CHAPTER II

REVIEW OF LITERATURE

Coronary heart diseases (CHD) are important cause of mortality in humans in many countries including Thailand. There is strong, continuous, positive relationship between total serum cholesterol levels and clinical manifestations of CHD (Lipid research clinics program, 1984; Martin et al., 1986 and Dart, 1990). Dietary and lifestyle changes are certainly the first goal in a primary prevention programme for hyperlipidaemia patients. If dietary control is unsuccessful in lowering lipid level, consideration should be given to the use of pharmacological agents. Nevertheless, hyperlipidaemia is not the only cause of CHD. Others cause include smoking, obesity, non-exercise, diabetes mellitus and hypertension (Thompson, 1988).

For further studies of hyperlipidaemia, consideration should be given to the understand of various human lipoprotein classes and the pathology of serum lipoprotein level.

Lipoprotein classes

Because lipids are essentially insoluble in water, they cannot be transported in blood as free molecules. Instead, they are complexed with phospholipid and amphipathic proteins called apoproteins to form particles known as lipoproteins. Lipoproteins have differences in chemical compositions, physical properties and metabolic functions. It is convenient to classify them according to their relative densities. The four major classes of human

lipoproteins are described as follows (Gurr and Harwood, 1991 and Horton et al., 1993).

1. Chylomicrons

Chylomicrons are the largest and the least dense of lipoproteins and their function is to transport exogenous lipids from the small intestine to the tissues. Shorty after the consumption of a fatty meal, the presence of chylomicrons is very apparent in a sample of plasma (lipaemia). Their half-life is very short (5-15 min) because they are hydrolysed by the enzyme lipoprotein lipase to chylomicron remnants, which are cleared by remnant receptors in the liver.

Because the role of chilomicrons is to transport the absorbed dietary fats, their principal components thus include triacylglycerols with small amounts of phospholipids and proteins and several apolipoproteins in the surface layer as shown in Table 1.

2. Very low density lipoproteins (VLDL)

These lipoproteins contain predominantly triacylglycerols (Table 1) and their function is to transport endogenous triacylglycerols, cholesterol and cholesteryl ester from the liver (their primary site of synthesis) to the tissues. VLDL are more dense and smaller than chylomicrons. The major synthesis site of VLDL is the liver, although some VLDL are produced in the enterocytes. Their half-life is about 6-12 hours. They are hydrolysed by the enzyme lipoprotein lipase to VLDL remnants, which are cleared by remnant receptors in the liver. However, a variable proportion of VLDL remnant remains in plasma and undergoes conversion to LDL.

3. Low density lipoproteins (LDL)

LDL are largely derived from VLDL by a series of degradation steps that remove triacylglycerols, resulting in a series of particles that are richer in cholesterol and phospholipids. Their role is to transport cholesterol to tissues where it may be needed for membrane structure or conversion into various metabolites. LDL provides the major carriers in plasma cholesterol in man. An average composition of LDL is shown in Table 1. Their half-life is about 3-4 days. LDL are recognized by LDL receptor on liver cell surface, taken up by endocytosis and metabolized by lipases.

Table 1 Characteristics of lipoproteins in human plasma (Horton et al., 1993).

	Chylomicrons	VLDL	LDL	HDL
Molecular weight x 10^{-6}	> 400	5 - 6	2.3	0.18 - 0.36
Density (g cm^{-3})	< 1.006	0.95-1.006	1.006-1.063	1.063-1.210
Chemical composition (%)				
Triacylglycerol	85	50	10	4
Free cholesterol	1	7	8	2
cholesteryl ester	3	12	37	15
Phospholipid	9	18	20	24
Protein	2	10	23	55
Diameter (nm)	> 70	30 - 90	18 - 22	5 - 12
Apolipoproteins	A1, B-48 C1, C2, C3	B-100, E	B-100	A1, A2

4. High density lipoproteins (HDL)

HDL are synthesized in the liver. they are the smallest and most dense of lipoproteins and their major role is to carry cholesterol and cholesteryl esters from peripheral cells back to the liver, a process generally termed reverse cholesterol transport. Table 1 summarizes their composition and properties. It is interesting that an increase in HDL level can protect against CHD and various methods have been reported to be capable of raising the HDL level without using pharmacological agents. These are non-smoking, decrease in body weight and aerobic exercise (Lipid research clinics program, 1984).

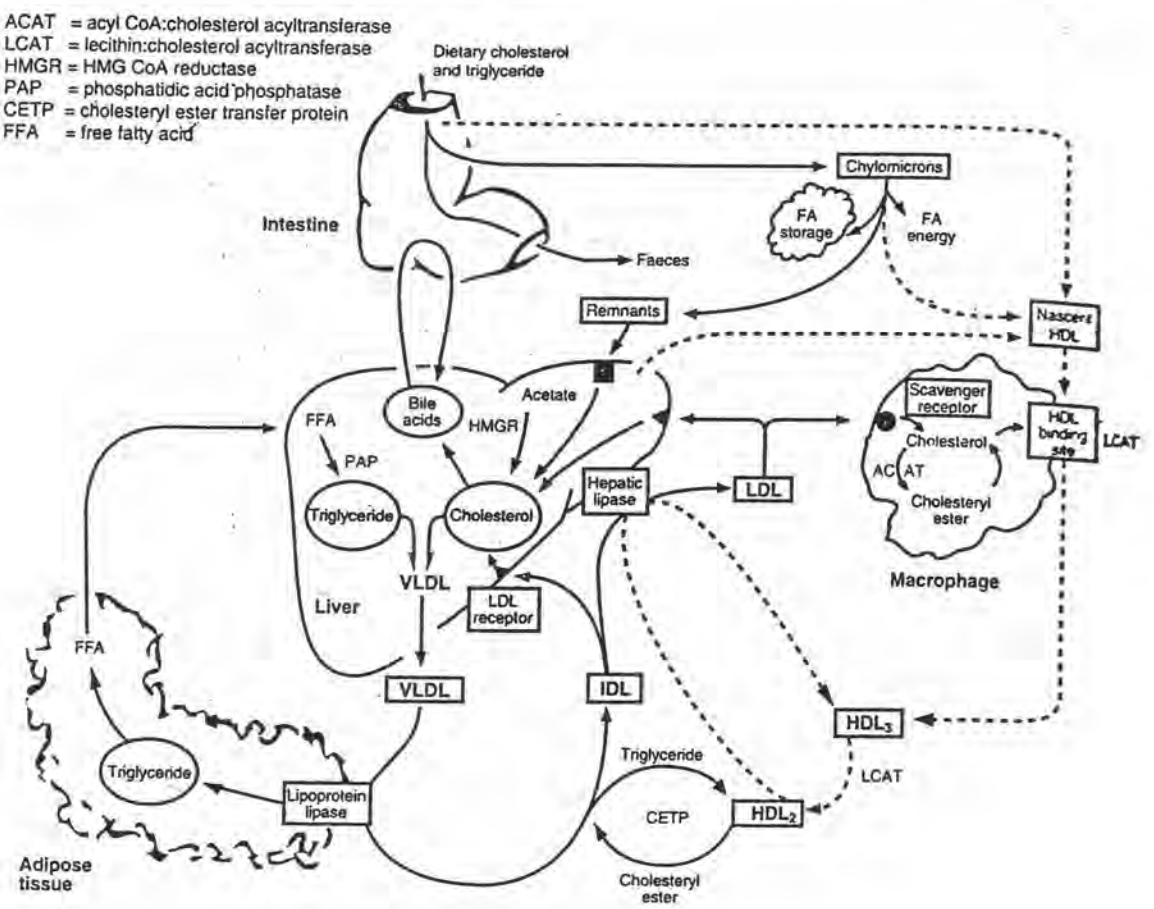


Figure 2 Lipoprotein metabolism.

Classification of hyperlipoproteinaemia

Lipoprotein phenotype was originally described by Fredrickson et al. (1967) and had been approved by World Health Organization practical use over many years.

Classification of primary hyperlipoproteinaemias is shown in Table 2.

Elevations of plasma lipids and lipoproteins have been divided into five phenotypes. Each of these phenotypes may be associated with a number of genetic diseases with primary effects on liprotein metabolism, or the dyslipidaemia may be secondary to other diseases. In type I hyperlipidaemia, plasma chylomicron level were elevated eventhough in fasting state. This abnormality was resulted from the absence of plasma lipoprotein lipase activity which lead to an ability to metabolize dietary triglyceride. Type I patients may develop lipimia retinatis, eruptive xanthomas, abdominal pain, pancreatitis. Type IIa hypercholesterolaemia is common, reflects an extremely increase in plasma LDL level due to the absence, reduction or impairment of function of the LDL receptor. A proportion of these patients have heterogenous monogenic familial hypercholesterolaemia (FH) which is associated with severe premature heart disease and tendon xantomata. Type IIb is hypercholesterolaemia accompanied by hypertriglyceridaemia . Patients of this type had defected in both lipoprotein receptor and VLDL catabolism. Type II is found in individuals who are obse, hypothyroid and impaired renal function. Type III is rare genetic disorder. Patients of this type have high plasma cholesterol and triglyceride level due to an abnormal apolipoprotein E. This type is associated with palmer xantomata, CHD and peripheral vascular disease. Type IV is common type of lipid abnormality presented in adulthood. Type IV patients had elevated plasma VLDL and triglyceride but LDL level is normal. Type IV

Table 2 Classification of primary hyperlipoproteinaemias.

Type[a]	Evaluated serum lipid[b]	Particular characteristics	Biochemical defect	Inheritance
Familial hyperchylomicronaemia (I)	TG (chylomicrons)	Juvenile onset, pancreatitis, eruption xanthoma, lipaemia retinatis	deficient lipoprotein lipase (some apolipoprotein CII deficient)	Monogenic recessive
Familial hypercholesterolaemia (IIa)	TC (LDL)	CHD, tendon xanthoma	Defective LDL receptor mechanism	Monogenic dominant
Polygenic hypercholesterolaemia (IIb)	TC (LDL),TG (VLDL) ±, TG (VLDL) ±	CHD		Polygenic
Familial type III hyperlipoproteinaemia (III)	TC (abnormal), TG (VLDL)	CHD, PVD, eruptive xanthoma, xanthoma striata palmaris	Homozygous for apolipoprotein E2, requires additional stimulus for clinical expression	Monogenic recessive
Hypertriglyceridaemia (IV) familial hypertriglyeridaemia	TG (VLDL), TG (VLDL), TC (chylomicrons) ±	Adult onset, pancreatitis, eruptive xanthoma	? Increased production, ? decreased clearance	Monogenic dominant
Familial combinedhyperlipidaemia (IIa , IIb , IV,V)	TG (VLDL) ± , TC (LDL) ±	CHD, xanthoma, ussually present with raised TG	Increased VLDL production	Monogenic dominant

a Roman numberals refer to the Fredrikson classification.

b Parentheses denote lipoprotein classes affected in each disorders ; ± denotes an inconsistent elevation.

Abbrevations ; TG = triglyceride ; TC = total cholesterol ; PVD = peripheral vascular disease.

may be associated with obesity, diabetes millitus and high alcohol intake. Type V is uncommon type having an elevated plasma triglyceride on chylomicrons and VLDL. Patients of this type are liable to develop pancreatitis. (Gurr and Horton, 1991; Oates and Wood, 1988).

SIMVASTATIN

Many attempts have been made to reduce risk of CHD by the use of drug with a lipid-lowering action, as dietary measures alone are rarely satisfactory. Some success has been obtained with bile acid sequestrants (cholestyramine and colestipol), nicotinic acid and fibrate (clofibrate, gemfibrozil, fenofibrate and ciprofibrate). More recently, the discovery of compounds that can lower blood lipid level by inhibiting the biosynthesis of cholesterol has marked a new approach to the treatment of hypercholesterolaemia. The principal rate-limiting factor in the synthesis of cholesterol is the enzyme HMG-CoA reductase, which converts HMG-CoA to mevalonic acid. No advance has been made in the search for specific inhibitions of HMG-CoA reductase until fungal metabolites, identified as mevastatin and lovastatin were found to have the desired action. Subsequent investigations have led to the introduction of simvastatin, a methyl analog of lovastatin, which was investigated and developed because of its improved biological activity.

1. Physicochemical properties (Ellison, Moore and Petts, 1993)

Generic name (USAN)	Simvastatin
Chemical name	(4R,6R)-6-[(1S,2S,6R,8S,8aR)-8-(2,2-Dimethylbutyryloxy)-2,6-dimethyl-1,2,6,7,8,8a-

hexahydro-1-naphthyl]ethyl]-4-hydroxytetrahydro pyran-2-one

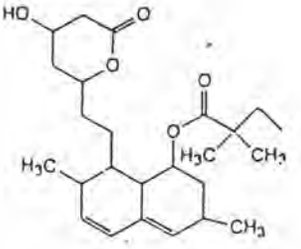
2,2-Dimethylbutyric acid, 8 ester with (4R,6R)-6-[2-[(1S,2S,6R,8S,8aR)-1,2,6,7,8,8a-hexahydro-8-hydroxy-2,6-dimethyl-1-naphthyl]ethyl]-tetrahydro -4-hydroxy-2H-pyran-2-one

2,2-Dimethylbutanoic acid 1S-[1α,3α,7β,8β,(2S*, 4S*),8aβ]]-1,2,6,7,8,8a-hexahydro-3,7-dimethyl-8-[(2-tetrahydro-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthaenyl ester

Trivial name — Synvinilin

Laboratory codes — L-644,128-000U (MK-0733)

Stucture



Molecular formula — $C_{25}H_{38}O_2$

Molecular weight — 418.57

Appearance — A white, crystalline powder

Table 3 Solubility of simvastatin.

Solvent	Solubility (mg/ml)
Chloroform	610
Dimethyl sulfoxide	540
Methanol	200
Ethanol	160
n-Hexane	0.15
Hydrochloric acid, 0.1 M	0.06*
Polyethylene glycol 400	70
Propylene glycol	30
Sodium hydroxide, 0.1 M	70**
Water	0.03

Hydrolysis of the lactone moiety of the molucule occurs in acid and in alkaline media. Solubility data are therefore for the free hydroxy acid* and the sodium salt of the hydroxy acid** of simvastatin.

Solubility

Simvastatin is insoluble in water, but is soluble in polar organic solvent. Solubility data obtained at room temperature are tabulated above

Dissociation constants

Simvastatin exhibits no acid / base dissociation constants. Potentiometric titration of a sample in 50% aqueous methanol revealed no observable buffering action in the pH range 2 - 10

Partition behavior

At room temperature, the partition cofficient of simvastatin ($K_{o/w}$) between octan-1-ol and either

pH 4 acetate or pH 7.2 acetate is > 1995

Stability and degradation

Solid state stability

Solid simvastatin stored under ambient condition undergoes very slow oxidation of the naphthalenyl diene bond system to give trace amounts of several polar oxidation products. These degradates are difficult to detect by HPLC with UV detection as they are present at low levels and have very little UV absorption. The oxidative degradation process has been studied by chromatography, isolation and identification of degradates, as well as differential scanning calorimetry. No degradation products other than those generated by oxidative processes have been found. Degradation is prevented by storage in an inert atmosphere.

Solution stability

In aqueous solutions, the lactone ring of simvastatin is readily hydrolysed to form the β-hydroxy acid. The hydrolysis is very slow in buffered aqueous /acetonitrile solutions and in buffered aqueous surfactant solutions, provided that the apparent pH of the system is approximately 7. In acid solutions, an equilibrium exists between the hydroxy acid and the lactone form. The lactone hydrolysis to hydroxy acid is rapid in alkaline solutions and is irreversible.

The equilibrium constants and the rate of the acid-

catalysed hydrolysis of simvastatin in pH 2.0 buffer at 37°C have been studied. The results indicate that the hydrolysis is reversible.

In aqueous surfactant solution in the presence of the initiator, simvastatin was shown to be susceptible to oxidation at the diene functional group.

In addition, oxidation of simvastatin in chloroform solution has been demonstrated, and the effects of oxidation inhibitors investigated.

2. Pharmacological properties

Simvastatin is an inactive prodrug. Studies in dogs have demonstrated that the lactone prodrug, unlike the open hydroxy acid form, undergoes preferential first pass sequestration in the liver (Slater and MacDonald, 1988). The prodrug is rapidly hydrolysed in the liver after absorption *in vivo* from the inactive lactone form to the active open β- hydroxy acid metabolite.

Mechanism in lowering plasma cholesterol concentrations of simvastatin are 1) inhibition of the enzyme HMG-CoA reductase with acts primarily in the synthesis of LDL cholesterol 2) increase in a number of LDL receptors expressed on the surface of liver cells resulting in greater uptake and degradation of circulating LDL. The concentrations of apolipoprotein B are also substantially reduced which further suggests a further decrease in a number of circulating LDL particles (Slater and MacDonald, 1988).

For the first mechanism, simvastatin is a competitive inhibitor of HMG-CoA reductase, an important rate-limiting enzyme which catalyzes the reduction of HMG-CoA to mevalonic acid in the biosynthesis of cholesterol. Usually, the end-products of mevalonate synthesis (chloesterol, dolichol, ubiquinone and isopentyl tRNA) can suppress HMG-CoA reductase when present in sufficient concentrations in the cell. The mechanism of the suppression is theorised to be a multivalent feedback system, as represented in Figure 2 (Todd and Gau, 1990).

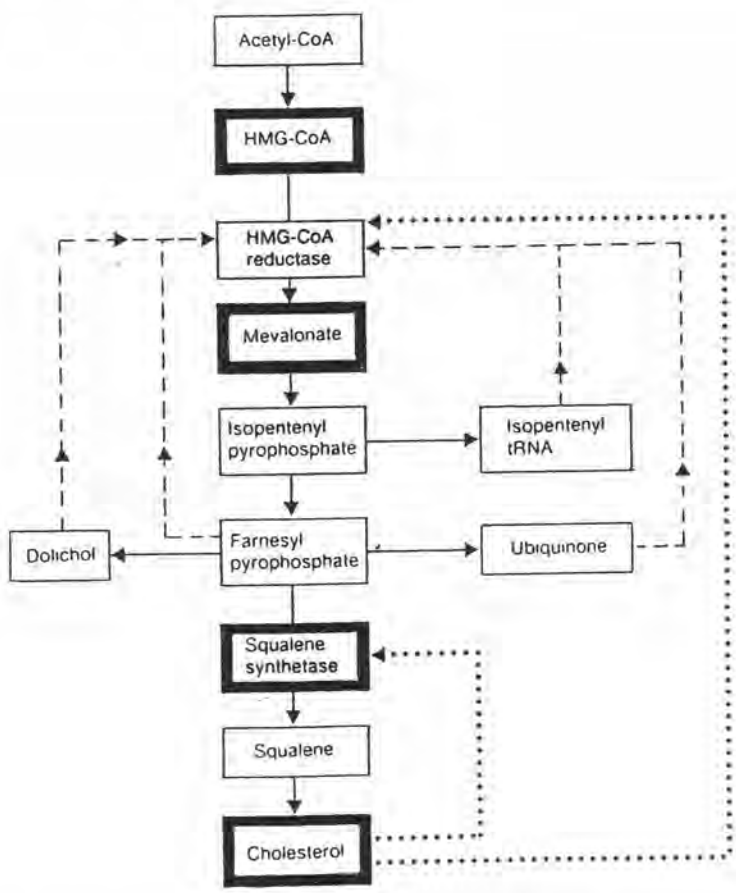


Figure 3 Schematic representation of multivalent feedback regulation of HMG-CoA reductase. The dashed lines indicate probably nonsterol regulators and the dotted lines indicate regulation by cholesterol which is derived from LDL ptake. This LDL cholesterol suppresses HMG-CoA reductase and to a limited extent squalene synthetase.

Inhibition of HMG-CoA reductase results in a moderate reduction in cholesterol synthesis. The effects have been examined *in vitro* and in animal models. Slater and MacDonald (1988) reported the mean IC_{50} values, or the concentration required to produce a 50% reduction in activity, for the inhibition of sterol synthesis in various cell culture lines *in vitro* to be 19.3 for mouse L-M (fibroblast), 13.3 for rat H411E (liver) and 15.6 nmol/L for human HEP G_2 (liver). In animal model, plasma cholesterol was reduced in dogs after single doses of simvastatin, and in rabbits fed with cholesterol-rich diets and administered with simvastatin in single doses or repeated doses for 2 to 12 weeks. Oral administration of simvastatin 1, 2 and 4 mg/kg/day to cholestyramine-treated dogs lowered plasma cholesterol by 2, 29 and 38%, respectively, compared with animals treated with cholestyramine alone (Slater and MacDonald, 1988). In primary hypercholesterolaemia, simvastatin significantly lowers total and LDL cholesterol. It also tends to reduce triglycerides and raise HDL cholesterol. In a short term treatment, simvastatin, at dose of 5 mg (n=109) and 10 mg (n=110), was administered in primary hypercholesterolaemia patients in a multinational, randomised trial for 6 weeks. For simvastatin 5 mg and 10 mg respectively, the mean reduction in total cholesterol levels was 19% and 23%, respectively. The mean reduction in LDL cholesterol levels was 26% and 30%, and triglyceride levels were 11.5% and 14.5%. HDL cholesterol levels were found to increase after simvastatin 5 mg and 10 mg with the respective value of 10% and 20% (Ose, Scott and the SV-FV study group, 1995). In long term treatment, Boccuzzi and coworker (1993) found that oral administration of simvastatin 10-40 mg/day to over 201 primary hypercholesterolaemia patients for 3 years led to a 28-30% mean reduction in total cholesterol, 36-39% mean reduction in LDL cholesterol, 11-14% mean reduction in triglyceride, and 10-14% mean increase in HDL cholesterol.

For second mechanism, LDL is regularly removed from the circulation via binding to the specific LDL receptors in the liver, the main site of LDL catabolism, and in other tissues. In animal and human, inhibition of liver cholesterol synthesis by HMG-CoA reductase inhibitor such as lovastatin leads to increased expression of a number of LDL receptors on the cellular surface, resulting in greater uptake and degradation of circulating LDL and a further decrease in total blood cholesterol (Slater and MacDonald, 1988). Similarly, simvastatin at the dose of 0.7 to 6 mg/kg produced a dose-related increase in LDL receptor-dependent binding and increased the number of hepatic LDL receptors in rabbits fed with a diet containing 0.25% cholesterol (Ishida et al., 1990). Moreover, high affinity degradation of radiolabelled LDL increased significantly from control in mononuclear leucocytes isolated from patients administered with simvastatin (Hagemenas et al., 1990).

Simvastatin also has influence on the adrenocortical function, bile acids composition, and lens opacity that would be described in detail later in safety evaluation.

Safety evaluation

In placebo-controlled trials evaluating the efficacy and safety of simvastatin monotherapy in the treatment of hypercholesterolaemia, clinically significant adverse events occur infrequently, and discontinuation because of drug-related events was rare. Discontinuation ranges between 0.3% and 0.7% (Boccuzzi et al.,1991). Therapies with simvastatin are generally well-tolerated. The most common drug-associated adverse effects are gastrointestinal disturbances, headache, sleep and central nervous system (CNS) disturbances. The rarely observed include increases in hepatic transaminase (defined as successive increases in either aspartate transaminase or alanine transaminase

concentration of more than 3 times the upper limit of normal), increases in creatine kinase (CK), and myopathy (defined as CK increases of more than 10 times the upper normal limit with associated muscle pain and/or weakness that in severe cases may lead to rhabdomyolysis and subsequent renal failure) (Plosker and McTavish, 1995).

Hepatotoxicity

Simvastatin can cause dose-related, asymptomatic and reversible increases in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) in a small proportion of individuals. Boccuzzi et al.(1991) reported the safety data from 2361 patients enrolled in controlled clinical trials of simvastatin and their open extentions for a mean duration of 1 year. Persistent increases in hepatic transaminase concentrations to more than 3 times the upper limit of normal occurred in 1% of the patients. Simvastatin has occasionally been associated with histological evidence of hepatitis, in at least one instance against a background of excessive alcohol consumption. Withdrawal of simvastatin and abstinence from alcohol was accompanied by a return to normal liver function test values (Thompson, 1993).

Muscular toxicity

The mechanism of these side effect of simvastatin still unknown but might be hypothesized as follow. HMG Co-A reductase is the rate-limiting enzyme in cholesterol synthesis at the level of mevalonate production. Mevalonate has a key role in the synthesis of several isoprenoid compound including ubiquinone. Coenzyme Q10 (CoQ10) is the natural occurring ubiquinone in humans. It is widely recognized as an essential component of the electron-transfer system in mitochondrial membranes, and it also an effective

lipid-soluble antioxidant at physiologic concentrations. Inhibition of cholesterol synthesis by HMG CoA reductase may reasonably led to a dimininution of CoQ10 plasma level and a reduction of it bioavailability with possible cellular damage. These side effect is rarely occurred but might especially occurred in patient with high risk of deficiency of CoQ10 such as in whom with higher metabolic requirement increased rate of lipid peroxidation and impaired biosynthesis of the quinolone moity (Ghirlanda et al., 1993).

Boccuzzi et al. (1991) observed increase in CK more than 10 times the upper limit of normal in 0.6% of the patients. Myopathy was observed in 2 patients who participated in an open-label extention (0.08%). Both patients had associated concomitant conditions, and myopathy was unlikely to be related to simvastatin therapy alone. The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent therapy with erythromycin, cyclosporin, niacin, gemfibrozil and fibrate agents. Ghirlanda et al. (1993) also reported that simvastatin significantly lower CoQ10 plasma level after a few week of 3 month treatment both in normal and in hypercholesterolemic subjects. Whereas Laaksonen (1995) reported that ubiquinone supply is not reduced during short-term (4 weeks) of simvastatin treatment in the musscle tissue of subjects.

Campana et al. (1995) reported that low-dosage simvastatin treatment seems to be safe in heart transplant patients receiving triple-drug immunosuppressive therapy (cyclosporin, prednisolone, and azathioprine). Plasma concentration profiles of simvastatin in kidney transplant recipients with cyclosporin indicated that simvastatin should be administered in a reduced dosage and monitored closely to cyclosporin patients (Arnadottir et al.,1993 and Thompson, 1993). The safety of combined simvastatin (up to 40 mg/day)-gemfibrozil (up to 1.2 g/day) therapy has been evaluated in 39 patients in 2

trials, and no case of myopathy was reported (Feussner, Eichinger and Ziegler, 1992 and da Col et al., 1993).

Ocular toxicity

In view of previous experience with triparanol, a drug which inhibits cholesterol synthesis at a much later stage than simvastatin, but also showed cataract-inducing properties, particular attention has been paid to the possibility of lens opacities in patients treated with simvastatin. But, simvastatin are biochemically hypocholesterolemic agent distinct from the previous later stage hypocholesterolemic agent. Hence, simvastatin would not caused the accumulation of the late-stage cholesterol biosynthesis intermediate (i.e., desmosterol) on the cholesterol synthesis sites (i.e., in the lens or any organ) after treatment. Ophthalmologic evaluations using slit-lamp examinations in 2014 simvastatin-treated patients revealed a 1-2% increase in the frequency of lens opacities. The magnitude of this increase was consistent with both the expected incidence related to the age of the population (mean age 50 years) and the calculated incidence caused by normal aging (Boccuzzi et al., 1991).

Influence on adrenal function

Investigation of the influence of HMG-CoA reductase inhibitors on adrenal function is warranted because reduction in the amount of LDL available for uptake may theoretically decrease the availability of cholesterol for ATCH-stimulated adrenal corticosteroid production. This could be of particular concern in patients with severe depletion in LDL receptors. The maximal increase in serum cortisol during ATCH stimulation was not significantly altered after simvastatin therapy compared with placebo baseline (0.50 VS 0.46 μmol/L) or during insulin tolerance testing (0.33VS 0.31 μmol/L) in 24

hypercholesterolaemic patients given simvastatin 40 mg/day for 8 weeks. In addition, there was no significant change in the excretion of free cortisol, 17-hydroxysterols and 17-ketosterols (Stalenhoef, Mol and Stuyt, 1989 and Mol and Stalenhoef, 1990).

Effect on gallstone formation

Cholesterol is hell in solution in bile by bile salt-lecithin micells, and an excessive secretion of cholesterol allows super saturation of the bile and so predisposes to formation of gallstones. Certain lipid-regulating agents have been shown to increase the saturation index of gallbladder bile and increase the possibility of cholesterol gallstone formation. Ursodeoxycholic acid reduces the hepatic secretion of cholesterol. It also lowers the activity of HMG-CoA reductase, which raise the possibility that simvastatin may also have some cholesterol-gallstone-dissolving activity. The effect of simvastatin on the saturation index of gallbladder bile was studied by Duane et al. (1988) in 10 patients with type IIa or IIb hypercholesterolaemia. After treatment with simvastatin 20 or 40 mg/day for 7 to 13 weeks, the mean cholesterol saturation index of gallbladder bile fell from 1.01 to 0.77 ($p<0.01$). This possibility that combined simvastatin and ursodeoxycholic acid treatment might have an additive effect in reducing cholesterol secretion and the cholesterol index may be worth in investigation as a non-invasive treatment of gallstones.

Elderly

The influence of age and gender on the pharmacokinetic profile was determined after administration of simvastatin 40 mg/day for several days in 16 elderly (aged 70 to 78 years) and 18 younger (aged 19 to 30 years) patients

with hypercholesterolaemia. Time to achieve peak plasma concentrations of active and total HMG-CoA reductase inhibitors was not significantly affected by age or gender. However, mean steady-state plasma concentrations of active and total HMG-CoA reductase inhibitors were 40 to 60% higher in elderly than younger patients and 20 to 50% higher amoung female than male patients. Cheng et al. (1992) concluded that the effects of age and gender on pharmacokinetic profile are not great enough to necessitate simvastatin dosage modifications, since the drug has a broad therapeutic window. In addition, Boccuzzi et al. (1991) studied clinical and laboratory safety in 349 elderly patients (≥ 65 years) who received simvastatin therapy (142 patients for a period ≥ 1 year, 62 patients for ≥ 1.5 years and 17 patients for ≥ 2 years). The incidence of clinical and laboratory adverse events in the elderly was similar to that seen in the non elderly population, suggesting that the elderly do not experience an increased frequency of adverse experiences. The trend for a slightly higher incidence of insomnia in the elderly must be viewed in light of the increased prevalence of sleep disturbances associated with this age group.

CNS side effects

Lovastatin and simvastatin, but not pravastatin, have been reported to cause CNS side effects such as headache, sleep disturbance, and insomnia, even though all three have similar chemical structure. Differences CNS side effects result from different abilities to permeate through the blood-brian barrier (BBB). Lovastatin and simvastatin are highly lipophilic, while pravastatin is hydrophilic (Serajudin, Ranadive and Mahoney, 1991 and Saheki et al., 1994). However, differences in sleep efficacy and sleep latency are difficult to evaluate, and polysomnographic differences indicating a physiologic or biochemical alteration in sleep pattern may not neccessarily result in significant subjective differences (Black et al., 1990). Susceptibility to the

CNS effects of more lipophilic HMG-CoA reductase inhibitors differs among individual patients, and individuals receiving prolong therapy at the higher doses may be more susceptible to these effects. Epidemiologic data on the comparative incidence of sleep disturbances associated with the use of HMG-CoA reductase inhibitors are lacking. Furthermore, since the data from clinical trials have demonstrated the incidence to be very low, a large sample size would be needed to detect a small difference, if it exists (Hsu, Spinler and Johnson, 1995).

Contraindication and precautions

Simvastatin is contraindicated in patients hypersensitive to the drug, in active liver disease or unexplained elevations of serum transaminase. It is also contraindicated in pregnancy and breast feeding. Liver function tests should be carried out before treatment and every 4 to 6 weeks subsequently. The drug should be withdrawn if transaminase levels rise progressively. Care is necessary in patients taking substantial amount of alcohol. Transient mild elevations of creatine phosphokinase (CPK) derived from skeleton muscles are not usually clinically significant, but the drug should be discontinued if markedly elevated CPK level occurs, or if myopathy is diagnosed discontinuation also should be considered in the differential diagnosis of chest pain in patients receiving simvastatin.

Dosage and administration

Simvastatin is indicated for patients with primary hypercholesterolaemia when the response to diet and other nonpharmacological measures alone has proved inadequate and with a cholesterol level in excess of 7.8 mmol/L. The usual starting dose is 10 mg/day given as a single dose in the evening.

Adjustments of dose should be made at intervals of not less than 4 weeks, depending on response. The dosage may be increased depending on the patients response to a maximum of 40 mg/day. A fall of total serum cholesterol levels below 3.6 mmol/L or a LDL cholesterol below 1.94 mmol/L indicates a need to review or reduce the dose of simvastatin. In Japan, a starting dose of 5 mg/day given as a single dose in the evening has been favoured in clinical trials.

3. Pharmacokinetic properties

Very little information has been published in the literature which addresses the pharmacokinetics of simvastatin, especially in humans, despite the fact that simvastatin has been available for general use in some countries for several years.

The half-life of simvastatin acid is 1.9 hr and total body clearance is 31.8 L/hr. Less than 10% of the peak HMG-CoA reductase inhibitory activity remains after 12 hours (Vickers et al., 1990a).

Absorption

Data from studies in rats and dogs suggest that approximately 61 to 85% of dose of simvastatin is absorbed from the stomach (Vickers et al., 1990a). It was unable to explain the results which demonstrated that peak plasma concentrations were 10 to 15 fold greater in female rats than in males (Vickers and Colleagues, 1990 and Uchiyama et al., 1990). When 100 mg of radiolabelled simvastatin was administered to 4 patients with hypercholesterolaemia, peak plasma radioactivity and peak enzyme inhibition occured after 4 hours. The inhibitory activity tended to correlate with plasma radioactivity

(Vickers et al., 1990a). Pentikainen and co-workers (1992) reported that peak enzyme inhibition in 12 healthy male volunteers occured 2.5 hours after receiving a single oral 40 mg dose. In humans, a linear increase in the inhibitory activity of simvastatin occurs as the dose is elevated from 5 to 120 mg. A low-fat diet does not alter simvastatin absorption (Mauro, 1993).

Distribution

Simvastatin is a relatively hydrophobic compound. Oral absorption allows simvastatin to quickly reach the liver, where it is converted to relatively polar metabolites, many of which are pharmacologically active. In dogs, only 7% of an oral dose reached the general circulation (Vickers et al., 1990a). Because of their increased polarity, the active metabolites are less lipophilic than the parent compound and tend to remain in the liver, allowing the potential HMG-CoA reductase inhibitory activity of a given dose of simvastatin to concentrate within the liver, the primary organ responsible for synthesis of most endogenous cholesterol (Germershausen et al., 1989 and Vickers et al., 1990a).

In rats and dogs, radiolabelled intravenous and oral dose of simvastatin concentrated in the liver and intestines, suggesting that the hepatically produced metabolites were eliminated via the biliary system (Vickers et al.,1990a). Based on both enzyme inhibition activity and radiolabelled drug studies, a relatively small portion of the metabolites do leave the liver and distribute to other organs in the body (Germershausen et al., 1989 and Vickers et al., 1990 a). Less than 5% of dose of simvastatin reached the circulation system in 9 healthy human volunteers (Duggan and Vickers, 1990). It has been demonstrated in animal models that intravenous simvastatin may distribute to other tissue to a relatively greater extent than orally administered drug (Vickers

et al., 1990a), but long term administration did not result in an accumulation of drug (Vickers et al., 1990a). Data on simvastatin with respect to possible effects on pregnancy and breast feeding are not currently available (Duggan and Vickers, 1990).

Metabolism

Simvastatin is extensively metabolised by the liver through the cytochrome P450 system (Vyas et al., 1990). Metabolism has been studied in both dogs and rodents but the dog model propably resembles human metabolism to greater degree because dogs and humans both lack plasma esterase. In rats, plasma esterase is involved in simvastatin metabolism, especially in the conversion of simvastatin to simvastatin acid (Vickers et al., 1990b).

Simvastatin exhibits a hepatic extraction ratio of 93% in dogs (Vickers et al., 1990a). The major active metabolite of pharmacologically inactive simvastatin is simvastatin acid (Vickers, et al., 1990b). Other metabolites identified from liver microsomal studies include 6′-hydroxy-simvastatin, 3″-hydroxy-simvastatin and 6′-exomethylene-simvastatin. 6′-Hydroxy-simvastatin readily rearranges in the presence of acid to form inactive 3′-hydroxy-simvastatin (Vickers et al., 1990b). Several metabolites not identified in the liver microsomal studies are present in the bile where they may exist in both lactone and acid forms. All the metabolites from liver microsomal production, with the exception of 3″-hydroxy-simvastatin, have been found in the bile. Two metabolites of 6′-exomethylene-simvastatin which were not isolated from the liver but have been identified in the bile are 6′-hydroxymethyl-simvastatin and 6′-hydroxycarbonyl-simvastatin (Vickers et al., 1990b). The chemical

structure of these metabolites are shown in Figure 4. Vyas and coworkers (1990) have shown that stereo- and regioselectivity are important with respect to the cytochrome P450 metabolism of simvastatin. 6′-Hydroxy-simvastatin, 3″-hydroxy-simvastatin. 6′-hydroxymethyl-simvastatin and 6′-hydroxycarbonyl -simvastatin, when converted to their acid forms, are respectively 50, 20, 90 and 40 % as active as simvastatin acid (Vickers et al., 1990b).

On the basis of animal studies, enterohepatic reabsorption of 6′-hydroxy-simvastatin is thought to occur (Vickers et al., 1990a). It has also been suggested that simvastatin acid may be capable of undergoing relactonisation to reform the parent compound (Vickers et al., 1990b).

3′-Hydroxy-simvastatin has been identified as the major end product of metabolism of simvastatin in rats (Vickers et al., 1990b). Rats have also demonstrated the ability to synthetize a unique acid metabolite which is not observed in dogs or humans (Vickers et al., 1990b).

Elimination

Regardless of whether the drug is administered orally or parenterally, simvastatin tends to be eliminated in feces, secondary to biliary secretion (Muaro, 1993). In humans receiving radiolabelled simvastatin, 13% of the radioactivity was collected in the urine and 58% in the feces (Muaro, 1993). Very little unchanged simvastatin or simvastatin acid is found in the feces.

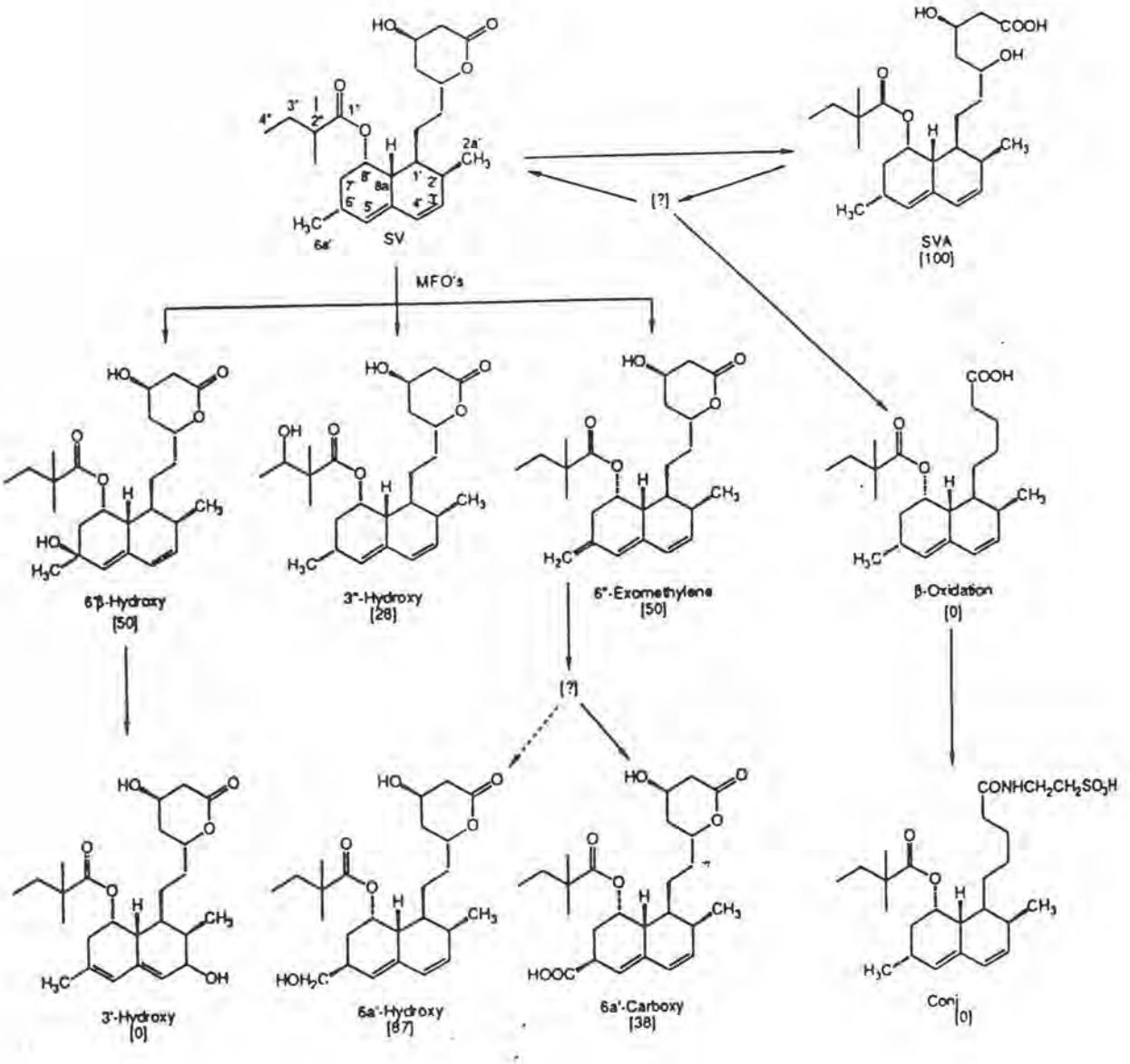


Figure 4 Biotransformation profile for SV. Value in brackets are HMG-CoA reductase inhibitory activities for the HO-acid forms relative to SVA.