Hyperlipidemia & its Management by using Pitavastatin : A review

Neeraj*, Rajesh Kumar, Ajeet Pal Singh & Amar Pal Singh

Department of Pharmaceutics, St. Soldier Institute of Pharmacy, Lidhran campus, Behind Nit(R.E.C.), Jalandhar-Amritsar By Pass, Nh-1, Jalandhar -144011, Punjab, India

***Address for correspondence:**

Neeraj*

Department of Pharmaceutics, St. Soldier Institute of Pharmacy, Lidhran campus, Behind Nit(R.E.C.), Jalandhar-Amritsar By Pass, Nh-1, Jalandhar -144011, Punjab, India

Email-neerajjarial28999@gmail.com

Abstract:

The main risk factor for cardiovascular illnesses is hyperlipidemia. Triglycerides and cholesterol combined restrict blood arteries, making it harder for blood to flow through them. Another term for high cholesterol in the body is hyperlipidemia.This review mostly addresses hyperlipidemia and Pitavastatin-based therapies.Pitavastatin is a HMG-CoA reductase inhibitor indicated for hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C).

Keywords: Pitavastatin, Hyperlipidemia, Cardiovascular diseases, Lipids, HMG-CoA ,Triglycerides, cholesterol, low-density lipoprotein cholesterol, High-density lipoprotein cholesterol.

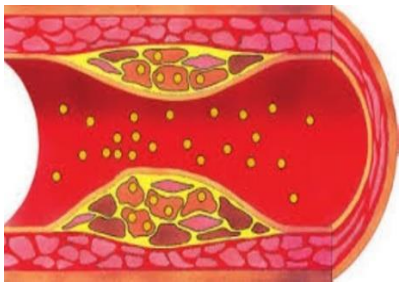
Introduction:

The most prevalent risk factor associated with the many types of cardiovascular illnesses is hyperlipidemia. Hyperlipidemia occurs frequently. Ninety-three million persons in the United States (aged 20 and above) have total cholesterol levels that are higher than the suggested threshold of 200 mg/dL. Cardiovascular disease (CVD) is almost twice as likely to occur in those with hyperlipidemia. It is a disorder that raises the body's lipid levels and combines a number of inherited and acquired illnesses. Cholesterol levels, lipoproteins, chylomicrons, VLDL, LDL, apolipoproteins, and HDL are examples of lipids.(10) There is a clear link between cholesterol and the prevalence of cardiovascular disease, according to epidemiological research. Low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) have an unfavorable relationship and a positive correlation, respectively, with the associated morbidity and mortality.(11)(12)

The synthesis of hormones and cell membranes involves cholesterol. Among its physiological functions are the following(13): (1) it is a component of cell membranes; (2) it is a precursor to the formation of oxysterols, bile acids, and steroid hormones; and (3) it modifies molecules that are involved in neural signaling.

About 80% of cholesterol is produced by the liver, with the remaining 20% coming from diets high in meat, fish, and eggs (14). High levels of low-density lipoprotein (LDL) cholesterol raise an individual's risk of atherosclerotic plaque formation and consequent vascular disease. Consuming a lot of different saturated fats is the primary cause of raised blood cholesterol (15).

Hyperlipidemia, sometimes referred to as hyperlipoproteinemia or high cholesterol, is a condition marked by unusually high blood lipid (fat) concentrations that are linked to the development of atherosclerosis, the underlying cause of both stroke and coronary heart disease (CHD). (16)



The illustration depicts the interior of an artery and the development of atherosclerotic plaques as a result of hyperlipidemia. (17) Plaque rupture may impede blood flow by causing a blood clot that may result in a heart attack.Plaque is made up of many blood-borne chemicals, fat, and cholesterol.

Lipoproteins are classified as five major groups(18):
• LDL (Low Density Lipoprotein)
• HDL (High Density Lipoprotein)
• VLDL (Very Low Density Lipoprotein)
• IDL (Intermediate-density lipoproteins)
• Chylomicrons (CM)

normal lipid profile:
1. Fasting triglyceride level:
• Normal: less than 150 mg/dL• Mild hypertriglyceridemia: 150 to 499 mg/dL
• Moderate hypertriglyceridemia: 500 to 886 mg/dL
• Very high or severe hypertriglyceridemia: greater than 886 mg/dL

2. LDL-C level:
• Optimal: less than 100 mg/ dL
• Near optimal/above optimal:100 to 129 mg/dL
• Borderline high: 130 to 159 mg/dL
• High: 160 to 189 mg/dL
• Very high: greater than 190 mg/dL

3. HDL level:
• Low: less than 40
• High: greater than or equal to 60

Total cholesterol is a measurement of all the cholesterol present in your blood. It consists of both HDL and LDL.
LDL cholesterol: Due to its larger ratio of cholesterol to protein, LDL is referred to as "bad" cholesterol and is associated with a higher risk of heart disease, stroke, and other conditions. It is the primary cause of artery obstruction and cholesterol accumulation.
HDL cholesterol is beneficial because it aids in the removal of cholesterol from the arteries.
Your total cholesterol less your HDL is your **non-HDL**. LDL and other forms of cholesterol, such as VLDL (very-low-density lipoprotein), are included in your non-HDL.
Another type of blood fat that can increase your risk of heart disease, particularly in women, is **triglycerides**.

Types of Hyperlipidemia: The following are the primary forms of hyperlipidemia, each with a unique impact on the body: (19)

Type I: This kind of hyperlipidemia primarily affects children. It may result in liver enlargement, pancreatic infections, and stomach pain. This is a genetic condition also referred to as an LPL deficit that can impair the digestion of lipids.
Type II: A high amount of low-density lipoprotein (LDL) can cause fat to accumulate around the eyes.
Type III: This essentially modifies the lipoprotein level. HDL is normal while the level of LDL is low. It could result in grayish-yellow plaques surrounding the eyes. It causes cardiovascular disease to manifest earlier.
Type IV: Triglycerides were raised while cholesterol was lowered, which could lead to obesity.

Complications of hyperlipidemia: (19)
Atherosclerosis
Coronary Artery Disease (CAD)
Myocardial Infarction (MI)
Ischemic stroke

Causes:

The following foods may increase blood lipid levels: dairy products. These foods contain cholesterol, saturated fat, and trans fat.

• Ice cream pastries.
• Junk food and fried food.
• Pork, etc.(20)

Hyperlipidemia has several significant causes, including other conditions including obesity, diabetes mellitus, and hypothyroidism. Hyperlipidemia can be caused by smoking and insufficient exercise (21).

Hyperlipidemia risk is also increased by excessive alcohol consumption. Hyperlipidemia can be brought on by several medications, such as β-blockers and steroids. Mutations in lipoprotein lipase(22).

• Obesity is one of the other causes of hyperlipidemia.
• Heredity or genetics.
• Cigarette smoking.
• Several medications, including betablockers, estrogen, and corticosteroids, increase the risk of hypertriglyceridemia.
• Steroids, alcohol, hypothyroidism, kidney failure, and so forth.
• Minimal exercise (23)

INDICATIONS OF HYPERLIPIDEMIA:

Hyperlipidemia typically presents with no symptoms and is typically detected during routine testing for atherosclerotic cardiovascular disease (24). It can also cause angina, heart attacks, strokes, and chest pain. If the levels are too high, cholesterol can build up in tendons or just under the skin under the eyes.

• blockage of blood vessels in the brain and heart; swelling of the liver, spleen, or pancreas.

The prevalence of glucose intolerance and obesity is higher.

• Lesions like pimples all over the body (25)

Diagnosis: Hyperlipidemia with no additional particular symptoms It can only be found with a blood test.

A routine blood test that measures LDL, HDL, VLDL, and triglycerides can identify hyperlipidemia. (26)

TREATMENT:

Pharmacological Treatments: (26)

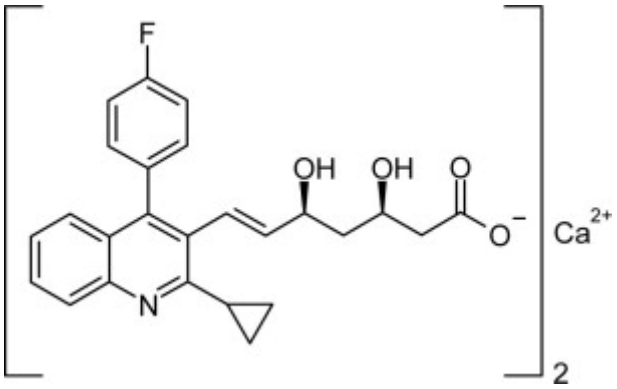
• Statins
• Fibrates
• Bile acid binding resins,
• Nicotinic acid derivatives

Non-Pharmacological Treatments: The following lifestyle modification may lower the cholesterol level:

• Proper diet. • Less weight of the body.
• Regular exercise.
• Having non-oily food

Pitavastatin(28) is an inhibitor of HMG-CoA reductase. It is a synthetic lipid-lowering agent for oral administration.

The chemical name for pitavastatin is (+)monocalcium *bis*{(3R, 5S, 6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-
dihydroxy-6-heptenoate}. The structural formula is:



The empirical formula for pitavastatin is C50H46CaF2N2O8 and the molecular weight is 880.98. Pitavastatin is odorless and occurs as white to pale-yellow powder. It is freely soluble in pyridine, chloroform, dilute hydrochloric acid, and tetrahydrofuran, soluble in ethylene glycol, sparingly soluble in octanol, slightly soluble in methanol, very slightly soluble in water or ethanol, and practically insoluble in acetonitrile or diethyl ether. Pitavastatin is hygroscopic and slightly unstable in light.

Pharmacodynamics:

An oral antilipemic medication called pitavastatin inhibits HMG-CoA reductase. It is used to increase HDL-C concentrations while lowering total cholesterol, trigleride (TG), apolipoprotein B (apoB), low density lipoprotein-cholesterol (LDL-C), and non-high density lipoprotein-cholesterol (non-HDL-C) plasma concentrations. Elevated quantities of LDL-C, decreased HDL-C, and elevated TG in plasma are linked to a higher risk of atherosclerosis and cardiovascular disorders. High ratios are linked to an increased risk of coronary artery disease. The total cholesterol to HDL-C ratio is a powerful predictor of the condition. Reduced cardiovascular risk is linked to higher HDL-C levels. Pitavastatin lowers the risk of cardiovascular morbidity and death by raising HDL-C and reducing TG and LDL-C.(29)(30)
174 healthy participants in a randomized, double-blind, placebo-controlled, 4-way parallel, active-comparator study using moxifloxacin did not experience a clinically significant prolongation of the QTc interval or heart rate at daily doses up to 16 mg (4 times the recommended maximum daily dose) when exposed to Pitavastatin.(28)

Mechanism of action:Pitavastatin decreases cholesterol production in the liver by competitively inhibiting HMG-CoA reductase, a rate-determining enzyme involved in the biosynthesis of cholesterol. This inhibition occurs through a competition with the substrate. This leads to an increase in the expression of LDL-receptors, an acceleration of the liver's absorption of LDL from the blood, and a subsequent decrease in plasma TC.
Moreover, very low density lipoprotein levels are lowered by the liver's persistent suppression of cholesterol synthesis.(28)

Pharmacokinetics:

Absorption and Distribution: Pitavastatin has a peak plasma concentration (Cmax) around an hour after oral administration; plasma levels rise in direct proportion to the dose. It is 51% bioavailable. When pitavastatin is taken with a high-fat meal, the drug's Cmax drops by 43% while the concentration's area-under-the-curve (AUC) is mostly same. When pitavastatin was administered in the morning or the evening, there was no difference in the Cmax or AUC concentration. In human plasma, pitavastatin is over 99% protein-bound, primarily to alpha1-acid glycoprotein and albumin.(28)
Metabolism and Excretion: Hepatic glucuronidation is the main metabolic pathway, with cytochrome P450 2C9 (CYP 2C9) and CYP 2C8 having a minor role. About 15% of the dose is eliminated in the urine, but the majority is eliminated in the feces. The half-life of the mean plasma concentration is 12 hours.(28)

Efficacy:(8)(9)

Saito et al, Japan carried out a multicenter, randomised, double-blind, controlled trial to assess the safety and effectiveness of pitavastatin versus pravastatin (Bristol-Myers Squibb) medication for 12 weeks. At week 12, a decrease in TC, TG, and LDL-C values was the trial's main goal.
In this trial, pitavastatin 2 mg/day showed a larger decrease in LDL-C levels compared with pravastatin 10 mg/day in patients with hyperlipidemia

Pitavastatin therapy compared with atorvastatin more may prevent cardiovascular events in hypercholesterolemic patients with one or more risk factors for atherosclerotic diseases despite similar effects on LDL-C levels.(31)

Indications:

Pitavastatin is currently FDA approved for the management of primary hyperlipidemia and mixed dyslipidemia as adjunctive therapy to dietary changes to help lower total cholesterol, low-density lipoprotein cholesterol (LDL), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL).(1)(2) It is also FDA approved to treat heterozygous familial hypercholesterolemia (HeFH) in pediatric patients over 8 years of age.(3)

Pitavastatin drug interactions:(4)

- Pitavastatin's serum levels may be lowered by the following medications: digoxin, ezetimibe, lopinavir/ritonavir, darunavir/ritonavir, and itraconazole.

- Pitavastatin's serum levels can be raised by the following medications: diltiazem, cyclosporine, erythromyncin, rifampin, atazanavir, gemfibrozil, fenofibrate, enalapril, and erythromyci.

Adverse Effects:

The adverse effects of pitavastatin that are most frequently mentioned include myalgia, back discomfort, diarrhea, constipation, and pain in the extremities. There are reports of urticaria, pruritus, and rash. Acute renal failure due to myopathy and rhabdomyolysis has also been reported. The usage of pitavastatin may also result in abnormalities in the lab, such as higher levels of glucose, bilirubin, alkaline phosphatase, creatine phosphokinase, and transaminases (aspartate aminotransferase [AST]/serum glutamic-oxaloacetic transaminase or alanine aminotransferase [ALT]/serum glutamic-pyruvic transaminase). Pitavastatin use has also been linked to elevated HgA1c and fasting blood glucose levels.(5)(6)(7)

Conclusion:

Pitavastatin is a powerful statin that offers benefits in terms of pharmacology and pharmacokinetics.Pitavastatin also significantly reduced triglycerides (TG) and increased HDL-C. Pitavastatin has cholesterol-lowering action stronger than that of other statins. Physicians, cardiologists, pharmacists, and nursing staff must communicate in order to prescribe and monitor patients. . Following a conversation on informed consent and shared decision-making, the doctor and patient should weigh the advantages and disadvantages of the medicine.

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