CHAPTER I

INTRODUCTION

Gemfibrozil , a lipid regulating agent which is generally classified as fibric acid derivative. Its chemical structure related to clofibrate but its pharmacological effects are different. Several studies indicated that gemfibrozil in the oral dose of 800-1600 mg/day is particularly effective in reducing total plasma triglyceride , very low density lipoprotein (VLDL), low density lipoprotein (LDL) and increasing high density lipoprotein (HDL) in patient with all types of dyslipidemia characterized by hypertriglyceridemia (except type I). Furthermore, gemfibrozil is also postulated to reduce the incidence of coronary heart disease . The drug is well tolerated in most patients. Gastrointestinal side effects is the most frequent symptomatic complication. There is no report of serious side effect. Because of the advantage of more potency and fewer side effects, gemfibrozil appears to be more available use in the treatment of patients with hyperlipidemia.

In Thailand, no less than eight different brands of gemfibrozil capsule are available in the market. One is the original product with high retail price, and the others are local manufactured products. The available of similar products from various manufacturers frequently has created the situation that health care persons must select one from several apparently equivalent products.

Because of the benefit of drug treatment upon the delivery of active drug in systemic circulation to the site of action , the alteration

of rate and extent of active drug reaching the systemic circulation or " bioavailability " would then affect the pharmacodynamic or toxicity of the drug. The rate and extent of drug absorption can be affected by various factors. The main one is the formulation factors which play an important role in controlling drug absorption. Drugs with pharmaceutical equivalence may not necessarily be absorbed in the same rate and extent owing to its individual formulation technique. Therefore, the concept of determining the bioequivalence between the well-accepted original product and the new local manufactured product is considered to be the regulation for evaluation of any new brands of pharmaceutical equivalent products. Gemfibrozil, as already mentioned contains a variety brands of local manufactured products that have never been reported for their bioequivalence and pharmacokinetic in Thais. Therefore, it is very interesting to conduct the experiment for determining the bioequivalence of one selected local brand gemfibrozil and the original product and also additionally determines the pharmacokinetic of gemfibrozil in Thai subjects.

Objectives of the study

1. To compare the bioavailability of one brand local manufactured product of gemfibrozil capsule to that of the original product.

2. To determine the pharmacokinetic parameters of gemfibrozil capsule after single oral administration in Thai healthy male volunteers.

Significance of the study

1. This study will provide bioavailability data of gemfibrozil capsule that would be a useful information for drug health care facilities in selecting more cheaper product which is bioequivalent to the original one.

2. This study will provide the pharmacokinetic of gemfibrozil following an oral administration in Thai healthy male volunteer, which would be useful for determining the optimum dosage regimen in certain patients.

REVIEW OF GEMFIBROZIL

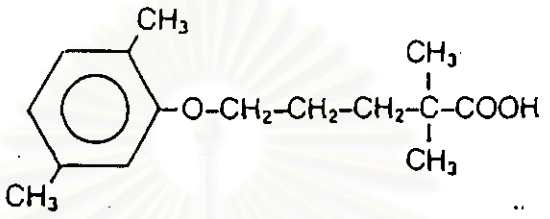

Figure 1 Chemical structure of gemfibrozil

1. Physicochemical Properties

Gemfibrozil, a nonhalogenated phenoxypentanoic acid , is 5-(2, 5-dimethylphenoxy) -2, 2-dimethylpentanoic acid. Its empirical formula is $C_{15}H_{12}O_{23}$. The chemical structure was depicted in Figure 1 appear as a white crystal compound with a molecular weight of 250.35 and a melting point of 58-61 °C. It is practically insoluble in water , slightly soluble in dilute alkaline and soluble in alcohol , chloroform and methyl alcohol. It contains acidic properties with the pKa value of 4.7. It is stable under room temperature (Reynolds, 1994 ; Gennaro ,1995).

2. Pharmacokinetics

Few reports on pharmacokinetics of gemfibrozil after oral administration in man were published. They were all conducted in healthy male volunteers in which they can be summarized as follows :

2.1 Absorption

Gemfibrozil is well absorbed from gastrointestinal tract after oral administration. Peak plasma concentration (Cmax) occured within 1-2 hours (Tmax) after drug administration. The mean peak plasma concentration of gemfibrozil in single oral administration at the dose of 600 mg was observed to be approximately 26 μg/ml. The plasma drug concentration is directly proportional to the dose and do not show accumulation following multiple dosing (Okerholm, et al., 1976 ; Smith, 1976 ; Knauf, Kölle and Mutschler, 1990).

2.2 Distribution

The in-vitro experiment demonstrated that gemfibrozil was highly bound to plasma protein (~ 99.0%) with the most binding to albumin (~ 97.0-98.6%). Approximately 0.8% of the drug was bound to erythrocyte but the binding to alpha-1 acid glycoprotein , lipoprotein and gamma-globulins were measured as negligible. The distribution of gemfibrozil to tissue and transferring of drug into breast milk or across the placenta have not been reported in humans. In contrast to animal studies, gemfibrozil can be transferred to monkey's placenta with fetal plasma gemfibrozil concentration being 1.47 times that of maternal plasma

and significant level of drug found in all fetal tissues and vital organs (Hamberger, et al., 1986 ; Todd and Ward, 1988).

2.3 Elimination

The elimination of gemfibrozil was studied in both animal and human experiment. The experiments that were studied including rats, dogs and monkeys. The data obtained from cannulated rats , dogs and monkeys indicated that there has been enterohepatic recycle whereby gemfibrozil and metabolites were excreted in bile and undergo intestinal reabsorption. (Okerholm, et al., 1976)

In human studies, oral administration of a tritiated dose of gemfibrozil after achieving steady-state (7 days) with 600 mg twice daily in healthy subjects showed that 66% of tritiated dose was recovered in urine within 48 hours and approximately 6% was recovered in feces over 5 days. Approximately 82.5% of the radioactivity in urine represented gemfibrozil (48%) , metabolite I (2.3%) , II (2.6%) , III (18.8%) and IV (10.7%). From this study, the metabolic pathway of gemfibrozil was also studied. The biotransformation of gemfibrozil in human can be proposed to contain three major metabolic pathways. Both phase I and phase II were hepatic biotransformation in which a number of oxidative metabolites and glucuronide conjugates were formed. Three metabolic pathways of gemfibrozil in man as depicted in Figure 2 was mainly involved with the hydroxylation process at different functional group. The first pathway has involved the hydroxylation at meta-methyl group of gemfibrozil to metabolite II which undergoes rapid oxidation to metabolite III . The second pathway has involved hydroxylation at aromatic ring of gemfibrozil to metabolite I and the third pathway has involved

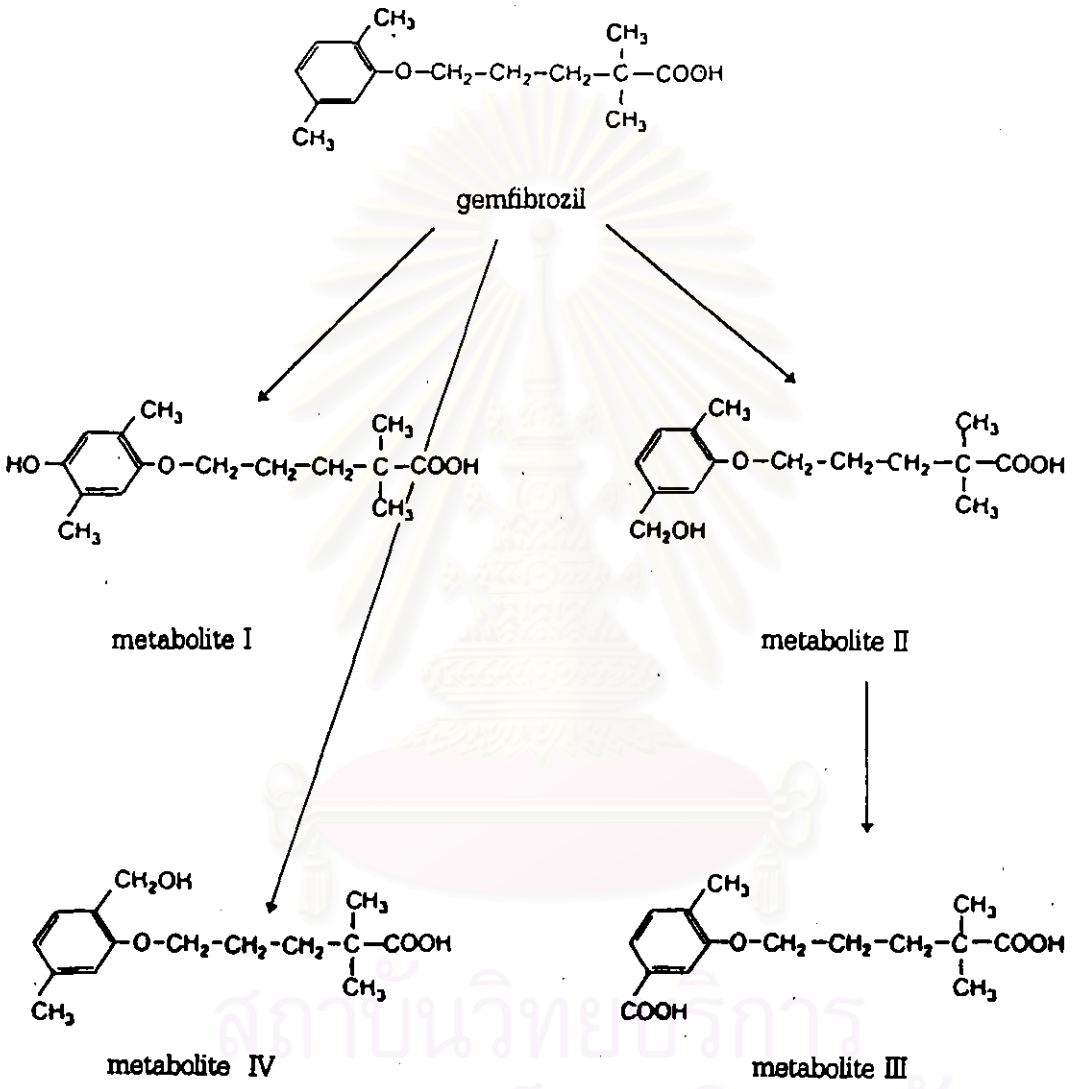

Figure 2 Metabolic pathway of gemfibrozil

hydroxylation of the ortho-methyl group of gemfibrozil to metabolite IV. All metabolites and its parent drug formed glucuronide conjugate in phase II reaction which were mainly excreted in urine. Only metabolite III was excreted in the unconjugated form to a significant degree in the urine (Okerholm, et al., 1976 ; Todd and Ward, 1988)

After administered a single oral dose of 600 mg gemfibrozil to healthy subjects , the elimination phase was characterized by a virtually loglinear declined of the plasma level up to 8 hours . The half-life of this time course was calculated to be 1.5 to 2.0 hours. After eight hour, the terminal elimination phase was appeared with the half-life of 6.5 to 7.9 hours (Okerholm, et al., 1976 ; Todd and Ward,1988 ; Knauf, et al., 1990).

3. Effect of renal and hepatic diseases on the elimination of gemfibrozil

There are only two studies so far that described the elimination of gemfibrozil affecting from renal or hepatic diseases (Evan , Forland and Cutler , 1987 ; Knauf , et al ., 1990)

Evan et al (1987) studied the effect of renal function on the pharmacokinetic of gemfibrozil following single and multiple oral doses. Approximately 17 male patients aged 57 to 74 years old selected for various levels of renal function, including end-staged renal disease. Patients received 600 mg of single oral gemfibrozil. The venous blood samples were collected up to 96 hours for serum gemfibrozil determination. Seven to 14 days later, the patients started receiving gemfibrozil 600 mg twice daily. Venous blood samples were obtained over the following 10 days. On day 11^{th} (final day) , blood samples were

collected up to 96 hours. The result showed that peak gemfibrozil concentration (Cmax) was 11.1 ± 3.9 mg/L (mean ± SD) for the single dose and 10.2 ± 3.8 mg/L for multiple dose study. Time to peak concentration (Tmax) was 2.1 ± 2.0 hrs and 1.8 ± 0.6 hrs, respectively. The mean elimination half-life in single dose study was 6.4 ± 11.8 hrs compared with the multidose study of 3.0 ± 3.1 hrs , (the mean elimination half-life was obtained from patients demonstrating monoexponential and biexponential elimination). It did not show statistical significance (p=0.25). The difference between the area under the concentration time curve (AUC) for the single versus the multiple dose study approached statistical significance (p=0.054). The coefficience of determination for renal creatinine clearance versus the plasma clearance of oral gemfibrozil was 0.009 (p=0.72) for single dose regimen and 0.331 (p=0.016) for multiple dose study. From this result, it could be concluded that the half-life of gemfibrozil was independent of renal function for both single and multiple dose regimens. Dosing schedule do not change in renal insufficiency.

More recently, Knauf et al (1990) studied the effect of renal or hepatic diseases on the elimination of gemfibrozil. Patients with either renal (n=8) or hepatic disease (n=8) and healthy volunteers (n=6) were selected. Single oral dose of 600 mg gemfibrozil was administered to every subjects. Venous blood samples were collected up to 36 hours after dosing. The peak gemfibrozil concentration was 46.1 ± 15.8 μg/ml and the time to peak concentration was 2.2 ± 1.1 hrs for healthy volunteer. In chronic renal failure and in liver cirrhosis the plasma concentration of gemfibrozil were not significantly different from a control group except in patients who concurrently took antacids. Cmax and AUC was significantly lower than control in these patients. The elimination half-life

was calculated within 8 hours. It was 1.5 , 2.4 and 2.1 hour in control group , renal failure and liver disease, respectively. It can be concluded that the elimination of gemfibrozil is not significantly influenced by renal or hepatic failure.

However, the manufacturer lists severe hepatic or renal dysfunction as a contraindication for the use of gemfibrozil (Warner-Lambert, 1982 cited in Todd and Ward,1988).

4. Mechanism of Action

The sites of action of gemfibrozil were partially established. Nevertheless , its mechanism of actions in decreasing plasma VLDL-triglyceride, plasma LDL-cholesterol and increasing HDL-cholesterol is still controversy.

In vitro studies, in rat's and human's adipose tissue studies the different results was observed at high therapeutic concentration of gemfibrozil. Gemfibrozil inhibited the basal lipolysis in rat's adipose tissue while it produced inconsistent effect on basal lypolysis in human adipose tissue (Carlson, 1976 ; Rodney, Uhlendorf and Maxwell, 1976).

The in vivo oral administration of gemfibrozil to rats at usual dose resulted in decreasing the incorporation of long chain fatty acids into newly synthesized triglycerides and thus decrease the hepatic systhesis of very low density lipoprotein (VLDL) fraction. It also decreased the synthesis of VLDL carrier apoprotein, so VLDL in systemic circulation decreased (Rodney, et al., 1976).

The mechanism of action of gemfibrozil has been investigated in several studies with dyslipidemia patients. The drug markly decreased plasma triglycerides level due to increase clearance of lipid from plasma. Lipoprotein lipase activity was stimulated so the catabolism of VLDL was promoted (Bremner, et al., 1976; Nikkilä, Ylikahri and Huttunen, 1976). More recently report indicated that the activity of lipoprotein lipase in normolipidemic subjects was also decreased by gemfibrozil (Horsmans, et al., 1993). Gemfibrozil may also decrease hepatic extraction of free fatty acid and thus reduce hepatic triglycerides synthesis (Kesaniemi and Grundy, 1984). In addition, the drug may also increase the capacity of intracellular triglyceride synthesis that can cause the increment of lipoprotein activity (Baldo, Sniderman and Cianflone, 1994).

It is still not clearly characterized that which of these afore mentioned action of gemfibrozil are primary or secondary drug related effect.

For the machanism of action that increase high density lipoprotein (HDL). Gemfibrozil is believed to raise HDL-cholesterol indirectly as a result of the decrement in the concentration of VLDL-triglyceride. VLDL normally exchanges lipids with HDL , the triglycerides of VLDL moving to HDL and the cholesteryl ester of HDL moving to VLDL. When VLDL concentration is reduced, this exchange is slow. Cholesteryl esters remain in HDL and thus the concentration of HDL-cholesterol increases.

The mechanism of gemfibrozil lower LDL-cholesterol is not known, but it may involve the enhancing of hepatic clearance of VLDL which would reduce the production of low density lipoprotein (LDL) (Gilman, 1991).

5. Pharmacological Effect

Oral administration of gemfibrozil to normolipidemic subjects causes significant change in plasma lipid. The concentration of triglycerides and total cholesterol decreases , and that HDL-cholesterol increases (Samuel , 1983).

Several previous studies stated that gemfibrozil has been shown to decrease LDL , VLDL and increase in HDL level in patients with type II a , II b and IV hyperlipidemia. The degree of these changes appeared to be proportional to dosage of gemfibrozil and duration of administration. Gemfibrozil appeared to be more effective in lowering triglycerides level than cholesterol level. The reduction in cholesterol level was significant only in patients with hypercholesterolemia (Eisalo and Manninen , 1976 ; Lageder and Irsigler , 1976 ; Wilkening and Schwandt , 1976 ; Nye , Sutherland and Temple , 1980 ; Fenderson , et al., 1982 ; Lewis , 1982 ; Nash , 1982b ; Manninen , 1985 ; Vaga and Grundy, 1985 ; Ojala , Helve and Tikkanen , 1990).

6. Adverse Effect

Gemfibrozil is well tolerated in most patients. No serious or life-threatening adverse effects have been reported in clinical trial. Only gastrointestinal symptoms were frequently occurred according to the adverse effect data from Helsinki Heart Study (Frick, et al., 1987 ; Todd and Ward, 1988).

However, the common adverse effects of gemfibrozil related to usual treatment were epigastric pain , constipation , anorexia (Nye, et al., 1980 ; Kaukola, et al., 198) , headache (Alvarez-Sabin, et al., 1988 ; Arellano , deCos

and Valiente, 1988) , impotence (Bain, Lemon and Jones, 1990 ; Pizarro, Bargay and D'Agosto, 1990) , myopathy , polymyositis (Fusella and Strosberg, 1990 ; Magarian, Lucus and Colley, 1991) , vasculitis and polyarthritis (Smith and Hurst, 1993).

7. Effect on Laboratory Values

Clinical laboratory data for patients receiving gemfibrozil has revealed no serious pattern of drug related toxicity (Frick, et al., 1987). Minor decrease in mean hemoglobin , hematocrit values and white blood cell count was occasionally occured at the onset of therapy but stabilize during continued treatment. Abnormal fluctuation in liver function test has occurred infrequently, however, there were no clinical symptoms indicating abnormal liver function (Samule, 1983 : Frick, et al., 1987). Abnormal results of blood urea nitrogen , serum creatinine , uric acid and urinalysis have occurred but were usually in elderly hypertensive patients recieving diuretics. Plasma glucose concentrations have been reported to be marginally increased, staying within the normal range during glucose tolerance testing in patient receiving gemfibrozil (Todd and Ward , 1988).

8. Drug Interaction

Gemfibrozil is highly protein binding drug. As such , it is expected to interact with other protein bound drug. In vitro study, Hamberger et al (1986) reported that gemfibrozil at therapeutic concentration did not influence the binding of nicoumalone , salicylic acid , vaproic acid,

frusemide , phenylbutazone, tolbutamide , warfarin and sulphamethoxazole. However , there were many reports about the drug interactions of gemfibrozil in patients who were treated with concomitant gemfibrozil and other drugs as follows :

8.1 Cholestipol

Concurrent use of cholestipol and gemfibrozil may result in reducing bioavailability of gemfibrozil if they are administered at the same time. This may due to the decrease in gemfibrozil effectiveness probably resulting from diminishing of gemfibrozil absorption. To avoid this consequence, they should be administered in different time at least 2 hours interval (Forland , Feng and Cutler, 1990).

8.2 Warfarin

Concomitant use of gemfibrozil and warfarin, hypoprothrombinemic and bleeding time disorder were happened in some patients. The mechanism of these interactions is still unknown. Therefore , If concomitant therapy is necessary, the dosage of the anticoagulant should be reduced for maintaining the prothrombin time at desired level to prevent bleeding complications (Ahmad, 1990).

8.3 Glyburide

Concurrent use of gemfibrozil and glyburide may result in enhancement of the hypoglycemic effect in some patients. It is possibly due to the displacement of gemfibrozil at glyburide protein binding site thus releasing more free glyburide in circulation. Therefore , blood glucose should be closely monitored when gemfibrozil is added to or discontinued

from glyburide or other sulfonylurea therapy to prevent hypoglycemic condition (Ahmad, 1991).

8.4 Lovastatin

In several case reports the concurrent use of lovastatin and gemfibrozil has resulted in severe myopathy and rhabdomyolysis. The actual mechanism is still unknown. Hence, if it is possible, concurrent use of these two drugs should be avoided. If it is essential, any occurrence of muscular pain , tenderness and weakness have to be recorded and the creatine kinase need to be controlled (East, Bilheimer, and Grundy, 1988 ; Pierce , Wysowski , and Gross , 1990).

9. Therapeutic Use

9.1 Coronary heart disease

In a large placebo-controlled with double blind study , the Helsinki Heart Study , involving 4081 asymptomatic middle aged men 40 to 55 years with primary dyslipidemia, recieved gemfibrozil 600 mg twice daily over 5-year study period. The drug was postulated to increase in HDL-cholesterol level with simultaneous reduction in VLDL , LDL and total triglycerides. A 34% reduction in incidence of coronary heart disease was observed. Beneficial effect on reducing evidence of coronary heart disease resulted in the second year of treatment and continued along the duration of the study (Frick , et al., 1987).

9.2 Hyperlipidemia

Gemfibrozil markedly reduces abnormally elevated serum triglyceride concentration in all types of dyslipidemia (except type I). In most patients with abnormally elevated serum total cholesterol concentration, gemfibrozil produces a mild reduction. However , there have been a large number of studies in patient with all types of primary dyslipidemia to assess the effect of gemfibrozil (Bremner, et al., 1976 ; Nye, et al., 1980 ; Kaukola, et al., 1981 ; Lewis, 1982 ; Samuel, 1983). All studies were designed by starting with a 4 to 8 wks run-in period on placebo to establish baseline lipid and lipoprotein measurements and the diet was controlled, then gemfibrozil was given at the dose of 800-1600 mg daily. In patient type II a , II b and IV dyslipidemia, the decrease of plasma triglyceride and total cholesterol were indicated to be 40-60% and up to 20%, respectively, HDL-cholesterol was increased to be 15-20% . The magnitude of lipid lowering effect was proportional to the duration of therapy , dosage and initial severity of the dyslipidemia. It takes several months to obtain maximum therapeutic response at the maintenance dose of 800 mg. This maximum therapeutic response can be enhanced by increasing dose from 800 to 1200 mg/day . Only a few patients show additional improvement by increasing the dosage to 1600 mg/day.

Gemfibrozil therapy should be used selectively in those patients who have not responsed to dietary control or other non-pharmacological measures for instance, exercise , weight loss , limiting alcohol intake (Gilman, 1991).

10. Dosage and Administration

Gemfibrozil (Lopid®) is available as 300 mg capsules and 600 mg tablets. The usually recommened dosage (for adult only) is 600 mg twice daily, taken 30 minutes before morning and evening meals. (Gilman, 1991).