Treated Patients Biochemical Studies on the Hepatotoxicity of Atorvastatin

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Abstract   Atorvastatin is the more potent drug to treat the hyperlipidemia patients. Unfortunately this drug has got hepatotoxicity and hence the patients on statin treatment have to be monitored for Liver function test frequently. This study is used to find the hepatotoxic effect of atorvastatin in hyperlipidemic patients. This study is planning to do the following biochemical parameters. Glucose, Urea, Creatinine, Uric Acid, Sodium, Potassium Chloride, Bicarbonate, Cholesterol, High Density Lipoprotein, Triglycerides, Ratio, Total Bilirubin, Serum Glutamic Pyruvate Transaminase, Alkaline Phosphatase, Gamma-glutamyl transpeptidase, Total Protein, Albumin Globulin.

Keywords   Atovastatin , Hyperlipidemia

1. Introduction

Hyperlipidemia is an excess of fatty substances called lipids, largely cholesterol and triglycerides, in the blood. It is also called hyperlipoproteinemia because these fatty substances travel in the blood attached to proteins. This is the only way that these fatty substances can remain dissolved while in circulation.[1]

Hyperlipidemia, in general, can be divided into two subcategories:

- hypercholesterolemia, in which there is a high level of cholesterol
- hypertriglyceridemia, in which there is a high level of triglycerides, the most common form of fat

Description of Hyperlipidemia

The fat-protein complexes in the blood are called lipoproteins. The best-known lipoproteins are LDL (low density lipoprotein) and HDL (high density lipoprotein).

Excess LDL cholesterol contributes to the blockage of arteries, which eventually leads to heart attack. Population studies have clearly shown that the higher the level of LDL cholesterol, the greater the risk of heart disease. This is true in men and women, in different racial and ethnic groups, and in all adult age groups. Hence, LDL cholesterol has been labeled the "bad" cholesterol.

In contrast, the lower the level of HDL cholesterol, the greater the risk of coronary heart disease. As a result, HDL cholesterol is commonly referred to as the "good" cholesterol.

Low HDL cholesterol levels are typically accompanied by an increase in blood triglyceride levels. Studies have shown that high triglyceride levels are associated with an increased risk of coronary heart disease.[2]

Causes and Risk Factors of Hyperlipidemia

Common secondary causes of hypercholesterolemia (specifically, high LDL cholesterol) include hypothyroidism (that is, low thyroid hormone levels), pregnancy, and kidney failure.

Common secondary causes of hypertriglyceridemia include diabetes, excess alcohol intake, obesity, and certain prescription medications (such as glucocorticoids and estrogen).

Hyperlipidemia, along with diabetes, hypertension (high blood pressure), positive family history, and smoking are all major risk factors for coronary heart disease.

Symptoms of Hyperlipidemia

Hyperlipidemia usually has no noticeable symptoms and tends to be discovered during routine examination or evaluation for atherosclerotic cardiovascular disease. However, deposits of cholesterol (known as xanthomas) may form under the skin (especially around the eyes or along the Achilles tendon) in individuals with familial forms of the disorder or in those with very high levels of cholesterol in the blood. Individuals with hypertriglyceridemia may develop numerous pimple-like lesions across their body. Extremely high levels of triglycerides may also result in pancreatitis, a severe inflammation of the pancreas that may be life-threatening.[3]

Diagnosis of Hyperlipidemia

Diagnosis is typically based on medical history, physical examination, and blood tests (done after overnight fasting) in order to determine the specific levels of LDL cholesterol,

HDL cholesterol, and triglycerides.

Treatment of Hyperlipidemia

It is necessary to first identify and treat any potential underlying medical problems, such as diabetes or hypothyroidism, that may contribute to hyperlipidemia. Treatment of hyperlipidemia itself includes dietary changes, weight reduction and exercise. If lifestyle modifications cannot bring about optimal lipid levels, then medications may be necessary.

Current national guidelines suggest a LDL cholesterol goal of <100 mg/dl for individuals already with heart disease or diabetes, <130 mg/dl for those with moderate risk of heart disease, and <160 mg/dl for everyone else. Your doctor can calculate your "risk score" for heart disease. This score can then be used to determine whether you need to start taking medications to lower your LDL cholesterol.

Although there are no firm treatment targets for HDL cholesterol or triglycerides, most experts agree that optimal HDL cholesterol and triglyceride levels are >40 mg/dl and <200 mg/dl, respectively.

Medications most commonly used to treat high LDL cholesterol levels are statins, such as atorvastatin (Lipitor) or simvastatin (Mevacor). These medications work by reducing the production of cholesterol within the body. Although safe and effective, statins very rarely cause muscle damage, typically when used in combination with other medications. Thus, it is important to let your doctor know whether you develop any generalized body ache or start a new medication when you are taking statins.

Other medications used to treat high LDL cholesterol levels include ezetimibe (Zetia), which decreases the absorption of cholesterol from the gut; bile-acid sequestrants (Questran), which eliminate cholesterol from the body; and nicotinic acid (Niacin), which, in addition to lowering LDL cholesterol, raises HDL cholesterol.

Hypertriglyceridemia is typically treated with a class of medications called fibrates. Included in this class are gemfibrozil (Lopid) and fenofibrate (Tricor). Similar to statins, fibrates are safe and effective but may cause muscle damage, usually when used in combination with other medications. [4]

Definition of Heart Disease

Heart disease is a general term that refers to any disease or condition of the heart, including coronary heart disease, hypertension, heart failure, congenital heart disease, disorders of the heart valves, heart infections, cardiomyopathy, conduction disorders, and heart arrythmias. This information item will focus on atherosclerotic changes – the changes that occur because of the build up of plaques or fatty streaks on the interior walls of the blood vessels that supply oxygenated blood to the heart muscle. This condition is also known as coronary artery disease. [5]

Description of Heart Disease

The heart is a muscular pump in the chest. Throughout life it beats continuously and rhythmically to send blood to the lungs and the rest of the body.

The normal heart weighs approximately 10 1/2 ounces and is about the size of your fist. It beats 60 to 120 times a minute, depending on whether you are excited or resting.

The average blood cell makes a round trip through the body's arteries and veins every 60 seconds, and can hit speeds of up to 10 mph. The heart pumps your five quarts of blood around your body 500 times a day.

When the arteries become clogged with deposits made up of "bad" cholesterol, plaque, scar tissue, or calcium, the heart has a harder time circulating blood. This clogging causes a myriad of heart problems from angina pectoris (chest pain) to heart failure to a heart attack.[6]

Causes and Risk Factors of Heart Disease

The primary risk factors for the development of atherosclerotic heart disease are smoking, sedentary lifestyle, hypertension, diabetes, hypercholesterolemia, and a genetic predisposition to the disease.

Symptoms of Heart Disease

In its early stages there are no symptoms. The first symptom is usually angina pectoris (chest pain) or heart attack.

Angina pectoris is discomfort or pain in the chest, typically, brought on by exertion and relieved by rest. The pain may be a dull ache in the middle of the chest or a feeling of pressure that may spread up to the neck or down the arms.

The major symptoms of a heart attack are intense chest pain, suddenly cold, sweating, weakness and nausea.

Cardiovascular diseases in the world
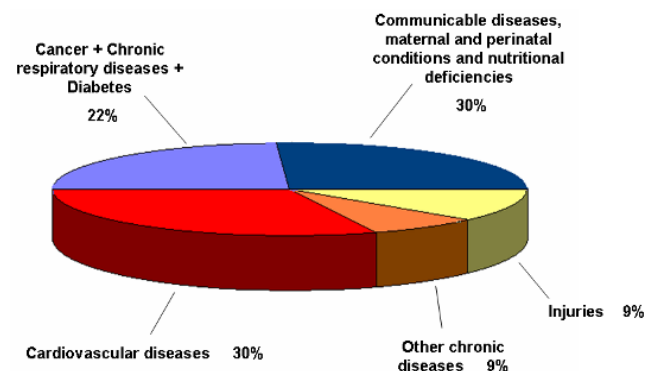
Cardiovascular disease is caused by disorders of the heart and blood vessels, and include coronary heart disease (heart attacks), cerebrovascular disease (cerebrovascular disease), raised blood pressure (hypertension), peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure. The major causes of cardiovascular disease are tobacco use, physical inactivity, and an unhealthy diet.

Cardiovascular disease is the number one cause of death globally and is projected to remain the leading cause of death. An estimated 17.5 million people died from cardiovascular

disease in 2005, representing 30 % of all global deaths. Of these deaths, 7.6 million were due to heart attacks and 5.7 million were due to stroke. Around 80% of these deaths occurred in low and middle income countries (LMIC). If appropriate action is not taken, by 2015, an estimated 20 million people will die from cardiovascular disease every year, mainly from heart attacks and strokes. [7]

Heart attacks and strokes are mainly caused by a blockage tat prevents blood from flowing to the heart or the brain. The most common reason for this is build-up of fatty deposits on the inner walls of the blood vessels that supply the heart or the brain. This makes the blood vessels narrower and less flexible. It is sometimes called hardening of the arteries or atherosclerosis. The blood vessels are then more likely to get blocked by blood clots. When that happens, the blood vessels cannot supply blood to the heart and brain, which become damaged.

There are three main reasons for fatty build-up, and you can control them all:

- Smoking and other tobacco use
- unhealthy diet
- not staying active.

An early form of fatty deposits, known as "fatty streaks", can even be found in some children younger than 10 years. These deposits get slowly worse as the person gets older. To find out more about how you can prevent this from happening to you and your family, read WHO publication "Avoiding heart attacks and strokes".

Diagnosis of Heart Disease

The diagnosis of this problem is based upon clinical history and physical exam. Confirmatory tests include electrocardiography (electrodes are connected to the chest and heart activity is monitored) and measurement of the level of serum creatine kinase enzymes released into the blood by the damaged muscle. Another method is the heart imaging technique called an angiography (injection of dye into the arteries followed by x-ray). [8]

Treatment of Heart Disease

There are several treatment methods that will help improve blood flow through the arteries.

Medications

Beta-blockers, such as atenol (Tenormin), nadolol (Corgard), metoprolol (Lopressor, Toprol XL), and propranolol (Inderal), lower blood pressure by reducing the amount of blood pumped by the heart. These drugs may also reduce the risk of a subsequent heart attack in patients who have already had one. Possible side effects include fatigue, impotence, abnormalities in fatty substances in the blood and interference with blood-sugar regulation. . (View list of beta-blockers)

Calcium channel blockers, such as amlodipine (Norvasc), diltiazem (Cardizen, Tiazac), nifedipine (Adalat, Procardia), nisoldipine (Sular), and verapamil (Calan, Isoptin, Verelan),

relax blood vessel walls, thereby lowering pressure. They are also quite expensive and may cause side effects such as constipation and swollen legs. There are also Nitrate-based drugs and vasodilator drugs. (View list of calcium channel blockers)

Diuretics, such as chlorothiazide (Diuril) and hydrochlorothiazide (Esidrix), lower blood pressure by causing the body to expel excess fluids and sodium through urination. If the desired effects aren't realized with diuretics alone, in combination they may enhance the effect of other blood pressure medications. (View list of diuretics).

Angiotensin-Converting Enzyme (ACE) Inhibitors, such as captopril (Capoten), enalapril (Vasotec), and lisinopril (Prinivil, Zestril), expand blood vessels and decrease resistance. This allows blood to flow more easily and makes the heart's work easier. (View list of ACE inhibitors).

Angiotensin-2 (AT-2) receptor antagonists, such as candesartan (Atacand) and Avapro, have been shown to achieve effects similar to those found in ACE inhibitors. Instead of lowering levels of angiotensin II (as ACE inhibitors do), angiotensin II receptor blockers prevent it from effecting the heart and blood vessels. This keeps blood pressure from rising.

Statins, such as atorvastatin (Lipitor), pravastatin (Pravachol), and rosuvastatin calcium (Crestor), are very effective in lowering LDL ("bad") cholesterol levels and have few short-term side effects. They work in the liver to interrupt the formation of cholesterol from the circulating blood. (View list of statins). Ezetimibe (Zetia) is a newer drug that lowers LDL ("bad") cholesterol by working in the digestive tract to reduce the absorption of cholesterol. It is sometimes prescribed along with a statin. [9]

Balloon Angioplasty

A nonsurgical procedure designed to dilate (widen or expand) narrowed coronary arteries. It works as follows:

First, a doctor inserts a thin plastic tube (a catheter) into an artery in your arm or leg. He or she then guides this catheter to the aorta (the large artery that conducts blood from the heart to the rest of the body). From there it passes into the coronary arteries.

As the doctor guides the catheter to the coronary arteries, the procedure is monitored by a special x-ray camera called a fluoroscope. Once the catheter is passed into the narrowed coronary artery, a second, smaller catheter with a balloon on its' tip is passed through the first catheter. You can think of this as one "pipe" passed through another.

As this second catheter is passed through the first, the balloon remains deflated; however, once the balloon tip reaches the narrowed part of the coronary artery, it's inflated. When the balloon is inflated, it compresses the plaque and enlarges the diameter of the opening within the blood vessel. After that, the balloon is deflated and the catheters are withdrawn.

The result of this procedure is that the blood vessel is dilated, and blood can flow more easily through the (formerly narrowed) part of the coronary artery.[10]

In some situations, a small hollow tube made of metal mesh, called a stent, is used to keep the blood vessel open after a balloon angioplasty. There are new types of stents, called drug-eluting stents, that are coated with immunosuppressants that are slowly released and help keep the blood vessel from reclosing. These new stents, a sirolimus-eluting stent (Cypher) and a paclitaxel-eluting stent (Taxus), have shown some promise for improving the long-term success of this procedure.

Bypass Graft Surgery

Bypass graft surgery was introduced as a way of treating coronary artery disease. In this operation (abbreviated as CABG and sometimes pronounced "cabbage"), cardiac surgeons remove part of the blood vessel (graft) from somewhere else in the body and attach it to a narrowed or blocked coronary artery so the muscle ordinarily supplied by the vessel can be nourished again. For many people who suffer from unremitting angina, CABG can provide dramatic relief.

The principle of bypass graft surgery is to construct a new channel so blood can get around the atherosclerotic blockages in the coronary arteries. Therefore, instead of trying to scrape out the plaques, the surgeon uses a segment of a vessel from another part of the body to transport blood to the far side of the obstruction. Usually the grafts are fashioned from one of the large, accessible saphenous veins that run down the inside of the leg, although recently there has been a trend towards using the internal mammary arteries located under the chest wall.[11]

Electrophysiologic devices (Pacemakers)

The job of the pacemaker is to maintain a minimum safe heart rate by delivering to the pumping chambers appropriately timed electrical impulses that replace the heart's normal rhythmic pulses.

The device designed to perform this life-sustaining role consists of a power source about the size of a silver dollar (containing the battery) and, control circuits, and wires, or "leads, that connect the power source to the chambers of the heart.

The leads are placed in contact with the right atrium or the right ventricle, or both. They allow the pacemaker to sense and stimulate in various combinations, depending on where the pacing is required.[12]

2. Prevention of Heart Disease

We can do several things to prevent heart disease:

Begin or sustain some regular physical activity:

Even a modest amount of activity each day will lower your LDL cholesterol and raise your HDL cholesterol. Exercise also improves your heart's pumping efficiency, benefits your circulation and increases your overall strength and endurance.

Increase our consumption of vegetables, fresh fruits, low-fat milk and other dairy products, grains, fish and poultry:

The main objective here is to replace foods high in saturated fat with healthier foods. Multiple sources of information exist that will help you create a heart-healthy diet.

Know our cholesterol, LDL, HDL and triglyceride levels:

The level of cholesterol in your blood is a good indicator of the health of your heart and blood vessels. Generally, the higher your cholesterol level, the greater your risk of heart disease.

LDL stands for low-density lipoprotein. LDLs carry cholesterol around the body. LDLs deposit cholesterol in blood vessels where they can eventually build up and restrict blood flow. The more LDLs you have, the higher your risk factor for heart disease.

HDL stands for high-density lipoprotein. HDLs remove cholesterol from artery walls and carry it to the liver, which breaks it down.

Triglycerides are a type of fat present in foods and manufactured in the liver. The higher your triglyceride level, the greater your risk of heart disease.

Obesity raises triglyceride levels, which in turn promotes heart disease. Diet and physical activity should help you lower and maintain your weight.

A family history of obesity, diabetes, heart attack, stroke or high blood pressure increases your risk of heart disease so consult a cardiologist before the age of 55 for males and 65 for females.

Pay attention to the pain:

If you feel your vitality generally slipping, have a checkup. If you are having chest pains go to the nearest emergency room. Atorvastatin is used together with lifestyle changes (diet, weight-loss, exercise) to reduce the amount of cholesterol (a fat-like substance) and other fatty substances in the blood. Atorvastatin is in a class of medications called HMG-CoA reductase inhibitors (statins). It works by slowing the production of cholesterol in the body.

Buildup of cholesterol and other fats along the walls of the blood vessels (a process known as atherosclerosis) decreases blood flow and, therefore, the oxygen supply to the heart, brain, and other parts of the body. Lowering blood levels of cholesterol and other fats may help to decrease your chances of getting heart disease, angina (chest pain), strokes, and heart attacks. In addition to taking a cholesterol-lowering medication, making certain changes in your daily habits can also lower your cholesterol blood levels. You should eat a diet that is low in saturated fat and cholesterol (see SPECIAL DIETARY), exercise 30 minutes on most, if not all days, and lose weight if you are overweight.

Statins, such as atorvastatin (Lipitor), pravastatin (Pravachol), and rosuvastatin calcium (Crestor), are very effective in lowering LDL ("bad") cholesterol levels and have few short-term side effects. They work in the liver to interrupt the formation of cholesterol from the circulating

blood. (View list of statins). Ezetimibe (Zetia) is a newer drug that lowers LDL ("bad") cholesterol by working in the digestive tract to reduce the absorption of cholesterol. It is sometimes prescribed along with a statin.

ATORVASTATIN: Brand name (LIPITOR):

Lipitor belongs to a group of medicines called HMG-CoA reductase inhibitors and is used to lower high cholesterol.

Everyone has cholesterol in their blood. It is a type of blood fat needed by the body for things such as building cell walls, making bile acids (which help to digest food) and some hormones. However, too much cholesterol can be a problem.

Cholesterol is present in many foods and is also made in your body by the liver. If your body makes too much cholesterol or you take too much cholesterol in your diet, then your level becomes too high.

A problem is more likely to occur with certain diseases or if you have a family history of high cholesterol.

There are different types of cholesterol. LDL is the 'bad' cholesterol that can block your blood vessels. HDL cholesterol is the 'good' cholesterol that is thought to remove the bad cholesterol from the blood vessels.

When you have high levels of 'bad' cholesterol in your blood, it may begin to 'stick' to the inside of your blood vessels instead of being carried to the parts of the body where it is needed. Over time, this can form hard areas, also called plaque, on the walls of your blood vessels, making it more difficult for the blood to flow. This blocking of your blood vessels can lead to several types of blood vessel disease, heart attack, angina and stroke.

There is another type of blood fat called triglyceride which is a source of energy. However, high levels of triglyceride can be associated with a low level of 'good' cholesterol and may increase your risk of heart disease.

In some patients, Lipitor is used to treat high cholesterol and high triglycerides together.Lipitor does not reduce the cholesterol that comes from fat in food.Therefore, when you are taking Lipitor, you also need to follow a low fat diet and other measures, such as exercise and weight control.In most people, there are no symptoms of abnormal cholesterol or triglyceride levels. Your doctor can measure your levels with a simple blood test.Your doctor may have prescribed Lipitor for another reason.Ask your doctor if you have any questions about why Lipitor has been prescribed for you.Lipitor is not addictive.

Atorvastatin comes as a tablet to take by mouth. It is usually taken once a day with or without food. Take atorvastatin at around the same time every day. Follow the directions on your prescription label carefully, and ask your doctor or pharmacist to explain any part you do not understand. Take atorvastatin exactly as directed. Do not take more or less of it or take it more often than prescribed by your doctor.Your doctor may start you on a low dose of atorvastatin and gradually increase your dose, not more than once every 2-4 weeks.Continue to take atorvastatin even if you feel well. Do not stop taking atorvastatin without talking to your doctor.[13]

Special dietary instructions

Eat a low-cholesterol, low-fat diet. This kind of diet includes cottage cheese, fat-free milk, fish (not canned in oil), vegetables, poultry, egg whites, and polyunsaturated oils and margarines (corn, safflower, canola, and soybean oils). Avoid foods with excess fat in them such as meat (especially liver and fatty meat), egg yolks, whole milk, cream, butter, shortening, lard, pastries, cakes, cookies, gravy, peanut butter, chocolate, olives, potato chips, coconut, cheese (other than cottage cheese), coconut oil, palm oil, and fried foods.Talk to your doctor about drinking grapefruit juice while taking this medication.

Take the missed dose as soon as you remember it. However, if it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Do not take a double dose to make up for a missed one.[14]

Side effects of Atorvastatin

Atorvastatin may cause side effects. Tell your doctor if any of these symptoms are severe or do not go away:
diarrhea
headache
difficulty falling asleep or staying asleep
dizziness
joint pain
sore throat
upper respiratory infection
Some side effects can be serious. The following symptoms are uncommon, but if you experience any of them, call your doctor immediately:
muscle pain, tenderness, or weakness
lack of energy
fever
chest pain ,swelling of the hands, feet, ankles, or lower legs
nausea
extreme tiredness
unusual bleeding or bruising
loss of appetite
pain in the upper right part of the stomach
flu-like symptoms
yellowing of the skin or eyes
rash
hives
itching
difficulty breathing or swallowing
swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
hoarseness
pain during urination
frequent urge to urinate [15]
Atorvastatin (Lipitor) changes the genetic material found in blood cells of people with vascular (blood vessel) disease. Vascular diseases affect the blood flow in the body and can lead to a heart attack or stroke. Information gained from this

study could be used to develop a more reliable blood test that predicts the risk of heart attack or stroke.

Storage conditions are needed for this medicine

Keep this medication in the container it came in, tightly closed, and out of reach of children. Store it at room temperature and away from excess heat and moisture (not in the bathroom). Throw away any medication that is outdated or no longer needed. Talk to your pharmacist about the proper disposal of your medication.

3. Review of Literature

HMG-CoA reductase inhibitors or statins are effective in both the primary and secondary prevention of coronary heart disease, the extent of benefit being proportional to the reduction in low density lipoprotein (LDL) cholesterol achieved. Atorvastatin, a newly licensed compound, reportedly lowers LDL with greater efficacy than other statins. The mechanism of this action was, therefore, explored in twenty patients with refractory familial hypercholesterolemia who received in a single-blind sequence simvastatin 40 mg/day, placebo and atorvastatin 10 mg/day each for 4 weeks. At the end of the placebo period the effects of single 40-mg doses of simvastatin and atorvastatin on plasma levels and urinary excretion of mevalonic acid, indices of HMG-CoA reductase activity, were compared. Administration of atorvastatin 10 mg daily for 1 month lowered LDL cholesterol by 32.5%, compared with placebo (P = 0.0001), which was 4.5% less than the decrease after simvastatin 40 mg daily (P = 0.33). The area under the plasma curve and urinary mevalonic acid/creatinine ratio were both significantly less during the 24 h after a single dose of atorvastatin 40 mg than after a single dose of simvastatin 40 mg (P < 0.01). These findings suggest that the greater efficacy of atorvastatin compared with simvastatin is due to more prolonged inhibition of HMG-CoA reductase, presumably reflecting longer residence of atorvastatin or its active metabolites in the liver.[16]

The benefits of cholesterol lowering for primary and secondary prevention of coronary artery disease (CAD) have been well established. However, to accurately assess a patient's risk for CAD, clinicians must be aware of their patients' specific levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides, and not just total serum cholesterol. Clinicians must also evaluate other factors in assessing a patient's risk profile. These include smoking, weight, family history of CAD, age, hypertension, and others. Absolute risk, rather than relative risk, can then be determined. Although LDL cholesterol may be the most potent predictor of risk, triglycerides are also an important indicator of CAD risk. Currently, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins") are first-line therapy for the reduction of elevated levels of LDL

cholesterol. All statins are effective in achieving some level of LDL cholesterol lowering. However, atorvastatin, which was recently introduced in the United States, has greater efficacy at maximal dosage in lowering LDL cholesterol, and also has a more beneficial effect on elevated levels of triglycerides, than other statins.[17]

Reduction in plasma lipids has been recognized as one of the primary cardiovascular risk reduction strategies in the secondary prevention of coronary heart disease (CHD). The primary end points of TARGET TANGIBLE were the safety (adverse events and laboratory measurements) and efficacy (responder rates) of therapy with atorvastatin versus simvastatin with the aim of achieving low-density lipoprotein (LDL) cholesterol lowering to < or =100 mg/dl (2.6 mmol/L). A total of 3,748 CHD patients with LDL cholesterol levels > or =130 mg/dl (3.4 mmol/L) entered a run-in diet phase of 6 weeks without any lipid-lowering drug therapy. At the end of the diet phase, 2,856 patients met the lipid criteria and were randomized to active treatment for 14 weeks. Patients received 10 to 40 mg of either drug in an optional titration design at 2:1 randomization for atorvastatin versus simvastatin. Adverse event rates were statistically equivalent (p<0.01) for simvastatin (35.7%) and for atorvastatin patients (36.3%). Both drugs were well tolerated; <5% of patients in both groups were withdrawn due to adverse events. In all, 37 atorvastatin patients (2%) and 27 simvastatin patients (3%) had serious adverse events. Drug-related side effects (elevations in creatine kinase, liver enzymes) occurred in both groups at similar rates with 10 atorvastatin patients (0.5%) and 5 simvastatin patients (0.5%) presenting confirmed transaminase elevations >3 x the upper limit of the normal range. Significantly fewer patients in the atorvastatin group (n = 724) required titration to 40 mg compared with the simvastatin group (n = 514) (38% vs. 54%, respectively; p<0.001). Atorvastatin resulted in a significantly greater number of patients reaching the LDL cholesterol goal than those treated with simvastatin, with 67% of atorvastatin patients and 53% of simvastatin patients reaching the target LDL cholesterol level of < or =100 mg/dl (2.6 mmol/L) (p<0.001). Both atorvastatin and simvastatin are safe for use by patients in the secondary prevention of CHD, with patients in both drug groups having similar adverse event rates. Despite the use of concomitant medications there was no drug-induced rhabdomyolysis with either atorvastatin or simvastatin. [18]

Although the levels of low-density lipoprotein (LDL) cholesterol remain the main therapeutic goal when treating dyslipidaemias, there is a need to consider high-density lipoprotein (HDL) concentrations. This conclusion is based on the findings of epidemiological surveys and appropriately designed trials using statins or fibrates. The importance of HDL, as a 'protective' lipoprotein fraction, has been recognised by major treatment guidelines. This review considers the differences in HDL-raising capacity of two of the most commonly prescribed statins--atorvastatin and simvastatin. When compared with simvastatin, atorvastatin is associated with progressively decreasing rises in the levels

of HDL as the dose increases (negative dose response), an effect not reported with other statins. In contrast, simvastatin shows a positive dose response (increasing concentrations of HDL with increasing dose). This effect is paralleled by changes in apolipoprotein A-I levels. Apolipoprotein A-I is the main apolipoprotein associated with HDL. This dissimilarity in HDL response is an example of several differences that have been reported when comparing various statins. If 'all statins are not created equal', we should focus prescribing on those statins that have end point evidence originating from appropriately designed trials. [19]

Primary and secondary prevention trials have shown that use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (also known as statins) to lower an elevated low-density lipoprotein cholesterol level can substantially reduce coronary events and death from coronary heart disease. In 1987 and 1993, the National Cholesterol Education Program promulgated guidelines for cholesterol screening and treatment. Thus far, however, primary care physicians have inadequately adopted these guidelines in clinical practice. A 1991 study found that cholesterol screening was performed in only 23 percent of patients. Consequently, many patients with elevated low-density lipoprotein levels and a high risk of primary or recurrent ischemic events remain unidentified and untreated. A study published in 1998 found that fewer than 15 percent of patients with known coronary heart disease have low-density lipoprotein levels at the recommended level of below 100 mg per dL (2.60 mmol per L). By identifying patients with elevated low-density lipoprotein levels and instituting appropriate lipid-lowering therapy, family physicians could help prevent cardiovascular events and death in many of their patients.[20]

Enhanced and prolonged postprandial lipaemia is implicated in coronary and carotid artery disease. This study assessed the effects of atorvastatin, a 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor, on postprandial plasma concentrations of triglyceride-rich lipoproteins (TRLs). Sixteen middle-aged men with combined hyperlipidaemia (baseline low density lipoprotein (LDL) cholesterol and plasma triglyceride concentrations (median (interquartile range) of 4.54 (4.17-5.26)) and 2.66 (2.04-3.20) mmol/l, respectively) and previous myocardial infarction were randomised to atorvastatin 40 mg or placebo once daily for 8 weeks in a double-blind, cross-over design. The apolipoprotein (apo) B-48 and B-100 contents were determined in subfractions of TRLs as a measure of chylomicron remnant and very low density lipoprotein (VLDL) particle concentrations (expressed as mg apo B-48 or apo B-100 per litre of plasma), in the fasting state and after intake of a mixed meal. Atorvastatin treatment reduced significantly the fasting plasma concentrations of VLDL cholesterol, LDL cholesterol and VLDL triglycerides (median% change) by 29, 44 and 27%, respectively, and increased high density lipoprotein (HDL) cholesterol by 19%, compared with baseline. The postprandial plasma concentrations of large (Svedberg flotation rate (Sf) 60-400) and small (Sf 20-60) VLDLs and chylomicron remnants were almost halved compared with baseline (mean 0-6 h plasma concentrations were reduced by 48% for Sf 60-400 apo B-100, by 46% for Sf 60-400 apo B-48, by 46% for Sf 20-60 apo B-100 and by 27% for Sf 20-60 apo B-48), and the postprandial triglyceridaemia was reduced by 23% during active treatment. In conclusion, atorvastatin 40 mg once daily causes profound reductions of postprandial plasma concentrations of all TRLs in combined hyperlipidaemic patients with premature coronary artery disease. [21]

The effects of the HMG CoA reductase inhibitor atorvastatin on electrophoretic characteristics of LDL particles were evaluated in 46 patients (28 males and 18 females) with heterozygous familial hypercholesterolemia (FH) aged 20-61 carrying either a negative or a defective LDL receptor gene mutation. Following a 6 week drug-free baseline period, FH heterozygotes were treated with atorvastatin (median dose: 20 mg/day, range 10-80 mg/day)) for 6 months to maintain their plasma LDL-cholesterol concentrations between 4.0 and 5.0 mmol/l. Atorvastatin treatment significantly reduced plasma total cholesterol, LDL-cholesterol and triglyceride levels and increased plasma HDL-cholesterol. Furthermore, atorvastatin treatment significantly increased LDL peak particle diameter (LDL-PPD) by 0.5% (from 255.0+/-6.2 to 256.4+/-5.5 A, P=0.004) and reduced the absolute concentration of cholesterol among small (<255 A) and large (>260 A) LDL particles by 35% (P<0.001). Changes in LDL-PPD and plasma triglyceride levels were inversely correlated (R=-0.34; P=0.02). Stepwise multiple linear regression analyses showed that 41.6% of the variation in the LDL-PPD response to atorvastatin was attributable to the initial LDL-PPD (14.4%, P=0.003), the apo E polymorphism (12.4%, P=0.02), the nature of the LDL receptor gene mutation (9.6%, P=0.01) and change in triglyceride levels (5.2%, P=0.04). Moreover, the reduction in the cholesterol content of LDL <255 A was directly correlated with the daily dosage of atorvastatin (P=0.05). Results of the present study showed that atorvastatin alters significantly LDL heterogeneity in patients at high risk of coronary heart disease (CHD) such as FH heterozygotes. These results also suggest that genetic and metabolic factors may be important determinants of atorvastatin-induced changes of LDL particle size and distribution among FH heterozygotes. [22]

The effects of atorvastatin at 20, 40, and 80 mg/day on plasma lipoprotein subspecies were examined in a randomized, placebo-controlled fashion over 36 weeks in 97 patients with coronary heart disease (CHD) with low-density lipoprotein (LDL) cholesterol levels of >130 mg/dl and compared directly with the effects of fluvastatin (n = 28), pravastatin (n = 22), lovastatin (n = 24), and simvastatin (n = 25). The effects of placebo and 40 mg/day of each statin were also examined in subjects with CHD with subjects in the fasting state and in the fed state 4 hours after a meal rich in saturated fat and cholesterol and compared with results in age- and gender-matched control subjects. At all doses tested in the fasting and fed states, atorvastatin was significantly (p

<0.01) more effective in lowering LDL cholesterol and non-high-density lipoprotein (HDL) cholesterol than all other statins, and significantly (p <0.05) more effective than all statins, except for simvastatin, in lowering triglyceride and remnant lipoprotein (RLP) cholesterol. At 40 mg/day in the fasting state, atorvastatin was significantly (p <0.01) more effective than all statins, except for lovastatin and simvastatin, in lowering cholesterol levels in small LDL, and was significantly (p <0.05) more effective than all statins, except for simvastatin, in increasing cholesterol in large HDL and in lowering LDL particle numbers. Our data indicate that atorvastatin was the most effective statin tested in lowering cholesterol in LDL, non-HDL, and RLP in the fasting and fed states, and getting patients with CHD to established goals, with fluvastatin, pravastatin, lovastatin, and simvastatin having about 33%, 50%, 60%, and 85% of the efficacy of atorvastatin, respectively, at the same dose in the same patients.[23]

Statins have become a cornerstone of treatment for dyslipidaemia primarily due to their marked lowering of low-density lipoprotein cholesterol (LDL-C). Studies show that statin treatment typically reduces relative risk of cardiovascular disease by 24-37%, regardless of age, sex, prior history of coronary heart disease (CHD), or other co-morbid conditions. There is also a growing body of evidence that statins can be effective in people whose LDL-C is not considered elevated under current guidelines. In both the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and the Collaborative Atorvastatin Diabetes Study (CARDS), participants randomised to atorvastatin (10 mg/day) experienced at least a one-third reduction in major cardiovascular events, even though at baseline, their LDL-C was within the normal range. Other studies have also provided evidence that more intensive lipid-lowering regimens could provide additional clinical benefits. In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, the first active-control clinical trial of CHD progression, an intensive lipid-lowering regimen using atorvastatin (80 mg/day) decreased atherogenic lipoproteins and atheroma volume in patients with established CHD, compared with a moderate regimen using pravastatin (40 mg/day). Furthermore, relative to baseline, there was no measurable atheroma progression in the atorvastatin group. While statin therapy does offer significant clinical benefit, 60-70% of major cardiovascular events are still not prevented, which underscores the need for alternative interventions. Targeting inflammatory mediators of atherosclerosis such as C-reactive protein (CRP), as well as combination therapy to simultaneously raise high-density lipoprotein cholesterol (HDL-C) and lower LDL-C, are among the promising new strategies for primary and secondary prevention of atherosclerotic disease. This article will summarise data concerning use of statins in patients without markedly elevated LDL-C. The issue of the ideal LDL-C target will also be considered before addressing future treatment options for dyslipidaemia. [24]

Atorvastatin has been shown to reduce coronary events and revascularization procedures in patients with multiple risk factors for coronary heart disease. Recent studies with atorvastatin 80 mg support the overall safety of this dose during long-term treatment. However, physicians appear reluctant to use high doses of statins. A retrospective analysis of pooled data from 49 clinical trials of atorvastatin in 14,236 patients treated for an average period of 2 weeks to 52 months was conducted. The study compared the safety of atorvastatin 10 mg (n = 7,258), atorvastatin 80 mg (n = 4,798), and placebo (n = 2,180) and included analyses on treatment-associated adverse events; nonserious and serious adverse events related to the musculoskeletal, hepatic, and renal systems; the incidence of elevations of creatine kinase >10 times the upper limit of normal (ULN); and hepatic transaminases >3 times ULN. Percentages of patients experiencing > or =1 adverse event were similar across all 3 groups. Withdrawals due to treatment-related adverse events were observed in 2.4%, 1.8%, and 1.2% of patients in the atorvastatin 10 mg, atorvastatin 80 mg, and placebo groups, respectively. Serious adverse events were rare and seldom led to treatment withdrawal with any dose. Treatment-associated myalgia was observed in 1.4%, 1.5%, and 0.7% of patients in the atorvastatin 10 mg, atorvastatin 80 mg, and placebo groups, respectively. No cases of rhabdomyolysis were reported in any group. Persistent elevations in hepatic transaminases >3 times ULN were observed in 0.1%, 0.6%, and 0.2% of patients in the atorvastatin 10 mg, atorvastatin 80 mg, and placebo groups, respectively. The incidence of treatment-associated adverse events for atorvastatin 80 mg was similar to that of atorvastatin 10 mg and placebo. In conclusion, the results of this analysis support the positive safety profile of atorvastatin at the highest dose. [25]

High-density lipoprotein (HDL) cholesterol levels are a strong inverse predictor of cardiovascular events. However, it is not clear whether this association is maintained at very low levels of low-density lipoprotein (LDL) cholesterolA post hoc analysis of the recently completed Treating to New Targets (TNT) study assessed the predictive value of HDL cholesterol levels in 9770 patients. The primary outcome measure was the time to a first major cardiovascular event, defined as death from coronary heart disease, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke. The predictive relationship between HDL cholesterol levels at the third month of treatment with statins and the time to the first major cardiovascular event was assessed in univariate and multivariate analyses and was also assessed for specific LDL cholesterol strata, including subjects with LDL cholesterol levels below 70 mg per deciliter (1.8 mmol per liter). The HDL cholesterol level in patients receiving statins was predictive of major cardiovascular events across the TNT study cohort, both when HDL cholesterol was considered as a continuous variable and when subjects were stratified according to quintiles of HDL cholesterol level. When the analysis was stratified according to LDL cholesterol level in patients receiving statins, the relationship between HDL

cholesterol level and major cardiovascular events was of borderline significance (P=0.05). Even among study subjects with LDL cholesterol levels below 70 mg per deciliter, those in the highest quintile of HDL cholesterol level were at less risk for major cardiovascular events than those in the lowest quintile (P=0.03). CONCLUSIONS: In this post hoc analysis, HDL cholesterol levels were predictive of major cardiovascular events in patients treated with statins. This relationship was also observed among patients with LDL cholesterol levels below 70 mg per deciliter.[26]

High-dose statin therapy has been demonstrated to provide incremental benefit when low-density lipoprotein (LDL) cholesterol concentrations are lowered well below recommended target levels. This secondary analysis of the Treating to New Targets (TNT) study was conducted to investigate whether the attainment of very low LDL cholesterol levels was associated with a further reduction in major cardiovascular events compared with higher LDL cholesterol concentrations and whether any incremental benefit was achieved without additional safety risk. Patients with coronary heart disease and LDL cholesterol levels <130 mg/dl (3.4 mmol/L) were randomized to therapy with atorvastatin 10 mg/day (n = 5,006) or 80 mg/day (n = 4,995). The primary end point was the occurrence of a first major cardiovascular event. Clinical outcomes and safety data were compared across on-treatment LDL cholesterol quintiles. There was a highly significant reduction in the rate of major cardiovascular events with descending achieved levels of on-treatment LDL cholesterol (p <0.0001 for trend across LDL cholesterol). Analysis of individual components of the primary end point demonstrated similar results. Death from any cause and from noncardiovascular causes was lowest in patients with the lowest on-treatment LDL cholesterol levels. Cardiovascular deaths were also reduced with lower levels of on-treatment LDL cholesterol. There were no clinically important differences in adverse event rates across quintiles. Specifically, no increase in muscle complaints, suicide, hemorrhagic stroke, or cancer deaths was observed at the lowest LDL cholesterol levels. In conclusion, the present analysis adds support to the concept that for patients with established atherosclerotic cardiovascular disease, a further risk reduction without sacrifice of safety can be achieved by reducing LDL cholesterol to very low levels.[27]

The lipid-lowering and anti-atherosclerotic effects of atorvastatin (10 mg/day) were investigated by measuring changes in the levels of oxidized low-density lipoprotein (LDL), serum lipids (total cholesterol [TC], LDL-cholesterol [LDL-C] and triglycerides [TG]), and in the protein adiponectin. This was undertaken in 22 patients with ischaemic heart disease and serum LDL-C levels > 100 mg/dl. After 3 months of therapy, atorvastatin significantly decreased serum lipids, oxidized LDL was reduced from 457.0 +/- 148.6 to 286.9 +/- 88.5 nmol/l, and adiponectin increased from 9.7 +/- 7.4 to 13.9 +/- 9.98 microg/ml. No significant correlation was observed between adiponectin and LDL-C, TG and high-density lipoprotein cholesterol. Atorvastatin therapy was not associated with side-effects,

such as myalgia and gastrointestinal disorders, and did not give abnormal laboratory test results. It is concluded that atorvastatin decreases serum lipid and oxidized LDL levels, and increases adiponectin levels in patients with ischaemic heart disease.[28]

4. Scope of the Present Investigation

Atorvastatin is the more potent drug to treat the hyperlipidemia patients.Unfortunately this drug has got hepatotoxicity and hence the patients on statin treatment have to be monitored for Liver function test frequently.This study is used to find the hepatotoxic effect of atorvastatin in hyperlipidemic patients.This study is plan to do the following biochemical parameters.

- Glucose
- Urea
- Creatinine
- Uric Acid
- Sodium
- Potassium
- Chloride
- Bicarbonate
- Cholesterol
- High Density Lipoprotein
- Triglycerides
- Ratio
- Total Bilirubin
- Serum Glutamic Pyruvate Transaminase
- Alkaline Phosphatase
- Gamma-glutamyl transpeptidase
- Total Protein
- Albumin Globulin

5. Materials and Methods

Estimation of Glucose

Estimation of Glucose By Ortho Toluidine Method.[16] [17]

PRINCIPLE

Glucose reacts with O-Toluidine in glacial acetic acid at 100˚C to form blue to green coloured N-glycosamine.The intensity of the colour is read at 620nm.

REAGENTS

1. 10% TCA
2. O-Toluidine reagent
3. Glacial Acetic Acid
4. Distilled Water
5. The O-Tolidine reagent ,Glacial acetic acid and water are mixed in the ratio of 15:75:10 and to this 2.5 gms of boric acid and 2.5 gms of Thiourea are addedand mixed well the solution is preserved in brown coloured bottle.

6. Stock Standard Glucose : 100 mg of glucose in 100 ml of distilled water.
7. Working Standard: 1 in 10 dilution of stock standard gives working standard.

PROCEDURE

To 2ml of blood , 2ml of 10% TCA was added to precipitate protein.Then it was centrifuged for 5 minutes. To 1ml of supernatant 4ml of O –Toluidine reagent was added and heated in a water bath for 15 minutes. Then the tube was cooled and measured at 620nm.Blank contains distilled water instead of filterate.
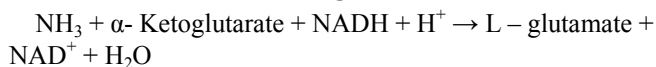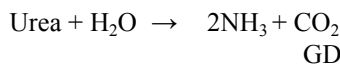
The values were expressed as mg % Blood.

Estimation of Urea

Estimation of blood urea by Kinetic UV assay method.(Neumann.U.,et al., 1977)[18] [19]

PRINCIPLE

Urease

$$Urea + H_2O \rightarrow 2NH_3 + CO_2$$
GD

$$NH_3 + \alpha\text{- Ketoglutarate} + NADH + H^+ \rightarrow L – glutamate + NAD^+ + H_2O$$

Urea is hydrolysed by urease to produce ammonia and water. The liberated ammonia reacts with α- Ketoglutarate in the presence of NADH to yield glutamate. An equimolar quantity of NADH undergoes oxidation during the reaction resulting in a decrease in absorbancs that is directly proportional to the urea nitrogen concentration in the sample.

REAGENTS

1. NADH 0.3M
2. Urease 1,500 U/L
3. α- Ketoglutarate Dehydrogenase > 1500 U/L
4. α- Ketoglutarate 4.0 mM
5. Buffer ph 8.2 ± 0.1
6. Activators and non-reactive stabilizers.
7. Reconstitute reagent with the volume of distilled water stated on the vial lable,swirl to dissolve.

PROCEDURE

Zero spectrophotometer with water at 340 nm is taken. Pipette 1.0 ml of reagent into test tubes and allow reagent to come to room temperature. Add 0.01 ml (10ul) of sample to test tube and immediately place in the spectrophotometer.After 30 seconds read and record the absorbance(A1).60 seconds after the first reading take another reading (A2). Determine the absorbance change between the two readings (A1- A2) .Repeat procedure foe each sample.

Using Hitachi Automatic analyzer Urea was estimated

CALIBRATION

Use an acqueous Urea standard (40mg/dl) or an appropriate serum calibrator.

CALCULATION

(A1-A2) = Absorbance change between reading

$$\frac{(A1- A2)\ Unknown}{(A1-A2)\ standard} \times Concentration\ of\ standard = Urea\ (mg/dl)$$

The values were expressed as ml/dl blood

Estimation of Serum Creatinine

Estimation of serum Creatinine by Alkaline Picrate method.[20] [21]

PRINCIPLE

Creatinine will form a red colour complex with picric acid in alkaline medium which can be measured at 590nm.

REAGENTS

1. 10% Sodium Tungstate
2. 2/3N,Sulphuric Acid
3. 0.04m Picric Acid
4. 0.75N Sodium Hydroxide
5. Stock Standard Creatinine:100mg of pure creatinine in 0.1N Hcl and made upto 100ml with acid itself.
6. Working Standard: 4ml of stock was diluted with 100ml of 0.1N Hcl.

PROCEDURE

0.2ml of serum was diluted with 2ml of distilled water and protein was precipitated by adding 2ml of 10% Sodium Tungstate and added 2ml of 2/3 N Sulphuric Acid and centrifuged for 10 minutes.3ml of the filterate was taken and added with 1ml of picric acid and 1ml of 0.75N Sodium Hydroxide.The colour developed after 15 minutes was read using green filter at 540 nm. A complete reagent blank was done replacing serum with water .

The values were expressed as ml/dl serum.

Estimation of Uric Acid

Estimation of uric Acid in Serum by Caraway method.[22] [23]

PRINCIPLE

The determination of uric acid is based on the reaction of uric acid with phosphor tungstic acid. The colour develop is read at 700nm.

REAGENTS

1. 10% Na_2Co_3
2. 2/3N H_2so_4
3. Phospho Tungstic acid
4. Stock Standard Uric Acid
5. 100mg of Uric Acid in 100ml distilled water.
6. Workng Standard
7. Dilute 1ml of stock standard to 500ml
8. Preparation of stock standard uric acid

Weigh out 100mgs of uric acid in a small beaker.Dissolved 16mg of Lithium Carbonate in 15 to 20 ml of water in a test tube.Heated the solution to 60˚C and poured

on to the uric acid until it dissolves, heating further in warm water if necessary. When dissolved, Transfer with washing to a 100ml flask added 2ml of 40% formalin and then slowly with shaking.Add 1ml of 50% water and mix kept in a well stoppered bottle from the light.

Preparation of tungstic acid

Added 50 ml of 10% sodium tungstate, 50ml 2/3 N sulphuric acid and a drop of phosphoric acid with mixing the 8ooml water.Discard when cloudy.

Preparation of Phospho Tungstic Acid:

To prepare a stock solution dissolved 50gms of sodium tungstate in about 400ml of water, added 40 ml 85% phosphoric acid and reflux gently for 2 hours. Cooled transfer to a 500ml flask made upto mark with water.

PROCEDURE

Added dy shaking 5.4ml of 10% sodium tungstate to 0.6ml of serum and centrifuged. 3ml of supernatant was taken in a test tube, 3ml of water was taken as blank, added 0.6 ml of 10% sodium carbonate to each followed by 0.6 ml phosphor tungstic acid and placed at 25°C in water bath for 30 minutes.The colour developed was read at 700nm.

The values were expressed as ml/dl serum.

Estimation of Electrolytes in the Blood

Estimation of electrolytes in the blood by SYNCHRON EL-ISE method

(Fullerton., 1999)[24][25]

PRINCIPLE

Measurement of electrolytes using iron selective electrodes housed in a flow cell.An LAS glass electrode is used for sodium measurement , a PVC / Valinomycin electrode for potassium analysis, a silver chloride (Ag / Agcl) electrode is provided for chloride measurement and a pH electrode is used for carbondioxide determination.

REAGENTS

1. SYNCHRON EL-ISE reference reagent
2. SYNCHRON EL-ISE electrolye diluent
3. SYNCHRON EL-ISE alkaline buffer
4. SYNCHRON EL-ISE acid reagents

PROCEDURE

Before calibrating the SYNCHRON EL-ISE electrolytesystems verify that sufficient volumes of reagents are on the systems and place fresh calibrators on the tray in their respective positions. Calidrate the systems and follow the " samp[le programming" and "start analysis" protocols.

Using Beckman Coulter, Electrolytes were estimated.

Estimation of Total Cholesterol

Total Cholesterol was estimated by the method of Zak's et al.,(1953) [26]

PRINCIPLE

Cholesterol in acetic acid gives purple colour with ferric chloride and sulphuric acid. The purple colour was then measured at 560nm.

REAGENTS

1. Glacial acetic acid
2. Ferric chloride:0.05% in acetic acid
3. Concentrated sulphuric acid
4. Stock cholesterol standard: 100mg of purified cholesterol in 100ml of purified acetic acid.Diluted the stock standard 1 to 25 with the ferric chloride-acetic acid reagent.The solution was kept in a cool dark place.

PROCEDURE

To 0.1ml of plasma, added 4.9ml of the ferric chloride-acetic acid reagent in a glass stoppered centrifuge tube. Mixed well and allowed to stand for 15 minutes for protein to flocculate.Centrifuged and transferred 5ml of the clear supernatant fluid to a glass stoppered centrifuge tube.A series of standard containing cholesterol in the range of 3-15g were made to 5ml with the reagent and a blank containing 5ml of the reagent were prepared.Added 3ml of sulphuric acid from a burette to all tubes stoppered tightly and mixed by repeated inversion.The tubes were allowed to stand for 20 minutes.The colour developed was read against the blank at 560nm.

The values were expressed as mg/dl plasma.

Estimation of High Density Lipoprotein (HDL)

Estimation of high density lipoprotein by Magnesium / Phospho tungstate method.[27][28]

PRINCIPLE

LDL,VLDL and chylomocrons are precipitated by poly anions in presence of metal ions to leave HDL in solution which reacts with ferric ions in acetic acid followed by sulphuric acid to give a final red coloured compound which is measured spectrophotometrically or colorimetrically.

REAGENTS

1. Phospho tungstate / Magnesium reagent or Mixed reagent:
2. Dissolve 2gms of phosphotungstic acid AR in 25 ml H_2O.Dissolve 5.08 gms of magnesium chloride GR in 10ml water .Mix two solutions.Adjust to pH to 6.15 using IN NaOH GR (3 Pellet in 10 ml water) make upto 50ml using distilled water.
3. Other reagents
4. Lipid c.fas

PROCEDURE

To 0.5ml of sample add 0.05ml of mixed reagent.Mix wellusing a cyclomixer,centrifuge well at 3000rpm for 30 mts.From the supernatant which only HDL fraction,take 0.4ml into a tube.Add 10ml of acetic acid ferric chloride mixture.Mix well and centrifuge for 20 mts.BIORAD control is done for quality check.

Calculation

Concentration of HDL mg/dl = $\underline{OD\ of\ Test}$ X Concentration of HDL in C.Fo.S

OD of Std

The values were expressed as ml/dl serum.

Estimation of Low Density Lipoprotein (LDL)

A homogeneous method based on an innovative detergent technology. [29] [30]

PRINCIPLE

Cholesterol LDL is a ready-to-use stable liquid reagent that directly measures the concentration of LDL cholesterol by a new homogeneous method based on an innovative detergent technology.This kit is readily adapted for use with most clinical chemistry analyzers without requiring any off-line sample pretreatment, centrifugation, or reagent reconstitution steps. Furthemore, the LDL cholesterol measurements with this kit show an excellent correlation with those of an ultra centrifugation method.

REAGENTS

Reagent 1:(Enzyme solution)
- Detergent 1
- 4-aminoantipyrine (0.5 mmol/L)
- cholesterol oxidase (1.2U/mL)
- Cholesterol esterase
- Peroxidase
- Good's buffer solution (pH 6.3)

Reagent 2:(Coloring solution)
- Detergent 2
- N,N-bis (4-sulfobutyl)-m-toluidine(1.0mmol/L)
- Good's buffer solution(pH 6.3)

Procedure

When reagent 1 is mixed with a serum specimen as the first step of the assay.Detergent 1 distrupts the structure of chylomicrons, VLDL, and causes release of cholesterol. The free cholesterol , which is formed by cholesterol esterase, reacts with hydrogen peroxide – producing cholesterol oxidase.Hydrogen Peroxide is consumed by a peroxidase in the presence of 4-aminoantipyrine to grnerate a colourless product .

The second step of the assay starts with the addition of reagent 2. Detergent 2 , which is contained in reagent 2 releases cholesterol from the remaining LDL, thereby allowing an enzymatic reaction to take place.Since Reagent 2 also contains a colouring agent.N,N'-bis-(4-sulfobutyl)-m-toluidine disodium salt (dSBmT),hydrogen peroxide formed by the enzymatic reaction produces a blue purple product. The intensity of colouration is proportional to the concentration of LDL cholesterol.

The values were expressed as ml/dl serum.

Estimation of Triglycerides

Triglycerides was estimated by the method of colometric test by Megraw et al.(1979)[31]

PRINCIPLE

Lipase

Triglycerides → Glycerol + Fatty acids

Glycerol Kinase

Glycerol + ATP → Glycerol -3Phosphate +ADP

Glycero phosphate oxidase

Glycerol -3phosphate→ Dihydroxyacetone phosphate +H_2O_2

peroxidase

H_2O_2 + TBHB → Quinonemine Dye + $2H_2O$

Triglycerides in the sample are hydrolysed by lipase to glycerol and fattyacids. The glycerol is then phosphorylated by adenosine- 5-Triphosphate (ATP) to glycerol -3-phosphate(G3P and Adenosine -5 – diphosphate in a reaction catalysed by glycerol kinase (GK), Glycerophatel - - phosphate is then converted to dihydroxyacetone phosphate (DAP) and hydrogen peroxide by glycerol phosphate oxidase (GPO).The hydrogen peroxide then reacts with 4-amino antipyrine (4- AAP) and 3-hydroxy2,4,6-Tri bromo benzoic acid (TBHB) in a reaction catalysed by peroxidase to yield a red coloured quinonemine Dye. The intensity of the red colour produced is directly proportional to the concentration of triglycerides in the sample when measured at 540nm.[32]

REAGENTS

The kit provided single reagent consists of the following chemicals.

ATP, Magnesium salt, TAHB, GPO, Lipase, GK, Peroxidase, Buffer, Surfactant, Stabilizers, Fillers, With Sodium Azide.The reagent is provided in the lyophilysed form.Reconstitute the reagent vial with volume of water slated on the lable.

PROCEDURE

Mark three test tubes as blank standard and test.Added 1ml tris reagent to all the tubes.placed all the tubes in incubator and bring reagent to 37˚C.Added 0.01ml of standard solution to Std tube and 0.01ml of sample was added to the test tube.1ml of tris reagent alone serves as a blank.Mix well and incubate all tubes for five minutes at 37˚C and read absorbance of the test (A_t) and standard (A_s) against reagent blank (A_b) at 540nm wavelength (530 to 570 nm) or with green filter.The colour developed is stable for 1 hour at room temperature , if protected from direct light.[33]

The values were expressed as ml/dl serum.

Estimation of Ratio

Ratio = Total Cholesterol

High Density Lipoprotein

Reference Range: < 4.5

Estimation of Total Bilirubin

Total Bilirubin was estimated by the method of Malloy

and Evelyn.[34]

PRINCIPLE

Bilirubin reacts with the diazo reagent to form azo bilirubin to give a purple coloured complex which can be measured calorimetrically at 540nm using green filter.

REAGENTS

1. Bilirubin Standard: 5mg of bilirubin is accurately weighed , dissolved and made upto 50ml with chloroform.(concentration 100mg/ml)
2. Sulphanilic Acid:(Diazo Blank) 10gms of Sulphanilic Acid is dissolved in 500ml of distilled water and 20 ml of concentrated hydrochloric acid is added and made upto 1 litre with water if necessary solution is warmed to dissolve the sulphanilic acid.
3. Sodium Nitrite (stock solution):20 mg of sodium Nitrite is dissolved in 100ml of distilled water.
4. Sodium Nitrite(Working Standard):Dilute 1ml of stock solution with 19ml of distilled water.
5. Diazo reagent:Mix 10ml of diazo blank and 0.3ml of sodium nitrite working standard solution. (Concentration 0.5gm/dl)

PROCEDURE

0.02-0.1ml of standard Bilirubin with concentration range of 2-10 mg was pipetted out into different test tubes. 0.7ml of diazo reagent alone is taken as blank. 0.1ml of given unknown solution is taken in duplicate and made upto 4.3ml with methanol. The contents are incubated for 5 minutes at room temperature. 2.7ml of distilled water is added to all the test tubes and then incubated for 5 minutes. The purple colour developed is read at 540nm using the green filter . From the standard graph the concentration of bilirubin is calculated.

ESTIMATION OF TOTAL BILIRUBIN

To the tubes marked test and blank 2.6ml of distilled water and 0.2 ml of serum is added.0.7ml of diazo blank alone is taken in the tube marked blank and 0.7ml of the diazo reagent is added to test.3.5ml of methanol is added to both the tudes and incubated for 10 minutes. The purple colour developed is read at 540nm . From the graph the total bilirubin concentration in serum is noted.

The values were expressed as ml/dl serum.

Assay of Serum Glutamate Pyruvate Transaminase Activity

Serum Glutamate Pyruvate Transaminase was assayed by the Colorimetric method.[35]

PRINCIPLE

Serum Glutamate Pyruvate Transaminase catalyses the following reaction.

SGPT

L-Alanine + α-Ketoglutarate ↔ L-Glutamate + Pyruvate

Pyruvate formed is coupled with 2,4 dinitro phenyl hydrazine to give a hydrazone in an alkaline medium which

is a brown coloured complex and can be read at 540nm using green filter.

REAGENTS

Buffer Solution:0.2M Phosphate buffer pH 7.4

Solution A: 0.2M solution of monobasic sodium dihydrogen phosphate (27.8gm in 100ml)

Solution B : 0.2M solution of dibasic sodium dihydrogen phosphate

19ml of solution A and 81ml of solution B is mixed and diluted to 200ml with water Adjust the pH to 7.4 by either adding sodium hydroxide or hydrochloric acid.

Stock Pyruvate Standard: 220mg of sodium pyruvate is accurately weighed and made upto 100ml with phosphate buffer.(concentration 200 μ mole / ml)

Working pyruvate standard: 10ml of stock pyruvate solution is diluted to 100ml with phosphate buffer.(concentration 20 μg/ml)

Buffered serum glutamate pyruvate transaminase susstrate:1.78 gm of Alanine and 29.2mg of α-Ketoglutarate are dissolved in 1N sodium hydroxide and made upto 100ml with phosphate buffer and pH is maintain at 7.4 and adjust with dilute sodium hydroxide

2,4 Dinitrophenyl hydrazine: 99mg of dinitrophenyl hydrazine is dissolved in 50ml of dilute hydrochloric acid and made upto 500ml with distilled water.

0.4N Sodium Hydroxide: 16gms of sodium hydroxide is dissolved in 1 litre of distilled water.

PROCEDURE

0.5-2.5ml of working pyruvate standard is pipetted out into tubes marked S1-S5 with serum glutamate pyruvate activity from 33.3 – 133.3 IU. 0.9-0.6ml of serum glutamate pyruvate transaminase substrate were added to the test tubes.1ml of serum glutamate pyruvate tramaminase substrate alone serves as blank.To all the tubes 0.2ml of distilled water and 1ml of dinitrophenyl hydrazine were added and incubated the tubes for 20 minutes at room temperature at 37˚C. Then added 10ml of sodium hydroxide to all the tubes and brown colour developed is read at 540 nm after 10 minutes using green filter.

Simultaneously added 0.5ml serum glutamate pyruvate transaminase substrate in two tubes marked Test and Blank.Keep the test tubes in a water bath at 37˚C for 10 minutes. Added 0.1ml of serum to the tube marked Test and incubated the tubes for 37˚C for 30 minutes.Added 0.5ml of dinitrophenyl hydrazine to both the tubes and allow to stand for 20 minutes. Then added 5ml of 0.4N sodium hydroxide and incubate for 10 minutes ,and the intensity of brown colour developed is read at 540nm using green filter.From the standard graph,the activity of serum glutamate pyruvate transaminase is calculated.

The activity of serum glutamate pyruvate transaminase is expressed as I.U.

Estimation of Alkaline Phosphatases

Plasma Alkaline Phosphatases was assayed by the method

of King.(1934)[36]

PRINCIPLE

Phosphatases are enzymes,which catalyses the splitting up of phosphoric acid from certain monophosphoric esters.Alkaline phosphatase acts on sodium β-glycerophosphate at pH 10 to liberate inorganic phosphorus.This phosphorus was allowed to react with molybdic acid to give phosphomolybdate which inturn was reduced by ANSA to molybdenum blue.The colour was read in a colorimeter at 620nm

REAGENTS

1. Substrate:0.1M of sodium β-glycero phosphate was dissolved in 100ml of sodium carbonate – bicarbonate buffer.(0.1M, pH 10)
2. Sodium carbonate-Bicarbonate buffer .(0.1M,pH10)
3. 10% Trichloro acetic acid (TCA)(W/V)
4. Ammonium Molybdate: 2-5% in $3NH_2SO_4$ (W/V)
5. Amino 2- Naphthol 4-Sulphonic acid (ANSA): 500mg ANSA was dissolved in a mixture of 195ml 15% Sodium Bisulphite solution.
6. Standard Phosphorus:

35.1mg potassium dihydrogen phosphate was dissolved in 100ml glass distilled water,10ml of this solution was diluted to 100 ml to prepare a working standard containing 8μg/ml phosphorus.

PROCEDURE

To 1ml buffered substrate added , 0.2ml plasma and incubated at 37˚C for one hour.The tubes were removed and 1ml 10%TCA was added,mixed and centrifuged for 10 minutes.To 1ml supernatant ,1ml ammonium moltbdate and 0.4ml ANSA were added.The colour developed was read in a colorimeter at 680nm.A system devoid of enzyme served as control.A series of standard in the concentration 0.156 to 0.781 μ moles were also processed similarly.

The enzyme activity was expressed as IU/L Plasma.

Estimation of gamma-glutamyl transpeptidase Activity

Quantitative in vitro determination of γ-glutamyl transferase (γ-GT) in serum or plasma.[37]

PRINCIPLE

Gamma-glutamyltransferase (γ-GT) in serum originates primarily from the hepatobiliary system.Therefore γ-GT is elevated in all forms of liver disease and has been shown to be more sensitive than alkaline phosphatase in detecting obstructive jaundice,cholangitis and cholecystitis.High levels of γ-GT are also seen in patients with primary or secondary liver cancer.[38]

REAGENTS

1.Buffer / Glycylglycine
2.Substrate

PROCEDURE

The substrate L-γ-glutamyl-3-carboxy-4-nitroanilide, in the presence of glyclyglycine is converted by γ-GT in the sample to 5-amono-2-nitrobenzoate which can be measured at 405nm. [39]   γ- GT

L-γ-glutamyl-3-carboxy-4-nitroanilide + glycylglycine → L- γ-glutamylglycylglycine + 5-amino-2-nitro-benzote

The enzyme activity was expressed as IU/L Plasma.

Estimation of Serum Total Protein

Estimation of serum protein by Lowry's method.[40]

PRINCIPLE

The amino acids like Tyrosine, Tryptophan and Phenylalanine reacts with phosphomolybdic acid and phosphotungstic acid in alkaline medium to give intence blue colour which is read at 650nm.

REAGENTS

1. 2 % sodium carbonate in 0.1N NaOH
2. 0.5 % $CuSO_4$ in 1 % sodium potassium tartarate.
3. Alkaline $CuSO_4$ reagent: Mix 1 and 2 in 50:1 ratio
4. Follins reagent
5. Working Standard:25mg of BSA in 100ml unknown solutions diluted to 200 times with distilled water.

PROCEDURE

0.2ml to 1ml of standard solution was taken in test tube and made upto 4ml with distilled water .Added 5.5ml of alkaline $CuSO_4$ kept in water bath for 10minutes. Then 0.5ml of Follins phenol reagent was added in all the test tubes and incubated for 30minutes at room temperature. Then OD was taken at 650nm. About 0.1ml and 0.2ml of test solution was taken and the same procedure was followed as done above. [41]

The values were expressed as ml/dl serum.

Estimation of Albumin

Estimation of Albumin by Dye binding (BCG) method.[42]

PRINCIPLE

At a pH lower than its isoelectric point, albumin is positively charged and has an affinity for anions.On combination with albumin , in presence of succinate buffer, anionic dyes like BCG change in colour from yellow to green which is measured at 610nm.The colour is directly proportional to the concentration of albumin.[43]

REAGENTS

1. Stock Bromo Gesol Green:

210 mg of BCG powder, BDH indicator with 50mg of sodium azide AR-loba is dissolved in 5ml of 0.1N sodium hydroxide GR and made upto 500ml with water.

2. Succinate Buffer:

11.8gms of succinic acid AR in 800ml of water + 100mg of sodium azide AR-l   oba. Adjust the pH to 4.15 with 10% sodium hydroxide .Make upto a litre (0.1 m)

3.   Working BCG:

125ml of stock BCG + 375ml of succinate Buffer + 2ml and 30% Brij 35 pH to be adjusted to 4.1 to 0.05.Store in a polythene container .(the dye sticks to glass containers when stored.

4.   Standard:

Commercial or in house quality sera.

PROCEDURE

Mark three tudes as blank ,standard and test.Added 2ml of working BCG, 3ml of distilled water to all the tubes.0.05ml of serum is added to the test tube.3.05ml of distilled water 2ml of working BCG serves as a blank.Mix and take readings in a red filter in a colorimeter or 620nm in a spectrophotometer against blank.
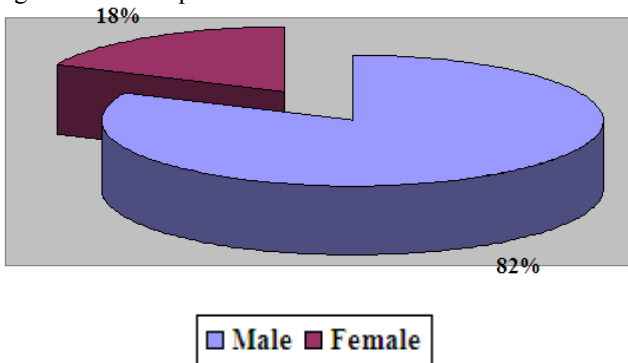
The values were expressed as gm/dl serum.

Estimation of Globulin

Globulin = Total Protein - Albumin

6. Results

Figure 1 shows the percentage of sex distribution of Atorvastatin treated patients selected for the study.The result shows the percentage of male patients are significantly higher when compared to female.

The age distribution of the study group patients were depicted in figure 2. This bar diagram shows 50-60 age group patients were significantly higher in number's when compared to other age group patients.
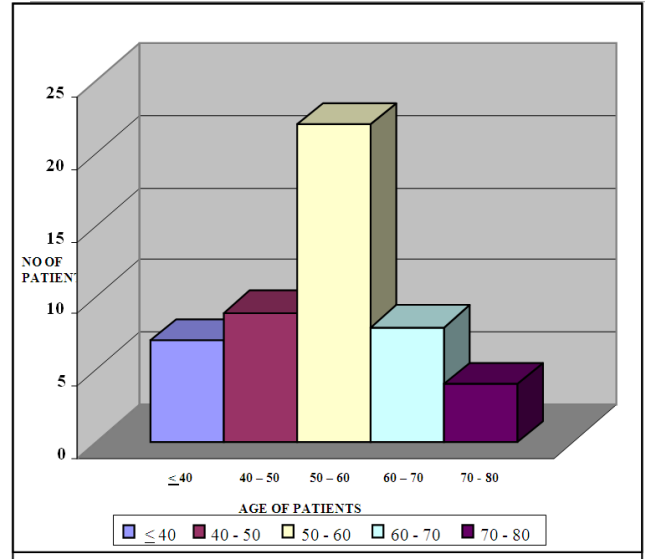

Table 1 shows the lipid profile levels. The result shows a significant increase in the level of Total Cholesterol,LDL and TGL in below and above 10mg of Atorvastatin patients when compared to normal.After Atorvastatin treatment the Total Cholesterol,LDL and TGL level were found to be significantly decreased whereas the HDL is significantly increased when compared to untreated groups.

The level of liver function test results where depicted in table 2.The result shows a significant increase in the level of Total Bilirubin, serum glutamate pyruvate transaminase,ALP,GGTP and significant decrease in total protein and albumin in below and above 10mg of atorvastatin patients when compared to normal.After Atorvastatin treatment the Total Bilirubin,SGPT,ALP,GGTP levels were found to be significantly increased whereas in Total Protein and Albumin the levels were found to be significantly decreased when compared to untreated groups.

Table 3 shows the level of Glucose, Urea , Creatinine and Uric Acid.The result shows a significant increase in the level of Glucose, Urea , Creatinine and Uric Acid in below and above 10mg of Atorvastatin patients when compared to normal.After AQtorvastatin treatment the Glucose, Urea , Creatinine and Uric Acid were found to be significantly decreased when compared to untreated groups.

Table 4 shows the electrolytes level of Sodium,Potassium,Chloride and Bicarbonate in normal and atorvastatin treated patients.The result shows there is no significant change in atorvastatin treated patients when compared to normal.

Table 1. Levels Of Lipid Profile in Atorvastatin Treated Patients
Values are expressed as Mean Standard Deviation

S.No	PARAMETERS	BELOW 10mg OF ATORVASTATIN		ABOVE 10mg OF ATORVASTATIN		NORMAL
		BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	
1.	TOTAL CHOLESTEROL	*** 213 ± 17	NS 163 ± 21	*** 245 ± 27	NS 176 ± 24	154 ± 9
2.	HIGH DENSITY LIPOPROTEIN	** 39 ± 2.2	NS 42 ± 3.1	NS 40 ± 3.6	NS 44 ± 2.8	46 ± 3.5
3.	LOW DENSITY LIPOPROTEIN	*** 125 ± 9	NS 92 ± 7	*** 156 ± 12	NS 97 ± 6	86 ± 11
4.	TRIGLYCERIDES	*** 185 ± 18	NS 105 ± 12	*** 201 ± 17	* 113 ± 15	97 ± 7
5.	RATIO	*** 5.8 ± 0.37	NS 3.8 ± 0.38	*** 6.1 ± 0.60	NS 4.0 ± 0.38	3.34 ± 0.23

Statistical significant variations are compared with Normal.
NS - Non Significant , * - $P < 0.01$, ** - $P < 0.05$, *** - $P < 0.001$

Table 2. Levels Of Liver Function Test In Atorvastatin Treated Patients
Values are expressed as Mean Standard Deviation

S.No	PARAMETERS	BELOW 10mg OF ATORVASTATIN		ABOVE 10mg OF ATORVASTATIN		NORMAL
		BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	
1.	TOTAL BILIRUBIN	NS 0.74 ± 0.10	** 0.84 ± 0.09	NS 0.77 ± 0.06	*** 0.93 ± 0.11	0.66 ± 0.05
2.	SGPT	NS 30 ± 3.7	*** 35 ± 4.2	* 32 ± 2.9	*** 47 ± 4.5	24 ± 2.9
3.	ALKALINE PHOSPHATASE	NS 187 ± 16	NS 209 ± 21	NS 194 ± 14	NS 216 ± 19	177 ± 16
4.	GGTP	NS 26 ± 3.1	** 29 ± 2.5	* 28 ± 2.7	*** 41 ± 3.7	23 ± 2.6
5.	TOTAL PROTEIN	NS 7.1 ± 0.54	NS 6.9 ± 0.62	NS 7.0 ± 0.88	NS 6.7 ± 0.65	7.4 ± 0.70
6.	ALBUMIN	NS 4.1 ± 0.37	NS 3.9 ± 0.35	NS 4.1 ± 0.43	NS 3.7 ± 0.30	4.5 ± 0.39
7.	GLOBULUN	NS 3.1 ± 0.40	NS 3.0 ± 0.45	NS 2.9 ± 0.62	NS 3.0 ± 0.45	2.9 ± 0.50
8.	A/G RATIO	NS 1.3 ± 0.1	NS 1.3 ± 0.12	NS 1.41 ± 0.16	NS 1.23 ± 0.09	1.55 ± 0.14

Statistical significant variations are compared with Normal.
NS - Non Significant , * - $P < 0.01$, ** - $P < 0.05$, *** - $P < 0.001$

Table 3. Levels Of Serum Glucose ,Urea, Creatinine and Uric Acid In Atorvastatin Treated Patients
Values are expressed as Mean Standard Deviation

S.No	PARAMETERS	BELOW 10mg OF ATORVASTATIN		ABOVE 10mg OF ATORVASTATIN		NORMAL
		BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	
1.	GLUCOSE	* 114 ± 12	NS 105 ± 9	** 121 ± 12	NS 110 ± 10	87 ± 8
2.	UREA	NS 24 ± 1.8	NS 24 ± 3.2	NS 25 ± 2.4	NS 23 ± 2.7	20 ± 1.9
3.	CREATININE	NS 0.8 ± 0.05	NS 0.7 ± 0.1	NS 0.9 ± 0.07	NS 0.8 ± 0.09	0.7 ± 0.05
4.	URIC ACID	NS 6.0 ± 0.75	NS 5.8 ± 0.68	NS 6.2 ± 0.49	NS 5.9 ± 0.53	5.1 ± 0.47

Statistical significant variations are compared with Normal.
NS - Non Significant , * - $P < 0.01$, ** - $P < 0.05$, *** - $P < 0.001$

<div align="center">

Table 4 .   Levels of Electrolytesin Atorvastatin Treated Patients
Values are expressed as Mean Standard Deviation

</div>

S.No	PARAMETERS	BELOW 10mg OF ATORVASTATIN		ABOVE 10mg OF ATORVASTATIN		NORMAL
		BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	
1.	SODIUM	NS 137 ± 12	NS 138 ± 10	NS 138 ± 14	NS 137 ± 11	137 ± 14
2.	POTASSIUM	NS 4.2 ± 0.40	NS 4.0 ± 0.34	NS 4.4 ± 0.34	NS 4.3 ± 0.34	4.2 ± 0.35
3.	CHLORIDE	NS 99 ± 11	NS 10 ± 9	NS 102 ± 13	NS 100 ± 8	100 ± 11
4.	BICARBONATE	NS 23 ± 2.5	NS 21 ± 1.8	NS 24 ± 2.2	NS 22 ± 2.0	24 ± 2.6

Statistical significant variations are compared with Normal.
NS - Non Significant , * - $P < 0.01$, ** - $P < 0.05$, *** - $P < 0.001$

7. Discussion

Cardiovascular disease

Cardiovascular disease is one of the disease that affect the heart ,the blood vessel system, especially the veins and arteries leading to and from the heart. Research on disease dimorphism suggests that women who suffer with cardiovascular disease usually suffer from forms that affect the blood vessels while men usually suffer from forms that affect the heart muscle itself. Known or associated causes of cardiovascular disease include diabetes mellitus, hypertension, hyperhomocysteinemia and hypercholesterolemia. Research has shown that a low fat,vegetarian diet can reduce the chance of cardiovascular disease and may also reverse conditions such as restriction of the blood vessels or "clogging."[44]

Symptoms of cardiovascular diseases

As stated above, CVD may exist with no obvious symptoms or pain. When symptoms are present, they vary depending on the extent to which the normal flow of blood to the affected organ is interrupted. When the interruption of blood supply to the brain or heart is severe, some or all of the following symptoms can be experienced. Heart attack symptoms include central chest pain with an oppressive or squeezing feeling that lasts for few minutes; chest pain that can spread to the neck, shoulders and/or arms; and chest discomfort, along with light-headedness, sweating, faintness, nausea or shortness of breath. Stroke symptoms include weakness of the arms or legs; a loss of feeling in the face or body; difficulty speaking; sudden loss of vision in one eye; dizziness; and a sudden, intense headache. [45]

Finally, congestive heart failure symptoms include a swelling of the lower extremities, referred to as "peripheral edema"; an intolerance to exercise followed by shortness of breath; fatigue; and a cough. [46]

8. Treatment of Cardiovascular Disease

The Response of Modern Medicine

The average cardiologist's approach to cardiovascular and heart disease consists of this: Invasive testing to demonstrate blocked arteries, drugs to control blood pressure, drugs to improve the flow of blood through narrowed arteries, and diet and/or medication to control elevated cholesterol levels. With more advanced cases of the disease, modern medical practitioners may advise surgery, such as cardiac catherization and angioplasty.[48]

Since high blood pressure is a common and serious risk factor associated with cardiovascular and heart disease, cardiologists usually prescribe beta-blockers, which lower blood pressure and slow the heart rate. The problem with this approach is that beta-blockers slow metabolism, which causes patients to gain weight and be even less inclined to exercise, both of which increase fat deposits. Unfortunately, all of this effectively adds to the underlying problem of cardiovascular and heart disease rather than eliminating it. [49]

The Natural Medicine Approach to Cardiovascular and Heart Disease

A better approach is to address the underlying cause of the disease by determining why blockages developed in the arteries in the first place. The best theory today about the cause of the initial insult to the lining of the artery (the endothelium) is that it results from some combination of mechanical stress (stretching of the arterial wall, as from high blood pressure, or nicks caused during the process of angiography) and oxidative stress (free radicals released in the process of metabolism that are not neutralized by internal antioxidants).[50]

The body attempts to heal all such damage, and under ideal circumstances is able to do so without trouble. However there are many things which can derail normal healing, and cause the beginning of plaque in the vessel wall. Such factors taken in total will predispose the patient to cardiovascular or heart disease, either damaging the artery lining or impairing the body's healing response.[51]

Stressors include hypertension (high blood pressure) and anything that creates it (like stress), and anything that produces more free radicals (like poor diet, smoking, heavy metal toxicity, increased homocysteine levels, elevated

blood fats, medications, and excess iron). Healing response interference would come from factors such as inadequate antioxidants, hormonal deficiencies or excesses, other nutritional deficiencies, insulin resistance, elevated blood sugars, increased lipoprotein levels, and increased clotting tendency of the blood.[52]

Among the above causes of cardiovascular disease hypercholesterolemia is one of the major risk factor in cardiovascular disease. This study evaluated the effect of Atorvastatin in reducing the level of hypercholesterolemia.[53]

Atorvastatin

Atorvastatin is used together with lifestyle changes (diet, weight-loss, exercise) to reduce the amount of cholesterol (a fat-like substance) and other fatty substances in the blood. Atorvastatin is in a class of medications called HMG-CoA reductase inhibitors (statins). It works by slowing the production of cholesterol in the body. Buildup of cholesterol and other fats along the walls of the blood vessels (a process known as atherosclerosis) decreases blood flow and, therefore, the oxygen supply to the heart, brain, and other parts of the body. Lowering blood levels of cholesterol and other fats may help to decrease your chances of getting heart disease, angina (chest pain), strokes, and heart attacks. In addition to taking a cholesterol-lowering medication, making certain changes in your daily habits can also lower your cholesterol blood levels. You should eat a diet that is low in saturated fat and cholesterol (see SPECIAL DIETARY), exercise 30 minutes on most, if not all days, and lose weight if you are overweight.[54]

Side effects

Headache, diarrhea, stomach/abdominal pain, or joint pain may occur. If any of these effects persist or worsen, notify your doctor or pharmacist promptly. Remember that your doctor has prescribed this medication because the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects. This drug may infrequently cause muscle damage (which can rarely lead to a very serious, possibly fatal, condition called rhabdomyolysis). Seek immediate medical attention if you develop: muscle pain/tenderness/weakness (especially with fever or unusual tiredness). Tell your doctor immediately if any of these highly unlikely but very serious side effects occur: yellowing eyes and skin, dark urine, severe fatigue, severe stomach/abdominal pain, persistent nausea, change in the amount of urine. A very serious allergic reaction to this drug is unlikely, but seek immediate medical attention if it occurs. Symptoms of a serious allergic reaction may include: rash, itching, swelling, severe dizziness, trouble breathing.[55]

1.   The percentage of male patients is significantly higher when compared to female

(figure 1).

Last year, 930,000 Americans died from heart disease, making it the No.1 or No. 2 killer of both men and women in the United States. But thousands more men die from heart disease every year than women, and they die at an earlier age. According to the Department of Health and Human Services (HHS), men are 30% more likely to suffer a stroke than are women, making it the third-leading cause of death in men. Both heart disease and stroke are cardiovascular diseases, or diseases of the blood vessels. One in three men can expect to develop some major cardiovascular disease before the age of 60, HHS says. [56]

Men avoid doctor visits far more than women, lest they appear weak or out of control. Thus, they often neglect getting recommended routine screening tests for blood sugar and cholesterol that can indicate increased heart disease risks. "Women visit doctors more, and they tend to be more compliant and willing to follow their doctors' orders. They are more caregivers for their children and themselves, inscribed in their DNA,"[57]

Men seem more prone to flying into a rage or venting their tempers than women do. "Emotional outbursts can increase blood pressure, heart rate and adrenalin levels. It's barbaric behavior today. Men need to learn to modulate their behavior, channel their emotions and convert their tempers to compassion."[58]

One risk factor where women are not setting an example for men is smoking, however. Although fewer women smoke than men, the percentage difference between the two continues to decrease every year. [59]

Cigarette smoking increases the risk of coronary heart disease by increasing blood pressure, decreasing ability to exercise, and increasing the tendency for blood to clot. [60]

This study results also confirms that men are more prone to get cardiovascular disease than woman.(figure 1)

2. Among the Atorvastatin treated patients 50-60 age group patients were found to be significantly higher in number when compared to other age group patients.

Type II diabetes starts after 40 years,Hypertension also high in this age group and after 50 years most of the people will live a sedentory life when compared to younger age groups. This study also confirms that 50 – 60 age groups patients where more prone to get cardiovascular disease of the risk factor like hyperlipidemia, diabetes, hypertension and less exercise.[61]

3. There is significant increase in the levels of Total Cholesterol,LDL and TGL in below and above 10mg of Atorvastatin patients when compared to normal.After Atorvastatin treatment the Total Cholesterol,LDL and TGL level were found to be significantly decreased whereas the HDL is significantly increased when compared to untreated groups.

Mixed hyperlipidemia is a major cause of coronary artery disease. Monotherapy with statins is considered the gold standard for treatment of mixed hyperlipidemia. But greater benefit may be expected by combination therapy. Combination may allow lower doses of statins and less

adverse effects. Hence, this preliminary study was designed to evaluate the efficacy and safety of low-dose atorvastatin in combination with fenofibrate in patients with mixed hyperlipidemia. Ninety patients were assigned into three groups and received atorvastatin (10-40 mg/day) or fenofibrate (160-200 mg/day) or combination of low-dose atorvastatin (5 mg/day) and fenofibrate (160 mg/day). [62]

There was a significant decrease in low-density lipoprotein (LDL), triglycerides (TG) and total cholesterol (TC), and a significant increase in high-density lipoprotein (HDL) in all the groups at the end of therapy. Combination therapy produced maximum decrease in LDL, TG and TC, and maximum increase in HDL when compared with monotherapies. To conclude, the results suggest that combination therapy with low-dose atorvastatin and fenofibrate is more efficacious, with no increase in adverse effects when compared with monotherapies with individual drugs for mixed hyperlipidemia. The results are preliminary and suggestive only, as the study was open and nonrandomized.[63]

4. The levels of Total Bilirubin, serum glutamate pyruvate transaminase,ALP,GGTP are found to be increased significantly and significant decrease in total protein and albumin in below and above 10mg of atorvastatin patients when compared to normal. After Atorvastatin treatment the Total Bilirubin , SGPT,ALP,GGTP levels were found to be significantly increased whereas in Total Protein and Albumin the levels were found to be significantly decreased when compared to untreated groups.

The drugs , have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the upper limit of normal [ULN] occurring on two or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. Specifically, the incidence of these abnormalities was 0.2% for atorvastatin 10 mg. In a pooled analysis of 10 placebo-controlled trials, increases in serum transaminases to >3 ULN occurred.[64]

5. There is significant increase in the levels of Glucose, Urea , Creatinine and Uric Acid in below and above 10mg of Atorvastatin patients when compared to normal.After Atorvastatin treatment the Glucose, Urea , Creatinine and Uric Acid were found to be significantly decreased when compared to untreated groups.

A total of 180 patients were enrolled; patients were randomly assigned to 40 mg/d of either atorvastatin or simvastatin. Serum lipid and metabolic parameters were measured at baseline and at 6 and 12 weeks of treatment; random urine samples were simultaneously obtained for creatinine, sodium, and uric acid determinations. Baseline serum uric acid levels correlated positively with the body mass index, serum insulin, creatinine, and triglyceride levels and inversely with serum HDL cholesterol levels. Both statins caused a favorable effect on lipids and a significant decrease in fibrinogen and high-sensitivity CRP levels.[65]

However, only atorvastatin reduced serum uric acid levels (from 5.6 +/- 1.7 to 4.9 +/- 1.5 mg/dL, P <.0001) by augmenting its urinary fractional excretion (from 10.4% +/- 7.9% to 12.0% +/- 7.4%, P <.01). In a multivariate logistic regression analysis, the reduction of uric acid levels was independently associated with baseline serum uric acid concentration but not to other variables, including lipid parameters (OR, 1.65; 95% CI, 1.14 to 2.40; P =.008). Atorvastatin (but not simvastatin) significantly lowered serum uric acid levels. This result may be in favor of a preferable choice of atorvastatin for the treatment of hyperlipidemic patients presenting with hyperuricemia.[66]

6. There is no significant change in electrolytes level in atorvastatin treated patients when compared to normal.

9. Summary

Atorvastatin is an oral drug that lowers the level of cholesterol in the blood. It belongs to a class of drugs referred to as statins which includes lovastatin (Mevacor), simvastatin, (Zocor), fluvastatin (Lescol), and pravastatin (Pravachol). All statins, including atorvastatin, prevent the production of cholesterol by the liver by blocking the enzyme that makes cholesterol, HMGCoA reductase. They lower total blood cholesterol as well as LDL cholesterol levels. (LDL cholesterol is believed to be the "bad" cholesterol that is primarily responsible for the development of coronary artery disease.) Lowering LDL cholesterol levels retards progression and may even reverse coronary artery disease. Unlike the other drugs in this class, atorvastatin also can reduce the concentration of triglycerides in the blood. High blood concentrations of triglycerides also have been associated with coronary artery disease. Atorvastatin was approved by the FDA in December of 1996.

10. Side Effects

Minor side effects of Atorvastatin include constipation, diarrhea, fatigue, gas, heartburn, and headache. Hepatotoxicity is one of the major adverse effect of Atorvastatin.

Cardiovascular disease patients who came for blood analysis to department of Biochemistry, Apollo Hospital at Chennai were selected for the study. This work was carried out under the guidance of Dr.S.Subramaniam, Head of Biochemistry department, Apollo Hospitals, Chennai.

In sex distribution of Atorvastatin treated patients, the male patients are significantly higher in percentage when compared to female patients.

In age group distribution of Atorvastatin treated patients, 50-60 age group patients are significantly higher in numbers when compared to other groups.

There is significant increase in the levels of Total Cholesterol,LDL and TGL in below and above 10mg of Atorvastatin patients when compared to normal .After

Atorvastatin treatment the Total Cholesterol, LDL and TGL level were found to be significantly decreased whereas the HDL is significantly increased when compared to untreated groups.

The levels of Total Bilirubin, serum glutamate pyruvate transaminase, Alkaline Phosphatase, Gamma-Glutamyl Transpeptidase are found to be increased significantly and significant decrease in total protein and albumin in below and above 10mg of atorvastatin patients when compared to normal. After Atorvastatin treatment the Total Bilirubin, serum glutamate pyruvate transaminase, Alkaline Phosphatase, Gamma-Glutamyl Transpeptidase levels were found to be significantly increased whereas in Total Protein and Albumin the levels were found to be significantly decreased when compared to untreated groups.

There is significant increase in the levels of Glucose, Urea , Creatinine and Uric Acid in below and above 10mg of Atorvastatin patients when compared to normal. After Atorvastatin treatment the Glucose, Urea , Creatinine and Uric Acid were found to be significantly decreased when compared to untreated groups.

There is no significant change in electrolytes level in atorvastatin treated patients when compared to normal.

11. Conclusions

In recent year there is increasing trend of cardiovascular disease patients among Indian, due to hyperlipedemia. Atorvastatin is one of the highly potent drug widely used for treating the hypercholesterolemia patients. Even though it reduces Cholesterol level drastically, it has got high adverse effect too. Hepatotoxicity is one of the major adverse effect of Atorvastatin and hence this study was planned to see the lipid lowering effect and toxic effect of it. The results showed decrease in lipid levels and elevated liver enyme levels. From this study we can conclude that atorvastatin is like a double edged knife. The patients on Atorvastatin has to be constantly monitored their liver function test. This will help the clinician to treat the patient effectively and safely.

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