เภสัชจลนศาสตร์ของยาอีโซเมปราโซลในผู้ป่วยโรคตับแข็งชาวไทย

นางสาวกัลยาณี อาชาสันติสุข

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PHARMACOKINETICS OF ESOMEPRAZOLE IN THAI PATIENTS WITH CIRRHOSIS

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โครงการวิจัยนี้มีวัตถุประสงค์เพื่อศึกษาเภสัชจลนศาสตร์ของยาอีโซเมปราโซลซึ่งเป็นยาใหม่ในกลุ่ม proton pump inhibitor ที่ได้รับการขึ้นทะเบียนในประเทศไทยเมื่อปี พ.ศ. 2543 โดยในการทดลองนี้ได้ทำการศึกษาในกลุ่มผู้ป่วยชาวไทยซึ่งเป็นโรคตับแข็งจำนวน 14 คน และกลุ่มอาสาสมัครชาวไทยที่มีสุขภาพดีซึ่งมีการทำงานของตับปกติจำนวน 12 คน โดยให้รับประทานยาอีโซเมปราโซล 20 มิลลิกรัม วันละครั้งติดต่อกัน 5 วัน

ผลการศึกษาพบว่าระดับยาสูงสุดในพลาสมา และเวลาที่ระดับยาสูงสุดในพลาสมาในผู้ป่วยโรคตับแข็งนั้นไม่ต่างไปจากกลุ่มอาสาสมัครที่มีสุขภาพดีทั้งในวันที่ 1 และวันที่ 5 ของการทดลอง ในขณะที่ระดับยาในพลาสมา และค่าครึ่งชีวิตของการขจัดยานั้นแตกต่างอย่างมีนัยสำคัญ และเป็นที่ทราบกันดีว่าอีโซเมปราโซลถูกเมตาบอไลต์ผ่านตับเป็นส่วนใหญ่ ความสามารถในการขจัดยาจึงลดลงในผู้ป่วยชาวไทยซึ่งเป็นโรคตับแข็ง โดยมีผลทำให้ระดับยาในพลาสมา และค่าครึ่งชีวิตของการขจัดยานั้นเพิ่มขึ้น ซึ่งสอดคล้องกับการศึกษาก่อนหน้านี้ของอีโซเมปราโซล 40 มิลลิกรัมในผู้ป่วยโรคตับแข็งชาวสวีเดน อย่างไรก็ตามค่าครึ่งชีวิตของการขจัดยาของอีโซเมปราโซลในชาวไทยที่มีการทำงานของตับปกติ และที่เป็นโรคตับแข็งในการศึกษานี้มีค่าสูงกว่าในชาวสวีเดน ทั้งนี้อาจเป็นผลเนื่องมาจากความแตกต่างของเอนไซม์ CYP2C19 ในแต่ละเชื้อชาติซึ่งใช้ในการเมตาบอไลต์ยานี้เป็นส่วนใหญ่ โดยพบว่าชาวเอเชียนั้นเป็นชนิด poor metabolizers ของ CYP2C19 ซึ่งการทำ ฟีโนไทป์ และจีโนไทป์ของ CYP2C19 นี้จะช่วยทำให้ข้อสันนิษฐานชัดเจนขึ้น ในการศึกษานี้พบว่าระดับยาในเลือดและค่าครึ่งชีวิตที่เพิ่มขึ้นทั้ง 2 กลุ่มการทดลองนี้ทำให้พบอาการที่ไม่พึงประสงค์ โดยส่วนใหญ่พบอาการท้องเสียอย่างอ่อน ซึ่งอาการจะหายไปเมื่อหยุดใช้ยานี้

จากผลการทดลองแสดงให้เห็นว่าในกลุ่มศึกษาทั้ง 2 กลุ่มนี้ สามารถทนต่อการใช้ยาอีโซเมปราโซล 20 มิลลิกรัมได้ดี และไม่จำเป็นต้องปรับขนาดยาในผู้ป่วยโรคตับแข็งแต่อย่างใด อย่างไรก็ตามควรมีการศึกษาเภสัชจลนศาสตร์ของยาอื่นที่มีช่วงการรักษาที่แคบ (narrow therapeutic range) ซึ่งเมตาบอไลต์ผ่านตับด้วยเอนไซม์ซึ่งมีความแตกต่างในแต่ละเชื้อชาติ

ภาควิชา.....เภสัชวิทยา.....ลายมือชื่อนิสิต.....

สาขาวิชา.....เภสัชวิทยา.....ลายมือชื่ออาจารย์ที่ปรึกษา.....

ปีการศึกษา.....2546.....ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

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The present studies aimed to investigate pharmacokinetic properties of esomeprazole, a new proton pump inhibitor which has been registered in Thailand since 2000 in 14 Thai cirrhotic patients compared to 12 Thai healthy volunteers with normal liver function. Each group received 20 mg of esomeprazole orally once a day for 5 consecutive days.

It was found that among all pharmacokinetic parameters tested, cirrhotic patients exhibit C_{max} and t_{max} similar to those observed in normal healthy volunteers whereas significantly higher values of AUC and $t_{1/2}$ were noted in both day 1 and day 5 of the experiments. As expected, clearance of esomeprazole which is extensively metabolized by hepatic cytochrome P450 was markedly reduced in Thai cirrhotic patients and subsequently AUC and $t_{1/2}$ were prolonged. Similar results have previously been reported in Swedish patients, with hepatic impairment, taking 40 mg of esomeprazole. However, $t_{1/2}$ of esomeprazole in both Thai healthy volunteers as well as Thai cirrhotic patients in the present studies was found to be higher than their corresponding value in Swedish patients. These might be explained by different activity of CYP2C19, a major hepatic metabolizing enzyme of esomeprazole, in which poor metabolizers is more prominent in Asian ethnic group. Additional phenotyping or genotyping study of CYP2C19 in Thai population are needed to clarify this finding. Despite higher values of AUC and $t_{1/2}$ in the study population, the adverse effect of esomeprazole observed in both groups was mild and reversible upon cessation of medication. Diarrhea was the most frequently reported side effects.

Based on these findings, it can be concluded that esomeprazole 20 mg is well tolerated in the population studied and dose adjustment in cirrhotic patients is not essentially required. However, for the sake of safety, it is suggestive to do the bridging pharmacokinetic studies of drugs that are metabolized mainly by hepatic enzymes that could be different in different ethnic groups, especially those drugs with narrow therapeutic index.

Department.....Pharmacology.....Student's signature.....

Field of study.....Pharmacology.....Advisor's signature.....

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LIST OF ABBREVIATIONS

AUC	=	area under the plasma concentration-time curve
BUN	=	blood urea nitrogen
$\overline{C}$	=	mean concentration
°C	=	degree Celcius
Cl	=	clearance
C_{max}	=	maximum concentration
cm	=	centimeter
dL	=	deciliter
hr	=	hour
kg	=	kilogram
m	=	meter
mg	=	milligram
mL	=	milliliter
ng	=	nanogram
PT	=	prothombin time
RBC	=	red blood cell
SGOT	=	serum glutamic oxaloacetic transaminase
SGPT	=	serum glutamic pyruvic transaminase
secs	=	seconds
$t_{1/2}$	=	half-life
t_{max}	=	time to maximum concentration
WBC	=	white blood cell
µL	=	microliter
µmol	=	micromole

CHAPTER I

INTRODUCTION

Esomeprazole

1. General information

For several years, proton pump inhibitors (PPIs) are commonly used in the treatment of patients with gartroesophageal reflux disease (GERD) and peptic ulcer. Since the PPIs have been developed, these agents provide the most rapid symptomatic control and best healing of oesophagitis of available agents. (Devault and Castel, 1999) Consequently, esomeprazole, the S-isomer of omeprazole (a racemic mixture of S- and R- optical isomers), is the first proton pump inhibitor which has been developed as a single optical isomer. It is generally used and accepted that it has a better pharmacokinetic profile and provides greater acid suppression than the other PPIs. (Caroline, Spencer and Faulds, 2000)

Chemical structure and characteristic

The empirical formula of esomeprazole is $(C_{17}H_{18}N_3O_3S)_2Mg.3H_2O$ with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis. The structural formula has shown on Figure 1.

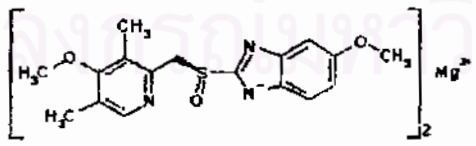


Figure 1. The structural formula of esomeprazole (Scott et al. 2002)

The stability of esomeprazole is a function of pH, it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half life is about 19 hours at 25 °C and about 8 hours at 37 °C.

2. Pharmacodynamic properties

Mechanism

Like other proton pump inhibitors, esomeprazole is a potent inhibitor of the final common pathway for hydrochloric acid secretion by gastric parietal cells. Esomeprazole contains a sulfinyl group, like other PPIs, in a bridge between substituted benzimidazole and pyridine rings. At neutral pH, esomeprazole is chemically stable, lipid soluble and weak base that are devoid of inhibitory activity. These neutral weak base reach parietal cells from the blood and diffuse into the secretory canaliculi, where the drugs become protonated and thereby trapped. The protonated agent rearranges to form a sulfenic acid and a sulfenamide. The sulfenamide interacts covalently with sulfhydryl groups at critical sites and irreversible in the extracellular (luminal) domain of the membrane spanning H^+/K^+ -ATPase. Esomeprazole must be considered as prodrug that need to be activated to be effective by acidic environment. (Huang and Hunt, 2001)

Antisecretory activity

The extent of gastroesophageal mucosal injury and symptoms associated with gastric reflux are dependent on pH. (Hunt, 1999) Refluxate with a pH<4 contains active pepsin and is associated with intensification of symptom, (Smith, Operkul and Larkai, 1989) with mucosal healing directly correlated with the proportion of each 24 hours period for which the pH of the intragastric compartment is held above this level. Accordingly, pharmacodynamic studies of esomeprazole have focused on the effect of the drug on intragastric pH.

The superior acid suppressant properties of esomeprazole 20 and 40 mg have been revealed by extensive 24 hours intragastric pH monitoring studies when compared with omeprazole 20 mg. (Lind et al. 2000) Esomeprazole 20 and 40 mg once daily for 5 days maintained intragastric pH>4 for 12.7 and 16.8 hours, respectively versus 10.5 hour for omeprazole 20 mg once daily for 5 days. ($p<0.001$ and $p<0.01$)

Twenty four hours median intragastric pH was significantly higher with esomeprazole 40 mg (pH 4.9) and 20 mg (pH 4.1) than with omeprazole 20 mg (pH 3.6) ($p<0.001$ and $p < 0.01$) Moreover, it has been reported that esomeprazole 40 mg provided more effective of acid secretion control than another drugs in PPIs, such as lansoprazole 30 mg (Rohss, Nilsson and Rydholm, 2000) and pantoprazole 40 mg (Wilder, Rohss and Lundin, 2000) once daily for 5 days. The percentages to control intragastric pH>4 for 12 hours in esomeprazole 40 mg and lansoprazole 30 mg were 90% and 57%, respectively ($p<0.01$) and for control intragastric pH>4 for 16 hours were 38% and 5 %, respectively ($p<0.05$). Also for a study in term of control intragastric pH>4 between esomeprazole 40 mg and pantoprazole 40 mg, the percentages to control for 12 hours were 90% and 30%, respectively ($p<0.0001$) and the percentages to control for 16 hours were 50% and 10%, respectively ($p<0.001$). Those investigators have proposed that high efficacy to control intragastric pH>4 in esomeprazole especially for dose 40 mg was resulted from higher area under the plasma concentration time curve (AUC) than did other PPIs.

Serum gastrin effects

The effect of esomeprazole on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1,300 patients for up to 6-12 months. (Scott et al. 2002) The mean fasting gastrin level increased in a dose related manner. This increase reached a plateau within 2-3 months of therapy and returned to baseline levels within 4 weeks after discontinuation of therapy.

Endocrine effects

Esomeprazole had no effect on thyroid function when given in oral doses of 20 mg and 40 mg once daily for 4 weeks. (Scott et al. 2002) Other effects of esomeprazole on the endocrine system were assessed using omeprazole studies. Omeprazole given in oral doses of 30 or 40 mg for 2-4 weeks had no effect on

carbohydrate metabolism, circulating levels of parathyroid hormone, cortisol, estradiol. testosterone, prolactin, cholecystokinin and secretin. (Huang and Hunt, 2001)

3. Pharmacokinetic properties

Absorption

A pharmacokinetic study of esomeprazole which given as a solution 20 mg or capsule 40 mg for 5 days to 32 healthy volunteers (Hassan, Rohss and Andersson, 2000) has shown that absorption of esomeprazole, which takes place in the small intestine is rapid with peak plasma levels occurring 1-2 hours after dosing. The absolute bioavailability (F) and AUC of esomeprazole increased from day 1 to day 5 of oral administration. F values increased from 50% to 68% with a dosage of 20 mg/day and from 64 to 89% with a dosage of 40 mg/day. AUC values increased from 1.34 to 2.55 μmol/L*h and 4.32 to 11.21 μmol/L*h with each dosage, respectively. The increase in systemic exposure to esomeprazole after repeated doses is attributed to reductions in total body clearance and first pass metabolism.

Distribution

The plasma protein binding to esomeprazole is 97%. The apparent volume of distribution at steady state of esomeprazole after intravenous administration was consistently around 0.25 L/kg. (Hassan, Andersson and Bredberg, 2000)

Metabolism

The drug is metabolized extensively in the liver by the cytochrome P450 (CYP) enzyme system to products that lack antisecretory activity. In vitro studies show that both optical isomers of omeprazole are converted chiefly to hydroxy and 5-O-desmethyl metabolites by CYP2C19 and to sulphone metabolite by CYP3A4. (Abelo, Andersson and Antonsson, 2000) The affinity of esomeprazole for CYP2C19 is

approximately 10 times that for CYP3A4, although the rate at which the hydroxy metabolite is formed is lower and the rate at which the sulphone and 5-O-desmethyl metabolites are formed is higher than with R-omeprazole. The sum of the intrinsic clearance values for formation of the 3 metabolites in vitro from R-isomer was 3 times that of the S-isomer. The suggestion that this would be reflected in reduced clearance and increased AUC of esomerprazole relative to omeprazole has been bome out by observations in healthy volunteers. (Andersson, Hassan and Hasselgren, 2001)

Elimination

Intravenous administration of single dose of esomeprazole 1-2 weeks before and the day after 5 days of oral administration showed that plasma clearance (CL) decreased and the plasma elimination half life ($t_{1/2}$) increased after repeated use. CL decreased from 22 to 16 L/h with a 20 mg dose and from 17 to 9 L/h with a 40 mg dose; correspondingly, $t_{1/2}$ increased from 0.8 to 1.2 hours with both drug doses. (Hassan, Rohss and Andersson, 2000) Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in urine and the remainder is found as inactive metabolites in the feces. (Hassan, Andersson and Bredberg, 2000)

4. Indications and therapeutic doses

Esomeprazole is indicated for healing of erosive esophagitis, the recommended dose is 40 mg once daily for 4 to 8 weeks. For long term prevention of relapse the recommended dose is 20 mg once daily. Clinical data are available for up to one year with 40 mg once daily. For treatment heartburn and other symptoms of GERD, a dose of 20-40 mg once daily for 2 to 4 weeks is recommended. Subsequent symptom control is achieved using an on demand regimen when esomeprazole 20 mg once daily is taken as needed. (Scott et al. 2002)

Esomeprazole is also indicated for the eradication of *Helicobacter pylori* infection in patients with duodenal ulcer disease or a history of duodenal ulcer disease within the past 5 years. The treatment of *H. pylori* eradication associated with duodenal ulcer, the recommend dose is 40 mg of esomeprazole combined with amoxicillin 1 g and clarithromycin 0.5 g, all given twice daily for 10 days. Healing of duodenal ulcer is achieved after the eradication of *H. pylori* without any further treatment with esomeprazole. (Caroline, Spencer and Faulds, 2000)

5. Adverse effects and tolerability

Adverse effects

The common side effects due to esomeprazole include headache, diarrhea, nausea, flatulence, abdominal pain and vomiting, the uncommon side effects are skin disorders, dry mouth, dizziness and vertigo. (Caroline, Spencer and Faulds, 2000)

Tolerability

Esomeprazole 20 or 40 mg/day was generally well tolerated in both 8 weeks and maintenance (up to 12 months) studies involving 6,000 adult patients with GERD. (Richter, Kahrilas and Johanson, 2001) The most commonly reported adverse events were headache, diarrhoea, nausea, abdominal pain and respiratory infection which occurred with an incidence of <9%. Adverse events associated with the long term administration of esomeprazole were generally similar to those observed with 8 weeks treatment. The nature and frequency of adverse events with esomeprazole were similar to those experienced with either omeprazole or lansoprazole in well designed 8 weeks trials. (Scott et al. 2002)

Maintenance therapy with esomeprazole 10, 20 or 40 mg once daily for up to 6 months was generally well tolerated in patients with healed GORD. (Johnson, Benjamin and Whipple, 2000) The most commonly reported adverse events were headache, respiratory infection, sinusitis, flatulence and diarrhea.

A noncomparative trial in 808 patients with healed erosive esophagitis in which esomeprazole 20 mg once daily was administered for 12 months (80.9% of patients received treatment for $\geq$ 6 months), showed that esomeprazole was generally well tolerated. Adverse events were reported by 37.4, 68.3 and 78.2% of patients at 1, 6 and 12 months, respectively, (cumulative percentages) and no patient reported a serious drug related adverse event. Laboratory changes were usually small and not clinically relevant. (Bardhan, 1996)

Dual or triple therapy 10 days regimens of esomeprazole 40 mg/day plus antibacterials were similarly tolerated with no serious drug related adverse events reported. (Scott et al. 2002)

6. Drug interactions

The potential for interactions of esomeprazole with other drugs is reported to be low and similar to that with omeprazole. (Andersson, Hassan and Hasselgren, 2001) However, esomeprazole inhibits gastric acid secretion, which interferes with the absorption of medications requiring an acid medium for absorption, such as ketoconazole and itraconazole. (Johnson and Hedge, 2002)

Esomeprazole has no apparent potential for interactions with drugs metabolized by the hepatic microsomal isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2D6 and CYP2E1. Possible interaction with drugs metabolised by CYP2C19 have been indicated by studies with diazepam, phenytoin and warfarin, but on the basis of available data these were considered unlikely to be of any clinical relevance. (Richardson, Hawkey and Stack, 1998)

The possibility of interaction of esomeprazole with either clarithromycin or amoxicillin is especially important, given that these are routinely co-administered for *H. pylori* eradication therapy. No effect was seen on either clarithromycin or amoxicillin pharmacokinetics, but the AUC of the active metabolite of clarithromycin, 14-hydroxyclarithromycin increased 50% during triple combination therapy. The significance of this finding is uncertain. (Andersson, Hassan and Hasselgren, 2001)

7. Special population

Pediatrics

Safety and effectiveness of esomeprazole have not been established in pediatric patients. However, the pharmacokinetics of orally administered omeprazole in children was studied (Andersson et al. 2000) and found that area under the plasma concentration time curve (AUC), plasma half life ($t_{1/2}$) and maximum plasma drug concentration (C_{max}) were lower in the younger age group because of higher metabolic with decreasing age, being highest at 1-6 years old. Therefore, esomeprazole is not recommended for using in pediatric patients.

Geriatrics

The pharmacokinetics of esomeprazole 40 mg once daily for 5 days were not significantly altered by increasing age. (Hasselgren et al. 2001) The AUC and C_{max} values were not significantly different in 14 healthy elderly volunteers, mean age 74 years old (range 71 to 80 years old) and 36 patients with symptoms of gastroesophageal reflux disease (GERD), mean age 45 years old (range 29 to 58 years old). The ratios of AUC and C_{max} values between elderly volunteers and patients with GERD were 1.25 (95% CI 0.94, 1.67) and 1.18 (95% CI 0.91, 1.52), respectively. The difference for AUC was 25% (95% CI –6% to +67%). Esomeprazole has a wide therapeutic window and the results do not indicate that dosage adjustment should be necessary in the elderly. (Hasselgren et al. 2001)

Renal impairment

The pharmacokinetic data of esomeprazole is not available on patients with renal impairment. However, since esomeprazole has less than 1% of the parent drug that is excreted in urine, approximately 80% as inactive metabolites and the remainder is found as inactive metabolites in the feces. It is reasonable to assume that a metabolism of esomeprazole as well as the antisecretory effect is unchanged in patients with impaired renal function. Therefore, a dose adjustment is not necessary in patients with impaired renal function. (Scott et al.2002)

The previous studies on the other PPIs in patients with renal impairment were examined. The results showed that the renal impairment had no effect on the pharmacokinetics of PPIs, such as omeprazole (Regardh, 1986), pantoprazole (Parsons, 1996), rabeprazole (Fuhr and Jetter, 2002) and lansoprazole. (Delhotal et al.1993) Therefore, dose adjustment in PPIs is not required in patients with renal impairment.

Hepatic Impairment

In a study of the pharmacokinetics of esomeprazole 40 mg once daily by oral administration for 5 days in patients with liver cirrhosis, it was found that AUC and $t_{1/2}$ were increased by 76% and 29%, respectively in 12 cirrhotic patients when compare with an historical control group of 36 GERD patients with normal hepatic function. However, when the cirrhotic patients were grouped according to the degree of liver function (Child Pugh Classification), AUC and $t_{1/2}$ values for patients with mild and moderate liver function were in the same range as those for GERD patients with no liver impairment. Therefore, dosage adjustment is not required in patients with mild to moderate liver impairment. However, a maximum dose of 20 mg of esomeprazole should not be exceeded in patients with severe liver impairment. (Sjovall et al. 2002)

Similar to other PPIs, esomeprazole is indicated to control intragastric pH> 4 for the treatment of peptic ulcer, erosive esophagitis and symptomatic of GERD. However, due to its superior anti-secretory effect when compare with the other PPIs, esomeprazole is generally used, especially in cirrhotic patients to prevent or decrease serious bleeding from peptic ulcer and esophageal varices.

With regards to incidence of bleeding in cirrhosis with peptic ulcer and esophageal varices, it has been reported that bleeding were resulted from peptic ulcer and esophageal varices by 60% and 20%, respectively. (Fraser, Pounder and Burroughs, 1993) The bleeding from esophageal varices is very dangerous and has a mortality rate 50% for the first bleeding. Epidemiology in cirrhosis with esophageal varices is about 15% and 30% of them has bleeding.

Cirrhosis

Definition

Cirrhosis is a chronic injury to a liver and alter to a fibrosis instead of a normal liver cell and become a nodule in finality. This changeover lead to an abnormal function of the liver, such as the flow of blood through the liver is blocked and lead to portal hypertention. Moreover, the function to produce albumin, cholesterol, bile or metabolize many drugs and the ability to eliminate waste material from a body is hindered. (Douglas et al. 1991)

Etiology

Cirrhosis can be a consequence of many liver diseases including alcohol, chronic viral hepatitis B, C and D (in association with B) which are the most common cause of cirrhosis worldwide. The other causes are chronic bile duct blockage which can occur at birth (biliary atresia) or develop later (primary biliary cirrhosis), chronic drug induced hepatitis (oxyphenisatin), toxic exposure (carbon tetrachloride, hypervitaminosis and methotrexate), autoimmune hepatitis and metabolic disorders such as Wilson's disease, alpha 1-antitrypsin deficiency and hemochromatosis. (Anastacio, Hector and Imogene, 1999)

Examination

Clinical observations

A careful physical examination can provide clues to the presence of cirrhosis, its complications or its cause. (alcoholism, chronic medication use, intravenous drug abuse, prior blood transfusions or hepatitis exposure) (Douglas et al. 1991)

Laboratory evaluation

The initial laboratory evaluation should include an etiologic profile. Viral studies for hepatitis B, C, D and disease specific markers including SGPT (serum glutamic pyruvic transminase), SGOT (serum glutamic oxaloacetic transminase), total bilirubin, alkaline phosphatase, serum iron, serum albumin and prothrombin time may assist in diagnosis. Macrocytic red blood cell may develop with cirrhosis or from folic acid deficiency. A liver biopsy should be performed to establish the presence of cirrhosis and provide clues to the cause. The diagnosis of cirrhosis requires demonstration of regenerative nodules or pseudolobules completely encircled by fibrosis. (Ponce et al. 1980)

Radiography

Ultrasonography can assist in the diagnosis of cirrhosis and its complications, such as portal hypertension and ascites. The size and shape of the liver can be estimated and change of ultrasound attenuation may indicate fibrosis. Computerized tomography (CT) provides similar hepatic information as ultrasound. However, early changes of cirrhosis and some vascular abnormalities may not be well seen. Vascular changes may also be observed by magnetic resonance imaging. (MRI) Esophagoscopy is considered the best examination to document the presence of esophageal and gastric varices. (Ponce et al. 1980)

Complications of cirrhosis

Cirrhosis takes several years to develop. During this time, there are usually no symptoms although fatigue, weakness and decreased appetite may occur and worsen with time. When cirrhosis is fully developed, the complications of cirrhosis are present jaundice, coagulation defect, fluid retention in the legs and abdomen, portal hypertension, varices, ascites, hepatorenal syndrome and hepatic encephalopathy. (Zetterman, 1991)

Fluid retention in the legs and abdomen occur when a protein called albumin that holds fluid in blood vessels which produced by the liver is decreased, so fluid seeps out of the tissues into the legs and abdomen, causing edema (fluid accumulation) and ascites. For jaundice, the liver produces bile that normally flows into the intestine, but advanced cirrhosis, bile can back up into the blood, causing the skin and eyes to tern yellow and the urine to darken. As we known coagulating factors can produce from the liver, but this function will be hindered in cirrhosis, therefore a prolong prothombin time will happen and make an easy bleeding to the cirrhotic patients.

Normally, blood from intestine and spleen came to the liver through the portal vein, but cirrhosis slows the normal flow of blood through the portal vein, therefore blood from intestine and spleen back up into blood vessels in the stomach and esophagus. These blood vessels may become enlarged which called varices, they have thin walls and carry high pressure and thus do burst at finally. A result from serious bleeding problem in the upper stomach or esophagus that requires immediate medical attention. (Simpson and Conn, 1968)

Gastroesophageal reflux is aggravated by increased intra-abdominal pressure from ascites and a reduction of lower esophageal sphincter pressure in cirrhosis. Medical therapy of esophagitis should be administered. Portal hypertension gastropathy may develop in the patient with portal hypertension and be a significant cause of upper gastrointestinal bleeding. (Arsene et al. 1987)

Moreover, a damaged liver from cirrhosis cannot remove toxins from the blood, causing them to accumulate in the blood and eventually the brain. Therefore, toxins can dull mental functioning and cause personality changes, coma and even death. The signs of a buildup of toxins in the brain include neglect of personal appearance, unresponsiveness, forgetfulness, trouble concentrating or changes in sleep habits. (Anthony, Ishak and Nayak, 1977)

The important thing to consider is sensitivity to medication. As we known that cirrhosis slows the liver's ability to filter medications from the blood. Because the liver does not remove drugs from the blood at the usual rate, they act longer than expected and build up in the body. This cause make a patient to be more sensitive to medications and their side effects.

Course and prognosis

The clinical course depends on the cause of cirrhosis and precipitating events leading to presentation. Cirrhosis is an irreversible disease and attempts should be made to stabilize the patient and to control the cause. Factors that indicate a poor outcome include an elevated prothombin time that does not correct itself with parenteral vitamin K, upper gastrointestinal bleeding caused by varices, ascites refractory to therapy, increased age of the patient, severe malnutrition, spontaneous bacterial peritonitis, a pronounced increase of serum bilirubin in the absence of hemolysis and hepatocellular carcinoma. For general, all causes of upper gastrointestinal bleeding are associated with an increased mortality in patients with cirrhosis. If ethanol consumption continues, mortality is higher. (Douglas et al. 1991)

Treatment

Liver damage from cirrhosis cannot be reversed, but treatment can stop or delay further progression and reduce complications. Treatment depends on the cause of cirrhosis and any complications a person is experiencing. Cirrhosis caused by alcohol abuse is treated by abstaining from alcohol. Treatment for hepatitis related cirrhosis involves medications used to treat the different types of hepatitis, such as interferon for viral hepatitis and corticosteroids for autoimmune hepatitis. Cirrhosis caused by Wilson's disease, in which copper builds up in organ, is treated with medications to remove the copper. The cirrhotic patients with portal hypertension, blood pressure medication such as a beta-blocker is necessary. (Zetterman, 1991)

Treatment will also include remedies for complications. A low-sodium diet or the use of diuretic, which are drugs that remove fluid from the body is recommended for ascites and edema. The build up of toxins in the blood and brain will decrease by having less protein and the laxatives can absorb the toxins and removed them from the intestines.

When complications cannot be controlled or when the liver becomes so damaged from scarring that it completely stops functioning, a liver transplant is necessary. In liver transplantation surgery, a diseased liver is removed and replaced with a healthy one from an organ donor. About 80-90% of people survive from liver transplantation. Survival rates have improved over the past several years because of drugs such as cyclosporine and tacrolimus, which suppress the immune system and keep it from attacking and damaging the new liver.

As described above, esomeprazole has a better pharmacokinetic profile and provides greater acid suppression than other PPIs. Therefore, esomeprazole is generally used, especially in patients with cirrhosis to prevent or decrease serious bleeding from peptic ulcer and esophageal varices.

As we known, hepatic impairment can affect of other drug's kinetic by increasing drug level in plasma as shown by previous study PPIs, such as pantoprazole (Ferron et al. 2001), lansoprazole (Delhotal et al. 1993) and omeprazole. (Rinetti, 1991) The relatively higher level of drugs in plasma when compared with the healthy volunteers could suggest that hepatic blood flow and the activity of their respective metabolizing enzyme were reduced. The decrease in clearance and the increase in bioavailability appear to be the kinetic changes that contribute most to the increase in plasma concentrations. Therefore, patients with hepatic impairment should be carefully monitored, especially when co-administered of PPIs with drug which has narrow therapeutic index, such as phenytoin. However, all of previous PPIs study demonstrateed that dose adjustment was not required in hepatic impairment, despite the high drug level in plasma, especially in patients with severe hepatic impairment.

Recently, a study on the pharmacokinetics of esomeprazole 40 mg once daily for 5 days in Swedish patients with cirrhosis showed that the area under the plasma concentration time curve (AUC) of esomeprazole in patients with mild to moderate cirrhosis is similar to that of healthy population. Therefore, dose adjustment is not required in these patients. However, it was suggested that the dose should not exceed 20 mg/day in patients with severe cirrhosis. (Sjovall et al. 2002)

Esomeprazole is metabolized extensively in the liver by CYP2C19 and as well as, to a minor extent by CYP3A4. It has been well recognized that CYP2C19 is different among different ethnic groups. Therefore, the pharmacokinetic studies of esomeprazole, which is a newly registered drug under safety monitoring program in Thai subjects are clearly needed in both healthy volunteers as well as cirrhotic patients.

CHAPTER II

MATERIALS AND METHODS

Materials

A. Study population

Ethics

Cirrhotic patients were recruited from the hospital of Tropical Medicine during the period of January to October 2003. The study was performed in an approval of the ethical committees of the Faculty of Tropical Medicine, Mahidol university, the Faculty of Medicine and the Faculty of Pharmaceutical Sciences, Chulalongkorn university. Written informed consent was obtained from all subjects prior to their enrollment. Subjects were free to discontinue their participation in the study at any time and could be withdrawn from the study at any time at the discretion of the investigator.

Inclusion criteria

The study enrolled 2 groups of subjects, the first group was 12 Thai healthy volunteers with normal hepatic function by blood chemistry test and the other group was 14 Thai patients with cirrhosis according to Child Pugh's Classification (see Appendix A), aged between 21–70 years in both groups.

Exclusion criteria

Patients with large or multiple hepatocellular carcinoma and those with significant unstable concomitant diseases or using drugs that were likely to interfere with the results of the study were excluded. In addition, patients with a history of severe allergic disease, renal failure (serum creatinine > 150 μmol/l), pregnant or nursing women were also excluded.

B. Reagents

1. Esomeprazole standard powder kindly supplied by AstraZeneca, Sweden
2. Esomeprazole tablet 20 mg kindly supplied by AstraZeneca, Sweden
3. Carbamazepine standard powder kindly supplied by Pharmaceutical Technology Service Center, Thailand
4. Methanol HPLC grade (Labscan, Thailand)
5. Acetic acid AR grade (Labscan, Thailand)
6. Triethylamine AR grade (Labscan, Thailand)
7. Diethylether AR grade (Labscan, Thailand)
8. Acetonitrile HPLC grade (Labscan, Thailand)

C. Apparatus

1. Analytical balance (Sartorius, 1615MP ; S/N 3209026, Germany)
2. Micropipet P1000 and P200 (Gilson, France)
3. Inertsil ODS-3 column, 4.6 * 250 mm (Shimadzu, Japan)
4. High performance liquid chromatography (LC-10A, Shimadzu, Japan)
5. Sonicator (Bransonic, USA)
6. Vortex mixer (Vortex-genie 2, G-560 E, USA)
7. Centrifuge (Kokusan, H-103N, Japan)
8. Glassware
9. Nylon mambrane filter 0.45 micron
10. Insert vial 200 µl
11. Heparinise tube 5 ml
12. Micro tube 2 ml

Methods

A. Study protocol

Subjects

On the day before and on the last day (day 5) of the study, physical examination, blood chemistry and urinalysis of each subject were carried out. The subjects were asked to refrain from food from 10 p.m. the day before to 8 a.m. of day 1 of the study.

Dose and drug administration

Esomeprazole 20 mg was taken together with 200 ml of water in the morning at 8 a.m. for 5 consecutive days. During the study, breakfast was allowed 30 minutes after drug administration.

Sample collection

5 ml of blood sample were serially collected on day 1 and day 5 at 0, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6 and 10 hours after drug administration. (Details of procedure were given in Appendix B)

Blood sample was collected in the heparinised tube and centrifuged at 3000 rpm for 15 minutes. Plasma was then collected and kept frozen at $-20^{\circ}C$ for further analysis by normal-phase liquid chromatography with ultraviolet (UV) detection method.

Adverse events

All spontaneously reported adverse events, as well as those elicited by open questioning or observed by the investigator were recorded.

Pharmacokinetic analyses:

The pharmacokinetic variables were estimated by non-compartmental analysis using WinNonlin Pro software.

Statistical method:

Data were analyzed descriptively. Kinetic parameters were compared between groups by student t-test.

B. Analysis of esomeprazole in plasma samples

Sample preparation

1. Frozen plasma sample was thawed and 1 ml of each sample was taken and being mixed by a vortex for 1 minute.

2. 30 µl of internal standard (carbamazepine) and 6 ml of diethylether were added and mixed by the vortex for 2 minutes.

3. Centrifuge at 3000 rpm for 15 minutes, the supernatant which was an organic solvent layer was collected and dried by nitrogen gas.

4. Residue was dissolved by 100 µl of acetonitrile and further analyzed by HPLC.

Chromatographic system:

Mobile phase	:	Methanol / H_2o / Acetic acid / Triethylamine
Flow rate	:	1.5 ml/min
UV detector	:	305 nm
Injection volumn	:	50 µl

Retention time : Esomeprazole ~ 16-17 minutes

Carbamazepine ~ 12-13 minutes

Standard calibration curve

Stock standard solutions of esomeprazole (200 and 2,000 ng/ml) were prepared in methanol to be used for the preparation of six different concentrations of esomeprazole (80, 150, 200, 300, 600 and 1,000 ng/ml) in plasma. These solutions were analyzed by HPLC technique. The peak area ratios of esomeprazole to that of the carbamazepine (internal standard) versus known concentrations of esomeprazole were fitted to straight line using linear regression.

C. Assay validation

Accuracy

Accuracy in terms of percent recovery was done by computing the ratio of inversely estimated concentration obtained using linear regression of a standard esomeprazole concentrations in plasma (150, 600 and 1,000 ng/ml) to known concentration of each standard esomeprazole concentration in plasma multiplied by one hundred.

$$\%\text{recovery} = \frac{\text{Inversely estimated concentration} * 100}{\text{Known concentration}}$$

$$\text{Inversely estimated concentration} = \frac{(\text{peak area ratio} + 0.0474)}{0.000908}$$

Within-run precision

This precision was determined by analyzing three sets of standard esomeprazole concentration in plasma (150, 600 and 1,000 ng/ml) on the same day. Peak area ratio of esomeprazole to carbamazepine was inversely estimated

concentration obtained using linear regression and the percent coefficient of variation (%C.V.) for each concentration was determined.

$$\%C.V. = (\text{standard deviation/mean}) * 100$$

Between-run precision

This precision was determined by analyzing three sets of standard esomeprazole concentration in plasma (150, 600 and 1,000 ng/ml) on five different days. Peak area ratio of esomeprazole to carbamazepine was inversely estimated concentration obtained using linear regression and the percent coefficient of variation (%C.V.) for each concentration was determined.

Linearity

Linearity in terms of the coefficient of determination (r^2) was read from the linear regression line of the calibration curve.

CHAPTER III

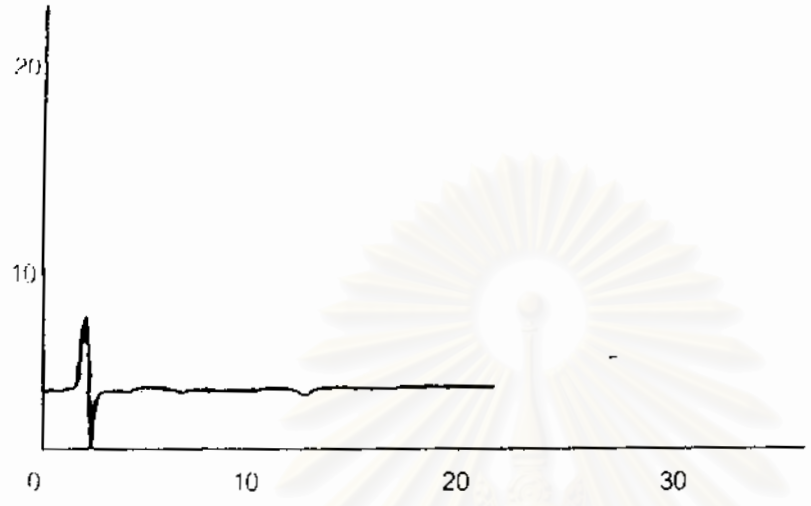
RESULTS

A. Analysis of esomeprazole in plasma

Chromatograms of blank plasma and plasma spiked with carbamazepine (internal standard) were shown in Figure 2. Chromatograms of plasma spiked with esomeprazole and carbamazepine were shown in Figure 3. The retention times of carbamazepine and esomeprazole were 13.09 and 17.14 minutes, respectively. No any interference peaks due to the presence of plasma protein and/or endogenous substances were observed, indicating selectivity of the analytical method used.

The method of analysis was validated by determining the accuracy, the within run and between run precisions. The percent recovery for accuracy was 98.92 to 99.56 percent as report in Table 1. The %C.V. in the within run and between run precision were 3.61 to 5.04 percent and 1.90 to 3.67, respectively. (Table 2 and 3) These results were within acceptance criteria for accuracy (>90%) and precisions. (<15%) The calibration curve of peak area ratio of esomeprazole to carbamazepine versus plasma esomeprazole concentrations as shown in Figure 4 was linear covered the range of concentrations used with the coefficient of determination (r^2) of 0.9985. The data including linear regression equation were reported in Table 4. The lower limit of quantitation was 80 ng/ml.

(A)



(B)

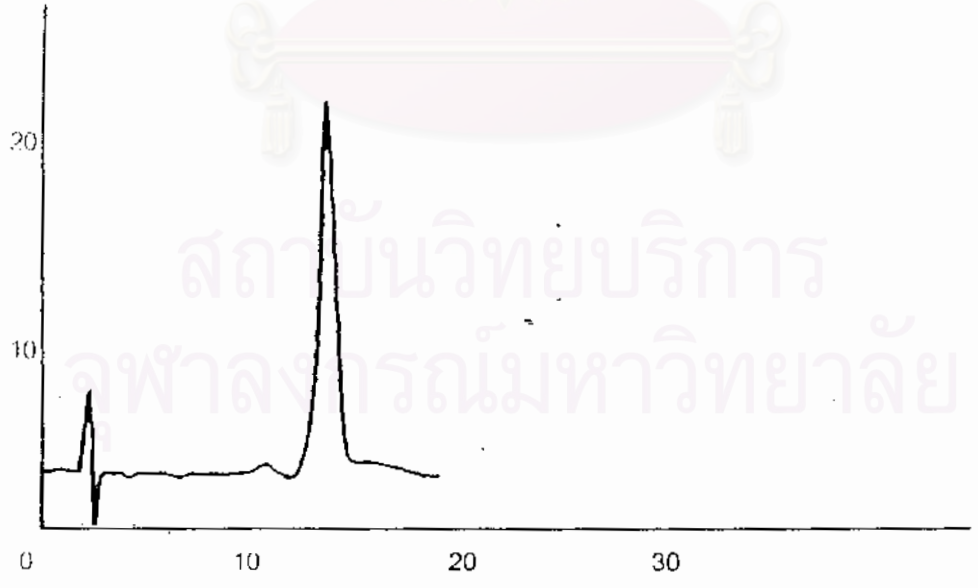


Figure 2. Chromatogram of blank plasma (A) and plasma spiked with carbamazepine (internal standard) 0.05 mg/ml (B)

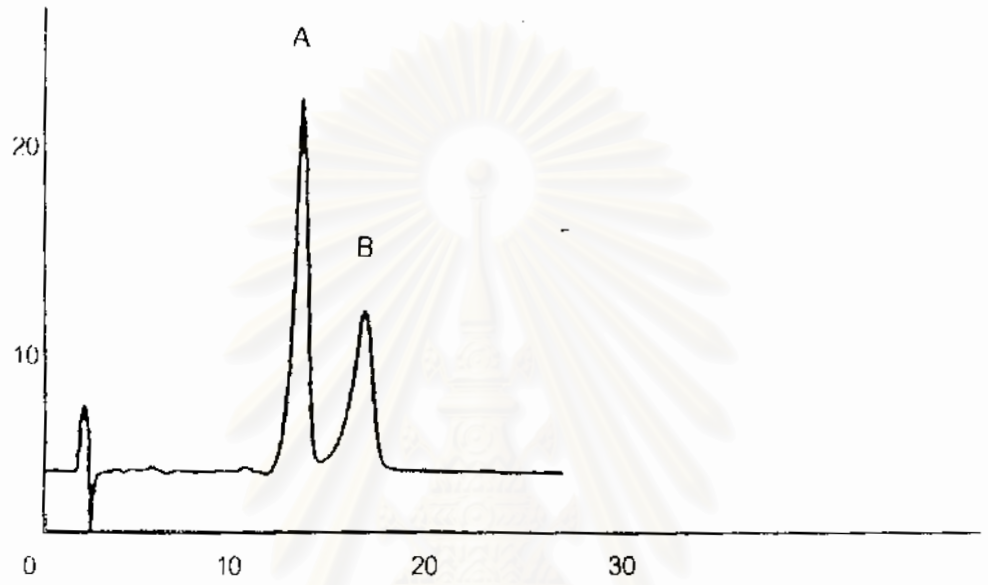


Figure 3. Chromatogram of plasma spiked with carbamazepine 0.05 mg/ml (A) and esomeprazole 0.002 mg/ml (B)

Peak A = carbamazepine, retention time 13.09 minutes

Peak B = esomeprazole, retention time 17.14 minutes

Table 1. Percent recovery of esomeprazole in plasma.

Standard No.	Concentration (ng/ml)	Peak Area Ratio*	Inversely Edtimated Concentration* (ng/ml)	%Recovery*
1	150	0.0882	149.339	99.56
2	600	0.4915	593.502	98.92
3	1,000	0.8534	992.070	99.21

* Results are mean of five samples per concentration on the same day

Table 2. Within run precision of analytical method for determination of esomeprazole in plasma.

Concentration (ng/ml)	Inversely estimated concentration					Mean ± S.D.	%C.V.
	1	2	3	4	5		
150	148.24	162.22	148.57	158.15	141.74	151.78 ± 7.39	4.87
600	649.23	608.70	595.48	584.36	606.39	608.83 ± 21.98	3.61
1,000	1008.45	10031.28	914.537	1040.09	1059.91	1010.85 ± 50.91	5.04

Table 3. Between run precision of analytical method for determination of esomeprazole in plasma.

Concentration (ng/ml)	Inversely estimated concentration					Mean ± S.D.	%C.V.
	Day 1*	Day 2*	Day 3*	Day 4*	Day 5*		
150	151.76	150.77	149.34	145.26	137.00	146.83 ± 5.39	3.67
600	608.81	595.93	593.50	569.38	563.00	586.12 ± 17.21	2.94
1,000	1010.79	1003.08	992.07	983.92	956.50	989.27 ± 18.78	1.90

* Results are mean of five samples per concentration in each day

Table 4. Linearity between concentrations and peak area ratio of esomeprazole to carbamazepine in plasma.

Standard No.	Concentration (ng/ml)	Peak Area Ratio*
1	80	0.0199
2	150	0.1045
3	200	0.1394
4	300	0.2167
5	600	0.4797
6	1,000	0.8703

* Results are mean of five samples per concentration

$r^2 = 0.9985, \quad y = 0.000908x - 0.0474$

where: y = Peak area ratio

x = Concentration

r^2 = Coefficient of determination

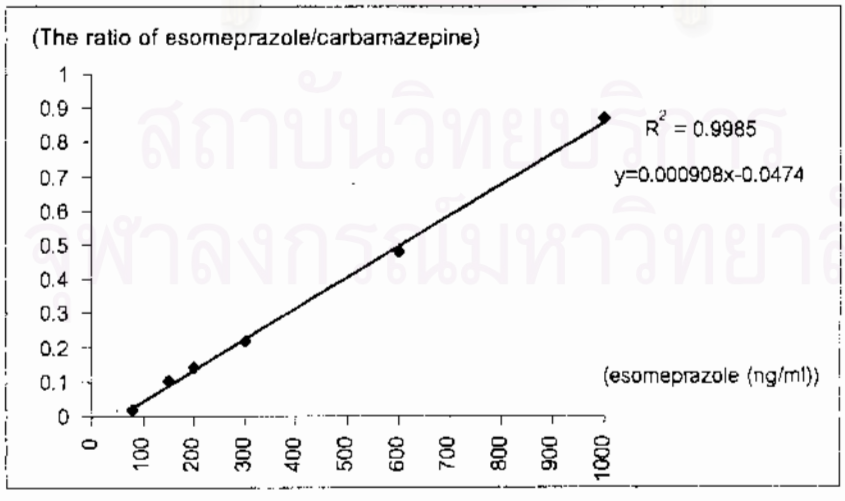


Figure 4. The calibration curve of peak area ratio of esomeprazole to carbamazepine versus plasma esomeprazole concentrations.

B. Study Population

Thai healthy volunteers with normal liver function were 7 men and 5 women, the average age and weight were 34 years (24-55 years) and 58 kgs (48-70 kgs), respectively. Their individual demographic data were shown in Table 5.

Thai cirrhotic patients were 8 men and 6 women with average age of 53 years (42 – 68 years) and average weight of 56 kgs. (45 – 72.2 kgs) Cirrhosis was rated as mild (Child Pugh Class A, n = 5), moderate (Child Pugh Class B, n = 5) and severe (Child Pugh Class C, n = 4). All patients who completed the study took the study drug in accordance with the study protocol. Their individual demographic data were shown in Table 6.

The liver and kidney function tests were performed in both healthy volunteers and cirrhotic patients on the first day and the last day of the study. The results were shown on Table 7 to 10.

Two cases (subject no. 13-14) in cirrhotic group concurrently taking lamivudine exhibited lower level of esomeprazole and were excluded from the comparison.

Table 5. Demographic data of 12 healthy volunteers.

Subject No.	Gender	Age (year)	Height (m)	Weight (kg)
1	F	26	1.68	51
2	F	42	1.60	58
3	M	31	1.65	55
4	M	32	1.75	56
5	M	25	1.70	65
6	M	24	1.68	55
7	F	50	1.62	55
8	F	29	1.65	56
9	M	55	1.77	70
10	M	32	1.70	62
11	M	36	1.70	58
12	F	28	1.60	55
Range	-	24-55	1.60-1.77	48-70
Average	-	34.17	1.67	58

Table 6. Demographic data of 14 cirrhotic patients.

Subject No.	Gender	Age (year)	Height (m)	Weight (kg)	Child Pugh's Classification	Concomitant Medication*
1	M	65	1.60	65.5	A	-
2	M	42	1.69	72.2	A	-
3	F	42	1.50	52.0	A	-
4	M	68	1.64	59.5	A	-
5	M	61	1.58	52.0	B	-
6	M	47	1.67	57.7	B	Propanolol
7	F	51	1.50	63.0	B	Propanolol
8	M	48	1.62	55.0	B	-
9	F	50	1.53	45.0	C	Furosemide
10	F	50	1.51	50.5	C	Furosemide
11	F	50	1.48	47.0	C	Furosemide
12	F	51	1.52	48.0	C	Furosemide
13	M	52	1.68	56.0	A	Lamivudine
14	M	62	1.63	61.0	B	Lamivudine
Range	-	42-68	1.48-1.69	45-72.2	-	-
Average	-	53	1.58	56.0	-	-

* Dosage regimen of concomitant medication was shown in Appendix C

Table 7. Clinical blood chemistry characteristics of Thai healthy volunte ers on the first day of the study.

Subject No.	SGPT (U/L) (7-40)*	SGOT (U/L) (7-40)*	Alkaline Phosphatase (U/L) (40-150)*	Total Bilirubin (mg/dl) (0.1-1.2)*	Creatinine (mg/dl) (0.6-1.4)*	BUN (mg/dl) (5-19)*	Albumin (g/dl) (3.5-5.0)*
1	21	28	58	1.10	0.80	6.0	4.9
2	17	25	42	0.83	0.60	6.1	4.4
3	18	27	50	1.00	0.77	8.0	4.3
4	15	23	40	0.75	0.70	6.2	4.8
5	20	27	62	0.86	1.00	8.6	4.0
6	22	28	48	0.89	1.11	8.8	4.5
7	17	27	53	0.74	0.94	7.6	4.2
8	21	28	60	0.98	0.64	8.2	4.5
9	20	28	52	1.00	0.60	6.0	4.4
10	18	26	48	0.84	0.96	9.0	4.5
11	24	29	62	0.88	0.80	10.0	4.0
12	17	25	55	0.72	0.60	11.8	4.6
Range	15-24	23-29	40-62	0.72-1.10	0.60-1.11	6.0-11.8	4.0-4.9
Average ± SD	19.17 ± 2.59	26.75 ± 1.71	52.50 ± 7.31	0.88 ± 0.12	0.79 ± 0.18	8.03 ± 1.80	4.43 ± 0.28

* = Normal Range

Table 8. Clinical blood chemistry characteristics of Thai healthy volunteers on the last day (day 5) of the study.

Subject No.	SGPT (U/L) (7-40)*	SGOT (U/L) (7-40)*	Alkaline Phosphatase (U/L) (40-150)*	Total Bilirubin (mg/dl) (0.1-1.2)*	Creatinine (mg/dl) (0.6-1.4)*	BUN (mg/dl) (5-19)*	Albumin (g/dl) (3.5-5.0)*
1	22	30	62	1.10	0.78	6.0	4.8
2	17	24	40	0.80	0.60	6.0	4.4
3	20	28	53	0.96	0.70	7.2	4.4
4	17	25	42	0.72	0.77	6.2	4.6
5	18	25	60	0.84	0.88	8.6	4.2
6	23	30	52	0.90	1.05	8.8	4.4
7	19	24	58	0.76	0.96	7.2	4.5
8	22	27	55	0.90	0.65	8.0	4.4
9	18	27	50	0.95	0.60	6.2	4.2
10	17	29	45	0.88	0.94	9.1	4.3
11	20	26	60	0.86	0.80	9.8	4.3
12	21	25	59	0.76	0.64	11.2	4.5
Range	17-23	24-30	40-62	0.72-1.10	0.60-1.05	6.0-11.2	4.2-4.8
Average ± SD	19.50 ± 2.15	26.67 ± 2.19	53.00 ± 7.43	0.87 ± 0.11	0.78 ± 0.15	7.86 ± 1.68	4.42 ± 0.17

* = Normal Range

Table 9. Clinical blood chemistry characteristics of cirrhotic patients on the first day of the study.

Subject No.	SGPT (U/L) (7-40)*	SGOT (U/L) (7-40)*	Alkaline Phosphatase (U/L) (40-150)*	Total Bilirubin (mg/dl) (0.1-1.2)*	Creatinine (mg/dl) (0.6-1.4)*	BUN (mg/dl) (5-19)*	Albumin (g/dl) (3.5-5.0)*
1	30	17	134	0.73	1.07	16.5	4.0
2	62	54	115	1.24	0.77	9.7	3.5
3	56	35	151	1.13	0.77	12.0	4.3
4	37	23	119	1.05	0.70	6.0	4.8
5	86	90	224	0.76	1.00	17.4	3.0
6	38	38	116	2.59	1.31	20.6	2.7
7	100	73	129	2.52	0.94	16.4	2.1
8	58	42	130	2.10	0.64	8.2	2.8
9	93	42	114	6.70	0.60	6.0	2.3
10	98	40	199	5.64	0.96	9.0	2.3
11	99	47	273	2.42	1.48	28.7	1.9
12	96	43	145	2.31	1.01	11.8	2.1
13	54	67	142	1.56	0.60	8.4	4.0
14	101	69	178	1.03	0.87	10.0	3.7
Range	30-101	17-90	114-273	0.73-5.64	0.60-1.48	6.0-28.7	1.9-4.8
Average ± SD	72.00 ± 26.69	48.57 ± 20.08	154.93 ± 47.45	2.27 ± 1.79	0.91 ± 0.26	12.91 ± 6.37	3.11 ± 0.94

* = Normal Range

Table 10. Clinical blood chemistry characteristics of cirrhotic patients on the last day (day 5) of the study.

Subject No.	SGPT (U/L) (7-40)*	SGOT (U/L) (7-40)*	Alkaline Phosphatase (U/L) (40-150)*	Total Bilirubin (mg/dl) (0.1-1.2)*	Creatinine (mg/dl) (0.6-1.4)*	BUN (mg/dl) (5-19)*	Albumin (g/dl) (3.5-5.0)*
1	29	16	135	0.70	1.00	16.2	4.1
2	56	49	130	2.71	0.81	10.1	3.6
3	43	29	128	1.25	0.76	11.8	4.25
4	82	48	140	0.78	0.76	8.4	4.5
5	95	84	218	0.75	0.98	14.8	3.0
6	37	50	84	2.58	1.33	19.6	3.0
7	90	80	113	2.76	0.85	15.2	2.4
8	51	38	128	2.11	0.60	7.6	2.9
9	70	33	114	6.50	0.60	6.2	2.3
10	93	38	247	5.00	0.90	8.4	2.4
11	85	38	235	2.20	1.24	22.1	1.7
12	90	37	144	2.33	0.96	10.2	2.3
13	50	67	135	2.31	0.60	8.0	4.0
14	90	52	168	1.03	0.76	9.6	3.8
Range	29-95	16-84	84-247	0.70-6.50	0.60-1.33	6.2-22.1	1.7-4.5
Average ± SD	68.64 ± 23.46	47.07 ± 19.06	151.36 ± 48.46	2.36 ± 1.65	0.87 ± 0.22	12.01 ± 4.83	3.16 ± 0.88

* = Normal Range

C. Pharmacokinetic data

The pharmacokinetic parameter in Thai healthy volunteers.

The mean C_{max}, $\overline{C}$, AUC and $t_{1/2}$ of esomeprazole 20 mg increased from day 1 to day 5 of the study by 28.31%, 13.22%, 13.22% and 11.42%, respectively. The value of mean C_{max} and $\overline{C}$ increased from 743.69 to 954.25 ng/mL and 104.33 to 118.12 ng/mL, respectively. The mean AUC and $t_{1/2}$ also increased from 2,503.82 to 2,834.90 ng/mL*hr. and 2.19 to 2.44 hr., respectively. In contrast, the mean CL/F decreased by 12.32% from 8.36 to 7.33 l/hr and the t_{max} were 1.52 to 1.06 hr. The individual pharmacokinetic parameters of Thai healthy volunteer group were presented in Table 11 and 12.

The pharmacokinetic parameter in Thai cirrhotic patients.

Similar to the results in Thai healthy volunteers, the mean C_{max}, $\overline{C}$, AUC and $t_{1/2}$ of esomeprazole 20 mg in Thai cirrhotic patients were increased from day 1 to day 5 by 7.34%, 15.11%, 15.11% and 0.49%, respectively. The value of mean C_{max} and $\overline{C}$ increased from 835.90 to 897.25 ng/mL and 145.65 to 167.66 ng/mL, respectively. The mean AUC and $t_{1/2}$ also increased from 3,495.67 to 4,023.71 ng/mL*hr. and 4.10 to 4.12 hr., respectively. In contrast, the mean CL/F decreased by 8.29% from 6.03 to 5.53 L/hr and the t_{max} were 1.38 to 1.04 hr. The individual pharmacokinetic parameters of Thai healthy volunteer group were presented in Table 13 and 14.

The mean plasma concentrations of esomeprazole 20 mg after oral administration in both 2 groups are shown in Figure 5 and 6. The mean of C_{max}, t_{max}, AUC, $t_{1/2}$ and Cl/F in Thai healthy volunteer group and Thai cirrhotic group were shown in Table 15 to 17.

Table 11. The individual pharmacokinetic parameters following oral administration of esomeprazole 20 mg once daily on the first day in healthy volunteer group.

Subject No.	C_{max} (ng/mL)	t_{max} (hr.)	AUC (ng/mL*hr.)	$\bar{C}$ (ng/mL)	$t_{1/2}$ (hr.)	CL/F (L/hr)
1.	536.12	1.50	2,858.13	119.09	2.97	6.99
2.	584.80	2.00	2,443.80	101.83	2.17	8.20
3.	513.44	1.25	1,603.38	66.81	1.63	12.5
4.	1,065.86	1.50	2,135.58	88.98	1.68	9.35
5.	781.94	1.25	3,219.60	134.15	3.31	6.21
6.	818.28	1.00	3,044.35	126.85	2.33	6.58
7.	727.64	1.00	2,156.46	89.85	1.26	9.26
8.	984.36	1.50	2,694.23	112.26	1.45	7.43
9.	783.48	1.50	2,709.18	112.88	2.31	7.38
10.	748.90	1.25	3,183.76	132.66	3.48	6.29
11.	700.33	1.25	1,840.43	76.68	1.45	10.87
12.	679.07	1.25	2,156.94	89.87	2.23	9.26
Average ± SD	743.69 ± 164.60	1.35 ± 0.27	2,503.82 ± 531.03	104.33 ± 22.13	2.19 ± 0.74	8.36 ± 1.95

Table 12. The individual pharmacokinetic parameters following oral administration of esomeprazole 20 mg once daily on the last day (day 5) in healthy volunteer group.

Subject No.	C_{max} (ng/mL)	t_{max} (hr.)	AUC (ng/mL*hr.)	$\bar{c}$ (ng/mL)	$t_{1/2}$ (hr.)	CL/F (L/hr)
1.	1,045.37	0.75	3,104.06	129.34	2.60	6.45
2.	995.93	1.25	3,315.80	138.16	2.07	6.02
3.	1,133.15	1.00	3,704.03	154.33	2.39	5.41
4.	795.93	1.00	2,455.73	102.32	2.73	8.13
5.	722.80	1.00	2,426.12	101.09	2.56	8.23
6.	1,145.37	0.75	2,968.84	123.70	2.59	6.73
7.	841.41	1.00	2,232.67	93.03	2.43	8.97
8.	818.39	1.00	2,037.67	84.90	3.12	9.80
9.	870.37	1.25	2,641.38	110.06	2.29	7.58
10.	816.74	1.25	2,482.51	103.44	2.24	8.06
11.	870.37	1.25	2,630.90	109.62	2.29	7.60
12.	1,395.15	1.25	4,019.01	167.46	2.02	4.98
Average ± SD	954.25 ± 194.42	1.34 ± 0.27	2,834.90 ± 602.38	118.12 ± 25.10	2.44 ± 0.30	7.33 ± 1.44

Table 13. The individual pharmacokinetic parameters following oral administration of esomeprazole 20 mg once daily on the first day in cirrhotic group.

Subject No.	C_{max} (ng/mL)	t_{max} (hr.)	AUC (ng/mL*hr.)	$\bar{C}$ (ng/mL)	$t_{1/2}$ (hr.)	CL/F (L/hr)
1.	680.95	0.75	2,083.25	86.80	4.24	8.62
2.	374.12	1.25	3,228.22	134.51	4.42	5.33
3.	711.34	1.00	3,754.19	156.42	3.15	6.19
4.	757.38	1.00	2,319.81	96.66	4.60	9.62
5.	947.14	1.25	4,406.33	183.60	3.64	5.93
6.	942.84	1.00	3,303.69	137.65	4.11	6.31
7.	863.11	1.00	3,169.25	132.05	2.97	6.06
8.	992.84	1.25	3,369.00	140.38	2.51	4.54
9.	981.28	1.00	4,114.46	171.44	4.46	4.37
10.	1,002.42	1.00	3,507.76	146.16	4.63	4.87
11.	963.77	1.00	4,112.65	171.36	6.05	5.70
12.	813.66	1.25	4,579.41	190.81	4.45	4.87
13.	592.84	1.25	2,741.96	114.25	5.04	7.30
14.	497.80	0.75	758.05	31.59	1.35	26.32
Total mean No. 1-12 ± SD	835.90 ± 184.35	1.06 ± 0.16	3,495.67 ± 765.32	145.65 ± 31.89	4.10 ± 0.94	6.03 ± 1.59

Table 14. The individual pharmacokinetic parameters following oral administration of esomeprazole 20 mg once daily on the last day (day 5) in cirrhotic group.

Subject No.	C_{max} (ng/mL)	t_{max} (hr.)	AUC (ng/mL*hr.)	$\bar{C}$ (ng/mL)	$t_{1/2}$ (hr.)	CL/F (L/hr)
1.	818.83	0.75	2,251.34	93.81	2.79	5.39
2.	725.77	1.50	2,887.91	120.33	3.88	8.66
3.	557.93	1.25	2,313.35	96.39	4.61	6.92
4.	789.76	1.75	3,707.12	154.46	3.29	8.89
5.	884.58	1.25	6,138.34	255.76	4.88	4.80
6.	765.42	1.00	3,088.92	128.71	3.79	6.25
7.	752.20	1.00	3,204.17	133.51	3.68	6.47
8.	764.10	0.75	4,173.97	173.92	4.43	3.26
9.	1255.18	0.75	5,215.98	217.33	4.64	3.36
10.	1,211.56	0.75	4,811.42	200.48	4.17	4.42
11.	1,254.85	0.75	4,529.20	188.72	4.68	4.16
12.	986.78	1.00	5,962.81	248.45	4.56	3.83
13.	180.84	4.00	1,984.42	82.68	5.90	10.10
14.	675.44	0.75	1,295.27	53.97	2.41	15.38
Total mean No. 1-12 ± SD	897.25 ± 229.89	1.04 ± 0.33	4,023.71 ± 1,333.29	167.66 ± 55.55	4.12 ± 0.64	5.53 ± 1.93

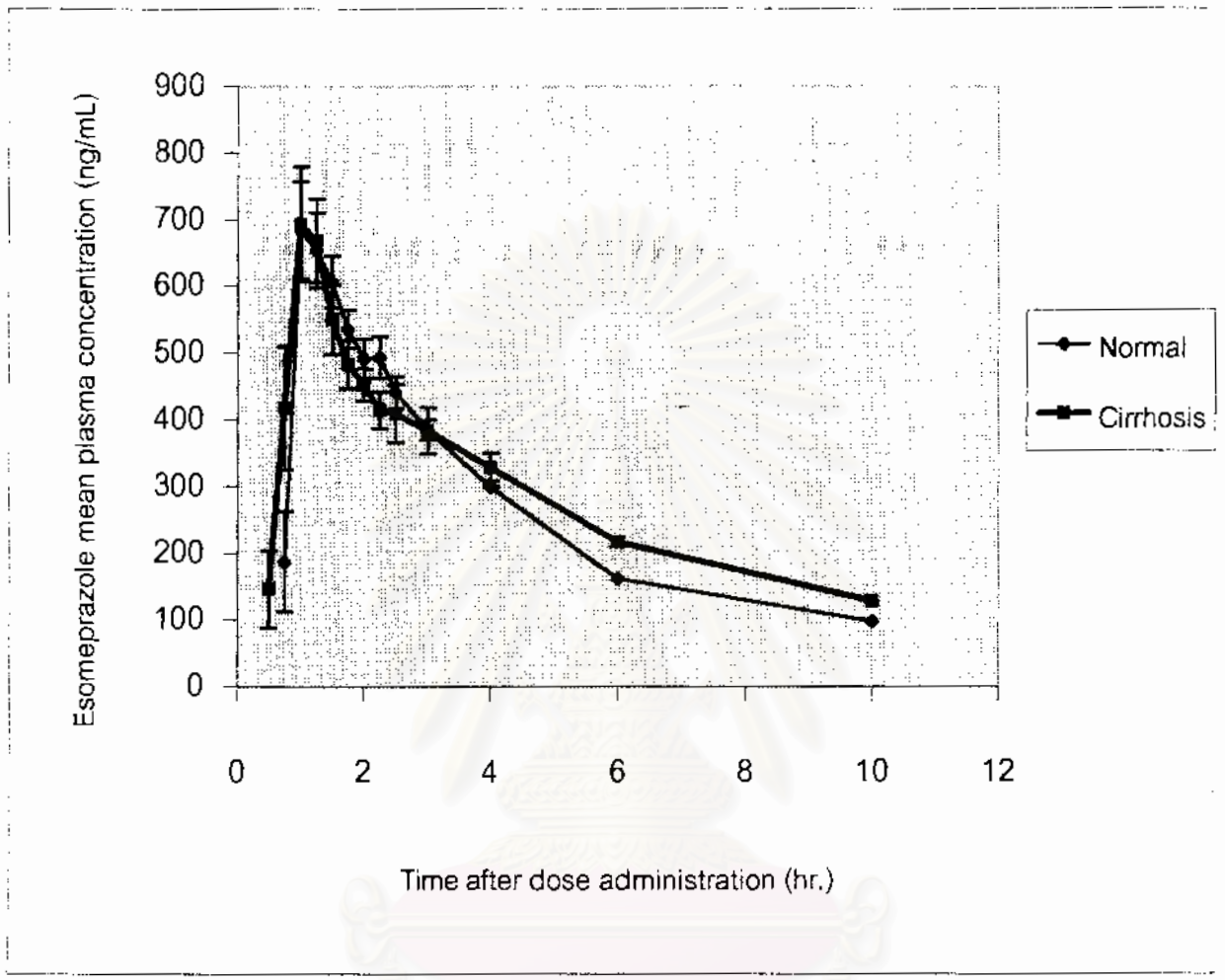


Figure 5. **Mean plasma concentration time profile on the first day following oral administration of esomeprazole 20 mg once daily in Thai healthy volunteer group (normal, n = 12) and Thai cirrhotic group. (cirrhosis, n = 12)**

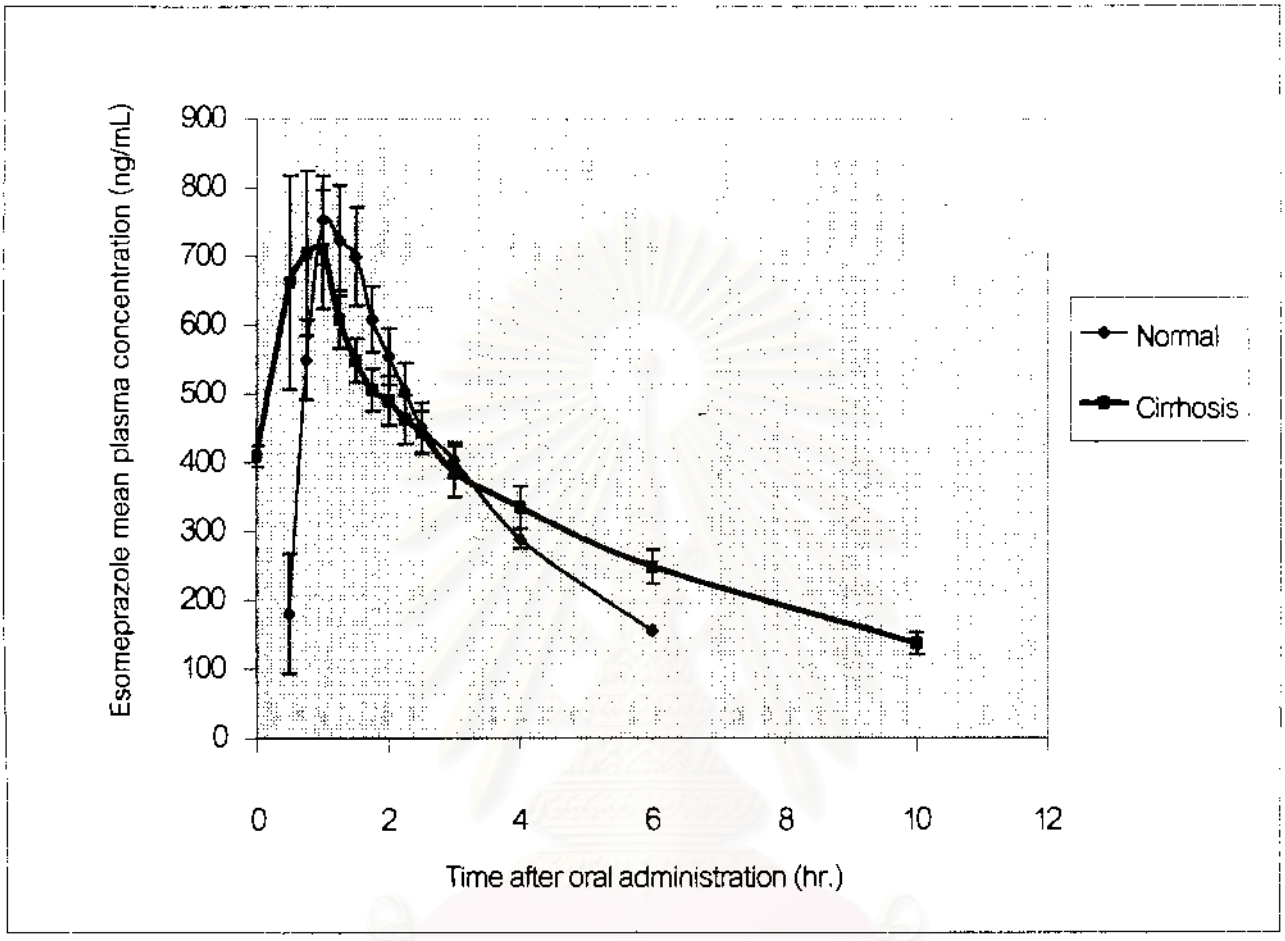


Figure 6. Mean plasma concentration time profile on the last (Day 5) day following oral administration of esomeprazole 20 mg once daily in Thai healthy volunteer group (normal, n = 12) and Thai cirrhotic group. (cirrhosis, n = 12)

Table 15. Pharmacokinetic parameters of the healthy volunteer and the cirrhotic groups following oral administration of esomeprazole 20 mg once daily on the first day.

Group	Pharmacokinetic parameters					
	C_{max} (ng/mL)	$\bar{C}$ (ng/mL)	t_{max} (hr.)	AUC (ng/mL*hr.)	$t_{1/2}$ (hr.)	CL/F (L/hr)
Normal hepatic function (n=12)	743.69 ± 164.60	104.33 ± 22.13	1.35 ± 0.27	2,503.82 ± 531.03	2.19 ± 0.74	8.36 ± 1.95
Hepatic impairment						
Mild (n=4)	630.95 ± 174.08	118.60 ± 32.54	1.00 - ± 0.20	2,846.37 ± 780.93	4.10 ± 0.65	7.44 ± 2.01
Moderate (n=4)	936.48 ± 53.89	148.42 ± 23.71	1.13 ± 0.14	3,562.67 ± 568.95	3.31 ± 0.71	5.71 ± 0.80
Severe (n=4)	940.28 ± 85.88	169.94 ± 18.31	1.06 ± 0.13	4,078.57 ± 439.36	4.90 ± 0.77	4.95 ± 0.55
Total mean of hepatic impairment	835.90 ± 184.35	145.65* ± 31.89	1.06 ± 0.16	3,495.67* ± 765.32	4.10* ± 0.94	6.03* ± 1.59

* $P < 0.05$, cirrhotic patients versus healthy volunteers

Table 16. Pharmacokinetic parameters of the healthy volunteer and the cirrhotic groups following oral administration of esomeprazole 20 mg once daily on the last day. (Day 5)

Group	Pharmacokinetic parameters					
	C_{max} (ng/mL)	$\bar{C}$ (ng/mL)	t_{max} (hr.)	AUC (ng/mL*hr.)	$t_{1/2}$ (hr.)	CL/F (L/hr)
Normal hepatic function (n=12)	954.25 ± 194.42	118.12 ± 25.10	1.06 ± 0.19	2,834.90 ± 602.38	2.44 ± 0.82	7.33 ± 1.44
Hepatic impairment						
Mild (n=4)	723.07 ± 116.76	116.25 ± 28.13	1.31 ± 0.43	2,789.93 ± 675.29	3.64 ± 0.78	7.47 ± 1.64
Moderate (n=4)	791.58 ± 62.29	172.98 ± 58.80	1.00 ± 0.20	4,151.35 ± 1411.21	4.20 ± 0.56	5.20 ± 1.49
Severe (n=4)	1,177.09 ± 128.52	213.75 ± 25.95	0.81 ± 0.13	5,129.85 ± 622.74	4.51 ± 0.23	3.94 ± 0.46
Total mean of hepatic impairment	897.25 ± 229.89	167.66* ± 55.55	1.04 ± 0.33	4,023.71* ± 1,333.29	4.12* ± 0.64	5.53* ± 1.93

*$P < 0.05$, cirrhotic patients versus healthy volunteers

Table 17. A summary of the pharmacokinetic parameters following oral administration of esomeprazole 20 mg once daily on the first day and the last day (day 5) of the study in the healthy volunteer and the cirrhotic groups.

Group	The mean of pharmacokinetic parameters											
	C_{max} (μmol/l)		$\bar{C}$ (ng/mL)		t_{max} (hr.)		AUC (μmol*hr./l)		$t_{1/2}$ (hr.)		CL/F (l/hr)	
	1st day	5th day	1st day	5th day	1st day	5th day	1st day	5th day	1st day	5th day	1st day	5th day
Normal hepatic Function (n=12)	743.69 ± 164.60	954.25 ± 194.42	104.33 ± 22.13	118.12 ± 25.10	1.35 ± 0.27	1.06 ± 0.19	2,503.82 ± 531.03	2,834.90 ± 602.38	2.19 ± 0.74	2.44 ± 0.82	8.36 ± 1.95	7.33 ± 1.44
Hepatic Impairment (n=12)	835.90 ± 184.35	897.25 ± 229.89	145.65* ± 31.89	167.66* ± 55.55	1.06 ± 0.16	1.04 ± 0.33	3,495.67* ± 765.32	4,023.71* ± 1,333.29	4.10* ± 0.94	4.12* ± 0.64	6.03* ± 1.59	5.53* ± 1.93

*$P < 0.05$, cirrhotic patients versus healthy volunteers

D. Adverse events

Adverse events were generally mild to moderate in intensity. Mild diarrhea was mostly frequent, 7 in healthy volunteers and 5 cirrhotic patients. Flatulence was reported by 4 healthy volunteers and 2 cirrhotic patients. The adverse events in cirrhotic patients occurred throughout the study period whereas they occurred only for the first few days in healthy volunteers. However, the adverse drug reaction from esomeprazole would disappear when discontinued. There was a severe cirrhotic patient with hepatic encephalopathy had moderate diarrhea when received esomeprazole and lactulose on the first day of the study, but when discontinue lactulose, the adverse effect from diarrhea was disappear. (Before this subject received esomeprazole, she was taking lactulose for excrete some toxic substance (NH_3) and treat for constipation) No adverse events were reported in the follow up period. (a period of one week after the last dosing of esomeprazole)

CHAPTER IV

DISCUSSION AND CONCLUSIONS

The present studies demonstrated the pharmacokinetics of esomeprazole 20 mg given once daily for 5 consecutive days in 14 Thai cirrhotic patients in relation to 12 Thai healthy volunteers. The repeated dose of esomeprazole 20 mg in Thai healthy volunteers for 5 days resulted in an increase, albeit to a lesser extent than a previously reported (Hassan, Andersson and Bredberg, 2000), in C_{max} , AUC and $t_{1/2}$ in comparison to its single dose pharmacokinetics. Rather similar profile of change between pharmacokinetic parameters of day 1 and day 5 were also observed in Thai cirrhotic patients. Decrease in clearance (Dose/AUC) was apparent in both study groups and that may underlie the results observed.

As expected, the pharmacokinetics of esomeprazole of both single and repeated dose in Thai cirrhotic patients are considerably changed from their corresponding values in Thai healthy volunteers. C_{max} and t_{max} in cirrhotic patients were not significantly differ from those in normal volunteers either at day 1 or day 5 implying that absorption of esomeprazole was unaltered in cirrhotic patients. However, AUC (3,495.67 $\pm$ 765.32 ng/mL*hr.) as well as $t_{1/2}$ (4.10 $\pm$ 0.94 hr.) of esomeprazole in cirrhotic patients at day 1 were significantly higher than those observed in their normal counterparts which exhibited the AUC of 2,503.82 $\pm$ 531.03 ng/mL*hr. and $t_{1/2}$ of 2.19 $\pm$ 0.74 hr. Statistical significance of AUC and $t_{1/2}$ between these two groups of patients was also noted at steady state when the AUC and $t_{1/2}$ in cirrhotic group were found to be 4,023.71 $\pm$ 1,333.29 ng/mL*hr. and 4.12 $\pm$ 0.64 hr., respectively whereas their corresponding values in normal volunteers were 2,834.90 $\pm$ 602.38 ng/mL*hr. and 2.44 $\pm$ 0.82 hr. Moreover, CL/F at day 1 of esomeprazole in cirrhotic patients (6.03 $\pm$ 1.59 L/hr.) were lower than in normal volunteers (8.36 $\pm$ 1.95 L/hr.) as the same direction on day 5. (5.53 $\pm$ 1.93 L/hr. and 7.33 $\pm$ 1.44 L/hr., respectively)

Previous study of oral administration of esomeprazole 40 mg once daily for 5 days in elderly (71-80 years) and middle-aged group (29-58 years) demonstrated that the pharmacokinetics of esomeprazole was not significantly affected by age and thus no dose adjustment is required in geriatric patients. (Hasselgren et al. 2001) Thus the impact of relatively older age of cirrhotic patients, in the present study, on an increment of AUC and $t_{1/2}$ was unlikely. On the other hand, the finding that clearance of esomeprazole in cirrhotic patients seemed to decrease proportionally to the degree of hepatic impairment in which clearance in severe hepatic impairment (Child pugh class C) was almostly 50% reduced, it is suggestive that enhancement of AUC and $t_{1/2}$ found in cirrhotic group could have been due to reduced hepatic metabolism in cirrhotic patients. Similar results have been reported in Swedish patients taking 40 mg of esomeprazole once daily for 5 days (Sjovall et al. 2002) as well as from other proton pump inhibitors such as omeprazole (Rinetti, 1991), pantoprazole (Ferron et al. 2001) and lansoprazole. (Delhotal et al. 1993)

Furthermore, it was found that $t_{1/2}$ of esomeprazole in Thai cirrhotic patients as well as Thai healthy volunteers in the present studies, were apparently higher than their Swedish counterparts. (Hassan, Andersson and Bredberg, 2000) Due to the fact that esomeprazole is extensively metabolized by hepatic cytochrome P450, mainly by CYP2C19 and to a minor extent by CYP3A4 (Abelo, Andersson and Antonsson, 2000), variation in activity of CYP2C19 may affect metabolism of esomeprazole. Poor metabolizers of CYP2C19 which has been reported to be prominent in Asian ethnic group (15-20%) than in Caucasian (3%) may underlie prolonged $t_{1/2}$ observed in both normal and cirrhotic Thai patients. Additional genotyping or phenotyping studies of CYP2C19 are further needed to clarify this finding. Furthermore, based on the finding that plasma level of esomeprazole, before the administration of the next respective dose of esomeprazole, was below detection limit of HPLC used, (except patients with severe cirrhosis) therefore, accumulation was hardly occur in people with normal hepatic function and patients with mild to moderate cirrhosis.

With regards to adverse effect, mild diarrhea was the most common form of adverse effect found in both healthy volunteers and cirrhotic patients. Flatulence was also noted in both groups but to a minor degree. Similar profile of adverse event have been reported in 6,000 adult patients with GERD who received 20 or 40 mg of esomeprazole up to 12 months. (Richter, Kahrilas and Johanson, 2001) Thus, special care should be taken to avoid excessive diarrhea when esomeprazole is co-administered with lactulose in hepatic encephalopathic patients. No other serious adverse effect than those mentioned above was found during the study in both 2 groups. Therefore, the mean plasma concentration to presume the efficacy and safety in healthy volunteers and cirrhotic patients for single dose (day 1) should be within the range of 66.81-134.15 ng/ml and 86.80-190.81 ng/ml, respectively and the corresponding value for multiple doses (day 5) should be within the range of 84.90-167.46 ng/ml and 93.81-255.76 ng/ml, respectively.

In conclusion, despite significant changes in AUC and $t_{1/2}$ in cirrhotic patients, esomeprazole in the dose of 20 mg seemed to be well-tolerated in patients with varying degree of hepatic impairment. Therefore dose adjustment of esomeprazole is not essentially needed in hepatic compromised patients. However, this might not be the case for drugs with narrow therapeutic index. Therefore, in order to assure safe use of medication in different populations, bridging pharmacokinetic studies of such drugs should be carried out especially for those drugs that are metabolized mainly by hepatic enzyme that could be different in different ethnic groups.

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APPENDICES

APPENDIX A

Documentary proof of ethical clearance and confidential form

Documentary Proof of Ethical Clearance

by the Ethics Committee

Faculty of Tropical Medicine

Mahidol University, Bangkok

Title of project : "Pharmacokinetics of Esomeprazole in Thai patients with liver cirrhosis"

Principal Investigator : Assist. Prof. Sombat Treeprasertsuk

Address : Department of Clinical Tropical Medicine
Faculty of Tropical Medicine
Mahidol University
420/6 Rajvithi Road, Bangkok 10400

Approved by the Ethics Committee, Faculty of Tropical Medicine

Chairman

(Prof. Polrat Wilairatana)

Dean

(Prof. Somchai Looareesuwan)

Date 7/03/2003

บันทึกข้อความ

ส่วนราชการ ฝ่ายวิจัย คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทร 4455, 4493

ที่ วจ21/2546 วันที่ 11 กุมภาพันธ์ พ.ศ. 2546

เรื่อง แจ้งผลพิจารณาจริยธรรมการวิจัย

เรียน รศ.พญ.วโรชา มหาชัย

จากการประชุมคณะกรรมการพิจารณาจริยธรรมการวิจัย ครั้งที่ 2/2546 ในวันอังคาร ที่ 4 กุมภาพันธ์ พ.ศ. 2546 ได้พิจารณาโครงการวิจัย (ฉบับแก้ไข) และ Patient informe consent (ฉบับแก้ไข) เรื่อง "เภสัชจลนศาสตร์ของยาอีโซเมปราโซลในผู้ป่วยโรคตับแข็งชาวไทย" ซึ่ง รศ.พญ.วโรชา มหาชัย เป็นหัวหน้าโครงการวิจัย

ที่ประชุมมีมติให้ผ่านปัญหาจริยธรรมได้

จึงเรียนมาเพื่อทราบ

(รองศาสตราจารย์ แพทย์หญิงธาดา สืบหลินวงศ์)

รองคณบดีฝ่ายวิจัย

บันทึกข้อความ

ส่วนราชการ ฝ่ายวิจัย คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทร. 2188261 โทรสาร. 2558227

ที่ ทม 0316 (วจ) / ภายใน วันที่ 4 ตุลาคม 2545

เรื่อง การพิจารณาด้านจริยธรรมทางโครงการวิจัย

เรียน นางสาวกัลยาณี อาชาสันติสุข

ตามที่ท่านได้เสนอโครงการวิจัยเรื่อง " เภสัชกรรมจลนศาสตร์ของยาอีโซเมปราโซลในผู้ป่วยโรคดับชาวไทย" เพื่อให้คณะภรรมการด้านจริยธรรมของการศึกษาวิจัยในสัตว์และมนุษย์ ได้พิจารณานั้น จากการประชุมคณะกรรมการฯ ครั้งที่ 4/2545 เมื่อวันอังคารที่ 1 ตุลาคม 2545 ได้พิจารณารับรองทางด้านจริยธรรมของโครงการดังกล่าว โดยมีข้อเสนอแนะเปลี่ยนความในชื่อโครงการวิจัย (ภาษาไทย) จาก "ผู้ป่วยโรค ดับ" เป็น "ผู้ป่วยโรคดับแข็ง"

จึงเรียนมาเพื่อทราบ

(รองศาสตราจารย์ ดร.บุญยงค์ ดันติสิระ)

คณบดีคณะเภสัชศาสตร์

ประธานคณะกรรมการด้านจริยธรรมของการศึกษาวิจัยในสัตว์และมนุษย์

สำเนาเรียน อาจารย์ที่ปรึกษาวิทยานิพนธ์ (รองศาสตราจารย์ ดร.มยุรี ดันติสิระ)

ฝ่ายวิจัย คณะเภสัชศาสตร์
โทรศัพท์ 02-2188251 หรือ 02-2188261

Subject Initials: _ _ _ _ Subject

Number: _ _ Date: _ _/_ _/_ _ _ _

Demography:

Date of Birth: _ _/_ _/_ _ _ _	Weight (kg): _ _ _ . _ _	Height (cm): _ _ _ . _ _
Gender: ☐ Male		Race: ☐ Thai
☐ Female		☐ Others.....

Written Informed Consent:

Subject's written informed consent obtained?	☐ Yes	☐ No
Date written informed consent was obtained: _ _/_ _/_ _ _ _		

Vital Signs:

Temperature (°C)	: _ _ . _	Heart Rate (beats/min)	: _ _
Blood Pressure (mmHg)	: _ _ _/_ _	Respiratory Rate (times/min)	: _ _

Physical Examination:

Body System	Normal	Abnormal	If Abnormal, please provide details
1. General appearance	☐	☐	
2. Head, ears, eyes, nose, throat	☐	☐	
3. Neck	☐	☐	
4. Heart	☐	☐	
5. Lungs	☐	☐	
6. Abdomen	☐	☐	
7. Lymph nodes	☐	☐	
8. Genitourinary	☐	☐	
9. Extremities	☐	☐	
10. Neurological	☐	☐	
11. Skin	☐	☐	
12. Musculoskeletal	☐	☐	
13. Others.....	☐	☐	

Are there any new clinically significant abnormalities or worsening of any existing abnormalities?

☐ No ☐ Yes → If 'Yes', please record in Adverse Event section.

Smoking Habits:

Is the subject currently a

☐ Non-Smoker

☐ Ex-Smoker → Stopped since _ _/_ _/_ _ _ _

Average number of cigarettes = _ _ _/day

☐ Smoker → Smoking since _ _/_ _/_ _ _ _

What does the subject smoke?

☐ Cigarette → _ _ _/day

☐ Cigar → _ _ _/day

☐ Pipe → _ _ _/day

Drinking Habits:

Does the subject consume alcohol on a regular basis?

☐ No ☐ Yes → _ _ _ units/week

(NB: 1 unit = 8g of alcohol = 1 standard drink = 250 ml of beer = 25 ml of spirit = 140 ml of wine)

Concurrent Illness:

Does the subject have any concurrent illness? ☐ No ☐ Yes .....

Concomitant Medication:

Is the subject currently taking any medication (s)? ☐ No ☐ Yes .....

Pregnancy:

Does the subject have a pregnancy now? ☐ No ☐ Yes

Dispensing of Study Medication:

Date of dispensing: _ _/_ _/_ _ _ _

Dose: ☐ 20 mg ☐ 40 mg

Adverse Events:

Are there any adverse experiences observed or elicited during the study?

☐ No ☐ Yes → _ _/_ _/_ _ _ _ Symptom: .....

Complete or Incomplete the study:

Does the subject terminate from the study?

☐ No ☐ Yes

Reason for Termination:

Date subject discontinuation from the study: _ _/_ _/_ _ _ _

Check one of the reasons below:

☐ Subject has adverse drug reaction from the study

☐ Subject is non-compliance to take Esomeprazole during the study period

☐ Subject drinks grapefruit juice or alcohol 2 days before and during the study period

☐ Subject eats grapefruit 2 days before and during the study period

☐ Subject takes OTC or other drugs 2 weeks before and during the study period

☐ Subject requests to discontinue the study by no reason

☐ Discontinuation of the study at the request of the sponsor, following consultation with the investigators

☐ Lost to follow-up

☐ Others.....

.....

Inclusion criteria for healthy volunteer subjects:

Complete the following inclusion criteria (✓ one box of each question)	Yes	No
1. Has signed and dated written informed consent been obtained from the subject prior to study participation?	☐	☐
2. Is the subject a male or female ≥ 20 and ≤ 65 years	☐	☐
3. Has the subject healthy and normal liver function?	☐	☐
4. Is the subject able to comply with study requirements and scheduled follow-up visits?	☐	☐

If any of the 'NO' boxes are ✓, This subject must not be entered into this study

Inclusion criteria for liver cirrhosis subjects:

Complete the following inclusion criteria (✓ one box of each question)	Yes	No
1. Has signed and dated written informed consent been obtained from the subject prior to study participation?	☐	☐
2. Is the subject a male or female ≥ 20 and ≤ 65 years	☐	☐
3. Has the subject liver cirrhosis?	☐	☐
4. Is the subject able to comply with study requirements?	☐	☐

If any of the 'NO' boxes are ✓, This subject must not be entered into this study

Exclusion criteria for both of healthy volunteer and liver cirrhosis subjects:

Complete the following inclusion criteria (✓ one box of each question)	Yes	No
1. Has the subject a large or multiple hepatocellular carcinoma?	☐	☐
2. Has the subject any disease or unstable concomitant diseases likely to interfere with the results of the study?	☐	☐
3. Has the subject a history of severe allergic disease?	☐	☐
4. Is the subject hypersensitivity to esomeprazole or benzimidazoles?	☐	☐
5. Is the subject renal failure? (serum creatinine >150 μmol/l)	☐	☐
6. Has the subject pregnancy or nursing women?	☐	☐

If any of the 'YES' boxes are ✓, this subject must not be entered into this study

Laboratory Results:

Haematology				
Collection Date: _ _/_ _/_ _ _ _	Units	Clinical Assessment		
		Normal	Abnormal, no Significance	Abnormal, significance
Haemoglobin _ _ _._		☐	☐	☐
RBC _ _._		☐	☐	☐
WBC _ _._		☐	☐	☐
Neutrophil _ _._ _		☐	☐	☐
Lymphocyte _ _._ _		☐	☐	☐
Monocyte _ _._ _		☐	☐	☐
Eosinophil _ _._ _		☐	☐	☐
Basophil _ _._ _ _		☐	☐	☐
Platelet Count _ _ _._		☐	☐	☐
Prothrombin Time _ _ _	secs	☐	☐	☐

Laboratory Results:

Biochemistry				
Collection Date: _ _/_ _/_ _ _ _	Units	Clinical Assessment		
		Normal	Abnormal, no Significance	Abnormal, significance
Albumin _ _ _._		☐	☐	☐
SGOT/AST _ _ _._		☐	☐	☐
SGPT/ALT _ _ _._		☐	☐	☐
Alkaline Phosphatase _ _ _._		☐	☐	☐
Total Bilirubin _ _ _._		☐	☐	☐
Creatinine _ _ _._		☐	☐	☐
Blood Urea Nitrogen (BUN) _ _ _._		☐	☐	☐
Sodium _ _ _._		☐	☐	☐
Potassium _ _ _._		☐	☐	☐

Laboratory Results:

Urinalysis					
Collection Date: _ _/_ _/_ _ _ _			Clinical Assessment		
			Normal	Abnormal, no Significance	Abnormal, Significance
PH _ . _			☐	☐	☐
Specific Gravity (SG) _ . _ _ _			☐	☐	☐
Protein	☐ Present	☐ Absent	☐	☐	☐
Glucose	☐ Present	☐ Absent	☐	☐	☐
Ketone	☐ Present	☐ Absent	☐	☐	☐
Bilirubin	☐ Present	☐ Absent	☐	☐	☐
Blood	☐ Present	☐ Absent	☐	☐	☐
Nitrite	☐ Present	☐ Absent	☐	☐	☐
Urobilinogen	☐ Present	☐ Absent	☐	☐	☐
RBC	☐ Present	☐ Absent	☐	☐	☐
WBC	☐ Present	☐ Absent	☐	☐	☐
Casts	☐ Present	☐ Absent	☐	☐	☐
Crystals	☐ Present	☐ Absent	☐	☐	☐

Grading system for cirrhosis: Child-Pugh Score (Pugh, Murray and Dawson, 1973)

Score	Bilirubin (mg/dl)	Albumin (gm/dl)	PT (sec) Longer than control	Hepatic Encephaolpathy (grade)	Ascites
1	<2	>3.5	1-4	None	None
2	2-3	2.8-3.5	4-6	1-2	Mild
3	>3	<2.8	>6	3-4	Severe

Grade A (Good operative risk) Total score 5-6 (mild)

Grade B (Moderate operative risk) Total score 7-9 (moderate)

Grade C (Poor operative risk) Total score 10-15 (severe)

Grading System for hepatic encephalopathy (Rowen, 1991)

Grade	Level of conciousness	Personality and Intellectual	Neurological abnormalities	EEG abnormal
0	Normal	None	Nil	Normal
1	Inverted sleep pattern, restless	Forgetful, irritable, mild confusion	Tremor, impaired hand writing	Slow triphasic wave
2	Slow responses	Amnesia, inappropriate behavior	Asterixis	Slow triphasic wave
3	Somnolent	Disorientation for place	Asterixis	Slow triphasic wave
4	Coma	Disorientation for place	Asterixis	Slow 2-3 CPS, delta activity

Test	Value	Score
Bilirubin (mg/dl)		
Albumin (gm/dl)		
PT (secs)		
Hepatic Encephalopathy (grade)		
Ascites		

Total score is ___ = Grade ___

APPENDIX B

The preparation of anticoagulant and blood collection

A. Preparation of anticoagulant

The preparation of anticoagulant for this study was heparin. It was diluted to 1:1000 in 0.9% normal saline for protection clotted blood while collecting blood sample. After preparation, it could keep for a month at a temperature of 4°C

B. A method of blood collection

The first of all we had to select a good vein, not too small and the subject felt comfortable to move a body. After that, cleaned a skin with 2.5% Iodine and 70% alcohol, then stab by IV. Catheter into the vein and waited until it had a blood flow, used three ways for lock and collection blood following time setting. The most important for blood collection was push the anticoagulant preparation 1 ml into a hole of three ways every time after drawn blood sample for protection blood clotting. Before collection blood sample for the next time, it had to drawn 1 ml of the preparation which was injected a moment and then collect blood sample 5 ml as a schedule.

APPENDIX C

Dosage regimens of concomitant medication in cirrhotic group

Subject No.	Concomitant medication with esomeprazole
1	-
2	-
3	-
4	-
5	-
6	Propanolol 40 mg 1*2 pc
7	Propanolol 40 mg 1*2 pc
8	-
9	Furosemide 40 mg 1*1 pc
10	Furosemide 40 mg 1*1 pc
11	Furosemide 40 mg 1*1 pc
12	Furosemide 40 mg 1*1 pc
13	Lamivudine 100 mg 1*1 pc
14	Lamivudine 100 mg 1*1 pc

All of concomitant medication with esomeprazole took after esomeprazole 2 hours.

APPENDIX D

The individual data of concentration at times after oral administration on day 1 in healthy volunteers

Time after oral administration (hr.)	Concentration (ng/mL)												Average	S.D.
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10	No. 11	No. 12		
0	*	*	*	*	*	*	*	*	*	*	*	*	*	*
0.5	*	*	*	*	*	*	*	*	*	*	*	*	*	*
0.75	*	*	370.04	106.39	418.60	*	*	*	*	86.56	*	*	245.4	173.29
1	*	*	468.06	948.57	778.52	818.28	727.64	794.71	505.07	649.01	621.81	527.42	683.91	156.13
1.25	197.25	155.18	513.44	989.65	781.94	763.11	659.58	976.89	677.86	748.90	700.33	679.07	653.60	258.4519
1.5	346.92	194.27	411.23	1065.86	436.56	603.19	501.87	984.36	783.48	720.04	638.88	589.65	606.36	254.883
1.75	208.04	175.33	404.52	738.88	526.65	575.99	499.45	827.75	703.63	608.81	604.19	555.65	535.74	196.0206
2	256.61	280.07	346.04	628.19	531.28	617.51	479.41	630.72	581.94	581.06	521.92	450.11	492.07	133.3291
2.25	503.30	497.80	354.95	467.29	646.37	630.40	631.94	703.63	550.44	557.71	475.66	480.95	541.70	97.88064
2.5	536.12	528.96	296.15	453.41	595.48	564.87	596.59	627.20	474.01	428.41	421.26	394.49	493.08	98.74714
3	526.98	584.80	297.69	275.22	522.25	518.28	492.40	523.35	426.54	384.58	336.23	325.88	434.52	106.6883
4	414.43	406.83	183.81	182.38	327.79	393.50	311.67	350.55	344.38	338.00	200.88	259.91	309.51	84.1036
9	223.57	213.47	82.21	*	204.41	188.44	96.41	116.74	171.40	193.87	*	130.84	162.14	51.35
10	100.55	*	*	*	92.40	*	*	*	*	98.90	*	*	97.28	4.31

* = Lower limit of quantitation (LLOQ)

The individual data of concentration at times after oral administration on day 5 in healthy volunteers

Time after oral administration (hr.)	Concentration (ng/mL)												Average	S.D.
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10	No. 11	No. 12		
0	*	*	*	*	*	*	*	*	*	*	*	*	*	*
0.5	160.35	*	222.80	*	*	*	*	*	185.79	*	151.98	*	180.23	31.81
0.75	1045.37	406.28	668.40	622.58	406.28	1145.37	559.80	577.42	456.83	169.27	356.60	175.77	549.16	300.3606
1	895.93	645.04	1133.15	795.93	722.80	1125.99	841.41	818.39	725.00	645.04	451.81	595.93	783.04	201.7126
1.25	722.80	995.93	1093.50	713.66	707.93	820.93	588.33	689.54	870.37	816.74	700.33	1395.15	842.93	223.8334
1.5	673.79	925.88	1008.59	614.21	357.27	353.19	445.37	599.45	714.98	733.81	638.88	1328.71	699.51	280.8042
1.75	393.94	791.08	920.93	540.86	391.52	408.26	439.76	337.22	644.93	665.53	604.19	1160.68	608.24	248.6878
2	698.46	741.74	754.52	461.89	478.08	477.86	325.55	477.64	567.07	586.12	521.92	923.68	584.54	185.7184
2.25	436.89	621.81	636.23	405.29	485.02	511.89	341.41	301.32	472.25	525.88	475.66	834.69	504.03	143.0812
2.5	539.43	622.25	634.80	386.23	431.72	466.96	384.25	270.93	438.99	472.14	421.26	816.30	490.44	144.2493
3	365.64	628.96	513.99	312.67	374.34	409.14	329.52	225.00	360.58	350.35	336.23	631.94	403.20	125.1607
4	333.66	381.15	368.72	232.38	255.84	311.45	240.33	147.47	252.53	263.66	200.88	479.85	288.99	90.55956
6	179.14	199.39	204.97	125.00	137.89	165.20	131.89	88.27	153.08	155.27	80.58	243.61	155.36	47.41141
10	*	*	*	*	*	*	*	*	*	*	*	*	*	*

* = Lower limit of quantitation (LLOQ)

The individual data of concentration at times after oral administration on day 1 in cirrhotic patients

Time after oral administration (hr.)	Concentration (ng/mL)														Average	S.D.
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10	No. 11	No. 12	No. 13	No. 14		
0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
0.5	83.26	*	*	89.65	*	*	*	*	*	*	*	*	*	267.18	86.46	4.52
0.75	680.95	*	*	680.07	183.37	543.83	575.44	173.02	462.44	448.90	372.81	174.78	217.95	497.80	429.56	198.97
1	635.24	85.57	95.86	757.38	863.99	942.84	863.11	854.19	981.28	1002.42	963.77	763.55	530.29	357.27	734.10	318.59
1.25	619.93	113.55	133.92	649.89	947.14	692.62	709.80	992.84	977.64	658.37	924.89	813.66	592.84	325.88	702.85	299.37
1.5	414.65	230.84	248.46	540.75	791.41	623.24	595.93	984.03	607.71	615.31	678.74	776.87	421.15	175.22	592.33	217.31
1.75	342.18	285.79	228.85	464.54	809.14	527.64	559.03	764.98	559.69	407.16	665.09	585.02	404.96	161.01	516.59	180.65
2	341.41	331.72	231.39	417.29	561.89	487.56	545.04	612.89	612.33	573.68	609.58	501.32	369.82	138.33	485.51	127.48
2.25	276.32	352.64	393.83	383.48	527.86	450.11	490.53	453.08	538.33	393.17	570.59	443.61	403.30	116.52	439.46	84.86
2.5	252.42	334.03	483.37	345.26	596.16	437.78	474.12	512.33	535.02	439.32	505.51	439.54	266.20	104.30	446.24	95.78
3	162.71	374.12	711.34	215.42	549.23	379.19	412.00	493.39	366.08	242.40	307.60	483.81	265.97	*	393.11	151.19
4	158.04	372.14	549.45	152.97	449.01	272.25	312.78	407.16	350.03	316.23	247.91	467.51	219.93	*	337.96	120.63
6	96.76	244.57	314.54	96.47	304.07	199.89	214.21	206.92	258.34	164.25	238.33	304.02	159.47	*	221.86	72.47
10	*	142.07	151.10	*	144.08	99.45	81.72	*	138.00	122.80	131.61	170.93	98.68	*	131.31	27.00

* = Lower limit of quantitation (LLOQ)

The individual data of concentration at times after oral administration on day 5 in cirrhotic patients

Time after oral administration (hr.)	Concentration (ng/mL)														Average	S.D.
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10	No. 11	No. 12	No. 13	No. 14		
0	*	*	*	*	*	*	*	*	415.21	458.19	353.67	*	*	*	409.02	52.53
0.5	*	*	*	*	80.95	209.69	222.47	80.25	1186.11	1109.47	1159.91	*	*	169.93	578.69	540.09
0.75	575.44	115.31	196.81	87.69	778.74	707.93	721.92	764.10	1255.18	1211.56	1254.65	814.97	*	675.44	707.06	414.12
1	863.11	249.23	349.34	254.63	881.94	765.42	752.20	579.96	977.20	1077.64	1000.66	986.78	*	489.43	728.18	299.73
1.25	709.80	480.57	557.93	625.99	894.58	598.02	556.83	519.93	891.19	846.81	720.93	889.54	71.92	384.03	671.84	144.27
1.5	595.93	725.77	496.59	745.70	703.63	483.44	528.63	462.33	809.48	834.69	538.22	760.46	119.49	300.22	605.24	109.51
1.75	559.03	617.29	402.53	789.76	609.25	463.88	489.21	438.44	670.81	566.19	499.01	668.94	153.96	250.66	556.20	107.83
2	545.04	720.59	478.30	744.60	671.59	445.15	416.41	403.85	431.28	539.54	428.06	648.48	153.52	230.40	539.41	125.96
2.25	490.53	681.61	332.93	696.81	616.41	441.08	438.11	415.42	494.60	522.69	366.51	633.15	157.27	200.55	509.90	122.73
2.5	474.12	623.02	332.27	634.69	577.31	346.48	338.55	489.76	524.23	489.43	445.59	587.78	152.53	182.93	488.80	107.70
3	412.00	398.13	254.30	511.67	662.33	269.16	281.28	423.90	446.81	408.59	396.59	627.09	171.26	144.82	424.32	128.34
4	312.78	255.29	191.41	414.21	543.72	288.27	306.20	398.57	416.68	393.80	334.43	547.39	180.84	105.44	366.06	107.43
6	214.21	155.63	123.77	243.22	383.18	197.11	219.48	294.04	306.41	291.74	251.42	408.79	140.98	*	257.42	84.77
10	81.72	85.02	*	117.95	241.06	95.93	99.87	156.17	169.71	143.19	137.89	220.46	89.10	*	140.08	53.22

* = Lower limit of quantitation (LLOQ)

APPENDIX E

A. The figures of plasma concentration time profile on the first day following oral administration of esomeprazole 20 mg once daily in Thai healthy volunteers.

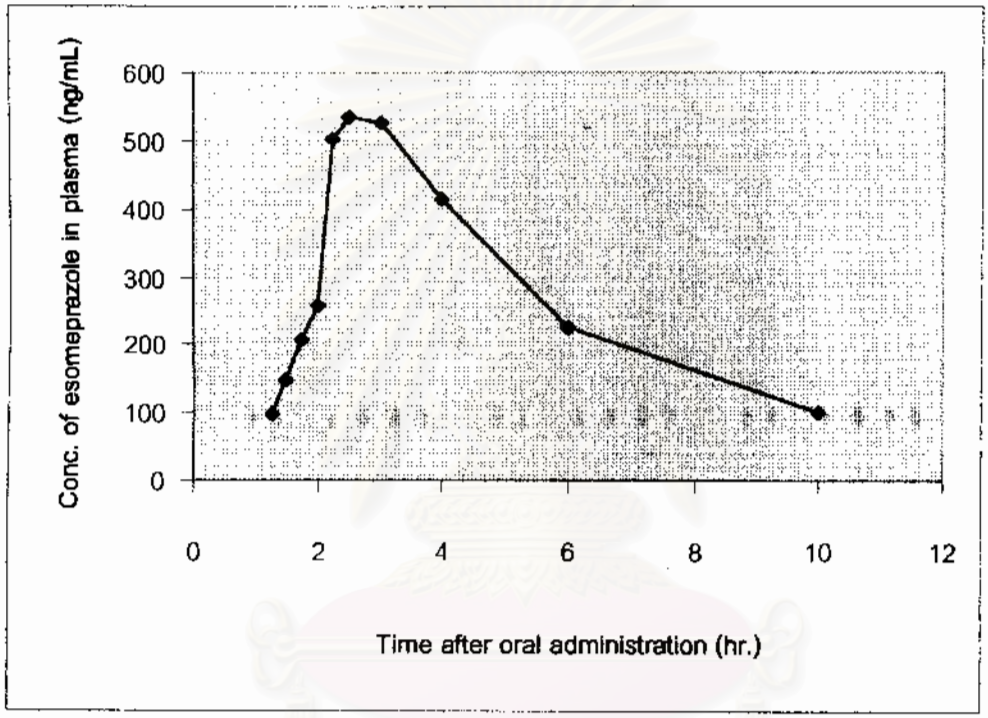

Figure 7. The plasma concentration time profile of subject No. 1

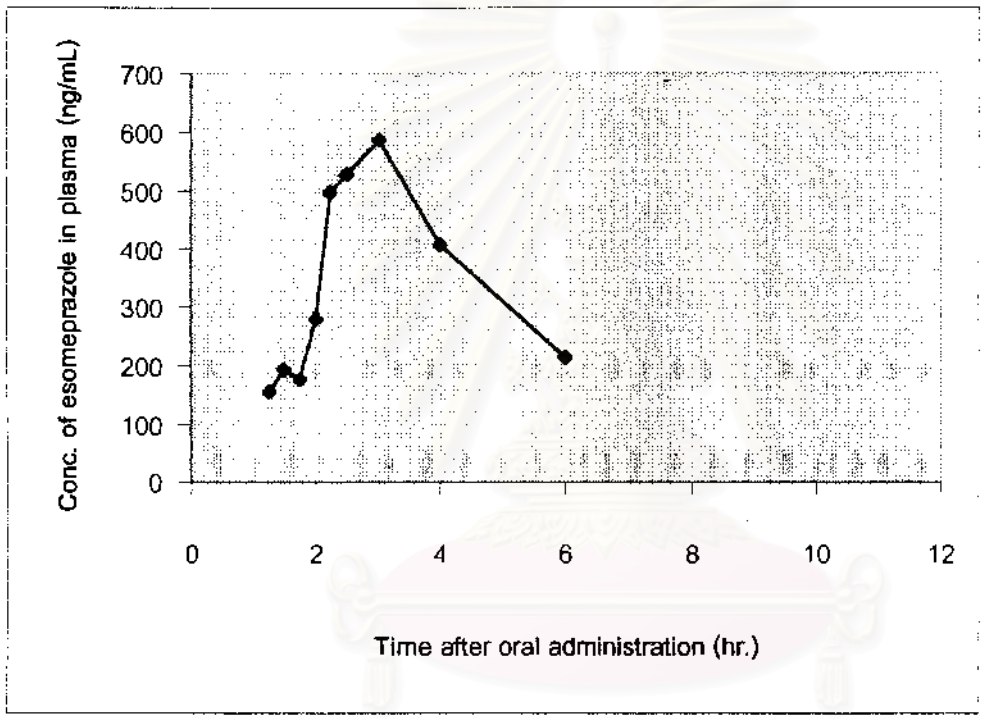

Figure 8. The plasma concentration time profile of subject No. 2

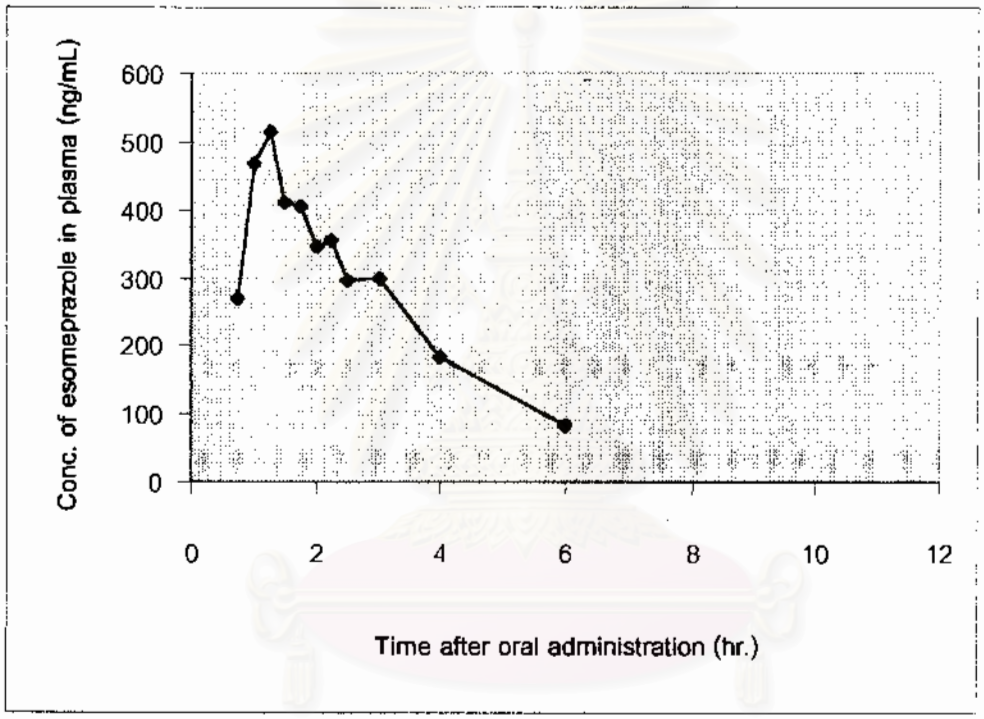

Figure 9. The plasma concentration time profile of subject No. 3

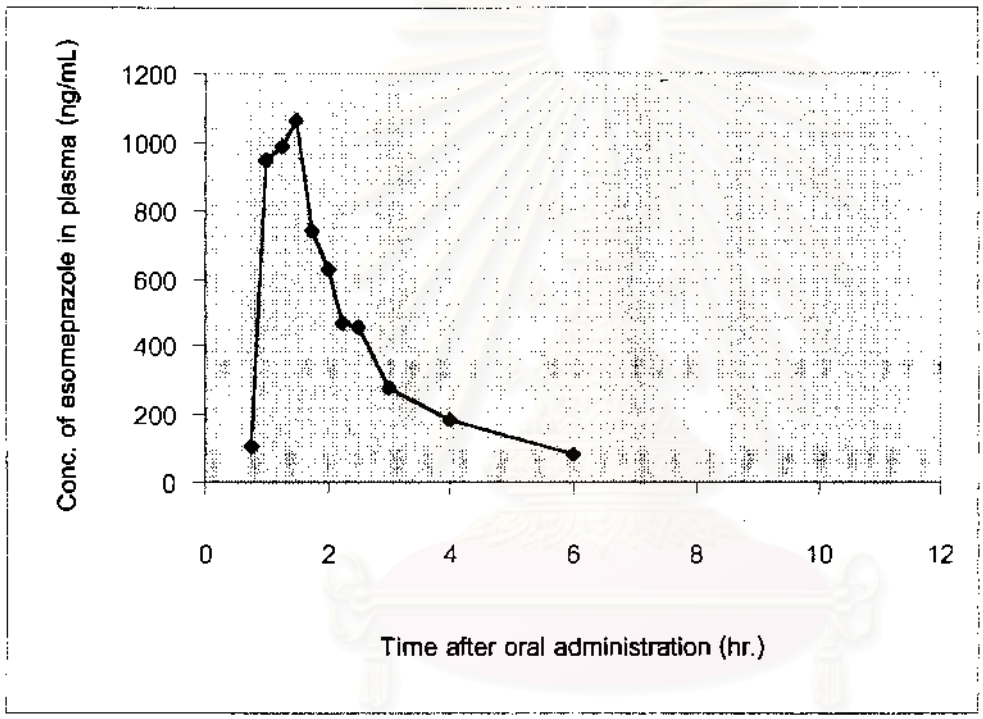

Figure 10. The plasma concentration time profile of subject No. 4

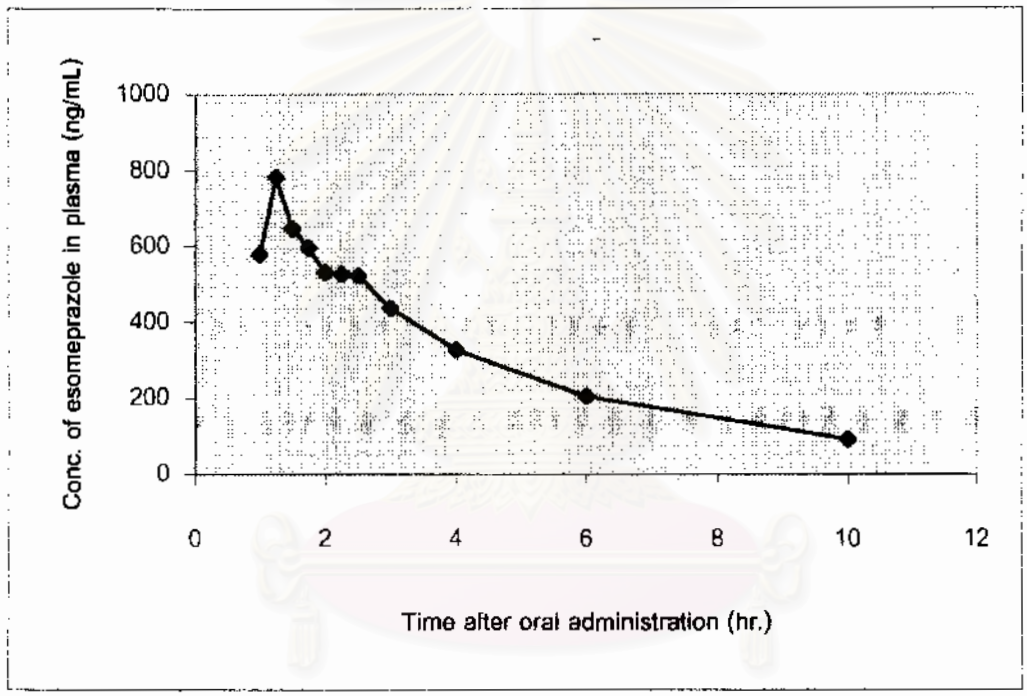

Figure 11. The plasma concentration time profile of subject No. 5

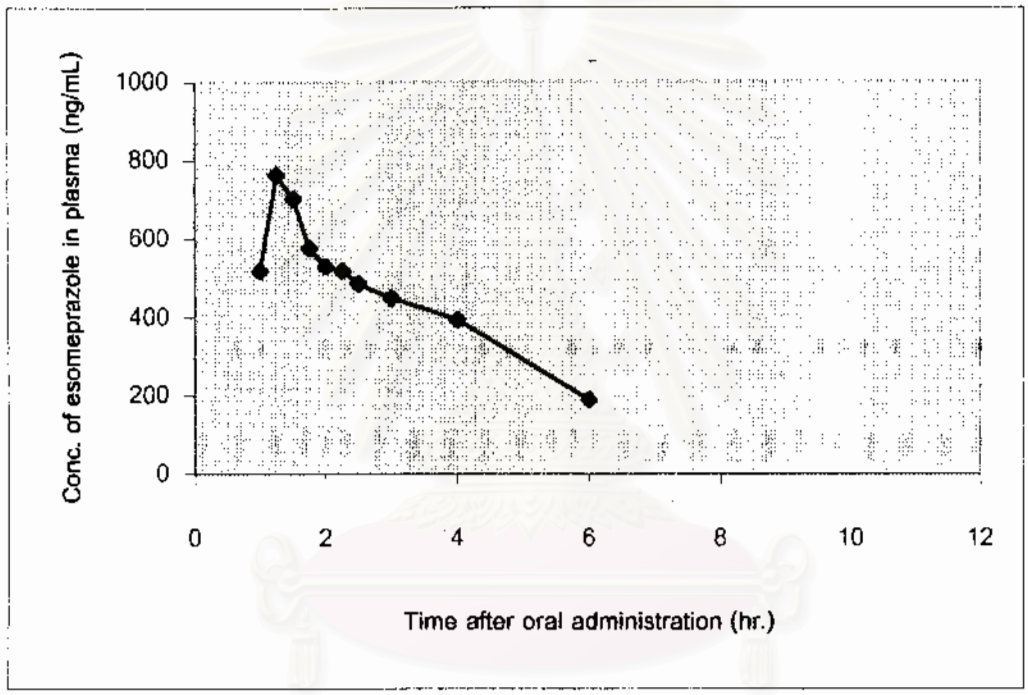

Figure 12. The plasma concentration time profile of subject No. 6

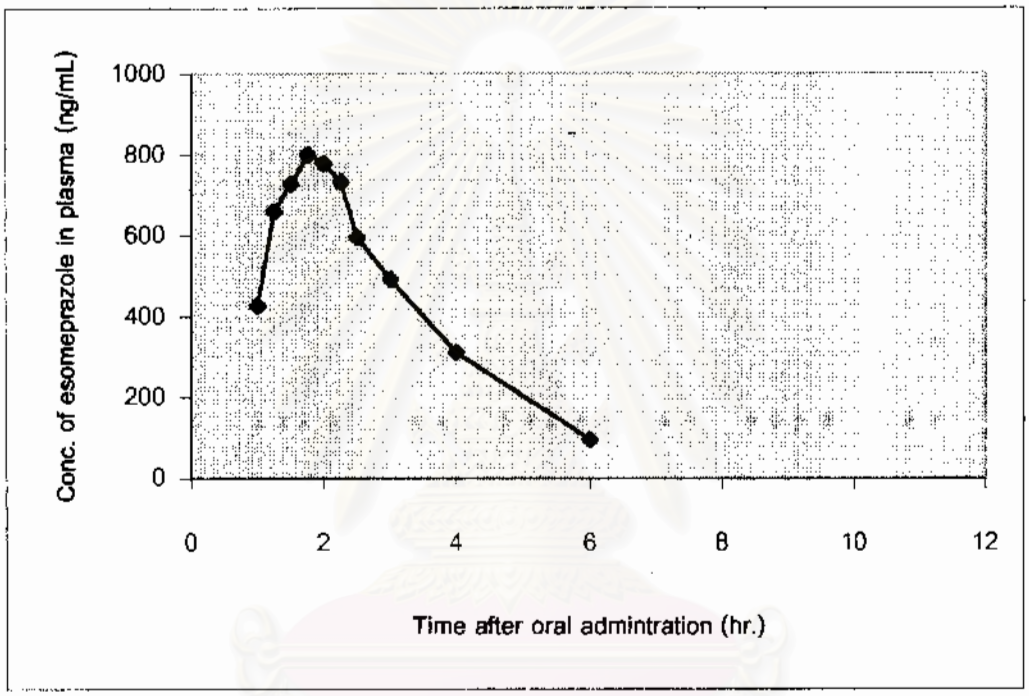

Figure 13. The plasma concentration time profile of subject No. 7

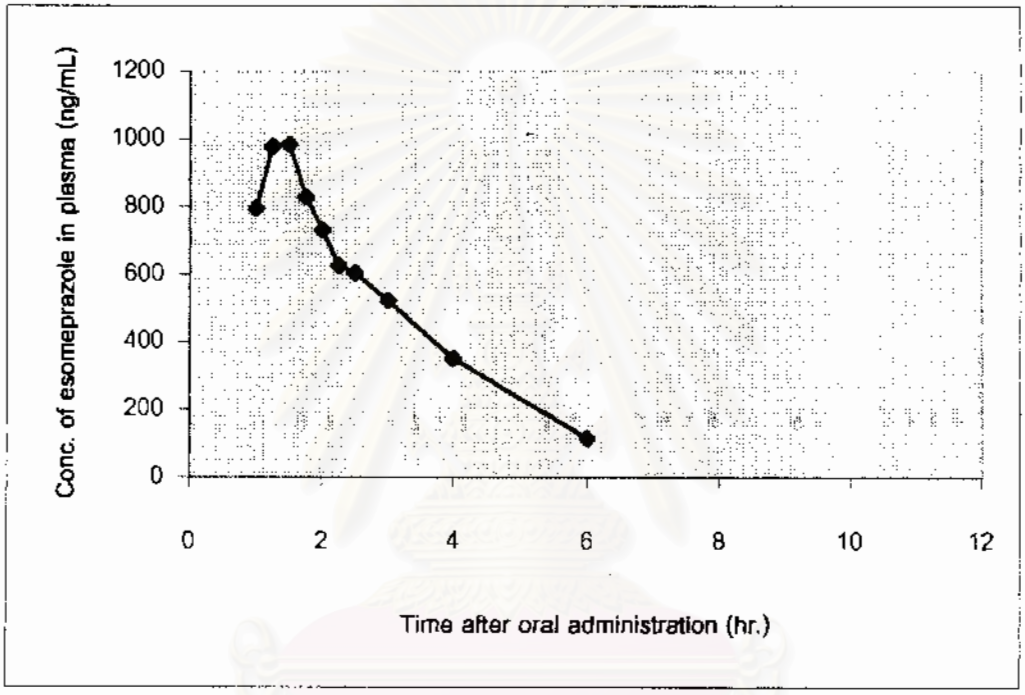

Figure 14. The plasma concentration time profile of subject No. 8

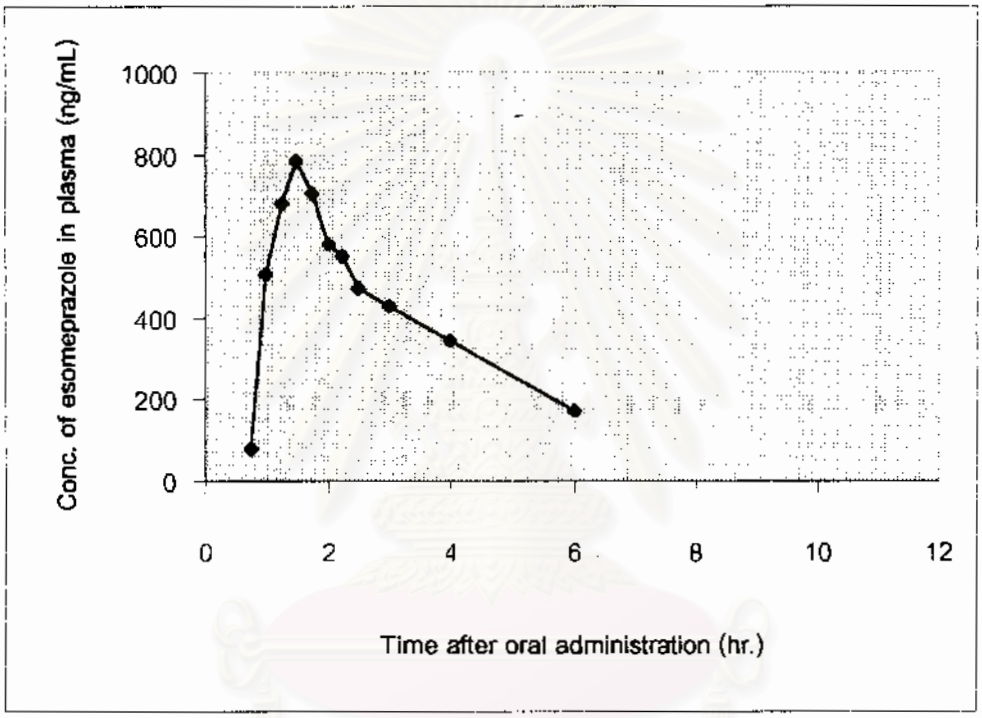

Figure 15. The plasma concentration time profile of subject No. 9

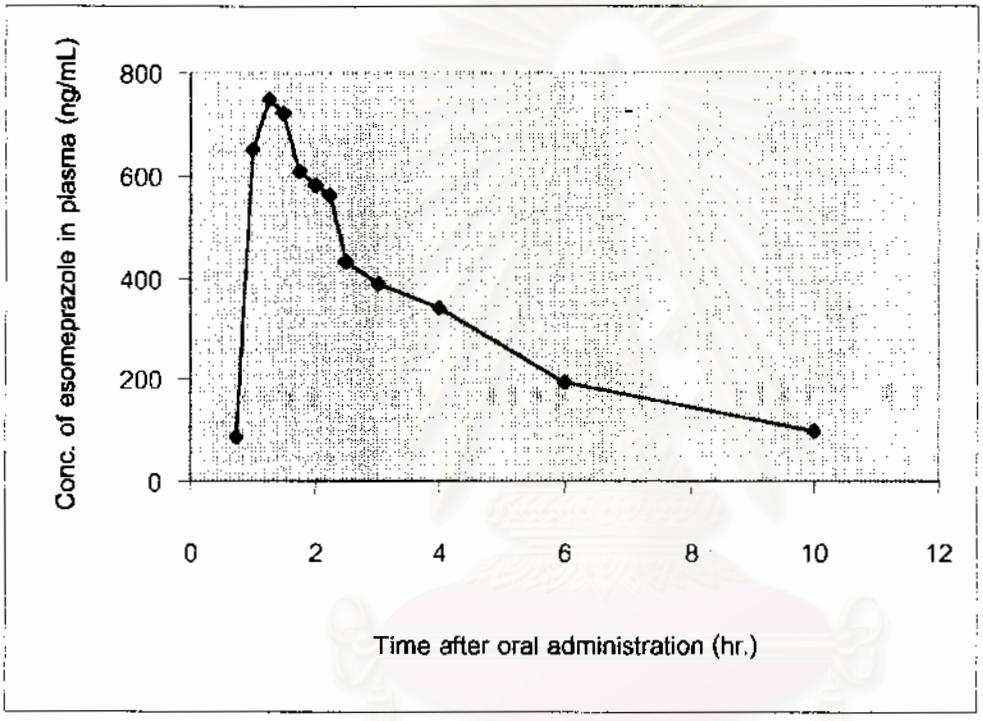

Figure 16. The plasma concentration time profile of subject No. 10

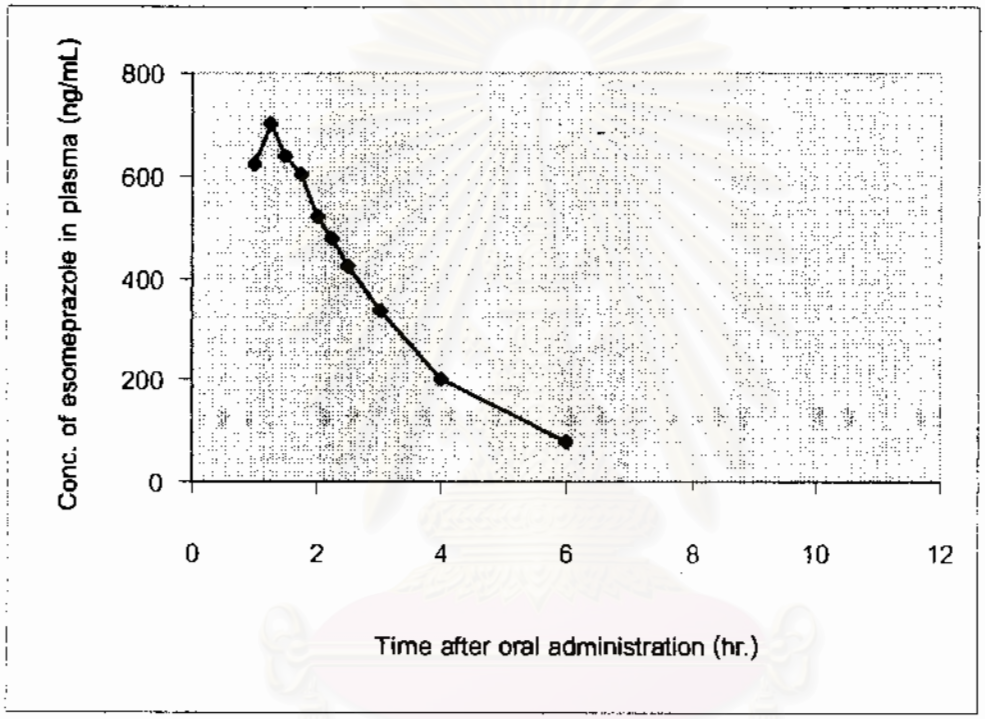

Figure 17. The plasma concentration time profile of subject No. 11

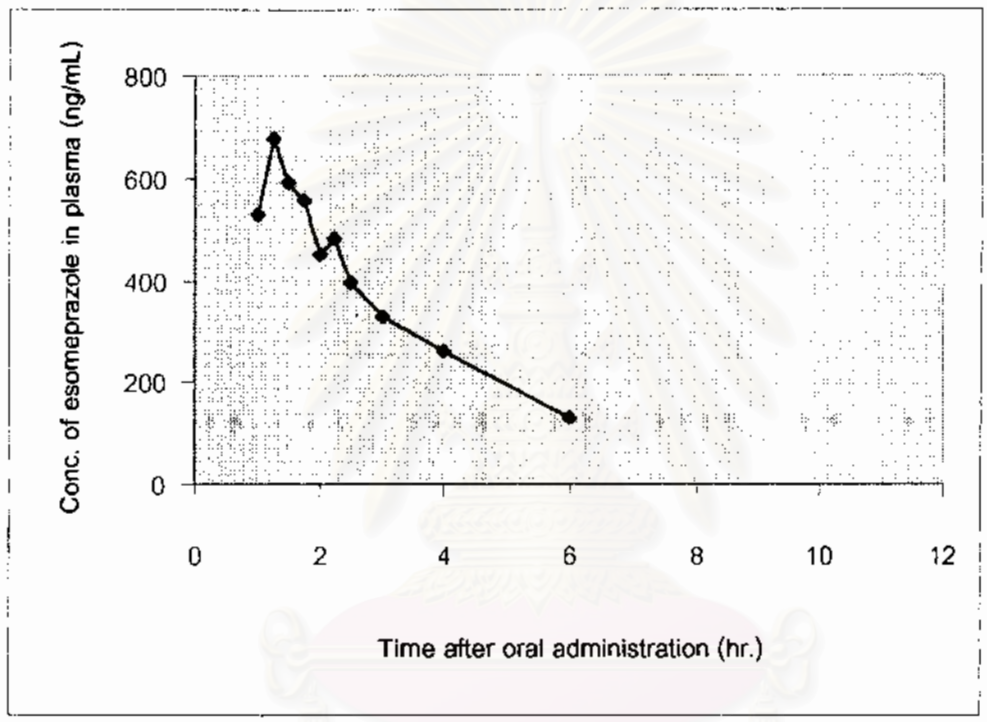

Figure 18. The plasma concentration time profile of subject No. 12

B. The figures of plasma concentration time profile on the last day (day 5) following oral administration of esomeprazole 20 mg once daily in Thai healthy volunteers.

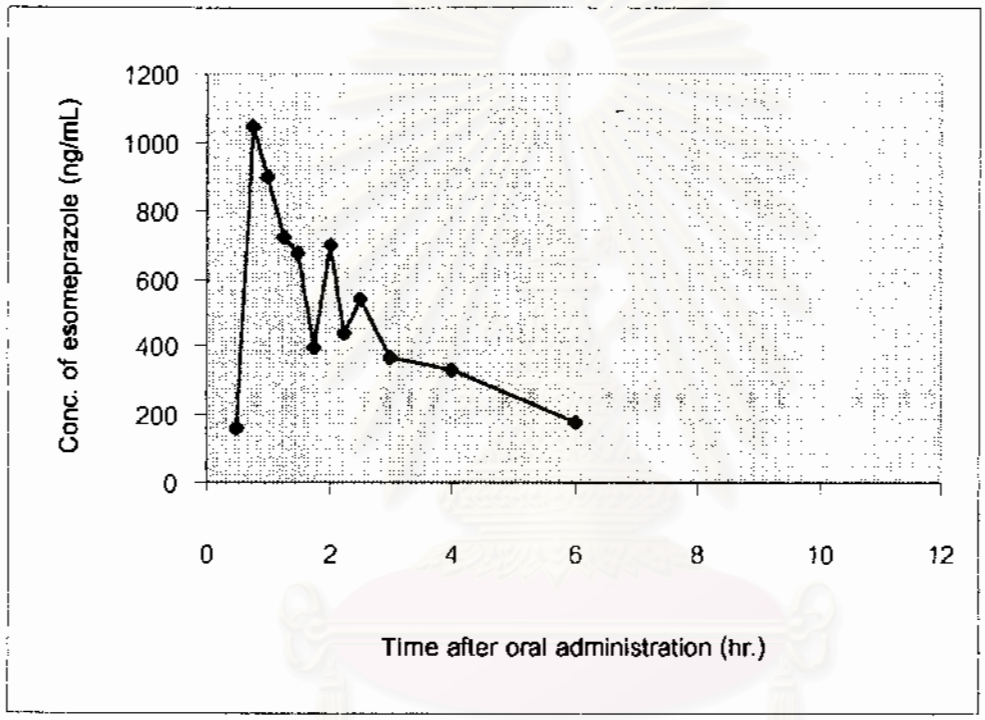

Figure 19. The plasma concentration time profile of subject No. 1

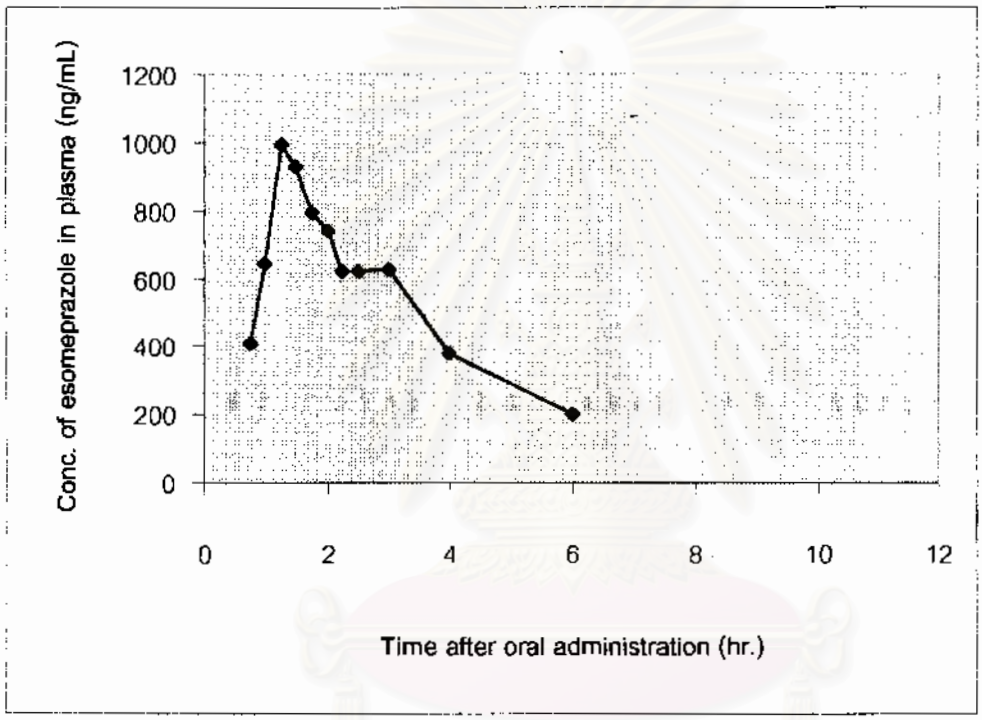

Figure 20. The plasma concentration time profile of subject No. 2

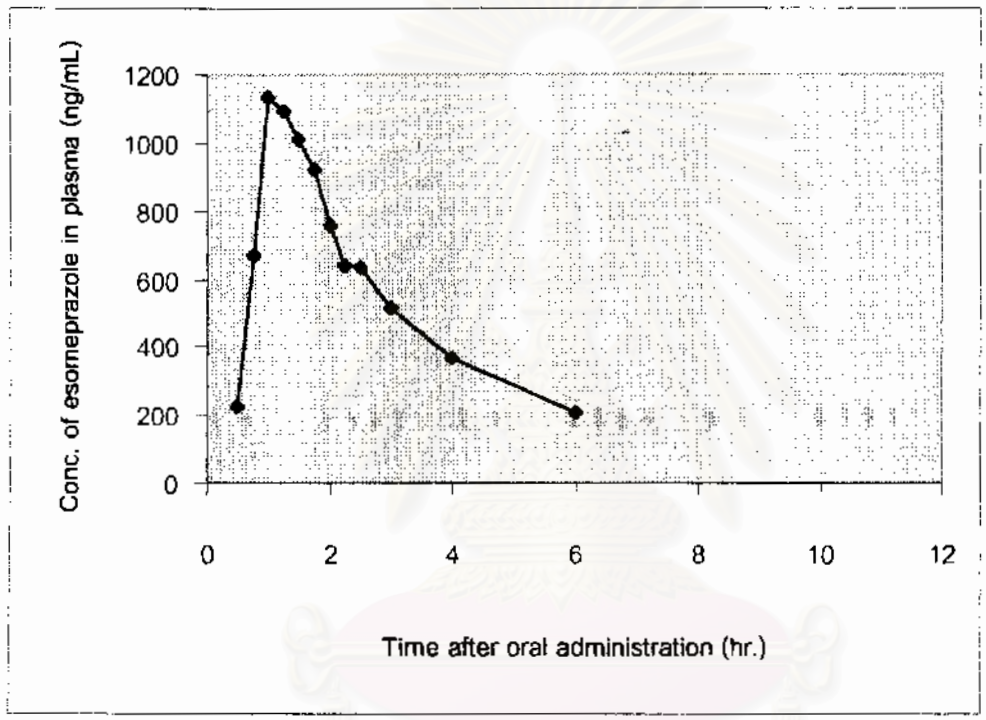

Figure 21. The plasma concentration time profile of subject No. 3

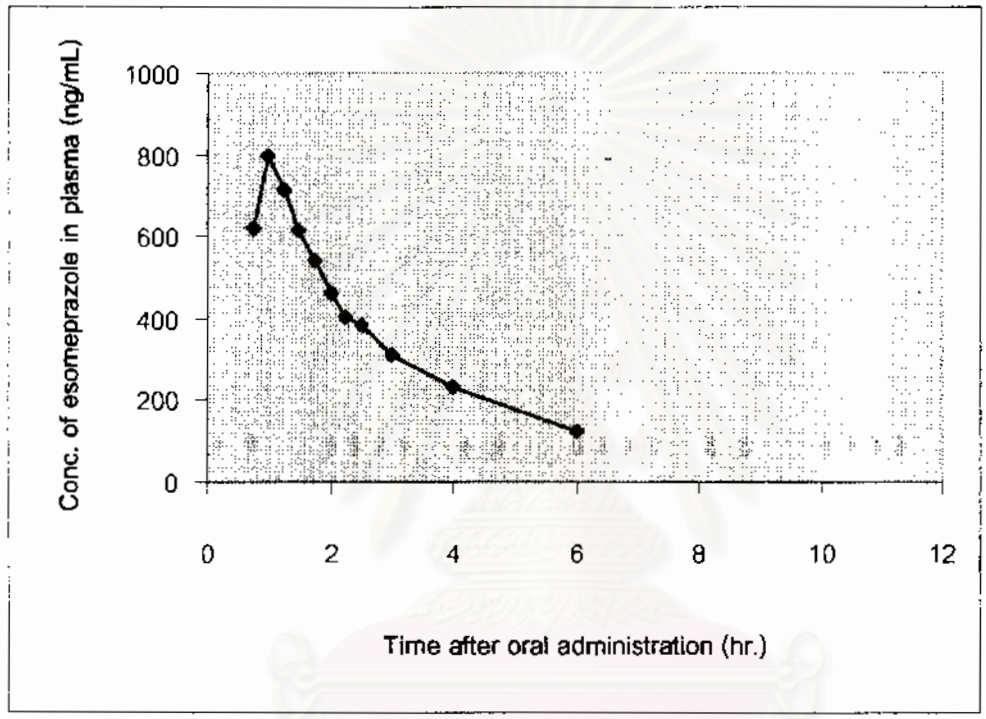

Figure 22. The plasma concentration time profile of subject No. 4

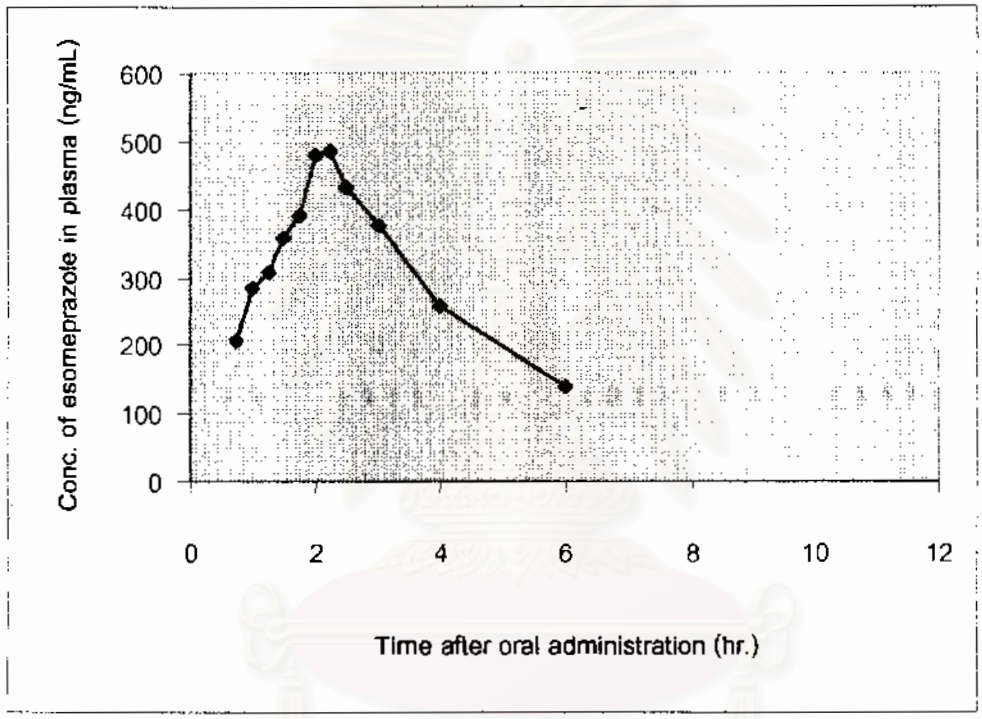

Figure 23. The plasma concentration time profile of subject No. 5

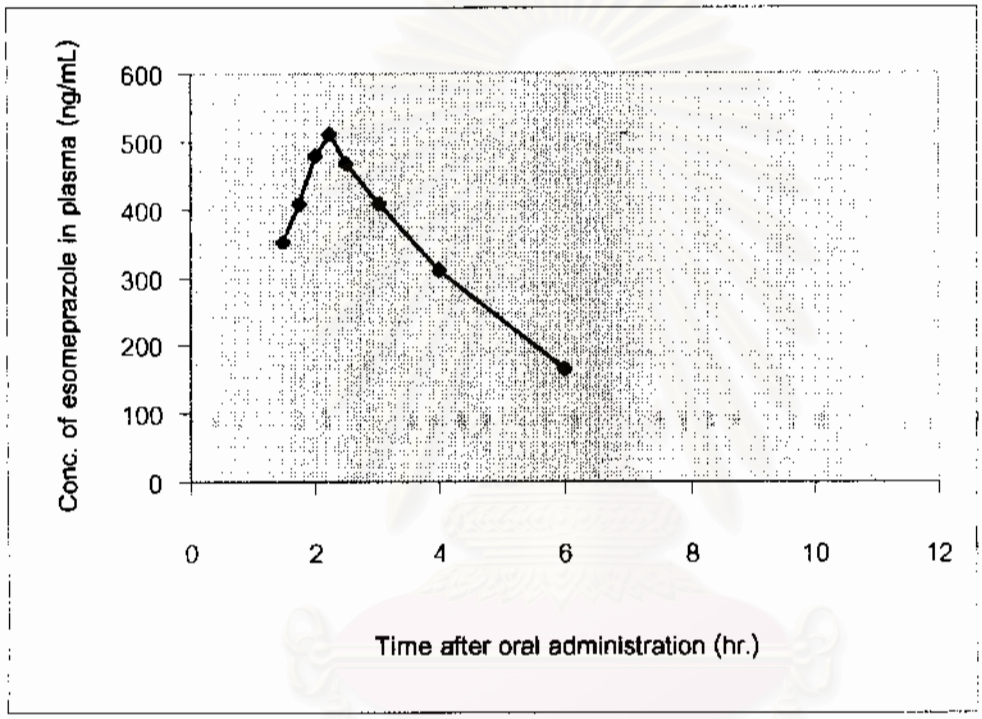

Figure 24. The plasma concentration time profile of subject No. 6

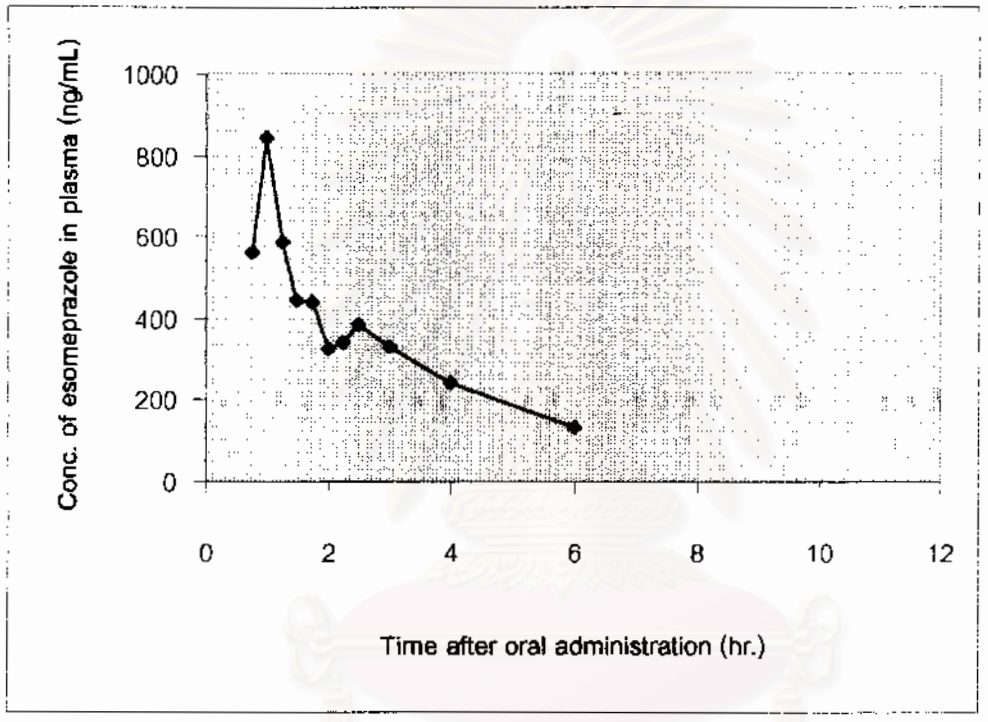

Figure 25. The plasma concentration time profile of subject No. 7

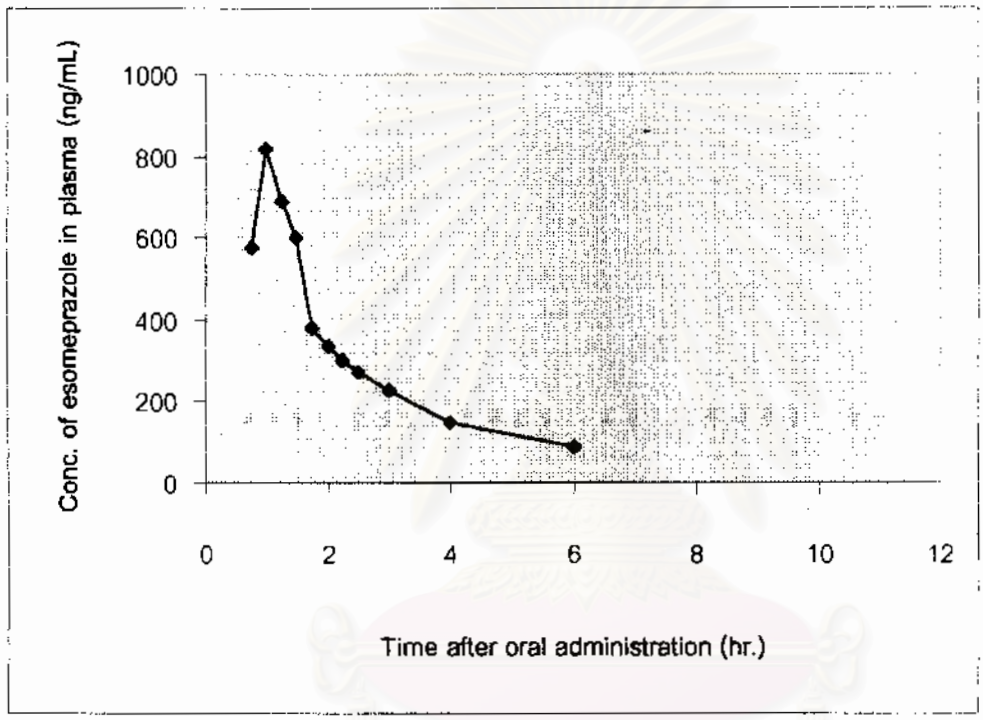

Figure 26. The plasma concentration time profile of subject No. 8

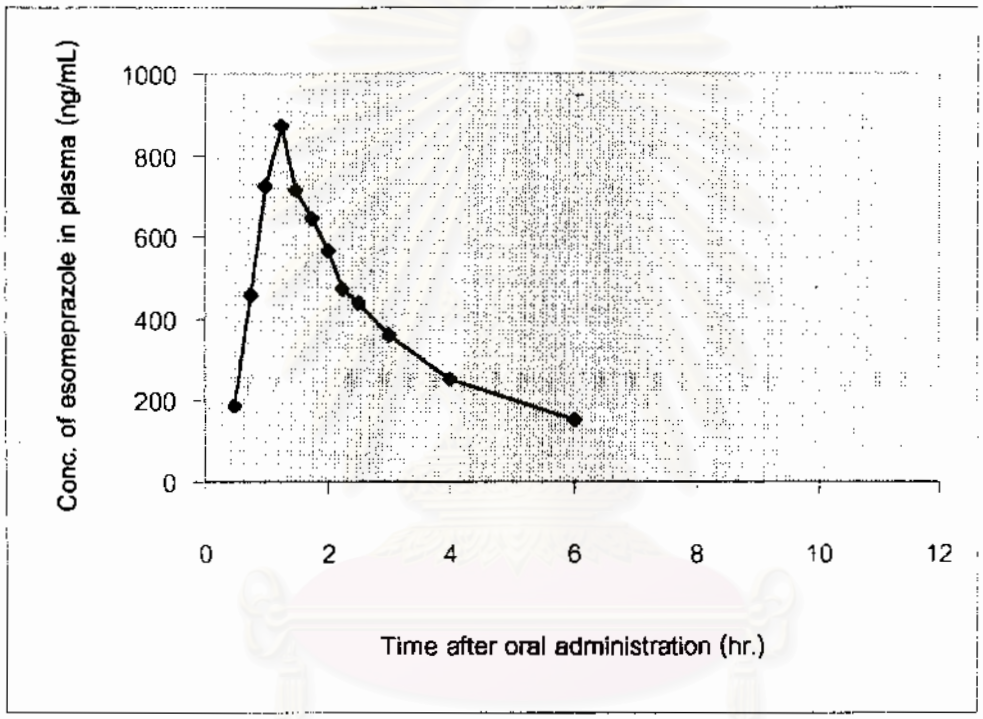

Figure 27. The plasma concentration time profile of subject No. 9

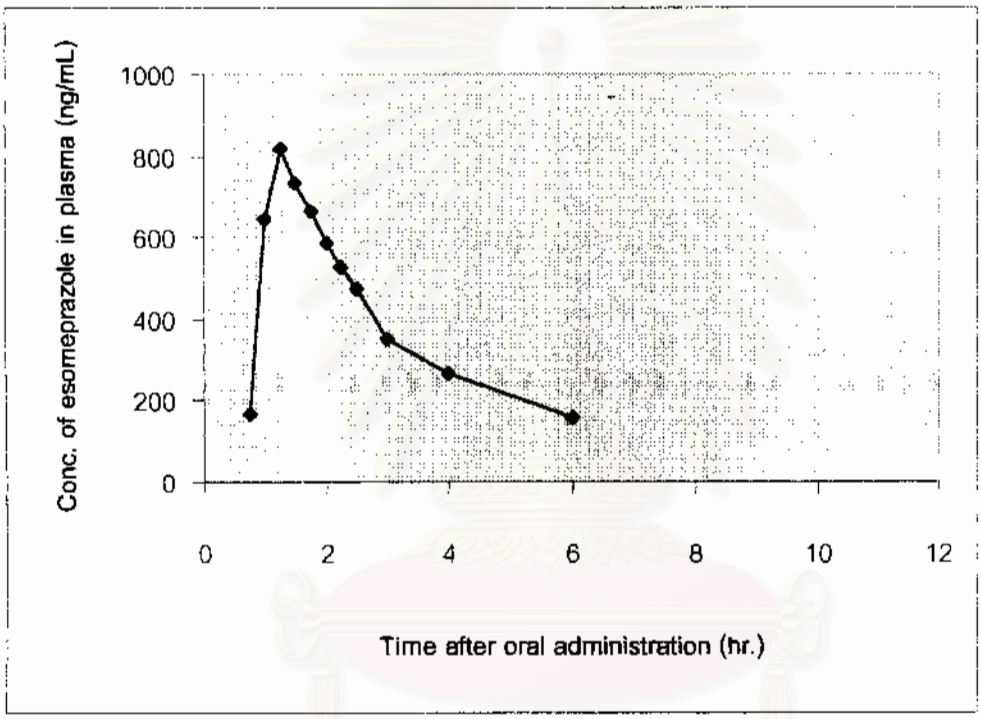

Figure 28. The plasma concentration time profile of subject No. 10

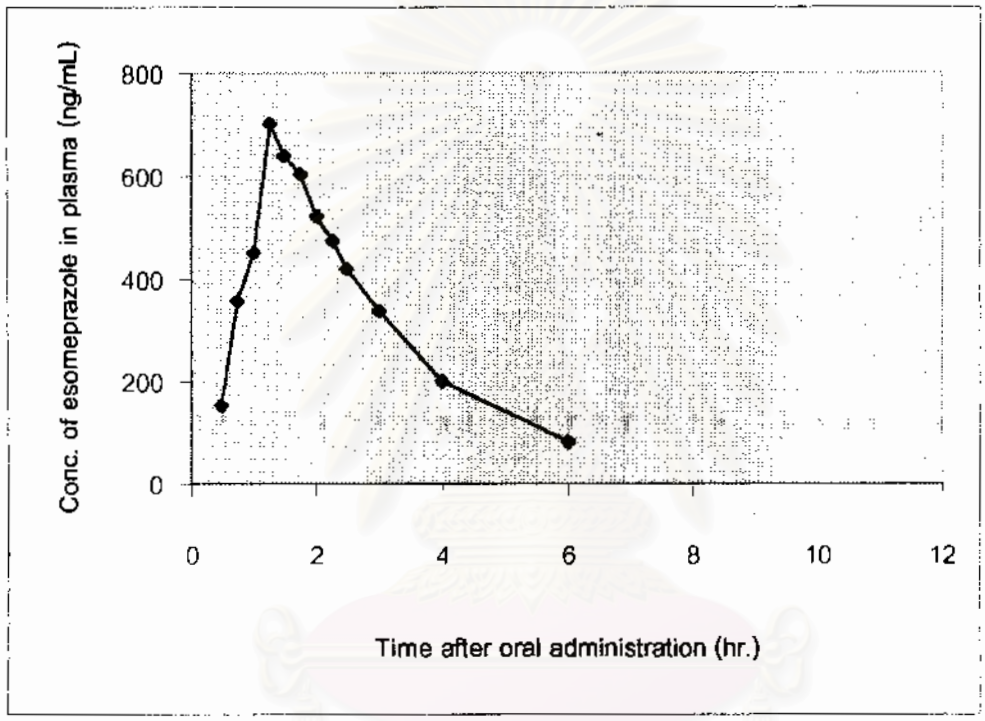

Figure 29. The plasma concentration time profile of subject No. 11

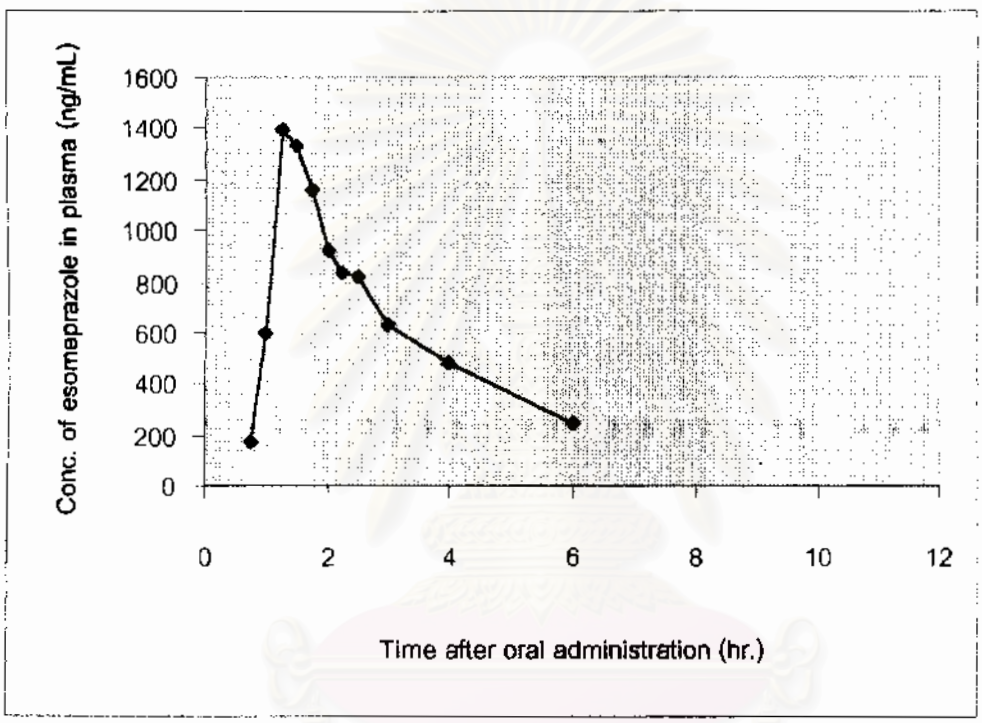

Figure 30. The plasma concentration time profile of subject No. 12

C. The figures of plasma concentration time profile on the first day following oral administration of esomeprazole 20 mg once daily in Thai cirrhotic patients.

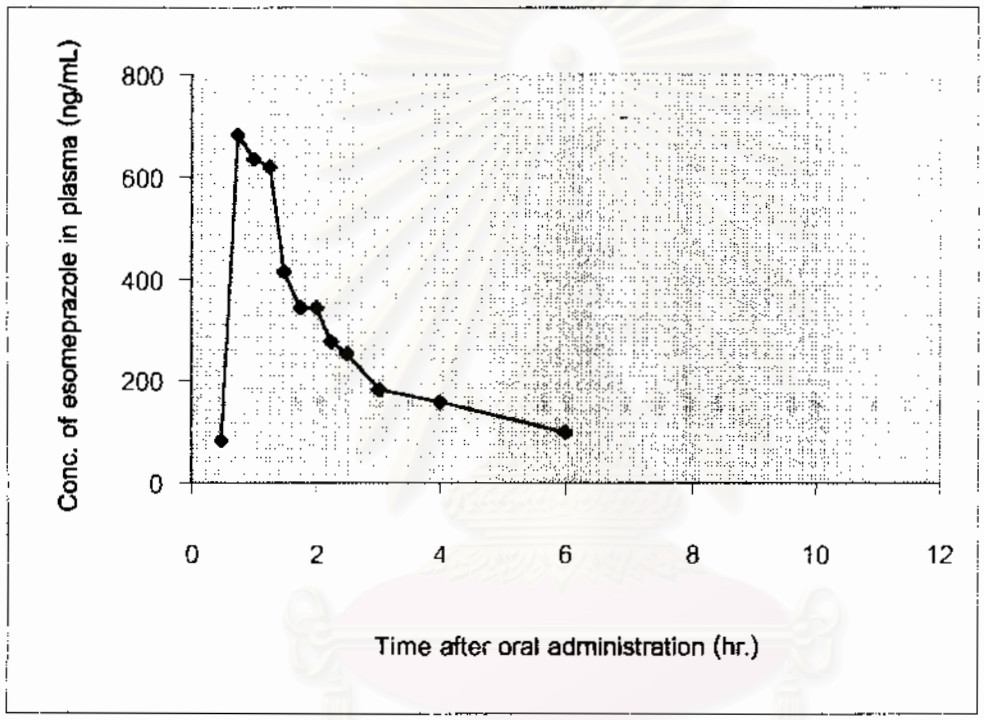

Figure 31. The plasma concentration time profile of subject No. 1

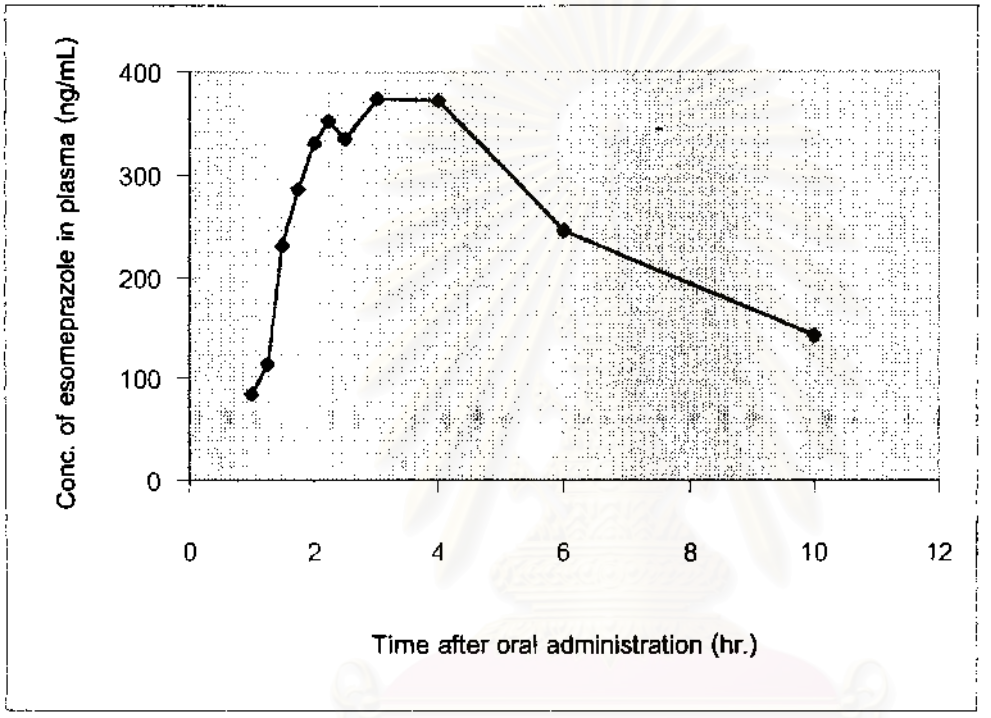

Figure 32. The plasma concentration time profile of subject No. 2

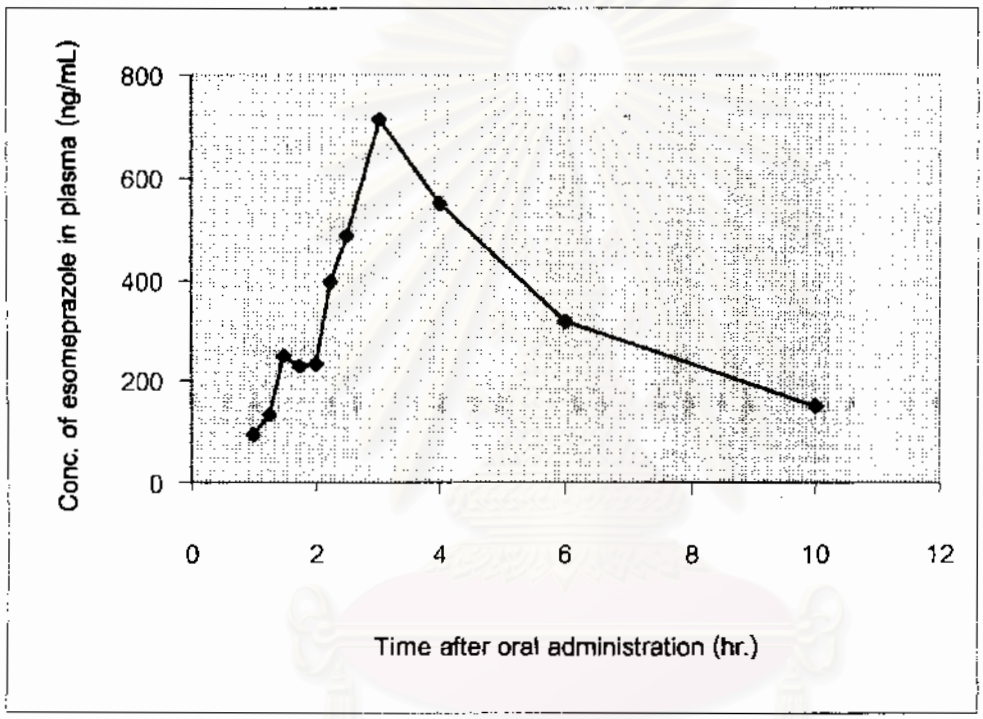

Figure 33. The plasma concentration time profile of subject No. 3

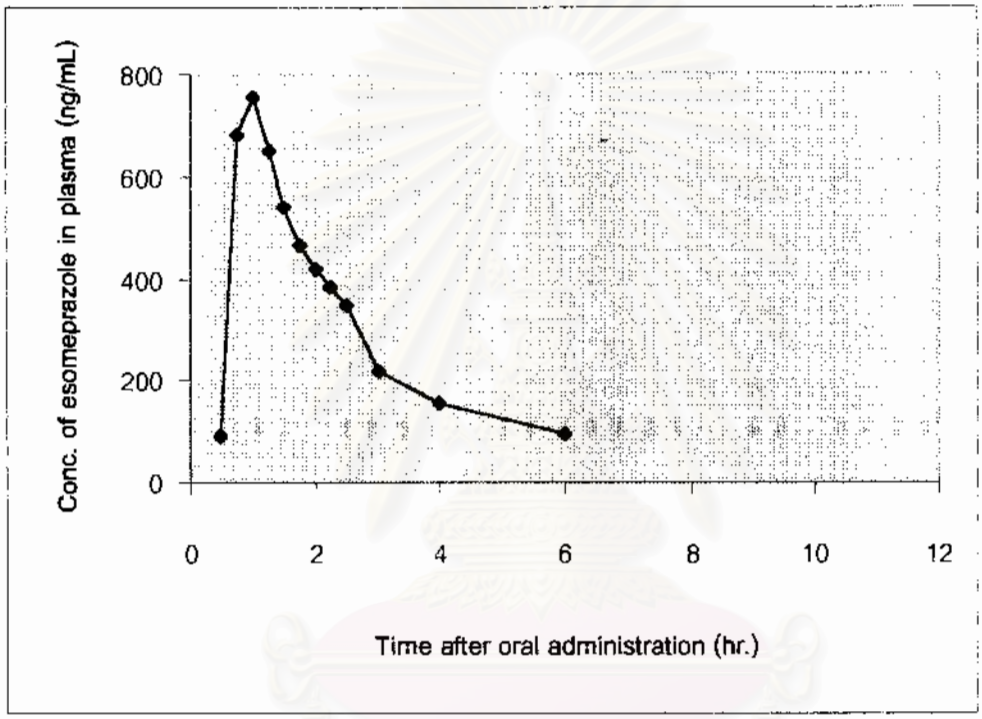

Figure 34. The plasma concentration time profile of subject No. 4

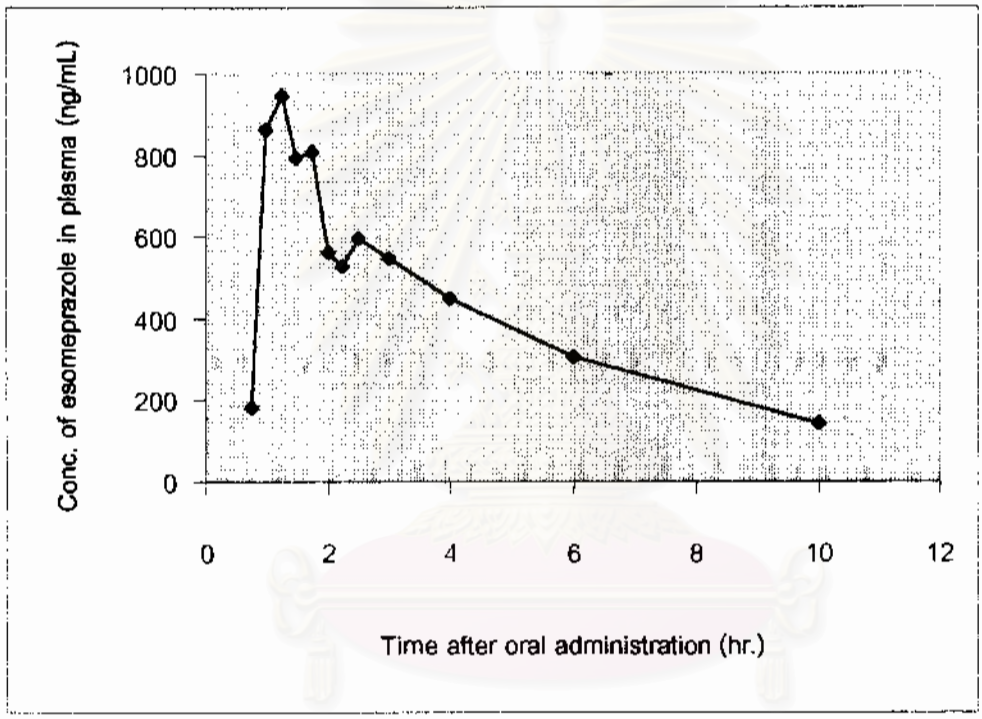

Figure 35. The plasma concentration time profile of subject No. 5

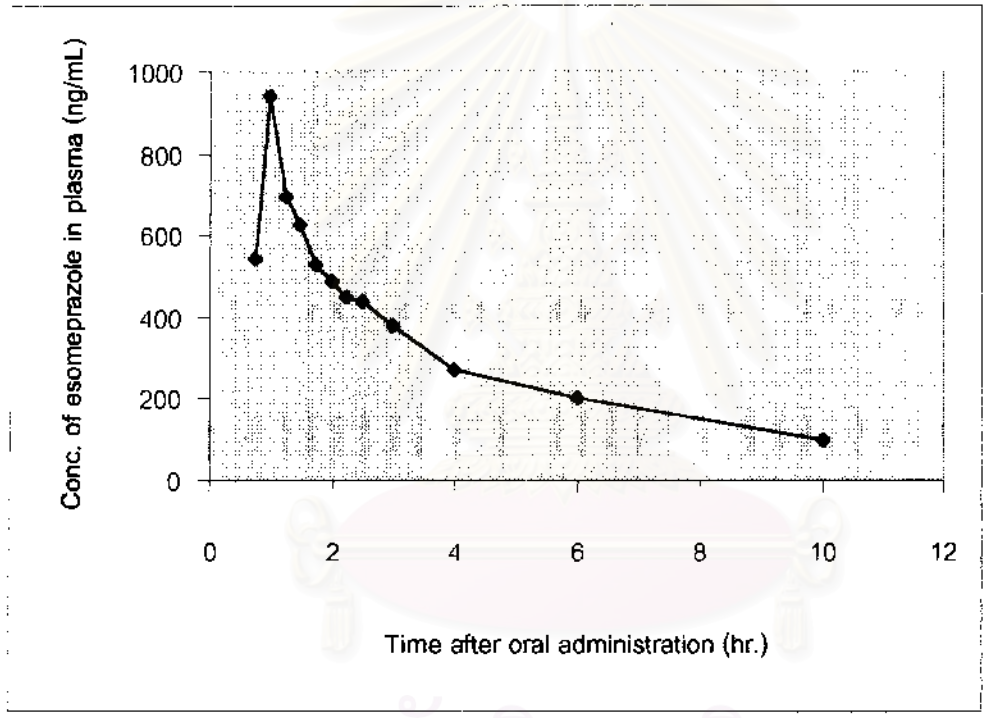

Figure 36. The plasma concentration time profile of subject No. 6

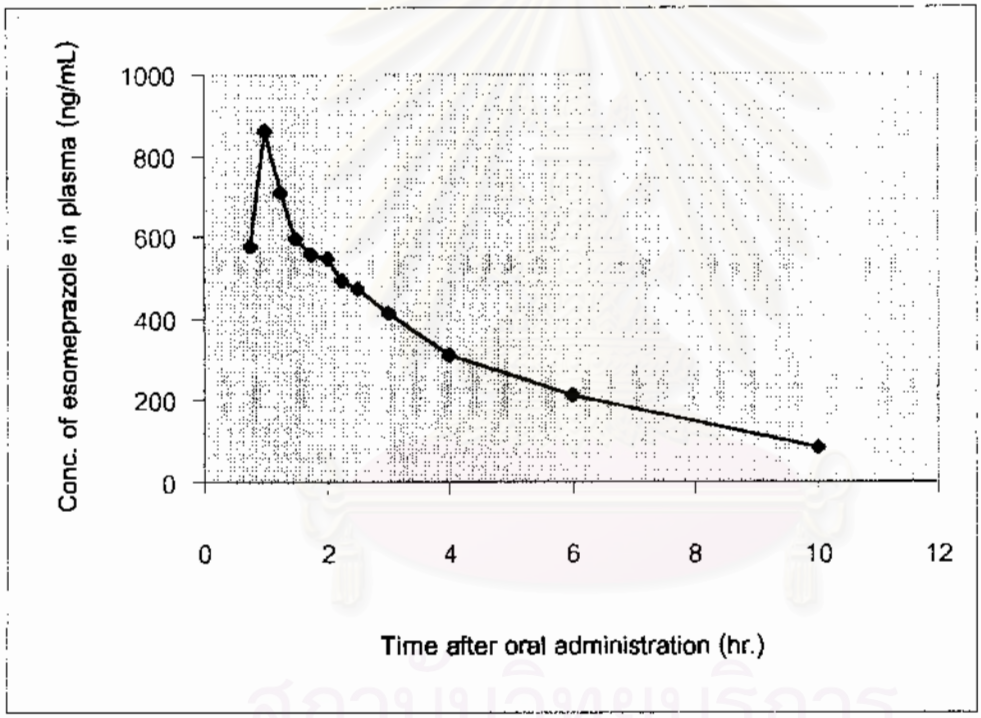

Figure 37. The plasma concentration time profile of subject No. 7

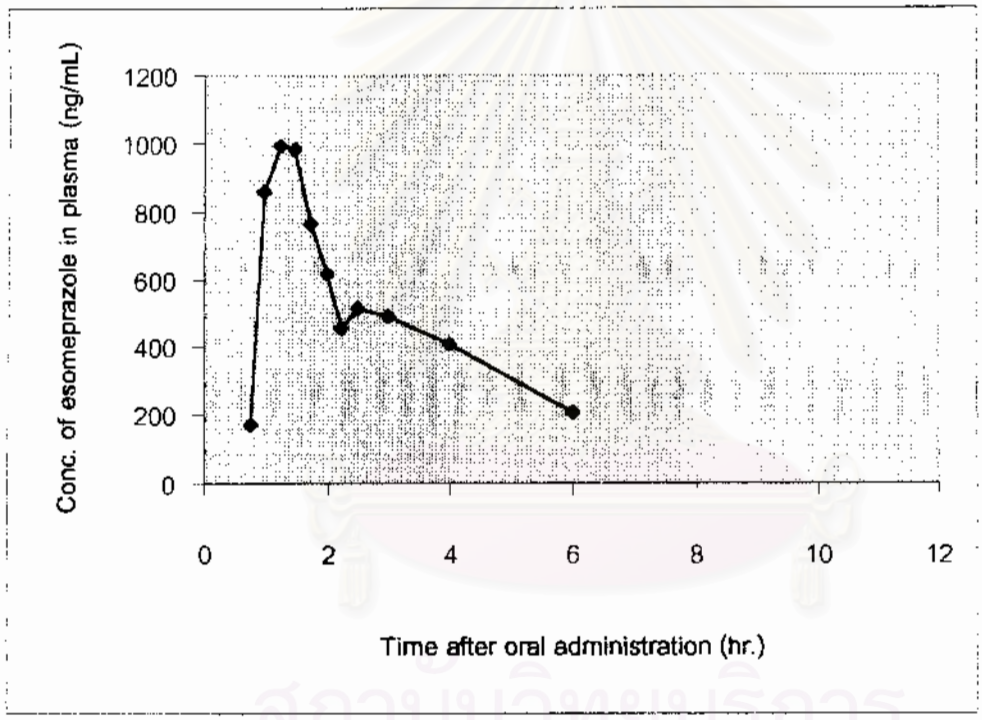

Figure 38. The plasma concentration time profile of subject No. 8

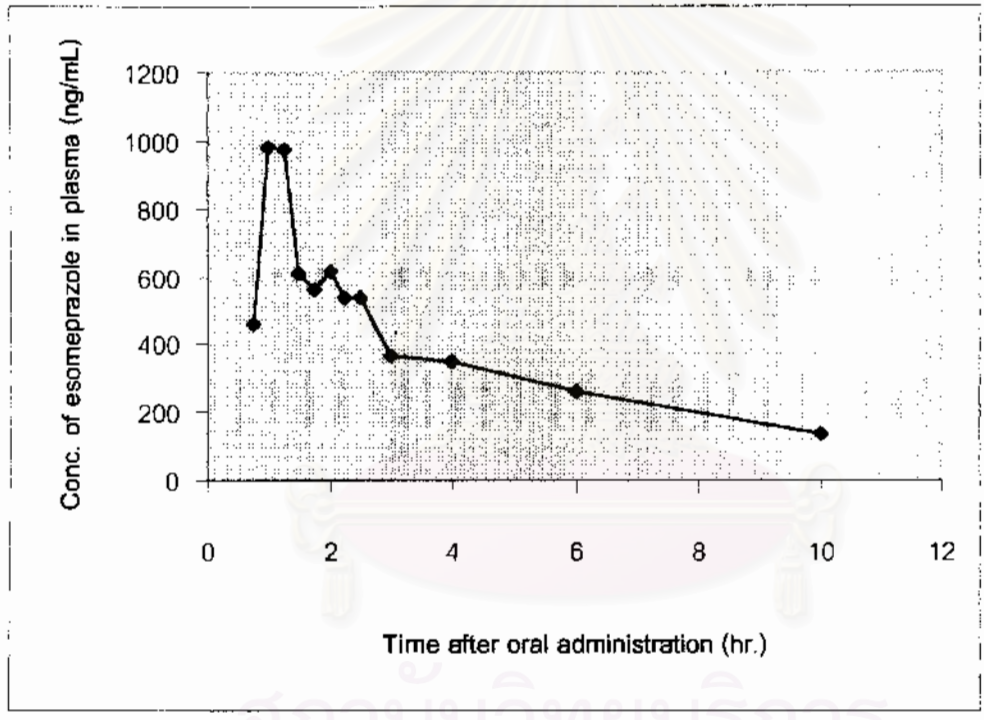

Figure 39. The plasma concentration time profile of subject No. 9

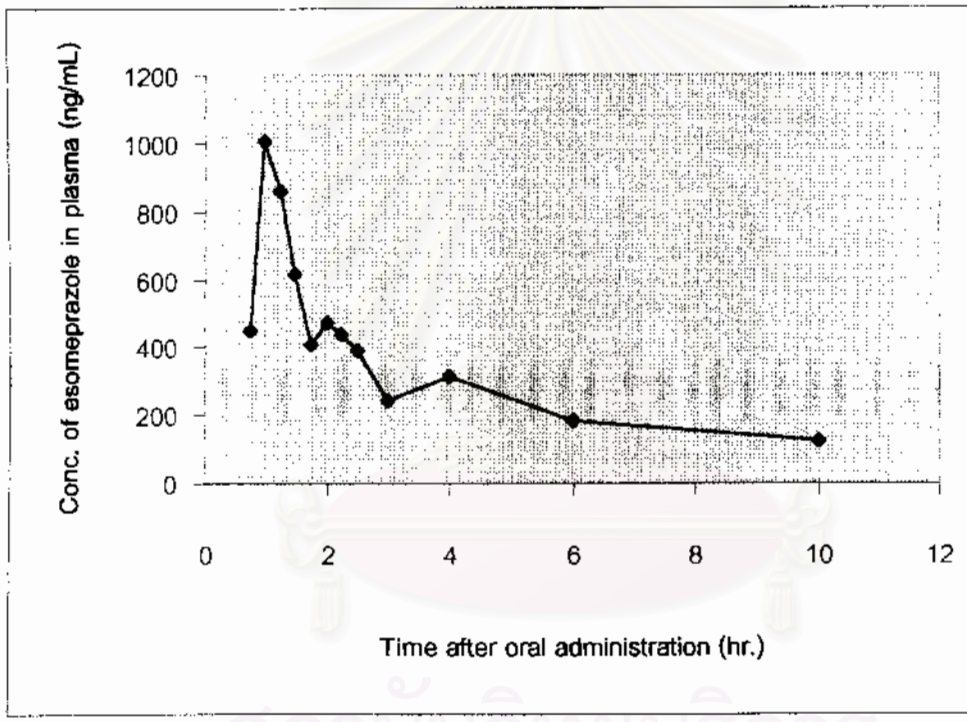

Figure 40. The plasma concentration time profile of subject No. 10

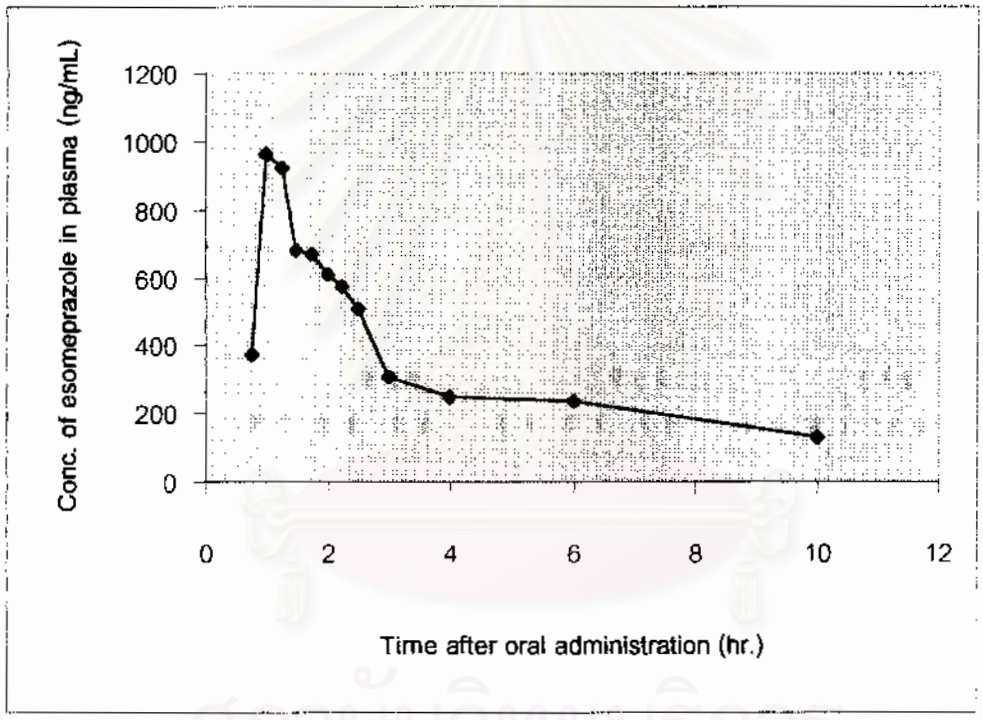

Figure 41. The plasma concentration time profile of subject No. 11

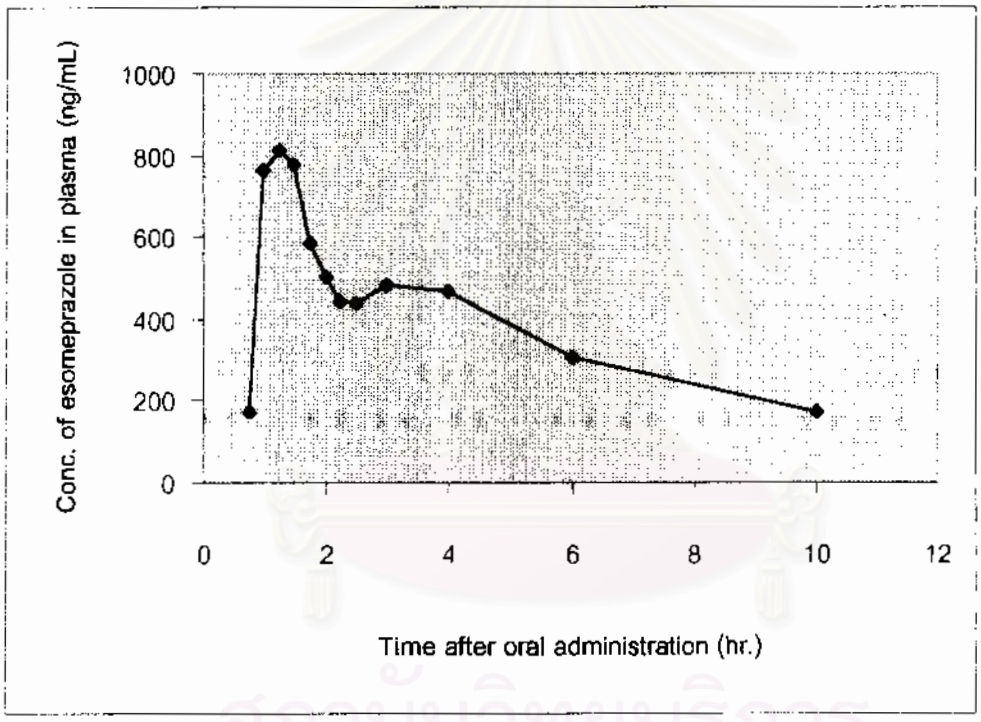

Figure 42. The plasma concentration time profile of subject No. 12

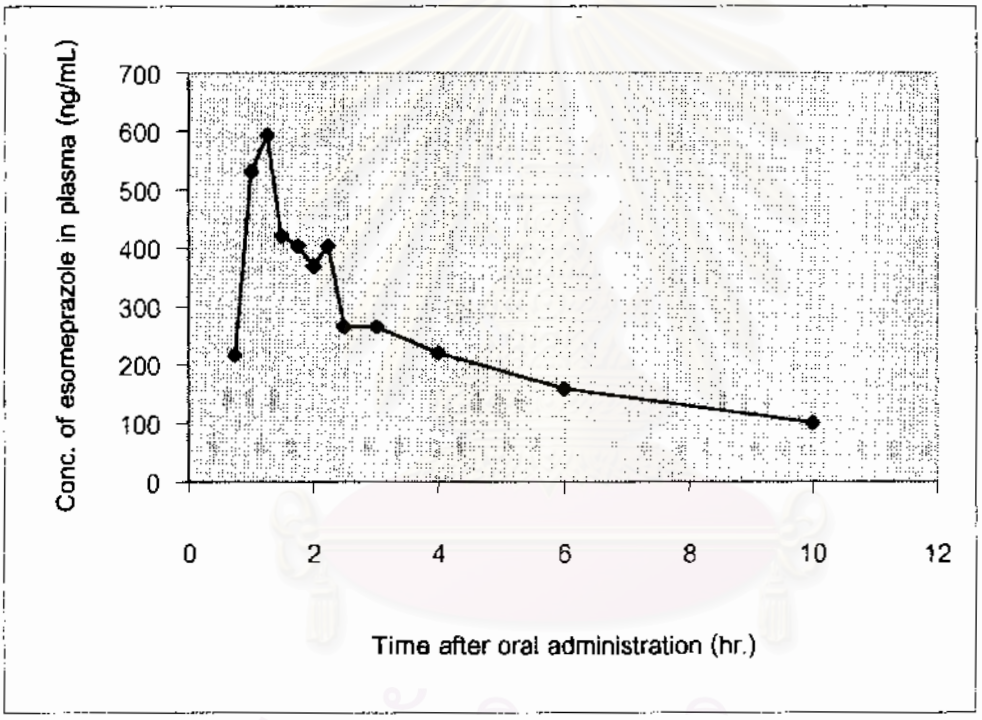

Figure 43. The plasma concentration time profile of subject No. 13

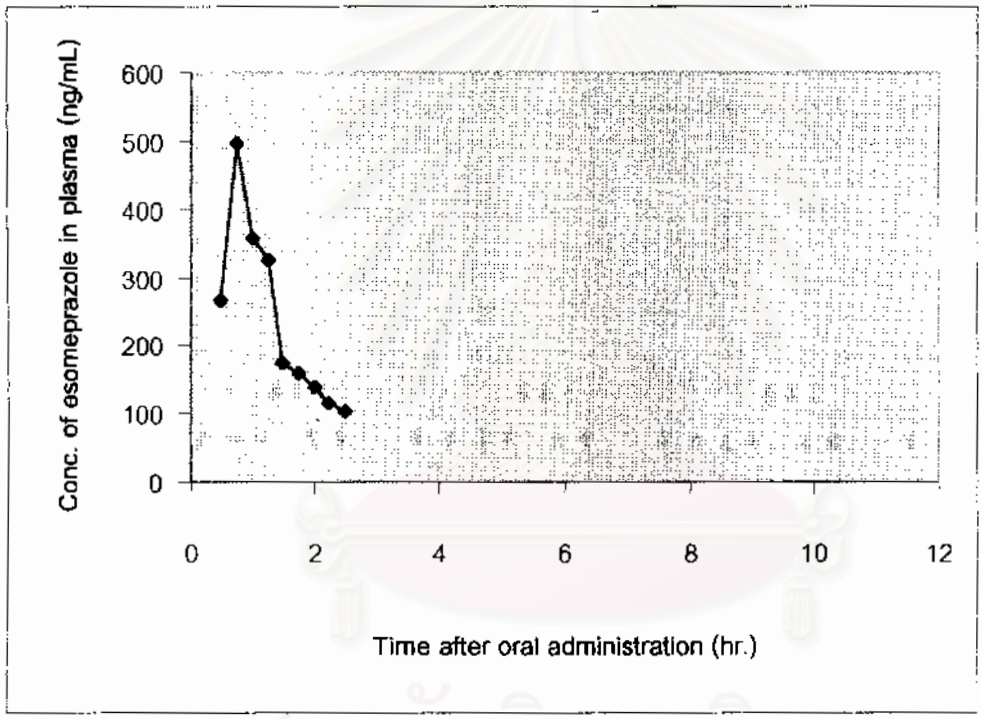

Figure 44. The plasma concentration time profile of subject No. 14

D. The figures of plasma concentration time profile on the last day (day 5) following oral administration of esomeprazole 20 mg once daily in Thai cirrhotic patients.

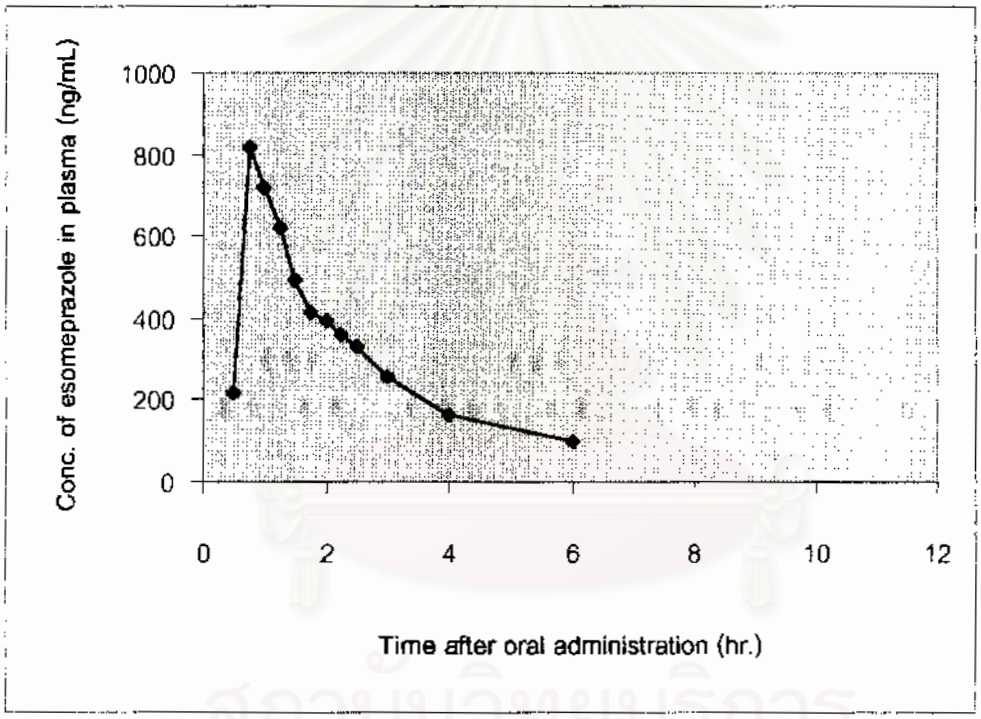

Figure 45. The plasma concentration time profile of subject No. 1

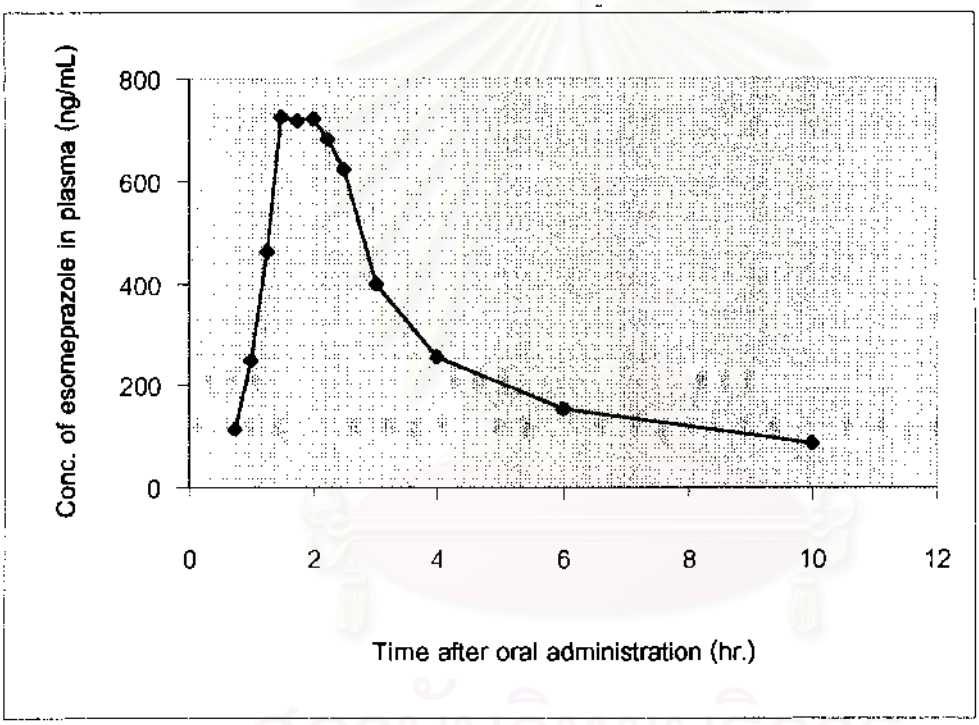

Figure 46. The plasma concentration time profile of subject No. 2

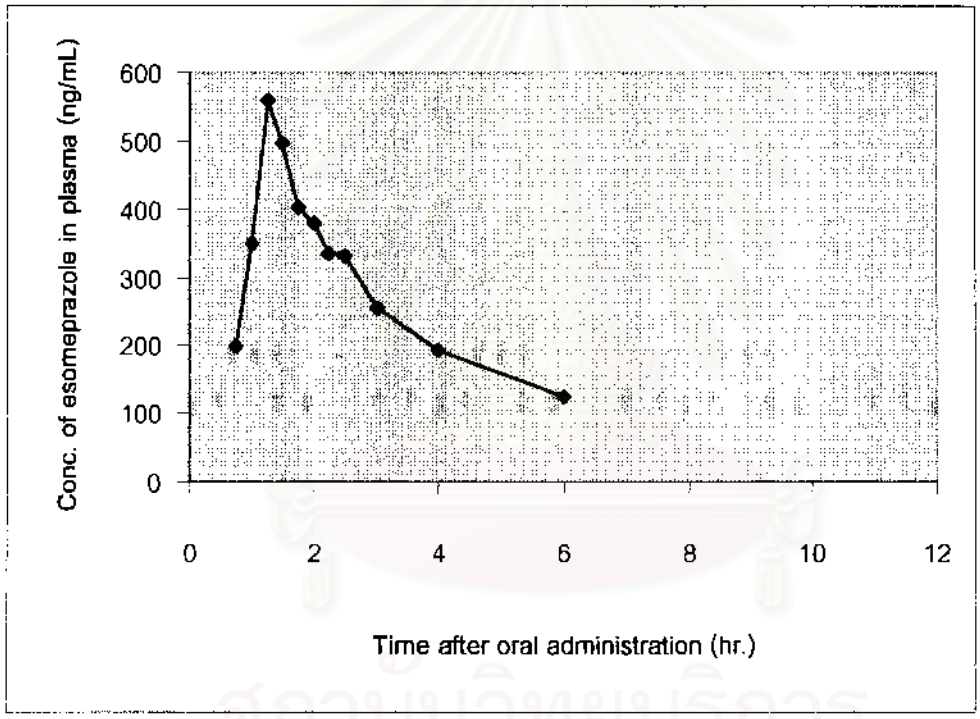

Figure 47. The plasma concentration time profile of subject No. 3

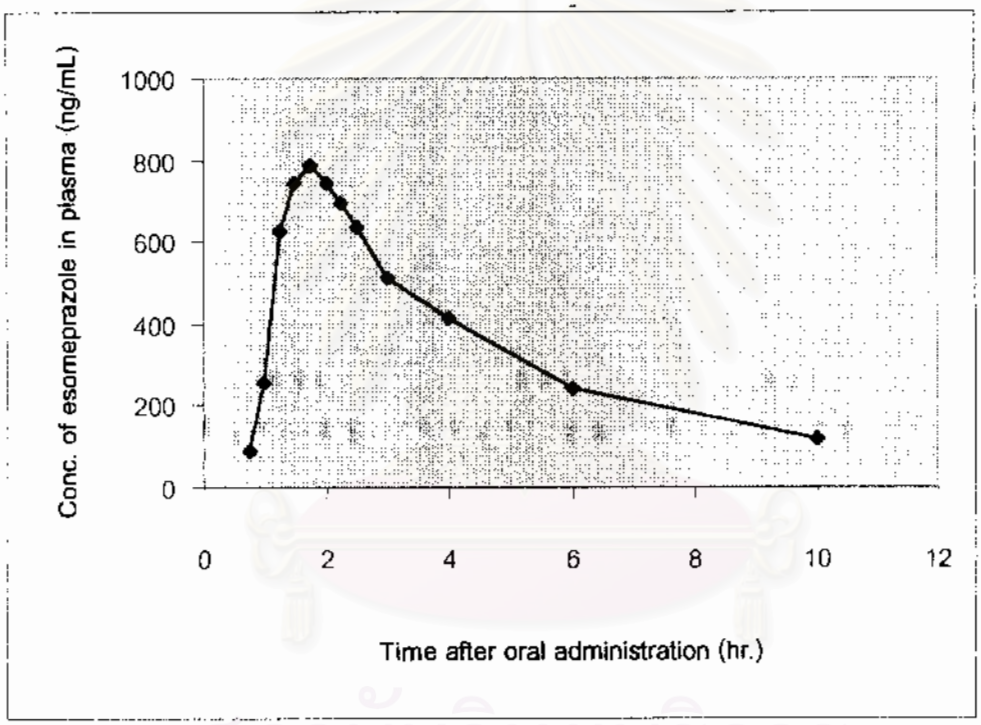

Figure 48. The plasma concentration time profile of subject No. 4

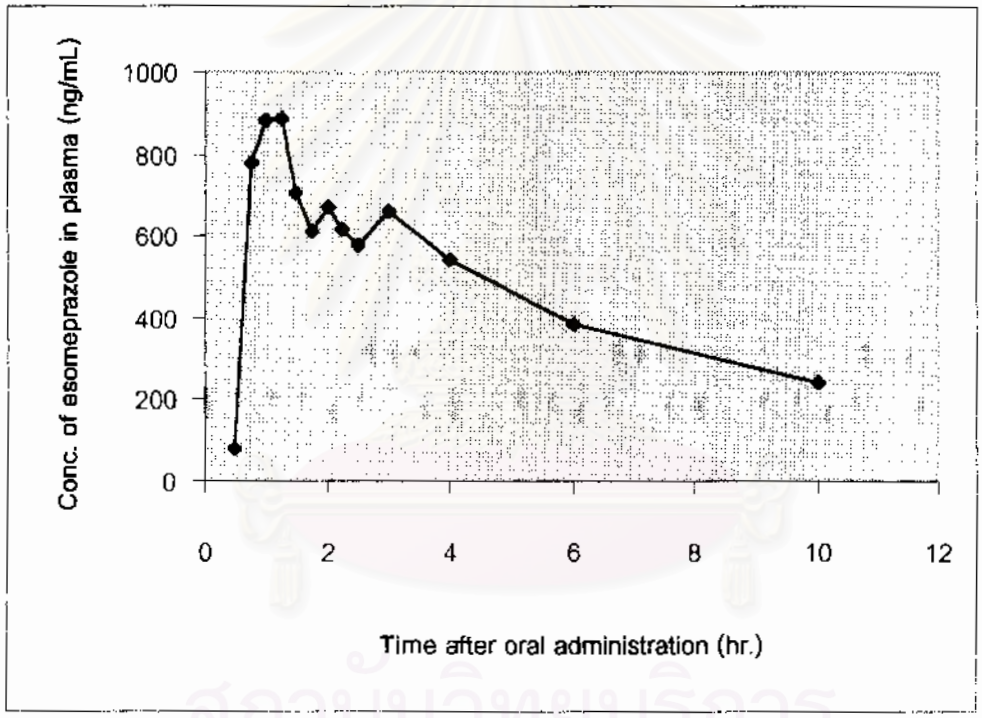

Figure 49. The plasma concentration time profile of subject No. 5

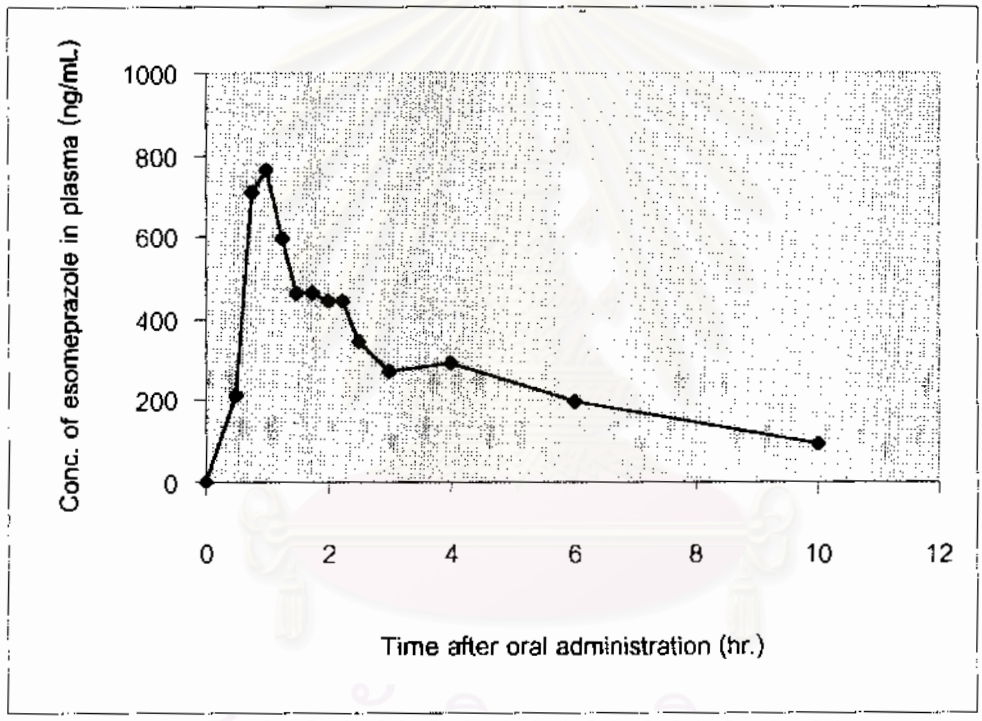

Figure 50. The plasma concentration time profile of subject No. 6

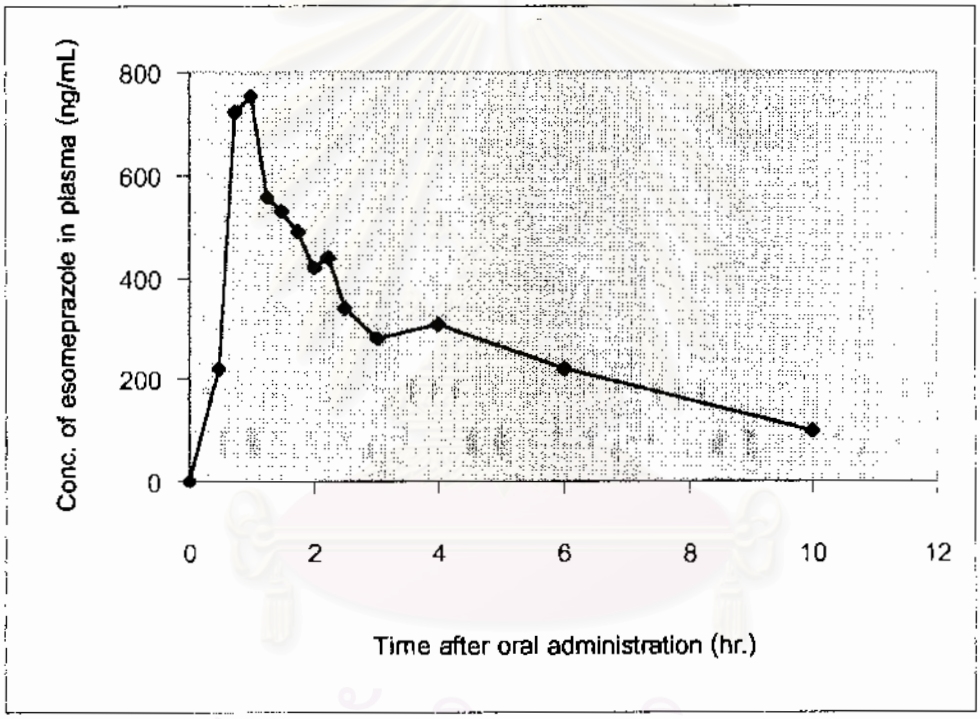

Figure 51. The plasma concentration time profile of subject No. 7

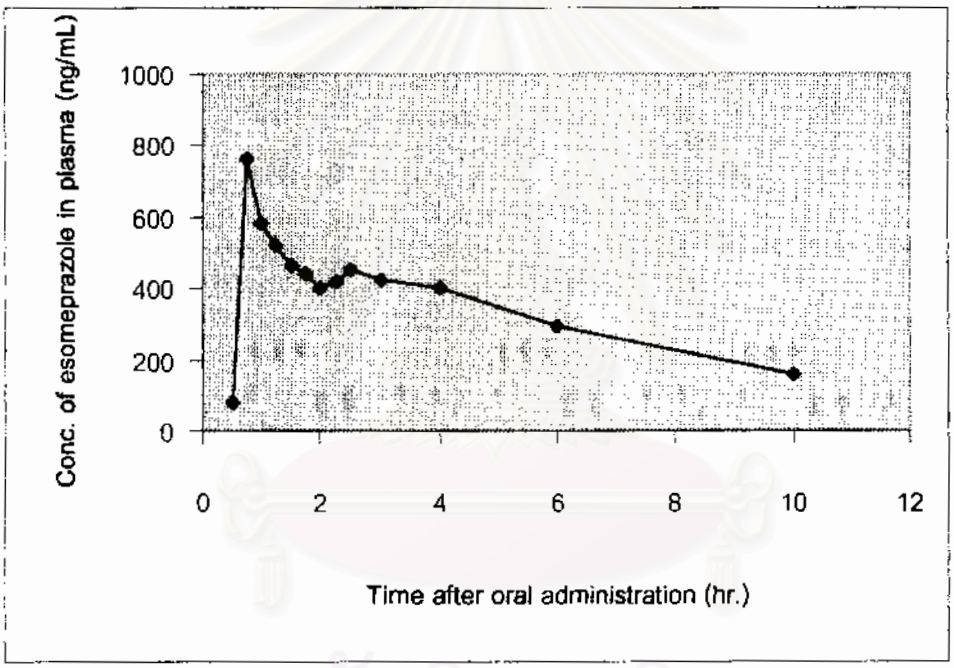

Figure 52. The plasma concentration time profile of subject No. 8

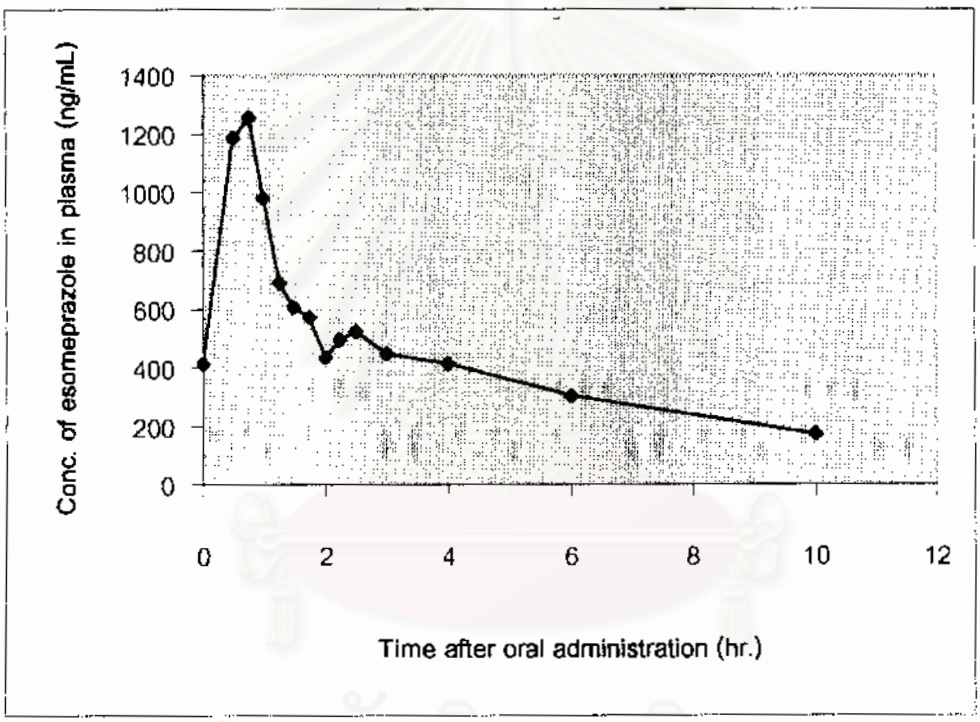

Figure 53. The plasma concentration time profile of subject No. 9

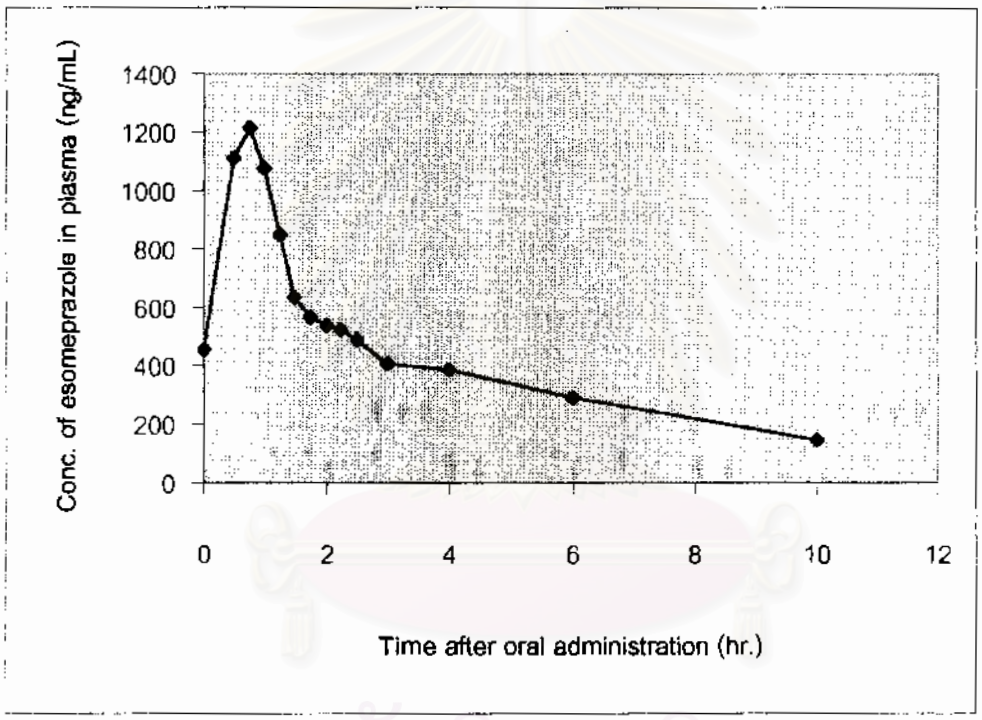

Figure 54. The plasma concentration time profile of subject No. 10

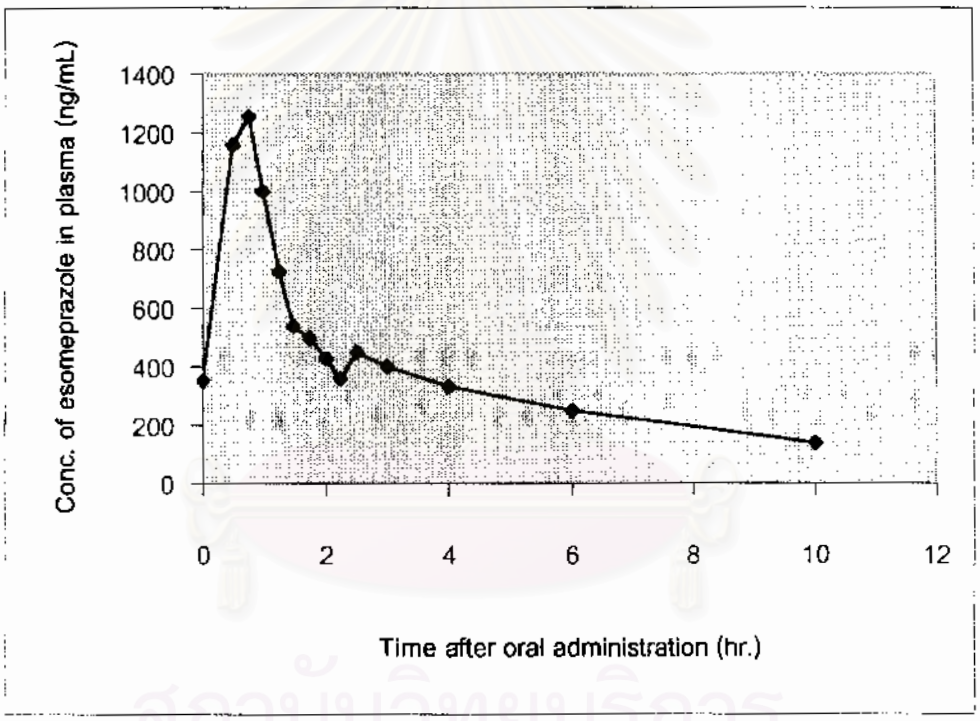

Figure 55. The plasma concentration time profile of subject No. 11

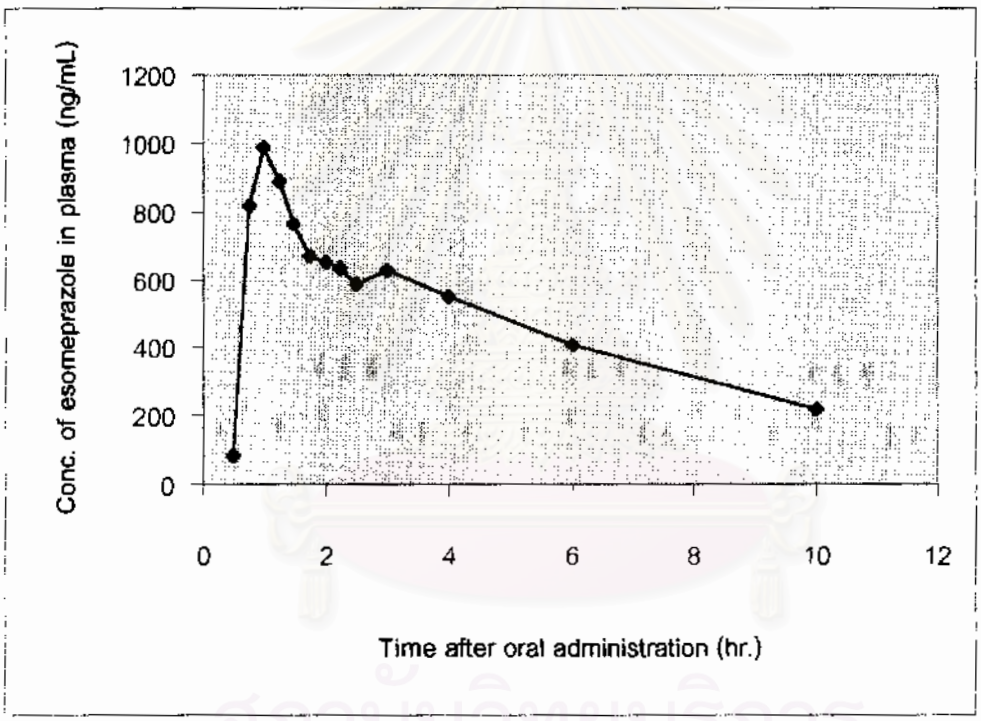

Figure 56. The plasma concentration time profile of subject No. 12

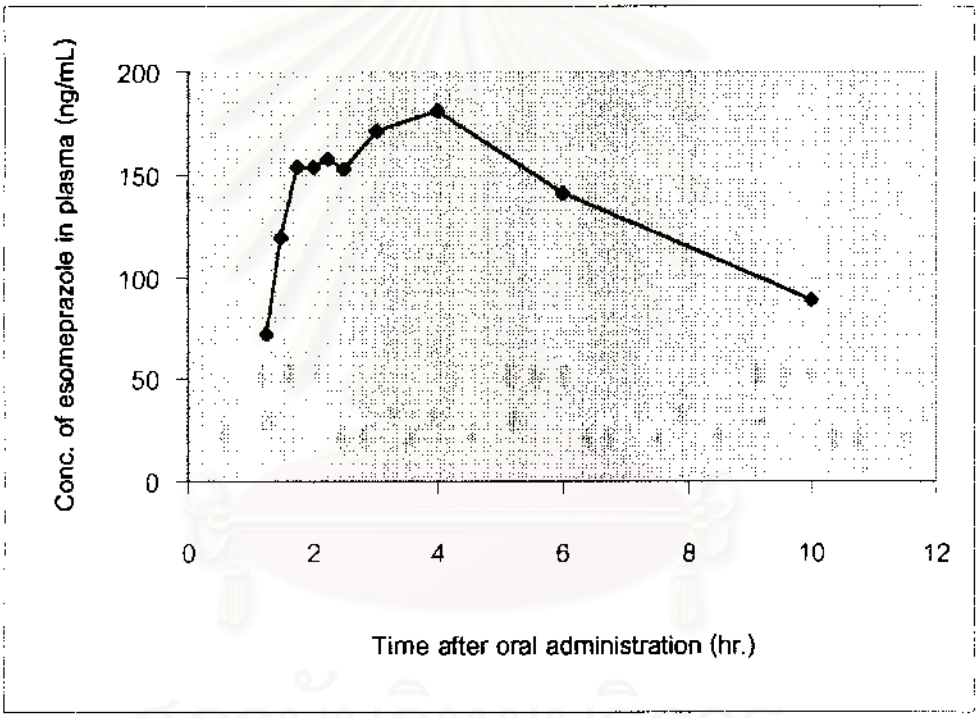

Figure 57. The plasma concentration time profile of subject No. 13

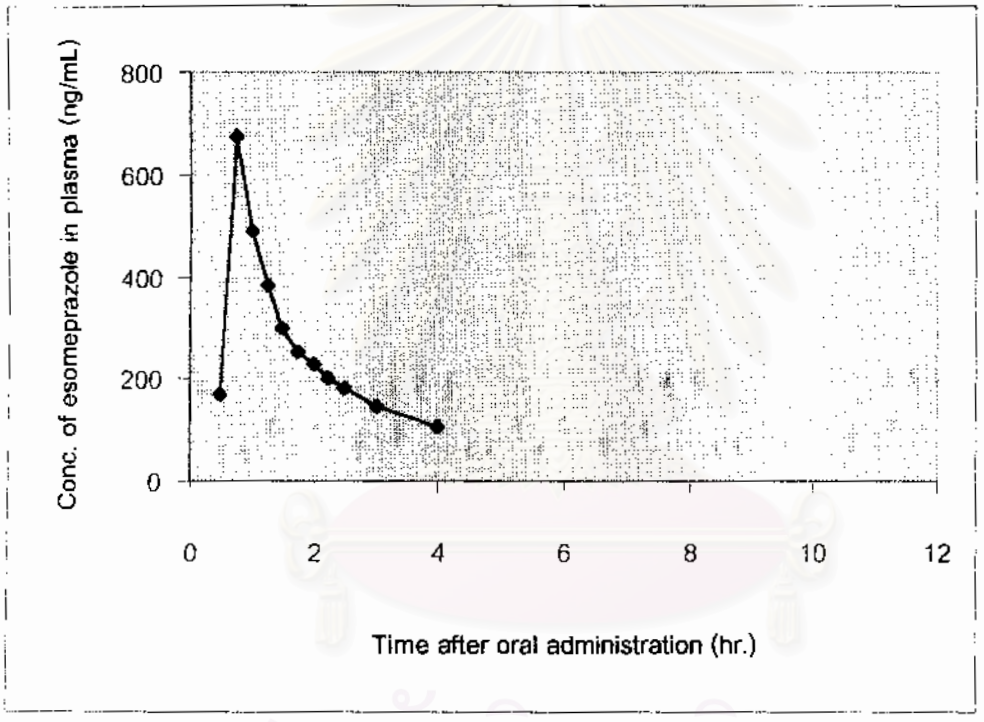

Figure 58. The plasma concentration time profile of subject No. 14

APPENDIX F

The formulas to calculate t-distribution test

When : $H_o : (S_1)^2 = (S_2)^2$

$H_1 : (S_1)^2 \neq (S_2)^2$

$(S_1)^2$ = variance of group 1 ; $(S_2)^2$ = variance of group 2

Equation 1 : $F_{calculation} = (S_1)^2 / (S_2)^2$; when $S_1 > S_2$

Degree of freedom (df) of group 1 = n-1

Degree of freedom (df) of group 2 = n-1

If $F_{index} > F_{calculation}$, accept $H_o : (S_1)^2 = (S_2)^2$ .....*Equation 2*

If $F_{index} < F_{calculation}$, accept $H_1 : (S_1)^2 \neq (S_2)^2$ .....*Equation 3*

When : $H_o : C_{max1} = C_{max2}$; $t_{max1} = t_{max2}$; $\overline{c_1} = \overline{c_2}$; $AUC_1 = AUC_2$; $t_{1/2(1)} = t_{1/2(2)}$; $CL/F_1 = CL/F_2$

$H_1 : C_{max1} \neq C_{max2}$; $t_{max1} \neq t_{max2}$; $\overline{c_1} \neq \overline{c_2}$; $AUC_1 \neq AUC_2$; $t_{1/2(1)} \neq t_{1/2(2)}$; $CL/F_1 \neq CL/F_2$

Equation 2 : If $(S_1)^2 = (S_2)^2$;

$$t = \frac{(\overline{x_1} - \overline{x_2})}{[S_p^{\,2}(1/n_1 + 1/n_2)]^{1/2}}$$

$$S_p^{\,2} = \frac{(n_1-1)(S_1)^2 + (n_2-1)(S_2)^2}{(n_1+n_2-2)}$$

$$df = n_1 + n_2 - 2$$

Equation 3 : If $(S_1)^2 \neq (S_2)^2$;

$$t = \frac{(\overline{x_1} - \overline{x_2})}{\{[(S_1)^2/n_1] + [(S_2)^2/n_2]\}^{1/2}}$$

$$df = \frac{\{[(S_1)^2 + (S_2)^2]/n\}^2}{\frac{[(S_1)^2/n_1]^2}{n_1-1} + \frac{[(S_2)^2/n_2]^2}{n_2-1}}$$

If $t_{calculation} < t_{index}$, accept $H_o : C_{max1} = C_{max2}$; $t_{max1} = t_{max2}$; $\overline{c_1} = \overline{c_2}$; $AUC_1 = AUC_2$; $t_{1/2(1)} = t_{1/2(2)}$; $CL/F_1 = CL/F_2$

If $t_{calculation} > t_{index}$, accept $H_1 : C_{max1} \neq C_{max2}$; $t_{max1} \neq t_{max2}$; $\overline{c_1} \neq \overline{c_2}$; $AUC_1 \neq AUC_2$; $t_{1/2(1)} \neq t_{1/2(2)}$; $CL/F_1 \neq CL/F_2$

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