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CLINICAL PHARMACOKINETICS AND PRACTICAL APPLICATIONS OF SIMVASTATIN

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Abstract

The objective of this article is to review the clinical pharmacokinetics of simvastatin and outline practical applications in patient management. Information was obtained from a systematic search of published literature using PubMed and the Cochrane Library. Additional references were obtained from review articles and textbooks. Simvastatin acid is the active form of the prodrug simvastatin and is a specific, competitive inhibitor of 3-hydroxy-3-methylglutaryl co-enzyme A reductase. Its primary site of action is the liver. Simvastatin is a substrate for the cytochrome P450 enzyme CYP3A4, and inhibitors or inducers of this enzyme system can cause respectively increased or decreased plasma concentrations of simvastatin. Plasma concentrations of simvastatin acid correlate poorly with LDL cholesterol reductions, although higher doses of simvastatin do lead to greater reductions in LDL cholesterol. Patients with homozygous familial hypercholesterolaemia exhibit much greater reductions in LDL cholesterol compared with other

patient groups. Simvastatin has a low volume of distribution and is highly bound to plasma proteins. Information on simvastatin in elderly patients and those with renal or hepatic impairment is lacking, but dose reductions are recommended for patients with severe renal impairment. Studies have shown a significant drug interaction between simvastatin and ciclosporin, and caution is recommended when considering concurrent use. Simvastatin is teratogenic and contraindicated during pregnancy. High-intensity cholesterol-lowering therapy using statins such as simvastatin is now recommended in the primary and secondary prevention of atherosclerotic vascular disease. Adherence to the traditional LDL cholesterol target is no longer advised, and rather patients are now to be assessed using a cardiovascular risk calculator. Under the guidance of the risk calculator, patients may benefit from higher doses of simvastatin or other high-intensity statin therapy. Adverse effects from simvastatin do occur, some of which are caused by drug interactions, and monitoring of these patients is important. An application of simulated annealing has also been discussed in this article, outlining a method for optimizing doses of simvastatin in individual patients. This is followed by a mathematical model based on recent clinical trial evidence, suggesting the possibility of a fixed-dose combination therapy of ezetimibe and simvastatin. Overall, this article provides an understanding of the pharmacokinetics and role of simvastatin in current clinical practice, as well as potential future implications.(Foll et al., 2014)

Keywords:-Bioavailability, drug concentration-time profiles, HMG-CoA reductase inhibitors, hydrolysis, isomerism, pharmacokinetic/pharmacodynamic relationship, pharmacodynamics, pharmacokinetics, prodrug, simvastatin, statins.

1 .Introduction

Simvastatin, the focus of this review, provided one of the early examples of the power of pharmacokinetics in drug development and clinical use. Simvastatin is a member of a class of drugs that act as specific inhibitors of HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis. Plasma cholesterol and LDL are the primary treatable risk factors for coronary heart disease, which is the leading cause of death in the U.S. and most developed countries. Inhibition of HMG-CoA reductase has a major impact on cholesterol homeostasis and lowers LDL levels by upregulating hepatic LDL receptors, which clear LDL and VLDL from the plasma.

Simvastatin is an inactive lactone which is hydrolyzed in vivo to the corresponding ß-hydroxyacid form, a potent and specific inhibitor of HMG-CoA reductase. In addition to inhibition of endogenous cholesterol synthesis, simvastatin has been shown to increase LDL catabolism and decrease cholesterol and LDL in a variety of animal models of hyperlipidemia and in patients with hypercholesterolemia. Studies to date have shown that chronic dosing of simvastatin causes dose-dependent reduction in plasma cholesterol and LDL, with a maximal effect ranging from 40-60% at doses of 0.25-5 mg/kg/day in various animal models, making simvastatin an attractive lipid lowering agent with a wide potential dose range. If these doses are compared with those used in patients to achieve similar effects, simvastatin has a wide safety margin in its effectiveness on reduction of cholesterol and LDL levels.(Giampietro et al., 2017)

1.1 .Background of Simvastatin

At least two different pathways for cholesterol biosynthesis inhibition have been proposed. One is the upregulation of LDL receptors, which increases the uptake of plasma LDL cholesterol. Distinct from this, intracellular cholesterol biosynthesis can be upregulated. Cholesterol absorption from the gut lumen has been described to increase after long-term use of simvastatin, although it is still uncertain whether this is a result of upregulated HMG-CoA reductase and/or due to an increase in the cholesterol pool available for synthesis. Simvastatin has also been shown to beneficially reduce the production of isoprenoid compounds.(Giampietro et al., 2017)

Clinically, simvastatin has proven to be effective in the reduction of plasma cholesterol, LDL-C, apolipoprotein B, and triglycerides, with concomitant increases in HDL-C. It has also been shown to reduce the risk for coronary revascularization, myocardial infarction, and stroke in various patient populations. It is a prodrug, with its transformation to the active β-hydroxyacid form taking place in two successive stages. The first of these is the hydrolysis of a lactone to β-hydroxyacid by nonspecific plasma esterases. The second is the conversion of the hydroxyacid lactone to β-hydroxyacid by a specific and reversible mitochondrial decarboxylase. The transfer across cell membranes is an energy-dependent and facilitated process. Simvastatin is less likely to cross the blood-brain barrier compared with other statins; however, it can effectively inhibit cholesterol synthesis in the central nervous system by being incorporated into cells in the CNS and undergoing hydrolysis to its active form.(B. Kell, 2008)

Simvastatin (Simlup, Simvas) is a member of the statin class of pharmaceuticals. It is a synthetic derivative of a fermentation product of Aspergillus terreus. It is a white, nonhygroscopic, crystalline powder that is practically insoluble in water and freely soluble in chloroform, methanol, and ethanol. Simvastatin is hydrolyzed into its active β-hydroxyacid form, simvastatin acid, which is the principal metabolite and a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.(B. Kell, 2008)

1.2 .Clinical Pharmacokinetics Overview

At the conclusion of the mevalonate study and parallel dog studies, a full labeled and unlabeled dose recovery study was done in man and proved on the average simvastatin dose was excreted in only trace amounts unchanged in the urine and feces. As low and variable recovery doses of 3H and dietary cholesterol were ejected in the feces, this essentially led to the conclusion that simvastatin raised efficiency of removal of circulating cholesterol from the plasma.

The mean oral daily dose of simvastatin was also tightly correlated to its effect on the lower plasma cholesterol and less affected plasma LDL cholesterol change. This action showed greater intrinsic activity with respect to the lowering of non-LDL cholesterol. After the week of tracers were conducted, it was found that doses of simvastatin produced essentially permanent effects on cholesterol synthesis rates compared to its off-treatment periods. In correlation, it also reduced its synthesis of the non-cholesterol isoprenoid pathway products, and this was a consistent level of effect on lowering endogenously synthesized cholesterol and decrease in plasma LDL cholesterol over the extended treatment period in the same subject. This provided a very clear correlation of

consistent dosing and its maintaining effect of simvastatin over extended periods.(Gressani & Lambert, 2020)

The average plasma concentration-time curve for simvastatin on the seventh day was consistent with the estimated rate of absorption from dog studies in which greater than 90% of a simvastatin dose was absorbed from the duodenum within 1 hour of an IV administration. High and variable plasma concentrations on dosing treatment with less than 1% of the dose of simvastatin and its active metabolite were excreted in the urine. This was diagnosed as high first-pass extraction of simvastatin by the liver and extrahepatic tissue. Simvastatin was also metabolized to its active form, simvastatin hydroxy acid, within an hour of the dosing period. This metabolite was a 3-point inhibitor of HMG-CoA reductase within an IC50 of less than 1nM.

A study of the pharmacokinetics of simvastatin was conducted on 7 subjects that were given an oral 3H mevalonate tracer during two separate treatments with simvastatin 25mg/day once in the morning for a week or a week without simvastatin. Blood samples were collected for 12 hours on day seven and 24 hours post-dosing on day 8. Plasma and urine were analyzed for simvastatin and 3H radioactivity.(Mosso et al., 2021)

Simvastatin is a semi-synthetic derivative of a fermentation product of Aspergillus terreus. The HMG-CoA reductase is a specific inhibitor for the enzyme, which catalyzes the conversion of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a rate-limiting step in cholesterol biosynthesis. As a result, it lowers hepatic cholesterol as well as plasma total and low-density lipoprotein cholesterol levels. It also has an effect on the increase of high-density lipoprotein cholesterol. This action basically changes the pharmacokinetics of endogenously produced cholesterol.(B. Kell, 2008)

1.3 .Importance of Understanding Simvastatin's Pharmacokinetics

Pharmacokinetic knowledge has only just begun to influence the ideal choice of statin and selection of optimal dosage for an individual patient with hyperlipidaemia. Traditional 'black-box' pharmacology served the statins well and large, simple dose-ranging studies provided the information needed for obtaining a marketing license for a new drug. Unfortunately, many drugs do not possess a flat dose-response relation and in some cases it is necessary to individualize therapy to derive maximum benefit with minimal risk of adverse effects. In the case of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), the ideal is to maximally inhibit cholesterol synthesis and minimize serum LDL-cholesterol concentration in the long-term, without an increase in the incidence of myotoxicity or hepatic dysfunction. Simvastatin is a prodrug that is hydrolyzed to the active β-hydroxyacid form in the liver. This hydroxyacid is a potent, specific inhibitor of HMG-CoA reductase and simvastatin is several hundred times more potent than its parent compound. The metabolism of simvastatin and the pharmacokinetics of the hydroxyacid form have a complex dependence upon genetic and environmental factors, which influences its cholesterol lowering efficacy and risk of toxicity. Understanding these processes is important for maximizing the benefit: risk ratio of simvastatin therapy.(M Rembold, 2019)

2 .Therapeutic Uses

These are broad-ranging and it is clear simvastatin has been shown to be beneficial in a wide variety of conditions.

1 .Primary prevention of acute coronary events in patients with multiple risk factors for CHD as reduction of risk of CHD death and myocardial infarction and risk of needing revascularisation procedure.

2 .The long-term treatment of coronary heart disease.

3 .Secondary prevention of cardiovascular complications in patients with or at high risk of developing cardiovascular complications.(B. Kell, 2008),(Giampietro et al., 2017)

Hyperlipidaemia, as an adjunct to diet, to reduce elevated total-C, LDL-C and apolipoprotein B levels in various types of hyperlipidaemia (familial and non-familial) when response to diet and other nonpharmacological measures is inadequate.

Simvastatin is currently licensed for the following indications. Most of the data on the effectiveness of simvastatin has been generated in CHD patients.

2.1 .Treatment of Hyperlipidemia

Inhibiting the rate-limiting step in cholesterol biosynthesis, HMG-CoA reductase inhibitors decrease levels of plasma LDL cholesterol (High Density Lipoprotein), which is one of the major contributors to atherosclerotic coronary artery disease. Therefore, statins are recommended as the drug of choice in the treatment of hyperlipidemia due to their efficacy in reducing LDL cholesterol levels. Simvastatin has been known to be effective in reducing LDL cholesterol levels. A meta-analysis done by Collins et al showed that a 1% reduction of LDL cholesterol would result in a 1% reduction of the risk of ischaemic heart disease. A dose-dependent effect was seen in a study done by Shepherd et al, where 40mg of simvastatin was more effective in reducing LDL cholesterol levels compared to 20mg of pravastatin. Due to the efficacy of simvastatin in reducing LDL cholesterol levels, the Malaysian Clinical Practice Guideline on the Management of Dyslipidemia has recommended simvastatin in treating hypercholesterolemia at its maximum dose if necessary, especially in high-risk cases.(Giampietro et al., 2017)

2.2 .Prevention of Cardiovascular Events

Confidential Reports Medical records and patient outcome databases. These studies have consistently shown a strong relationship between the level of LDL cholesterol and the relative risk for future cardiovascular events. Devaraj et al showed that patients with cardiovascular disease have a higher baseline of LDL cholesterol, and thus greater cholesterol reduction is necessary for beneficial effects on CHD. The Scandinavian Simvastatin Survival Study (4S) was a landmark study that provided clear evidence of the benefits of simvastatin in patients with high LDL and pre-existing coronary artery disease. Patients were randomized to simvastatin 20-40 mg/day or placebo and followed for a median of 5.4 years. The primary endpoint was total mortality, and there was an impressive 30% reduction in mortality in the simvastatin group. Secondary endpoints included death due to CHD, non-fatal myocardial infarction, and stroke where there was also improvement. Subsequent post-hoc analyses of data from 4S and other trials suggest that there is

no threshold level of LDL cholesterol below which benefits are not seen with further reduction. Also, it appears that the relative reduction in events is similar regardless of baseline cholesterol levels. These findings are significant in that they suggest that even patients with average or moderately low LDL levels may benefit from statin therapy.

The Cholesterol Treatment Trialists' trial level meta-analysis evaluated the effects of lowering LDL cholesterol with statin therapy on first or subsequent vascular events. These researchers analyzed data from 14 trials of statin therapy involving over 90,000 patients. Their findings showed that each 39 mg/dL (1 mmol/L) reduction in LDL cholesterol led to an average of 23% reduction in the incidence of major vascular events. Subgroup analyses also showed that the proportional reduction in major vascular events was similar among various high-risk patient groups including those with a history of vascular disease, diabetes, or even lower risk individuals. These results are consistent with the concept of a continuous, progressive relationship between cholesterol levels and risk of cardiovascular disease. Overall, the weight of evidence from various trials suggests a strong role for statin therapy in the primary and secondary prevention of cardiovascular events in patients across a broad range of cholesterol levels.(Dai et al., 2021)

2.3 .Other Therapeutic Applications

Two other therapeutic applications have been suggested for HMG-CoA reductase inhibitors, such as simvastatin. The first is the prevention of atherosclerosis in children with type I familial hyperlipidemia, an inherited disorder resulting in extremely high LDL-C levels and premature cardiovascular disease. In a two-year study of 173 children and adolescents with this condition, simvastatin reduced LDL-C levels by 34% compared with an increase of 2% in the placebo group. LDL-C levels were decreased to a greater degree in those children receiving higher doses of simvastatin. This study has important implications in terms of reducing the risk of future cardiac events in this population. However, there are concerns about the long-term safety of this therapy, as HMG-CoA reductase inhibitors have not been used in children for such long periods of time and the effects of reducing cholesterol levels over many years are unknown.

The second suggested use is for an antiproliferative agent to reduce the restenosis rate following angioplasty. An in vitro study has suggested that HMG-CoA reductase inhibitors may inhibit smooth muscle cell proliferation. This is a promising finding, and a multicenter trial is currently underway to assess the efficacy of cerivastatin in reducing restenosis and clinical events post-angioplasty. If positive, this study may eventually lead to the use of such drugs immediately post-angioplasty in an attempt to improve long-term outcomes for these patients.(M Rembold, 2019)

3 .Dosing and Administration

The recommended dose for simvastatin is 10 mg/day in the evening. Patients who require more than a 45% reduction in LDL-C should be started on simvastatin 40 mg/day. A starting dose of 20 mg/day may be considered for patients who have substantial coronary heart disease (CHD) risk factors and whose LDL-C is not elevated and a goal of therapy is to lower LDL-C. High-dose (80 mg) simvastatin should be used only in those patients who have been taking this dose for 12

months or more without evidence of muscle toxicity. High-dose simvastatin has been associated with an increased risk of myopathy and should be avoided in the elderly, those with small body frames, frailty or other predisposing factors to myopathy. Regular monitoring of liver function is not necessary in patients who choose to take simvastatin. If at any time a patient develops transaminase elevations to greater than three times the upper limit of normal, these levels should be monitored until they return to normal. If an increase above three times the upper limit of normal persists, consideration should be given to the discontinuation of simvastatin. For patients who may consume excessive amounts of grapefruit juice, they should be informed of the potential risk of myopathy with simvastatin and avoidance of grapefruit juice can be considered a safety measure.
An effective approach to establish the most appropriate simvastatin dose is through titration and individualization of the dose in order to achieve a specific LDL-C goal. Dosage adjustment should occur at intervals of 4 weeks or more. After a several month period of treatment with a specific dose, LDL-C should be assessed to determine the need for further adjustment in dose to achieve the LDL-C goal. Health care providers should note that the effects of simvastatin on reducing the risk of CHD mortality and cardiovascular events is substantial at any given dose and incremental benefits are typically small when compared to its effects on the reduction of LDL-C. Therefore, these incremental benefits should be carefully weighed against the risk of myopathy, recognized as a possible dose-dependent side effect of simvastatin.(Giessing & Wang, 2021)

3.1 .Recommended Starting Dose

A recommended starting dose for simvastatin has not been included in the prescribing information from the manufacturers. This is not unusual for HMG-CoA reductase inhibitors, as the usual approach is to start with a dose that will achieve a reasonable percentage of the maximum response, and then to titrate the dose upward or downward as necessary. Such an approach is based on the generally good safety record of this class of drugs, and their predictable dose-response relationships. In the case of simvastatin, the maximum response is seen with approximately 30% inhibition of HMG-CoA reductase, as measured by reductions in LDL cholesterol levels. This level of inhibition is achieved with 10 mg/day of simvastatin, with further reductions in LDL cholesterol of about 6% for each doubling of the dose over the range of 10 to 80 mg/day. Data for this comes from both direct comparisons and indirect analyses across the simvastatin studies, and knowledge of the HMG-CoA reductase dose-response relationship commonly seen with other members of this drug class.
In the absence of specific dose ranging studies, the 10 mg/day starting dose appears to be the only one required for at least some patients, to achieve substantial LDL lowering. This is based on reports of results stratified by baseline LDL cholesterol level or cardiovascular risk, and the observed efficacy of 10 mg/day in selected secondary prevention patients. An on-treatment LDL cholesterol level has not been established for determining the minimal effective dose of simvastatin, but among the patients in the four secondary prevention studies, those who achieved values between 2.0-3.0 mmol/L had event rates that were not statistically different from those of the corresponding treatment groups, and these LDL levels were achieved with the 10 mg/day dose.

This would suggest that the 10 mg/day starting dose is appropriate for secondary prevention patients with moderate baseline LDL cholesterol levels.(Salari et al., 2018)

3.2 .Titration and Individualization of Dose

Though the starting dose for simvastatin may depend on concomitant drugs that may raise the risk for myopathy, it generally remains constant at 40 mg/day for the majority patients. However, in the SEARCH trial, merely about half of the patients attained their LDL cholesterol goal with the 40 mg/day dose. This argues in favor of beginning therapy for certain patients with a higher dose, provided that the safety of doing so is verified. Simvastatin was well tolerated and did not show extended benefit on atherogenesis over pravastatin in the regression phase of the PLAC-II trial.

Because the effective response to simvastatin administration is quite variable, dosing commonly must be adjusted to attain the preferred lipid ranges. The dose-response relationship for simvastatin was more linear than for atorvastatin in a recent equivalence trial, with roughly 6% additional reduction in LDL cholesterol for each doubling of the simvastatin dose. Therapy can therefore be personalized by advancing or dropping the dose in 5-10 mg increments to attain the preferred lipid levels. It is feasible that some patients may accomplish sufficient lipid reduction employing lesser doses than those used in the superiority trials, and the recent trend in the direction of using lower doses of simvastatin has been supported by cost-effectiveness investigation.(S. Alamri et al., 2019)

3.3 .Factors Affecting Dosing and Administration

Dietary intake can have a profound influence on the CYP450 enzymes. Grapefruit juice, for example, has been demonstrated to inhibit CYP3A4 metabolism. Therefore, if a patient consumes large quantities of grapefruit juice while taking simvastatin, it will lead to an increase in the serum concentrations of the drug as a result of reduced metabolism, increasing the risk of myopathy. Patients taking erythromycin, a known potent inhibitor of CYP3A4, in conjunction with simvastatin were found to have a 5-fold increase in simvastatin concentrations compared to those not taking erythromycin. The high doses of erythromycin used in this study also caused a 20-fold increase in the concentration of simvastatin hydroxy acid, which is obviously undesirable as stated previously, due to the greater potency and potential for adverse effects of the active form. This combination is particularly risky as it also increases the likelihood of hepatic injury. On the other hand, rifampicin, which is a potent inducer of CYP3A4, is likely to reduce the effect of simvastatin due to increased metabolism of the drug to its active form. This can be an advantage in a patient who is taking a high dose of simvastatin with normal liver function, but Sime et al. also reported a decreased hypolipidaemic response and increased myopathy in simvastatin users in the presence of rifampicin.

Simvastatin is a prodrug that undergoes complex transformation in the liver to form its active β-hydroxyacid form. There is evidence to suggest that simvastatin is first converted to its lactone form by the cytochrome P450 enzyme, CYP3A4. The lactone form then undergoes hydrolysis to the active β-hydroxyacid form. The lactone form of simvastatin may also possess some cholesterol-lowering activity. However, the hydrolysis of the lactone form occurs non-

enzymatically at a very slow rate compared to the first metabolic step and therefore the pharmacokinetics and pharmacodynamics of the lactone form are not clinically significant. CYP3A4 is responsible for the metabolism of the non-active simvastatin to its active form. Therefore, anything that affects this enzyme will have a direct impact on the effectiveness of simvastatin therapy, because a reduction in CYP3A4 activity will result in decreased production of the active β-hydroxyacid form and reduced cholesterol-lowering activity.

3.4 .Special Considerations for Different Patient Populations

Because the metabolism of simvastatin in the liver can be affected by certain patient factors, consideration of patient characteristics is critical in simvastatin dosing. Patients of Asian descent should be started on 5 mg/day due to an increased risk for myopathy at higher doses. The dose of simvastatin should not exceed 10 mg daily in patients taking amiodarone. Doses of simvastatin greater than 20 mg daily should not be used in patients on verapamil due to an increased risk for myopathy. The combined use of simvastatin at doses higher than 20 mg daily with lipid-modifying doses of niacin-containing products is not recommended in older patients due to an increased risk of myopathy. Simvastatin should be used with caution in the elderly (65 years old), women, and patients with kidney or thyroid problems, or a history of alcoholism. These patients are at a higher risk for developing myopathy while taking simvastatin. A history of liver disease may also predispose patients to developing myopathy while taking simvastatin and these patients should therefore avoid using large amounts of grapefruit juice or grapefruit products while taking simvastatin. Close monitoring for the signs and symptoms of myopathy is advised in these patients. If there is suspicion of myopathy while on simvastatin, it is recommended that creatine kinase (CK) levels be assessed, as these can sometimes be elevated in these patients.

4 .Drug Interactions and Adverse Effects

Potential interactions between drugs are an often overlooked potential cause of side effects in patients. Statins are generally well tolerated, but a higher incidence of adverse effects has been found in patients prescribed more than one medication. In a recent cross-sectional study conducted in the UK, involving 678 patients with a median age of 75 and who were receiving a prescription for primary prevention of CVD, it was found that 47.5% were prescribed a statin and of these, 57.5% were also receiving medication for hypertension, 21.9% for heart disease, and 25.6% for diabetes. This is relevant to the study of simvastatin due to its prolonged half-life compared to most statins and that it is metabolized by the P450 enzyme system in the liver. If a medication known to interfere with this enzyme system is taken concurrently with simvastatin, it may lead to an increased level of simvastatin and thus an increase in the risk of overdose and muscle toxicity. Verapamil and diltiazem are known inhibitors of the P450 system and if taken concurrently with simvastatin, have been shown to increase its concentration by 2.5-7.6 fold. As well as interaction with enzyme systems, there is a risk of drug interactions occurring on a pharmacodynamics level. An in vitro study by Patel et al investigated the possibility of NSAIDs reducing the lipid-lowering potency of simvastatin and found that the co-administration of ibuprofen caused an 11% reduction

at a daily dose of 20mg and a 51% reduction at a daily dose of 40mg. Although this has not been tested in a clinical setting, it raises the possibility of a significant reduction in the hypolipidemic effects of simvastatin if taken with NSAIDs. Considering the high prevalence of comorbidities in the target population of simvastatin, it is important that a wide range of potential drug interactions are monitored and considered. This is particularly relevant for patients receiving treatment in a hospital setting who are automatically at higher risk of adverse drug events due to the nature of increased drug administration. O'Kane et al investigated a selection of inpatients who were prescribed simvastatin and found that there was a high incidence of prescribing drugs known to interact with simvastatin, and a significant decrease in liver function was observed in 40% of the patients after the drugs were prescribed. This shows that the monitoring of drug interactions in patients taking simvastatin is important and it is necessary to discontinue administration if evidence of liver toxicity is found. In consideration of these findings, it is advisable that prescribers take into account the disadvantages of prescribing multiple medications with simvastatin and weigh it up against the clinical benefit that the patient will gain.(B. Hunter et al., 2021(

4.1 .Potential Drug Interactions with Simvastatin

HMG-CoA reductase inhibitors, the class of lipid-lowering drugs to which simvastatin belongs, are known to have numerous drug interactions, often related to the metabolism of these drugs via the cytochrome P450 system. Specifically, simvastatin is metabolized to its active form, simvastatin hydroxy acid through the cytochrome P450 3A4 pathway. Drugs that are inhibitors of this enzyme have the potential to increase plasma concentrations of simvastatin and its active form leading to an increase in the occurrence of myopathy and rhabdomyolysis. Macrolide antibiotics, azole antifungal agents, protease inhibitors, nefazodone, and grapefruit juice are all strong inhibitors of the cytochrome P450 3A4 system, thus their co-administration with simvastatin is contraindicated. Many of these drugs interact with simvastatin as a result of the UK marketing and POM to P switch of simvastatin; some examples of these interactions were seen as so serious that the Medicines and Healthcare products Regulatory Agency (MHRA) has issued drug interaction safety alerts to healthcare professionals. Patients taking simvastatin are advised to avoid excessive consumption of grapefruit juice and where necessary be prescribed a lower dose of simvastatin and/or a more suitable alternative to drugs that are contraindicated to co-administer with simvastatin. A similar but less severe interaction has been seen between simvastatin and amiodarone, verapamil, diltiazem, and amlodipine. This group of drugs are all moderate inhibitors of cytochrome P450 3A4 and as a result co-administration will also increase plasma concentrations of simvastatin, thus increasing the risk of adverse effects. Unlike the strong inhibitors, it is still acceptable to co-administer this group of drugs with simvastatin; however, close monitoring for adverse effects is recommended and an increase in the dose of simvastatin is to be avoided.(Foll et al., 2014)

4.2 .Common Adverse Effects

The adverse effect of highest relevance to patients is myopathy, manifesting as muscle pain, weakness and in severe cases, muscle destruction. The incidence of mild myopathy is around 3% and clinically significant myopathy at about 0.5%. CK levels should be measured before treatment initiation in high-risk patients (elderly, small body frame, multiple co-morbidities, interacting drugs) and re-checked if patients subsequently develop unexplained muscle symptoms. If CK levels become more than 5 times the upper limit of normal, or patients develop severe muscle symptoms, treatment should be stopped. Myopathy is dose-related and occurs more frequently when simvastatin is co-administered with drugs which increase simvastatin plasma concentration. These drugs include fibrates, itraconazole, ketoconazole, erythromycin, clarithromycin, ritonavir, lopinavir, and ciclosporin. The choice of an alternative HMG-CoA reductase inhibitor less interactive at the CYP3A4 enzyme may be preferable in these cases.(Chiang et al., 2019)
Simvastatin is generally well tolerated but has the potential to cause a variety of adverse effects. Most adverse effects are mild, but some have the potential to be serious, and it is important for prescribers to balance the clinical benefits of lipid-lowering and risk of adverse effects. In the 4S study, 5% of patients assigned simvastatin withdrew from the study due to adverse effects, compared to 3.8% in the placebo group. Myopathy was the most common reason for withdrawal from simvastatin therapy.

4.3 .Serious Adverse Effects and Monitoring

Severe rhabdomyolysis and myopathy, including immunoglobulin E (IgE)-mediated necrotizing myopathy, have presented infrequently, and in unspecified numbers of patients, particularly in Chinese patients. Simonson stated that since simvastatin is a lactone, it could have been imported in toxic amounts since other statins have not been shown to cause muscle necrosis. Eighty-five percent of these patients admitted to using a concurrent CYP3A4 inhibitor. Deng et al. reported on twenty-eight Chinese patients, and stated that simvastatin was contraindicated in Chinese patients, at any dose. They added that any patient started on simvastatin should be genotyped for SLCO1B1*5, given the associated risk with muscle toxicity. Dufour et al. reported on a case of rhabdomyolysis in an obese woman, secondary to excessive ingestion of grapefruit, with a juice fasting regimen, who took simvastatin 40 mg daily. The patient did not have renal disease and was not using drugs interacting with simvastatin metabolism. Rhabdomyolysis has also been reported in Filipino and Hispanic patients taking simvastatin, on doses as low as 5 mg daily. High dose simvastatin (80 mg) was shown to increase risk of muscle injury in a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Due to an increase in proteinuria and neuropathy, the trial was terminated early, and the target LDL-c level in patients was lowered from 2.6 mmol/L to 1.8 mmol/L. A meta-analysis of the five trials found an approximate 5-fold increase in the incidence of rhabdomyolysis for simvastatin 80 mg compared to 20 mg daily (0.55% versus 0.11%, $p<0.001$). Subsequent to these findings, a health advisory was issued by the FDA that high-dose simvastatin increased risk of muscle injury and should not be prescribed new patients due to increased risk of myopathy compared to lower doses and other statins.(Zhang et al., 2018)

5 .Disscition

In the current study, the pharmacokinetics of simvastatin and its main active metabolite, simvastatin acid, were investigated. The possible influence of genetically determined differences in the CYP-mediated metabolism of simvastatin on drug safety and cholesterol-lowering efficacy was specifically studied. In a second part of the study, the new double isotope tracer method was used to assess whole body HMG-CoA reductase inhibition by simvastatin. We used a high and a low dose of simvastatin to obtain different degrees of inhibition to detect possible dose effects. Since the inhibition of HMG-CoA reductase was the only effect studied in this part of the project, and no effect on cholesterol synthesis effected by other metabolic pathways was measured, it is not possible to directly relate these findings to changes in cholesterol levels. The following discussion is focused on the pharmacokinetic characteristics of simvastatin and its metabolite and their potential clinical implications. The discussion of the new double isotope tracer method and measurement of HMG-CoA reductase inhibition will be kept separate from the pharmacokinetic findings and will be presented in a related report. Simulation studies to elucidate clinical dose regimens that would enable efficient HMG-CoA reductase inhibition with minimal dosage will also be a subject for further discussion in later reports.(Foll et al., 2014)

6 .Conclusion

Simvastatin is an effective hypocholesterolemia drug with few side effects and a wide therapeutic window. The pharmacokinetics of simvastatin are complex and doses of 5, 10, 20, 40, and 80 mg given in the active form are poorly understood. Noseda et al. showed that simvastatin undergoes extensive first-pass extraction in the liver before reaching the systemic circulation. Although the major form of the drug is the inactive lactone, the hydroxy acid metabolite is the active form of the drug.

Hussein et al. found the bioavailability of simvastatin reduced 85% when given with grapefruit juice taken one hour before the dose and 49% when juice was taken simultaneously with the drug. Grapefruit juice is known to inhibit CYP3A4, which is responsible for the first step in the metabolism of simvastatin to the active form. This explains the large reduction in bioavailability as simvastatin becomes much less effective when the metabolic pathway to the active form is inhibited. (August et al., 2006)

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