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Pharmacokinetic of simvastatin study in Malaysian subjects

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Abstract:- The pharmacokinetic of simvastatin 40 mg tablet was assessed in 9 healthy Malaysian male subjects after a single oral dose in Pinang Hospital, Malaysian. Blood samples were collected at specified time intervals, plasma separated and analyzed for simvastatin using validated LC-MS-MS method at unversiti sains Malaysia. The pharmacokinetic parameters AUC_{0-24} C_{max}, T_{max}, $t_{1/2}$, K_e, Cl and V_d were determined from plasma concentration-time profile for simvastatin. The results of this current method were consistent with other methods previously reported.

Keywords:- Malaysian subjects, Pharmacokinetic study, Simvastatin

I. INTRODUCTION

Cardiovascular disease is an increasingly important health problem in Malaysia. It is the most common cause of death reported in government hospitals [1]. The majority of these cases are due to coronary heart disease (CHD), of which hyperlipidaemia is one of the major risk factors. The primary and secondary prevention of CHD should therefore be directed against hyperlipidaemia as well as the other risk factors. However, dietary modifications, cessations of smoking, exercise and weight reduction form the cornerstone of coronary prevention strategy. Where appropriate, pharmacotherapy with lipid modifying statin drugs should be instituted. Therefore, simvastatin is one of the major four most important drugs used to treat hyperlipidaemia. Simvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, is an established drug treatment for hypercholesterolemia. At doses of 10, 20 and 40 mg/day, it produces a substantial reduction in low density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG), and a modest increase in the cardio protective high density lipoprotein cholesterol (HDL-C) [2-3]. Simvastatin at 20 and 40 mg/day has been shown to improve survival in patients with CHD. The majority of simvastatin studies have used doses of 10, 20, or 40 mg/day; however, a dose of 80-mg/day may provide additional reductions in LDL-C and a more substantial increase in HDL-C [4-5].

Most published studies on the pharmacokinetics of simvastatin have been done on animals and Western populations. Indeed, many of the internationally accepted guidelines for cholesterol management are not based on local pharmacokinetic data. In this study the work will be concerned on pharmacokinetic of simvastatin with fasting healthy Malaysian male subjects.

II. METHODS

2.1 Subjects and study design

Nine healthy Malaysian male subjects participated in this study were consenting healthy males between ages of 22 and 49 years (all non smokers). The subjects were informed that they could withdraw from the study any time. Subjects were 18 years of age or older and were in good health as assessed by history, physical examination and laboratory studies. The study protocol of oral single dose 40 mg simvastatin following guidelines of the Helsinki Declaration of 1975 and its amendments was approved by the Ethics Committee of the joint Pinang Hospital/School of Pharmaceutical Sciences, Universiti Sains Malaysia Committee on Bioavailability Studies. Written informed consent was obtained from each subject before entering the study.

The fasting subjects were given a single dose of 40 mg tablet of simvastatin at 8.00 a.m., with 200 mL of water after 10-hour overnight fast. Blood samples were drawn 10 mL into a labeled glass tubes immediately before administration of simvastatin and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after administration. Tubes were inverted to ensure proper mixing with anticoagulant and left for 30 minutes then centrifuged at 3000 rpm for 15 minutes. The plasma was isolate from whole blood by centrifugation at 3000 rpm and then transferred into a glass tube, placed in a freezer -20^0C until frozen, and then stored in a -85^0C freezer until analysis.

2.2 Sample analysis

Simvastatin was quantified by liquid chromatography tandem mass spectrometry (LC-MS-MS). The simvastatin was extracted from serum using ethyl acetate and hexane (90/10%, v/v) by using lovastatin as internal standard. The solutes were separated on a C_{18} column with mobile phase consisting of mixture of acetonitrile and 3 mM formic acid (75/25%, v/v) at flow rate 500 µL/min. For quantitation in the selective reaction monitoring (SRM) in positive ion mode, the daughter ions m/z 325 for simvastatin and m/z 285 for lovastatin were used. Parent ions in positive ion mode were m/z 441.3 for simvastatin and m/z 405.1 for lovastatin. The lower limit of quantitation of 0.25 ng/mL was achieved. The within day coefficient of variations were less than 14.00% and the accuracies were between 90.00 and 109.33%. The day-to-day coefficients of variation were less than 10.00% and accuracies were between 97.70 and 106.60%.

2.3 Pharmacokinetic Analysis and Statistical Analysis

The pharmacokinetic of simvastatin was characterized by peak concentration in serum (C_{max}), concentration peak time (T_{max}) and area under the concentration-time curve from time zero to the last quantifiable plasma concentration (AUC_{0-t}) was calculated using the linear trapezoidal rule for each incremental trapezoid. The apparent terminal elimination rate constant K_e was derived from the log linear disposition phase of the concentration time curve using least squares regression with visual inspection of the data to determine the appropriate number of terminal points to calculate K_e, not less than 4 points. The apparent terminal phase elimination half-life ($t_{1/2}$) was calculated as $ln_{(2)}/K_e$.

The data are expressed as mean values ± SD, except for T_{max} which is expressed as median with range.

III. RESULTS

Nine subjects completed the study. There are no adverse effects were observed during the treatment. Biodata of nine subjects were shown in "Table" 1. The mean plasma of 40 mg simvastatin tablet concentration versus time profile of subjects after dosing with fasting, state is shown in "Fig". 1. "Table" 2 lists the pharmacokinetic parameters derived in this current study.

The AUC_{0-24} ranged from 6.20 to 15.86 $ng.mL^{-1}hr$. The mean (± SD) AUC_{0-24} of the simvastatin was 10.90 ± 3.21. The peak concentration ranged from 0.93 to 4.96 ng/mL. The mean (± SD) C_{max} of the simvastatin was 2.61 ± 1.42. The mean observed T_{max} for simvastatin was 1.33 hr ± 0.71. The half-life obtained in this study was 3.16 ± 1.68. The mean observed K_e (elimination rate) determined for simvastatin was 0.29 ± 0.16. The mean observed V_d (volume distribution) determined for simvastatin was 232.57 ± 132.54. Finally, the mean observed Cl (clearance) determined for simvastatin was 52.59 ± 23.87.

IV. DISCUSSION

The principle of this study have provided a means of quantitatively assessing simvastatin lactone form absorption and this assessment has shown that, for simvastatin, only a small and sometimes variable fraction of the administered dose is absorbed. Indeed, much of the variability in the response of certain drugs can be attributed to variability in the rate as well as the extent of drug absorption from various drug products (i.e the bioavailability). Therefore, bioavailability testing must be a primary consideration in the quality control of drug products.

There are many factors for incomplete absorption and for variation in the rate and extent of absorption. These include the food eaten by the patient, the effect of the disease state on drug absorption, the age of the patient, the site(s) of absorption of the administered drug, the co-administration of other drugs, the physical and chemical properties of the administered drug, the type of dosage form, the composition and method of manufacture of the dosage form, the size of the dose and the frequency of administration [6-8].

Bioavailability is pharmacokinetic term that describes the rate and extent to which the active drug ingredient is absorbed from product and becomes available at the site of drug action. The definition would not be valid in the case of prodrugs, whose therapeutic action normally depends on their conversion into a therapeutically active form prior to or on reaching the systemic circulation. It should also be noted that, in the context of bioavailability, the term systemic circulation refers primarily to venous blood (excluding the hepatic portal vein, which carries blood from the gastrointestinal tract to the liver in the absorption phase) and the arterial blood, which carries the intact blood to tissues. Therefore, for a drug which is administered orally to be 100% bioavailable, the entire dose must move from the dosage form to the systemic circulation. However, the drug must be completely released from the dosage form, fully dissolved in the gastrointestinal fluids, stable in the solution of the gastrointestinal fluids, pass through the gastrointestinal barrier into mesenteric circulation without being metabolized and pass through the liver into the systemic circulation unchanged [9-10].

Simvastatin is an inactive prodrug which is well absorbed (60 to 80%) in animal and humans studies, but undergoes extensive first pass hepatic metabolism following oral administration [2,3,11]. 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 [2,3,11]. 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 organ responsible for synthesis of most endogenous cholesterol [3]. Bioavailability of the simvastatin was less than 5% relative to that after intravenous administration of the simvastatin [2,11]. In general, AUC of active inhibitors increased linearly with increasing oral simvastatin doses over the range of 5 to 120 mg in healthy volunteers [11]. Simvastatin and its corresponding β-hydroxy acid metabolite are approximately 95% bound to human plasma proteins [2,3,11]. The elimination half-life of the major active β-hydroxy acid metabolite is 1.9 hours and total body clearance is 31.8 L/h [11].

When a drug is given intravenously it is administered directly into the blood, and therefore we can be sure that the entire drug reaches the systemic circulation. The drugs are therefore said to be 100% bioavailable. However, if a drug is given by another route there is no guarantee that the whole dose will reach the systemic circulation intact. The fraction of an administered dose of the drug that reaches the systemic circulation in the unchanged form is known as the bioavailable dose. The relative amount of an administered dose of a particular drug that reaches the systemic circulation intact and the rate at which this occurs is known as the bioavailability. Variability in the bioavailability exhibited by a given drug from different formulations of the same type of dosage form, or from different types of dosage forms, or by different routes of administration, can cause the plasma concentration of the drug to be too high and therefore causes side effects, or it may be too low and therefore the drug will be ineffective [7,12].

To the best of the researcher's knowledge, one of the studies which had been performed in Jordon (Middle East), addressed and compared the pharmacokinetic profiles of simvastatin single dose 40 mg in healthy fasting volunteers [13]. Meanwhile, our current study revealed that pharmacokinetic parameters results (AUC, C_{max}, T_{max}, $t_{1/2}$ and K_e) were similar to the above mentioned study. However, other studies, in China [14] and in Japan [15] showed that the value of C_{max} was higher than the value of the current study. While the $t_{1/2}$ value in China and Japan studies was similar to the value of the current study.

Simvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, is administered in the form of lactone prodrug. The lactone ring is hydrolyzed *in vivo* to produce the hydroxyl acid derivatives which are the pharmacologically active forms of this drug, and this is believed to take place predominantly in the liver [2,3,11].

Since lactone hydrolysis reactions are strongly accelerated by general acid catalysis, [16] it is anticipated that conversion of lactone into its hydroxyl acid may occur in the strongly acidic gastric environment. Obviously, the desirable tissue selectivity of the lactone form is not realized if hydrolytic conversion in the GIT occurs rapidly relative to lactone absorption. In addition, *in vitro* study showed that the lactone form in aqueous solution is susceptible to pH dependent hydrolysis at pH 2 [17]. The maximum stability of lactone form is at pH 5 and no degradation of the lactone in 24 hours at pH 5 was observed [16]. Thus, the study presented herein is to determine the rate and extent of simvastatin lactone form prodrug absorption under fasting condition.

Drug stability in the GI fluids may also play a role in the efficiency of absorption of a given dose of a therapeutic agent. Drugs must remain sufficiently stable, not only during storage, but also in the gastrointestinal fluids, since reactions which result in a product that is pharmacologically inactive or less active will reduce biological availability and therapeutic effectiveness. Generally, the most important reactions that drugs undergo in the gastrointestinal tract are acid and enzymatic hydrolysis [6,18].

Fasting tends to decrease the pH of gastric fluids [19]. The values of gastric pH in the fasted state can fluctuate on a minute to minute basis over the range pH 1 to pH 7, but in healthy young Caucasians gastric pH lies below pH 3 during 90% of the fasted state [19], with an interquartile range of pH 1.4 to pH 2.1.

One study that has been conducted by Cheng *et al* (1992) showed that the effect of simvastatin on 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. The results showed that total of HMG-CoA reductase inhibitors were 40 to 60% higher in elderly than younger and 20 to 50% higher among female than male. The time to achieve peak plasma concentration of active and total HMG-CoA reductase inhibitors was not significantly affected by age or gender. But this effect was explained in more detail by Russell *et al* (1993). They state that achlorhydria (the absence of gastric acid secretion) is more in elderly (60-70 years) than younger (20-30 years), pH of gastrointestinal tract in elderly between 5 to 6, so the lactone form of simvastatin is stable at this pH.

Additionally, Mauro, (1993) reported the results from studies performed in the United Stated and Europe. He states that the daily doses of simvastatin 10 and 40 mg reduce total plasma cholesterol by 20 and 30%, respectively. While, studies performed with Japanese patients indicate that an approximately 20% reduction in cholesterol occurs with a 5 mg daily dose of simvastatin. This difference in effect has been attributed to differences in genetic and physical factors [22]. But this effect was explained in more detail by

Russell *et al*., (1993). He states that the incidence of achlorhydria appears to be much higher in Japanese people than European and American people. In addition, in Japanese people a 60% incidence of elevated gastric pH even in the 55 to 59 age bracket, whereas most of the European and American studies report incidences well below 5% in a similar age range.

Finally, the study was performed in young men (age 31 ± 9.3 years), not in patients who often receive other medications that may have different influences on absorption of simvastatin under fasting. Furthermore, plasma simvastatin level after a single-dose administration under fasting was used, which may not be readily predictive of the magnitude of corresponding change in electro-physiologic effects of the drug in clinical situations. This current study is recommended further clinical studies of the in patients who often receive other medications and elderly age should be explored.

V. CONCLUSION

The pharmacokinetic study of simvastatin 40 mg tablet was done in nine fasting healthy Malaysian male subjects. The parameters were determined from plasma concentration-time profile for simvastatin.. The results were consistent with other results previously reported

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Table 1 Biodata of 9 healthy volunteers

Volunteer	Age (year)	Weight (kg)	Height (cm)	Body Mass Index (BMI)
V1	49	58	163	21.8
V2	40	55	165	20.2
V3	22	67	169	23.5
V4	33	70	162	26.7
V5	24	85	167	30.5
V6	23	64	170	22.2
V7	22	67	170	23.2
V8	31	78	179	24.3
V9	34	70	163	26.4
Mean	**30.89**	**68.22**	**167.56**	**24.31**
± SD	**9.31**	**9.24**	**5.29**	**3.12**

Table 2 Pharmacokinetic parameters of simvastatin in 9 Malaysian volunteers after 40 mg oral simvastatin in fasting group

PK parameters	V1	V2	V3	V4	V5	V6	V7	V8	V9	Mean	(±SD)
K_e (/hr)	0.16	0.3	0.11	0.61	0.18	0.23	0.18	0.47	0.35	**0.29**	**0.16**
$t_{1/2}$ (hr)	4.30	2.20	6.50	1.14	3.93	3.10	3.80	1.48	1.97	**3.16**	**1.68**
AUC $_{0\text{-}24}$ (ng.mL^{-1}.hr)	15.86	6.20	8.95	12.70	10.93	6.97	10.40	14.40	11.70	**10.90**	**3.21**
C_{max} (ng/mL)	2.13	1.23	0.93	3.90	1.90	1.86	2.33	4.28	4.96	**2.61**	**1.42**
T_{max} (hr)	1.00	1.00	3.00	1.00	1.00	1.00	1.00	2.00	1.00	**1.33**	**0.71**
V_d (L/Kg)	223.00	335.30	463.90	71.10	194.90	341.80	260.39	71.73	130.99	**232.57**	**132.54**
Cl (L/hr)	35.94	105.60	49.50	43.20	34.40	77.40	47.60	33.60	46.10	**52.59**	**23.87**

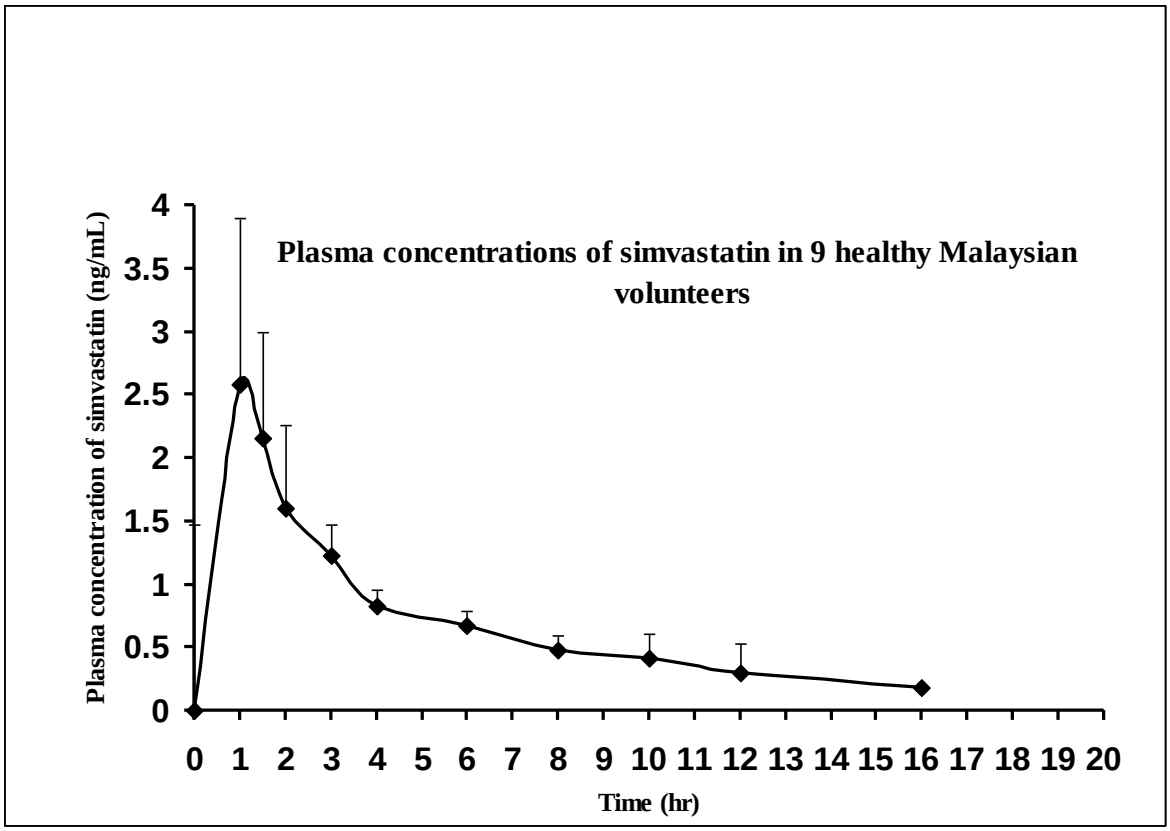

Figure 1. The mean plasma concentration versus time plot for simvastatin. Mean ± SD, N=9