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Esomeprazole Pharmacokinetics in Patients with Cirrhosis and Healthy Controls

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ABSTRACT

Objectives: To determine the pharmacokinetic properties of esomeprazole,a new proton pump inhibitor, which is mainly metabolized by the liver, in Thai cirrhotic patients of various etiologies and healthy controls.

Patients and Methods: The study population included two groups, including 12 cirrhotic patients with different Child Pugh's classification (Child A = 4, Child B = 4, Child C = 4) and 12 healthy controls. Each group received 20 mg. of esomeprazole OD. for 5 consecutive days. Serial blood samples were collected over 10 hours period on the first day (D1) after single dose and the fifth day (D5) of the study after multiple doses for measurement of plasma esomeprazole levels.

Results: All pharmacokinetic properties of esomeprazole, except T max, were higher in D5 than in the D1 in both groups. However, when compared between both groups, AUC and half-life in the cirrhotic patients were higher than those in the healthy group on both D1 and D5. AUC. on D1 of the cirrhotic patients and healthy controls were 4.7 and 3.2 micromol.hr/l while AUC. on D5 of both groups were 5.9 and 4.2 micromol.hr/l, respectively. Cirrhotic patients had longer half-life of esomeprazole than healthy controls on both D1 (4.1 and 2.1 hr.) and D5 (4.1 and 2.4 hr.). Although, plasma levels of esomeprazole were elevated in cirrhotic patients when compared with control group, these findings usually confined to the patients with severely impaired liver function.

Conclusions: Esomeprazole given 20 mg.OD by oral administration for 5 consecutive days resulted in comparable pharmacokinetic parameters including AUC, half-life in cirrhotic patients and healthy controls. Plasma levels of esomeprazole were elevated in cirrhotic patients especially in Child C when compared with the control group. Dose adjustment should not be required except those with Child C cirrhosis and further study need to be done .

Key words : Esomeprazole, pharmacokinetic, cirrhosis

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BACKGROUND

For several years, proton pump inhibitors (PPIs) are commonly used in the treatment of patients with gastro esophageal 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[1]. 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[2].

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.

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. 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. Esomeprazole must be considered as prodrug that need to be activated to be effective by acidic environment[3].

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[4]. 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 $p < 0.01$). 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.

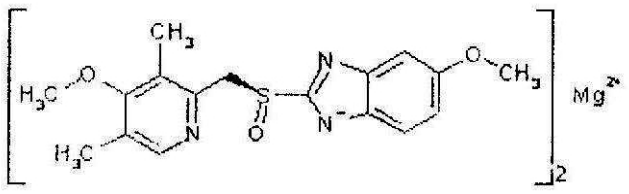

Figure 1 The structural formula of esomeprazole (Scott, *et al*. 2002)

A pharmacokinetic study of esomeprazole which given as a solution 20 mg or capsule 40 mg for 5 days to 32 healthy volunteers[5] 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 (mol/L*h and 4.32 to 11.21 (mol/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.

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[6]. The drug is metabolized extensively in the liver by the cytochrome P450 (CYP) enzyme system to products that lack antisecretory activity.

The most commonly reported adverse events were headache, diarrhea, 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[7].

The potential for interactions of esomeprazole with other drugs is reported to be low and similar to that with omeprazole[6]. However, esomeprazole inhibits gastric acid secretion, which interferes with the absorption of medications requiring an acid medium for absorption, such as ketoconazole and itraconazole[8].

In a study of the pharmacokinetic of esomeprazole 40 mg once daily by oral administration for 5 days in patients with liver cirrhosis, it was found that AUC and t1/2 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 t1/2 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[9].

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[10], lansoprazole[11] and omeprazole[12]. 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 demonstrated 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[9].

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.

PATIENTS AND METHODS

A. Study population 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.

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, 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 >1.5 mg/dl), pregnant or nursing women were also excluded.

B. 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.

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˚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 analysis Data were analyzed descriptively. Kinetic parameters were compared between

groups by student t-test.

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.

RESULTS

Analysis of esomeprazole in plasma

Table 1 showed the result of standard calibration study.

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 2.

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 3.

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 4.

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

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 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 3 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 4 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*

The Pharmacokinetic Parameter in Thai Healthy Volunteers.

The mean C_{max}, c, AUC and t1/2 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 c increased from 743.69 to 954.25 ng/mL and 104.33 to 118.12 ng/mL, respectively. The mean AUC and t1/2 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 tmax were 1.52 to 1.06 hr.

The Pharmacokinetic Parameter in Thai Cirrhotic Patients.

Similar to the results in Thai healthy volunteers, the mean C_{max}, c, AUC and t1/2 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 c increased from 835.90 to 897.25 ng/mL and 145.65 to 167.66 ng/mL, respectively. The mean AUC and t1/2 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 tmax were 1.38 to 1.04 hr.

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 no adverse events were reported in the follow up period. (a period of one week after the last dosing of esomeprazole).

DISCUSSION

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 t1/2 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 tmax 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 ± 765.32 ng/mL*hr.) as well as t1/2 (4.10 ± 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 ± 531.03 ng/mL*hr. and t1/2 of 2.19 ± 0.74 hr. Statistical significance of AUC and t1/2 between these two groups of patients was also noted at steady state when the AUC and t1/2 in cirrhotic group were found to be 4,023.71 ± 1,333.29 ng/mL*hr. and 4.12 ± 0.64 hr., respectively whereas their corresponding values in normal volunteers were 2,834.90 ± 602.38 ng/mL*hr. and 2.44 ± 0.82 hr. Moreover, CL/F at day 1 of esomeprazole in cirrhotic patients (6.03 ± 1.59 L/hr.) were lower than in normal volunteers (8.36 ± 1.95 L/hr.) as the same direction on day 5. (5.53 ± 1.93 L/hr. and 7.33 ± 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[13]. Thus the impact of relatively older age of cirrhotic patients, in the present study, on an increment of AUC and t1/2 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 almost 50% reduced, it is suggestive that enhancement of AUC and t1/2 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[9] as well as from other proton pump inhibitors such as omeprazole[12], pantoprazole[10] and lansoprazole[11].

Furthermore, it was found that t1/2 of esomeprazole in Thai cirrhotic patients as well as Thai healthy volunteers in the present studies, were apparently higher than their Swedish counterparts[6]. Due to the fact that esomeprazole is extensively metabolized by hepatic cytochrome P450, mainly by CYP2C19 and to a minor extent by CYP3A4[14]. 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 t1/2 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[15]. Thus, special care should be taken to avoid excessive diarrhea when esomeprazole is co-administered with lactulose in hepatic encephalopathy patients. There was 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 t1/2 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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