrhythmia, bradycardia, chest pain, postural hypotension, hypoesthesia, peripheral neuropathy, tremor, vertigo, anorexia, constipation, dyspepsia, diarrhea, vomiting, allergic reaction, asthenia, back pain, hot flushes, malaise, arthralgia and myalgia.

DOSE
Usual antihypertensive oral dose is 5 mg once daily with a maximum dose of 10 mg once daily. The dose for chronic stable or vasospastic angina is 5 – 10 mg, with the lower dose suggested in elderly patients with hepatic insufficiency.

2.2.3 HYDROCHLOROTHIAZIDE

NOMENCLATURE:

Chemical Name $^{156}$: 6-chloro-3,4-dihyro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Molecular weight $^{156}$: 297.7

CAS Number $^{156}$: 58-93-5.

Formula:

Empirical formula $^{156}$: C$_7$H$_8$ClN$_3$O$_4$S$_2$

PHYSICAL PROPERTY

Appearance $^{156}$: It is white odouless crystalline powder.

Solubility $^{156}$: Slightly or very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone; freely soluble in dimethylformamide; practically insoluble in ether, chloroform and dilute mineral acid.

Melting point: 273-275°C

UV spectrum $^{164}$: $\lambda_{max}$ at 317 nm, 271 nm, 226 nm (methanol and HCl).

$pK_a$ $^{164}$: 7.9 & 9.2

PHARMACOKINETICS $^{156}$

Hydrochlorothiazide is rapidly absorbed from the gastro intestinal tract. It is having bioavailability of 65-70%. It is having plasma half life of 5-15 hours. It is excreted unchanged in urine. Hydrochlorothiazide crosses the placental barrier and is excreted in breast milk.

MODE OF ACTION $^{165}$

The mechanism of anti hypertensive effect of thiazide is unknown. Hydrochlorothiazide do not affect normal blood pressure. It affects the distal renal tubular mechanism of electrolyte reabsorption. It increases excretion of sodium and chloride in approximately equivalent amounts.
INDICATION & USAGE

Hydrochlorothiazide is used in the treatment of edema associated with heart failure, hepatic and renal disorders. It is also used in hypertension, either alone or in combination with other antihypertensive agents, such as angiotensin-converting enzyme inhibitors (ACE) and beta blockers.

It is also indicated in the treatment of edema accompanying premenstrual tension, the prevention of water retention associated with corticosteroids and estrogens, the treatment of diabetes insipidus and prevention of renal calculus formation in patients with hypercalciuria.

TOXIC EFFECTS

Hydrochlorothiazide may cause a number of metabolic disturbances especially at high doses. It may cause hyperglycemia and glycosuria in diabetic and other susceptible patients. Administration of thiazide diuretics is associated with electrolyte imbalances including hypochloraemic alkalosis, hyponatraemia and hypokalaemia.

Other side effects like anorexia, gastric irritation, nausea, vomiting, dizziness, photosensitivity reactions, postural hypotension, pulmonary oedema, cholestatic jaundice, thrombocytopenia and haemolytic anemia have been reported.

DOSE

In the treatment of edema the usual dose is 25 – 100 mg daily. For the treatment of hypertension the recommended dose of hydrochlorothiazide is 25- 50 mg daily either alone or in combination with other antihypertensive agents. In the treatment of nephrogenic diabetes insipidus an initial dose of up to 100 mg is recommended.

2.3 NON STEROIDAL ANTI-INFLAMMATORY DRUG

2.3.1 ASPIRIN

NOMENCLATURE:

Chemical Name: 2-Acetoxybenzoic acid
Molecular weight: 180.2
CAS Number: 50-78-2

Formula:
Empirical formula: C₉H₈O₄
Structural formula:
PHYSICAL PROPERTY

Appearance\textsuperscript{166}: It is a white crystalline powder.

Solubility\textsuperscript{166}: It is slightly soluble in water, freely soluble in alcohol, soluble in chloroform and ether.

Melting point\textsuperscript{167}: 135°C

UV spectrum\textsuperscript{167}: $\lambda_{\text{max}}$ at 229 nm in 0.1 N H$_2$SO$_4$

$\lambda_{\text{max}}$ at 277 nm in chloroform

pK$_\alpha$\textsuperscript{167}: 3.49

PHARMACOKINETICS\textsuperscript{166}

Aspirin is absorbed rapidly from gastro-intestinal tract. A portion of the absorbed aspirin is hydrolyzed to salicylate in the gut wall. After absorption aspirin is rapidly converted to salicylate but during the first 20 minutes following oral administration, aspirin is the predominant form of the drug in the plasma. Aspirin is 80-90% bound to plasma proteins and is widely distributed. Salicylate is mainly eliminated by hepatic metabolism; the metabolites include salicylic acid, salicylphenolic glucuronide, gentisuric acid.

MODE OF ACTION\textsuperscript{168}

Aspirin is potent inhibitor of both prostaglandin synthesis and platelet aggregation. Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclooxygenase and thus inhibits the generation of thromboxane A2, a powerful inducer of platelet aggregation and vasoconstriction. The difference in activity between aspirin and salicylic acid are due to acetyl group present in aspirin. This acetyl group is responsible for the inactivation of cyclooxygenase via acetylation.

INDICATION & USAGE\textsuperscript{166}

Aspirin is used for the relief of mild to moderate pain such as headache, dysmenorrheal, myalgia and dental pain. It is also used in acute and chronic inflammatory disorder such as rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aspirin is also used for its antiplatelet activity in cardiovascular disorder. It is given with a thrombolytic in the early treatment of myocardial infarction and for secondary prophylaxis of myocardial infarction and stroke in patients at risk. It is given after angioplasty and coronary bypass surgery to prevent restenosis.
TOXIC EFFECTS

The most common adverse effects occurring with therapeutic doses of aspirin are gastro-intestinal disturbances such as nausea, dyspepsia and vomiting. Irritation of the gastric mucosa with erosion, ulceration, haematemesis and melaena may occur.

DOSE

The usual dose of aspirin as an analgesic and antipyretic is 0.3-0.9 g which may be repeated every 4 to 6 h as per need. In the treatment of rheumatoid arthritis the recommended dose is 3 g per day in divided doses. The recommended dose for juvenile rheumatoid arthritis is 80-100 mg per kg body weight daily in 5 to 6 divided doses.

For the secondary prevention of myocardial infarction and stroke the recommended dose is 75-100 mg per day.

2.4 PEPTIC ULCER

Pepetic ulcer is one of the common gastrointestinal disorders in clinical practice. The common form of peptic ulcer are duodenal ulcer, gastric ulcer, NSAID induced ulcer and stress ulcer. Gastric acid and pepsin are the pathogenic factors in the peptic ulcer diseases. While inherently caustic, acid and pepsin in the stomach normally do not produce damage or symptoms because of intrinsic defense mechanisms. Barriers to the reflux of gastric contents into the esophagus comprise the primary esophageal defense. If these protective barriers fail and reflux occurs, dyspepsia and/or erosive esophagitis may result. Therapies are directed at decreasing gastric acidity, enhancing the lower esophageal sphincter, or stimulating esophageal motility. In the stomach, mucus and bicarbonate, stimulated by the local generation of prostaglandins, protect the gastric mucosa. If these defenses are disrupted, a gastric or duodenal ulcer may form. The treatment and prevention of these acid-related disorders are accomplished either by decreasing the level of gastric acidity or by enhancing mucosal protection. The appreciation that an infectious agent, Helicobacter pylori, plays a key role in the pathogenesis of acid-peptic diseases has stimulated new approaches to prevention and therapy.
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Drugs used to treat peptic ulcer are

Proton pump inhibitors: Omeprazole, esomeprazole, lasnoprazole, rabeprazole and pantoprazole

H2 receptor antagonist: Cimetidine, ranitidine, famotidine and nizatidine

Agent that enhances mucosal effect: Misoprostol, Sucralfate

Antacids: Magnesium hydroxide, aluminium hydroxide, calcium carbonate, magnesium trisilicate, magnesium carbonate, sodium bicarbonate

Acid suppressants and cytoprotectant: Pirenzepine, telenzepine

Gastro esophageal reflux disease

Gastro esophageal reflux disease (GERD) results from the reflux of gastric or duodenal contents into the esophagus. Symptoms include heartburn, acid regurgitation and dysphagia, esophageal inflammation, ulceration and stricture formation. Term GERD is broader one, which include reflux esophagitis, non-erosive reflux disease and extra esophageal manifestations.

Protracted reflux over several years can lead to development of Barrett’s esophagus (ulceration with presence of columnar epithelium). GERD is associated with transient relaxation of the lower esophageal sphincter or loss of sphincter tone, although impaired esophageal clearance, reduced gastric emptying, and impaired mucosal resistance have been implicated.

Treatment requires a multifactorial approach starting with life style and dietary modification. As mucosal damage correlates with the extent of acid exposure, drug treatment is aimed at either neutralizing the acid refluxate or to promote peristalsis (prokinetics) 170, 171.

Drugs used to treat GERD are

Antacid: Calcium carbonate, magnesium hydroxide, magnesium oxide, aluminium hydroxide, sodium bicarbonate etc.

H2 receptor blockers: Ranitidine, famotidine, nizatidine, cimetidine

Proton pump inhibitors: Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole

Prokinetics: Cisapride, mozapride, Itopride, Domperidone

Combination drug therapy: Prokinetics with H2 receptor blockers or proton pump inhibitors
2.4.1 RABEPRAZOLE SODIUM

NOMENCLATURE:
Chemical Name: 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridynyl]-methyl]sulfinyl]-1H-benzimidazole sodium.
Molecular weight: 381.43
CAS Number: 117976-90-6
Formula:
Empirical formula: C_{18}H_{20}N_{3}NaO_{3}S
Structural formula:

![Structural formula of Rabeprazole Sodium](image)

PHYSICAL PROPERTY

Appearance: It is a white to slightly yellowish white solid.
Solubility: It is very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate and insoluble in ether and n-hexane.
Melting point: 140-141°C
UV spectrum: λmax at 284 nm in methanol.

pKa: 5.0

PHARMACOKINETICS

Rabeprazole is extensively degraded in acidic media and is more stable in alkaline conditions. It is formulated in enteric coated formulation. The absolute bioavailability of rabeprazole is approximately 52% compare to intravenous administration. It is 96% bound to plasma protein. Rabeprazole is extensively metabolized. Thioether and sulphone are the major metabolites in human plasma which are devoid of antisecretory activity. Approximately 90% of the drug is eliminated in urine as thioether carboxylic acid; its glucuronide and mercapturic acid metabolites.
MODE OF ACTION

Rabeprazole is substituted benzimidazole proton pump inhibitor. It does not exhibit anticholinergic or histamine H2 receptor antagonist properties but suppress gastric acid secretion by inhibiting the gastric H⁺, K⁺ ATPase at the secretory surface of the gastric parietal cell. Rabeprazole blocks the final step of gastric acid secretion.

INDICATION & USAGE

It is indicated in the healing of erosive or ulcerative gastro esophageal reflux diseases (GERD). It is also indicated in the treatment of healing and symptomatic relief of duodenal ulcers. In combination with amoxicillin and clarithromycin it is indicated for the treatment of patients with H. Pylori infection and duodenal ulcer disease to eradicate H. Pylori.

TOXIC EFFECTS

Rabeprazole treatment is well tolerated in patients. The adverse events like asthenia, fever, allergic reaction, chills, malaise, chest pain, neck rigidity and photosensitivity reactions have been reported in patients.

DOSE

For the treatment of GERD and duodenal ulcer the recommended dose is 20 mg twice a day.

2.4.2 ITOPRIDE HYDROCHLORIDE

NOMENCLATURE

Chemical Name: N-[P-[2-[dimethyl amino]ethoxy]benzyl] veratramide hydrochloride
Molecular weight: 394.90
CAS Number: 122892-31-3
Formula:
Empirical formula: C₂₀H₂₆N₂O₄. HCl
Structural formula:

PHYSICAL PROPERTY

Appearance: It is a white crystalline powder.
**Solubility:** It is soluble in water, methanol and sparingly soluble in acetic acid.

**Melting point:** 191-195 °C

**UV spectrum:** λmax at 258 and 282 nm in methanol

**pKα:** 8.72

**PHARMACOKINETICS**

On oral administration, Itopride is rapidly and extensively absorbed and peak serum concentrations are achieved within 35 minutes after oral administration. Thus it has a rapid onset of action, unlike cisapride and mosapride, which take around 60 minutes to reach peak plasma concentrations. Food does not affect its absorption. Itopride is metabolized in the liver by N-oxidation to inactive metabolites by the enzyme flavin-containing monooxygenase (FMO). The half-life of Itopride is about 6 hours. It is excreted mainly by the kidney as metabolites and unchanged drug.

**MODE OF ACTION**

Itopride has anticholinesterase (AchE) activity as well as dopamine D2 receptor antagonistic activity and is being used for the symptomatic treatment of various gastrointestinal motility disorders. The enzyme AchE hydrolyses the released Ach, inactivates it and thus inhibits the gastric motility leading to various digestive disorders. Besides Ach, dopamine is present in significant amounts in the gastrointestinal tract and has several inhibitory effects on gastrointestinal motility, including reduction of lower esophageal sphincter and intragastric pressure. These effects appear to result from suppression of Ach release from the myenteric motor neurons and are mediated by the D2 receptor.

Itopride, by virtue of its dopamine D2 receptor antagonism, removes the inhibitory effects on Ach release. It also inhibits the enzyme AchE which prevents the degradation of Ach. The net effect is an increase in Ach concentration, which in turn, promotes gastric motility, increases the lower esophageal sphincter pressure, accelerates gastric emptying and improves gastro-duodenal coordination. This dual mode of action of itopride is unique and different from the actions of other prokinetic agents.

**INDICATION & USAGE**

Various prokinetic studies were conducted in patients of non ulcer dyspepsia (NUD), reflux esophagitis and chronic gastritis, diabetic gastroparesis and functional dyspepsia. The results of these studies indicated that itopride is an effective...
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prokinetic agent for the treatment of symptoms caused by altered gastrointestinal motility in all the above mentioned conditions. Few studies have shown that itopride is superior in efficacy to metoclopramide and cisapride in patients of NUD.

TOXIC EFFECTS

Itopride is well tolerated with few minor adverse drug reactions in the form of diarrhea, headache and abdominal pain. It has no significant effects on central nervous system and thus is devoid of extra pyramidal side effects and hyperprolactinaemia as is seen with other prokinetic drugs such as metoclopramide and domperidone. It has no effect on the cardiovascular system. Preclinical and clinical studies till date indicate that this drug is not having the potential to cause prolongation of QT intervals unlike cisapride and mosapride. The affinity of cisapride for 5HT4 receptors in the heart has been implicated in the undesirable cardiac effects of the drug but itopride has no affinity for 5HT4 receptors which makes this drug a better and safer prokinetic agent.

DOSE

The usual daily dosage for adults is 50 mg of itopride hydrochloride orally in three divided doses before each meal.

2.5 COMBINATION DRUG THERAPY

2.5.1 Statins and Ezetimibe combination therapy

Clinical study reported that a combination therapy of ezetimibe with statins, produces significant reductions in LDL-C and triglycerides compared to statin monotherapy. Ezetimibe has a favorable safety and tolerability profile without any clinically important drug interactions. A clinical study reported that a ezetimibe and atorvastatin combination therapy produced a significantly greater adjusted mean change from baseline in LDL-C compared with ATV monotherapy, equating to an additional 14.1% reduction in LDL-C. Clinical chemistry profiles and the incidence of adverse events were similar in both combination and monotherapy. The combination therapy was well tolerated by patients of CHD compare to atorvastatin monotherapy.

Clinical study using ezetimibe and simvastatin combination therapy led to significant reduction in LDL-C, non-HDL-C, apo B, triglyceride and C-reactive protein compared to simvastatin alone. Combination therapy improved the lipid and
inflammatory profiles of hypercholesterolemic patients with metabolic syndrome and was well tolerated 176.

2.5.2 **Atorvastatin and Aspirin combination therapy**

Clinical study reported effect of atorvastatin and aspirin combination therapy on inflammatory responses, endothelial cell function and blood coagulation system in patients undergoing coronary artery bypass grafting (CABG) to aspirin monotherapy. The combination therapy proved beneficial to the patients after CABG 177.

A clinical study reported that a combination therapy of ASP and ATV has an additive effect in reducing cardiovascular events in dyslipidemic patients with coronary heart disease 178.

2.5.3 **Atorvastatin and Nicotinic acid combination therapy**

Safety and efficacy of combination therapy of extended release (ER) niacin and atorvastatin in patients with low HDL-C was compared with atorvastatin monotherapy. The Combination therapy exhibited beneficial effects on lipid profile with significant elevation of HDL-C cholesterol and further lowering of LDL-C compared to monotherapy 179.

A study reported that statin/niacin ER combination therapy increased HDL-C and large HDL (HDL2) and lowered triglycerides and lipoprotein-a significantly more than statin monotherapy. No drug-related myopathy or hepatotoxicity was observed with combination therapy. Low to moderate dose combination therapy with a statin and niacin ER provided broad control of lipids and lipoproteins independently associated with CHD 180.

2.5.4 **Atorvastatin and Amlodipine combination therapy**

A clinical study reported that combination therapy of amlodipine and atorvastatin showed significant dose-related reductions in systolic blood pressure (SBP) and LDL-C compared to placebo, with no overall modification of effect of either component on SBP and LDL-C. Coadministered atorvastatin and amlodipine was well tolerated without adverse pharmacodynamic interactions 181.

Study reported that combination therapy with ATV and AML decreases inflammatory status of atherosclerotic patients more compare to ATV monotherapy. The combination therapy has beneficial additive effects 182.
A clinical study reported early and sustained improvement in small artery compliance with combination therapy of AML and ATV from baseline, which was significantly greater than with either treatment alone\textsuperscript{183}.

A clinical study reported marked reduction in blood pressure and reverses left ventricular hypertrophy with combination therapy compare to amlodipine monotherapy. Combination therapy produced more beneficial effect in the treatment of hypertensive and hypercholesterolemic patients\textsuperscript{184}.

### 2.5.5 Nebivolol and Hydrochlorothiazide combination therapy

A clinical study reported that a combination therapy of NEB and HCTZ was effective in reducing clinic and 24 h ambulatory blood pressure in patient with ambulatory hypertension. The combination therapy was well tolerated\textsuperscript{185}.

A study reported significant dose related reduction in blood pressure among patients receiving different combination of NEB and HCTZ. Lipid, lipoprotein and apolipoprotein levels were not significantly modified after the treatment with combination therapy\textsuperscript{186}.

### 2.5.6 Rabeprazole and Itopride combination therapy

Proton pump inhibitors are drug of choice in the treatment of peptic ulcer diseases, GERD, and non ulcer-dyspepsia\textsuperscript{187,188}. Itopride has been proved to be effective prokinetic agent for the treatment of non ulcer dyspepsia, GERD, gastritis caused by altered gastric motility. Proton pump inhibitors are combined with prokinetics which induces peristalsis to achieve synergistic effect in the treatment of GERD and peptic ulcer diseases\textsuperscript{171}. 