Hypertension condition. Atorvastatin is an HMG CoA reductase inhibitor and widely used in the treatment of hyperlipidemia conditions. Combination of irbesartan and atorvastatin is used in the treatment of cardiovascular diseases like hypertension and hyperlipidemia. So this combination therapy gives antihypertensive and antilipidemic effects in the treatment of coronary artery diseases.

ABSTRACT

Hypertension and hypercholesterolemia are a major public health problem in the developed countries recently. Hypertension and hypercholesterolemia are frequently treated with antihypertensive drugs like calcium-channel blockers, angiotensin-converting enzyme inhibitors, and angiotensinII (AT1) receptor blockers, and statins. Irbesartan is an angiotensin II receptor type 1 antagonist and widely used in treatment of hypertension condition. Atorvastatin is an HMG CoA reductase inhibitor and widely used in treatment of hyperlipidemia condition. Combination of irbesartan and atorvastatin is used in the treatment of cardiovascular diseases like hypertension and hyperlipidemia. So this combination therapy gives antihypertensive and antilipidemic effects in the treatment of coronary artery diseases.

Keywords: Irbesartan, Atorvastatin, Antihypertensive, Antilipidemic, Pharmacology, Combination Therapy.

INTRODUCTION

In recent years, two major problems are being observed in among people like hypertension and hyperlipidemia. So irbesartan is used in combination with atorvastatin to treat hypertension and hyperlipidemia, respectively, in cardiovascular patients.

Irbesartan, an angiotensin II receptor antagonist [1], is used mainly for the treatment of hypertension. It is an orally active nonpeptide tetrazole derivative and selectively inhibits angiotensin II receptor type 2. Angiotensin II receptor type 1 antagonists have been widely used in treatment of diseases like hypertension, heart failure, myocardial infarction and diabetic nephropathy. Irbesartan, classified as high permeability and low solubility drug, is slightly soluble in alcohol and methylene chloride, and practically insoluble in water. It is a lipophilic drug and possesses rapid oral absorption. Hypertension is one of the most prevalent cardiovascular diseases in the world, affecting a big proportion of the adult population. Furthermore, hypertension is an independent risk factor for cardiovascular disease and is associated with an increased incidence of stroke and coronary heart disease. Although there have been many advances in treatment over the past several decades, less than 25% of all hypertensive patients have their blood pressure adequately controlled with available therapies.

Irbesartan blocks the potent vasoconstrictor and aldosterone-secreting effects [2]. Of angiotensin II by selective antagonism of the angiotensin II (AT1 subtype) receptors localized on vascular smooth muscle cells and in the adrenal cortex. It has no agonist activity at the AT1 receptor and a much greater affinity (more than 8500-fold) for the AT1 receptor than for the AT2 receptor (a receptor that has not been shown to be associated with cardiovascular homeostasis). So irbesartan is highly specific for angiotensin receptor.

Atorvastatin is used as a lipid-lowering agent [3]. Especially 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. It is also used in coronary artery disease (CAD), Dyslipidemia, atherosclerosis and other cardiovascular diseases. Atorvastatin is potent inhibitors of the rate-limiting enzyme involved in sterol synthesis, HMG-CoA reductase. The ability of statins to markedly reduce serum levels of TC, LDL-C, and triglycerides (TGs) and Apo lipoprotein B (Apo B). This effect on serum lipids and lipoprotein lipids has dramatically changed the relative risk of cardiovascular morbidity and mortality and on total mortality. The effect of atorvastatin on high-density lipoprotein cholesterol (HDL-C) is usually modest (5% to 10% increase).

Atorvastatin competitively inhibits HMG-coenzyme a reductase, which is involved in the rate limiting step of cholesterol biosynthesis in the liver [4]. In addition, statins (atorvastatin, simvastatin, pravastatin, lovastatin, rosuvastatin) increase levels of HDL which has cardiovascular protective effects. Furthermore, atorvastatin reduce the susceptibility of lipoproteins to oxidation, both in vitro and ex vivo. Oxidative modification of LDL appears to play a key role in mediating the uptake of lipoprotein cholesterol by macrophages.

Hypertension frequently coexists with hyperlipidemia and both are considered to be major risk factors for developing cardiovascular disease ultimately resulting in adverse cardiovascular events. This clustering of risk factors is potentially due to a common mechanism. Further, patient compliance with the management of hypertension is generally better than patient compliance with hyperlipidemia. It would therefore be advantageous for patients to have a single therapy which treats both of these conditions.

Coronary heart disease is a multifactorial disease in which the incidence and severity are affected by the lipid profile, the presence of diabetes and the sex of the subject. Incidence is also affected by smoking and left ventricular hypertrophy which is secondary to hypertension. To meaningfully reduce the risk of coronary heart disease, it is important to manage the entire risk spectrum. For example, hypertension intervention trials have failed to demonstrate full normalization in cardiovascular mortality due to coronary heart disease. Treatment with cholesterol synthesis inhibitors in patients with and without coronary artery disease reduces the risk of cardiovascular morbidity and mortality and beneficial effect for treatment in coronary heart disease.

Mechanism of action

Irbesartan

Irbesartan is a nonpeptide tetrazole derivative [5, 6], and an angiotensin II antagonist that selectively blocks the binding of angiotensin II to the AT1 receptor. In the renin-angiotensin system, angiotensin I is converted by angiotensin-converting enzyme (ACE) to form angiotensin II. Angiotensin II stimulates the adrenal cortex to synthesize and secrete aldosterone, which decreases the excretion of sodium and increases the excretion of potassium. Angiotensin II also acts as a vasoconstrictor in vascular smooth muscle.

Irbesartan blocking the binding of angiotensin II to the AT1 receptor promotes vasodilation and decreases the effects of aldosterone. Negative feedback regulation of angiotensin II on renin secretion is...
also inhibited, but the resulting rise in plasma renin concentrations and consequent rise in angiotensin II plasma concentrations do not counteract the blood pressure–lowering effect that occurs.

Fig. 1: Chemical mechanism of Irbesartan [7].

The action of ARBs is different from ACE inhibitors, which block the conversion of angiotensin I to angiotensin II, meaning that the production of angiotensin II is not completely inhibited, as the hormone can be formed via other enzymes. Also, unlike ACE inhibitors, irbesartan and other ARBs do not interfere with response to bradykinins and substance P, which allows for the absence of adverse effects that are present in ACE inhibitors (e.g. dry cough).

Fig. 2: Structure of Irbesartan [8].

Chemical derivative is also gives effective change in mechanism of action [9]. The "acidic group" is thought to mimic either the phenol or the Asp1 carboxylate of angiotensin II. Groups capable of such a role include the carboxylic acid (A), a phenyl tetrazole or isostere (B), or a phenyl carboxylate (C). In the biphenyl series, the tetrazole and carboxylate groups must be in the ortho position for optimal activity. The n-butyl group of the model compound provides hydrophobic binding and, most likely, mimics the side chain of Ile5 of angiotensin II. As seen with azilsartan, candesartan, telmisartan, and olmesartan, this n-butyl group can be replaced with either an ethyl ether or an n-propyl group. The imidazole ring or an isosteric equivalent is required to mimic the His6 side chain of angiotensin II. Substitution can vary at the "R" position. A variety of R groups, including a carboxylic acid, a hydroxymethyl group, a ketone, or a benzimidazole ring, are present in currently available ARBs and are thought to interact with the AT1 receptor through either ionic, ion-dipole, or dipole–dipole bonds.

Renin-angiotensin system is responsible for effects such as vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium [10]. Irbesartan is a specific competitive antagonist of AT1 receptors with a much greater affinity (more than 8500-fold) for the AT1 receptor than for the AT2 receptor and no agonist activity. Irbesartan's inhibition of angiotensin II binding to the AT1 receptor leads to multiple effects including vasodilation, a reduction in the secretion of vasopressin, and reduction in the production and secretion of aldosterone. The resulting effect is a decrease in blood pressure.

Fig. 3: Irbesartan Much Greater Affinity For The AT1 Receptor Than For The AT2 Receptor [11].

Atorvastatin selectively and competitively inhibits the hepatic enzyme HMG-CoA reductase [12,13]. As HMG-CoA reductase is responsible for converting HMG-CoA to mevalonate in the cholesterol biosynthetic pathway, this results in a subsequent decrease in hepatic cholesterol levels. Decreased hepatic cholesterol levels stimulateup regulation of hepatic LDL-C receptors which increases hepatic uptake of LDL-C and reduces serum LDL-C concentrations. Atorvastatin, a selective competitive HMG-CoA reductase inhibitor, is used to lower serum total and LDL cholesterol, Apo II, and triglyceride levels while increasing HDL cholesterol. High LDL-C, low HDL-C and high TG concentrations in the plasma are associated with increased risk of atherosclerosis and cardiovascular disease. The total cholesterol to HDL-C ratio is a strong predictor of coronary artery disease and high ratios are associated with higher risk of disease. Increased levels of HDL-C are associated with lower cardiovascular risk. By decreasing LDL-C and TG and increasing HDL-C, atorvastatin reduces the risk of cardiovascular morbidity and mortality. Atorvastatin has a unique structure, long half-life, and hepatic selectivity, explaining its greater LDL-lowering potency compared to other HMG-CoA.

Fig. 4: Structure of Atorvastatin [14].

The activity of HMGRIIs is sensitive to the stereochemistry of the lactone ring, the ability of the lactone ring to be hydrolyzed, and the length of bridge connecting the two ring systems. Additionally, it was found that the bicyclic ring could be replaced with other lipophilic rings and that the size and shape of these other ring systems were important to the overall activity of the compounds. The ring system is a complex hydrophobic structure, covalently that is involved in the binding interactions to the HMG-CoA reductase. The binding interactions of the ring are able to reduce the competition for the binding site between the statin and the endogenous HMG-CoA substrate because keeping the statin closed to the enzyme precludes the possibility of statin displacement by the endogenous substrate [15].
In recent years, Hanmi Pharmaceutical has patented the combination purpose of lowering hypertension with diabetic patients and also for cholesterol lowering. Atorvastatin gives a safe and effective treatment. It is mainly used in antilipidemic drug for coronary artery disease [19]. Here the use of newly developed combination of antihypertensive and inhibitors of HMG-CoA reductase lower plasma cholesterol levels by enhancement of receptor-mediated LDL uptake, and reduction of VLDL precursors. [17]. HMG-CoA reductase is the rate-limiting step in cholesterol biosynthesis. Inhibition of this enzyme causes an initial decrease in hepatic cholesterol. Compensatory mechanisms result in an enhanced expression of both HMG-CoA reductase and LDL receptors. The net result of all these effects is a slight to modest decrease in cholesterol synthesis, a significant increase in receptor-mediated LDL uptake, and an overall lowering of plasma LDL levels. Evidence to support the theory that enhanced LDL receptor expression is the primary mechanism for lowering LDL levels comes from the fact that most statins do not lower LDL levels in patients who are unable to produce LDL receptors (i.e., homozygous familial hypercholesterolemia). The increased number of LDL receptors also may increase the direct removal of VLDL and IDL. Because these lipoproteins are precursors to LDL, this action may contribute to the overall lowering of plasma LDL cholesterol. Finally, all HMGs can produce a modest (8% to 12%) increase in HDL.

Combination therapy

In recently, Hanmi Pharmaceutical gave patent for the combination use of newly developed combination of antihypertensive and antilipidemic drug for coronary artery disease [19]. Here the antihypertensive agent used as irbesartan and antilipidemic agent is atorvastatin give safe and effective treatment. It is mainly used in hypertension with diabetic patient and also for cholesterol lowering purpose.

This combination of atorvastatin and antihypertensive agents like irbesartan and losartan treat subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and to treat subjects presenting with symptoms of cardiac risk, including humans. additive and synergistic combinations of atorvastatin and irbesartan whereby these synergistic combinations are useful in treating subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and those subjects presenting with symptoms of cardiac risk, and congestive heart failure and coronary artery disease.

Ibesartan and atorvastatin combination is also used in Postprandial Endothelial Dysfunction, Oxidative Stress, and Inflammation in Type 2 Diabetic Patients [20]. The possibility of reducing NT generation during acute hyperglycemia with irbesartan. Atorvastatin and angiotensin and type 1 (AT-1) receptor blockers (irbesartan) are widely used in preventing CVD and diabetic complications, and it has been suggested that many of their ancillary effects are due to strong intracellular antioxidant activity. Mechanisms underlying the biological effects of atorvastatin and irbesartan differ, even in terms of intracellular antioxidant activity.

Pharmacokinetics profile

Atorvastatin

After oral administration, Atorvastatin is rapidly absorbed, with peak serum concentrations reaching within 1 to 2 hours. Extent of absorption increases in proportion to Atorvastatin dose. The absolute bioavailability of Atorvastatin is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. Mean volume of distribution is approximately 381 liters. Atorvastatin is 98% bound to plasma proteins. Atorvastatin is extensively metabolized to ortho- and para-hydroxylated derivatives and various beta-oxidation products. Approximately 70% of circulatory inhibitory activity for HMG-CoA reductase is attributed to active metabolites. Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extrahepatic metabolism, however the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of Atorvastatin in humans is approximately 14 hrs but the half-life of inhibitory activity for HMG-CoA reductase is 20-30 hours due to contribution of active metabolites [21].

Ibesartan

Ibesartan is an orally active agent that does not require biotransformation into an active form. The oral absorption of ibesartan is rapid and complete with an average absolute bioavailability of 60-89%. Following oral administration, ibesartan is extensively metabolized to active metabolites [21]. The pharmacokinetics of ibesartan has been extensively studied in patients with and without cardiovascular disease. Ibexartan peak plasma concentrations of ibesartan are attained at 1.5-2 h after dosing. Food does not affect the bioavailability of ibesartan. The pharmacokinetics of ibesartan has been compared to the other available angiotensin receptor antagonists.

The oral bioavailability of this AT1 antagonist is relatively high. Ibesartan is more completely absorbed from GI tract than other AT antagonists and reaches peak plasma concentrations within 2 h. Ibesartan is not as extensively bound to plasma proteins and does not require metabolism to the active form. It is metabolized hepatically to inactive metabolites via cytochrome P450 2C9 (CYP29). It is excreted by both biliary and renal routes and has a longer elimination half-life (11-15 h) than other angiotensin antagonists [22].

CONCLUSION

Presentsystematic review gives new combination approach for antihypertensive and antilipidemic drug treatment. In this first drug Ibesartan is an effective antihypertensive agent in patients with mild to moderate hypertension. Atorvastatin are highly effective cholesterol-lowering agents, and have been shown to reduce cardiovascular morbidity and mortality in patients with and without cardiac vascular disease. The fixed-dose combination therapy with ibesartan and atorvastatin is efficacious in patients with hypertension and dyslipidemia and may be possess additive effects over endothelial function and inflammatory markers. This may be
due to combined effects of the respective monotherapies to improve lipid profile and blood pressure.

REFERENCES