Scandinavian Journal of Gastroenterology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/igas20

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To cite this article: Hólmfríður Helgadóttir, Sigrún H. Lund, Sveinbjörn Gizurarson, Helge Waldum & Einar S. Björnsson (2021) Pharmacokinetics of single and repeated oral doses of esomeprazole and gastrin elevation in healthy males and females, Scandinavian Journal of Gastroenterology, 56:2, 128-136, DOI: 10.1080/00365521.2020.1859610

To link to this article: https://doi.org/10.1080/00365521.2020.1859610

SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY
2021, VOL. 56, NO. 2, 128–136
https://doi.org/10.1080/00365521.2020.1859610

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ORIGINAL ARTICLE

Pharmacokinetics of single and repeated oral doses of esomeprazole and gastrin elevation in healthy males and females

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ABSTRACT

Objective: Gastrin elevation secondary to proton pump inhibitor (PPI) therapy is well documented. Recent studies have demonstrated a sex-related difference where females on PPIs have significantly higher baseline gastrin levels than males. The aim of the study was to analyse the pharmacokinetics of esomeprazole and short-term effect on serum gastrin levels and evaluate potential sex-related difference.

Materials and methods: Healthy volunteers received 40 mg of esomeprazole daily for five days. After the 1st and 5th dose blood samples for fasting gastrin and pharmacokinetic analysis were collected at scheduled time-points for eight hours. Esomeprazole was analysed by liquid chromatography and gastrin concentrations were measured using radioimmunoassay.

Results: A total of 30 volunteers were enrolled. Females had higher median baseline gastrin (pM) than males 12 (IQR 10–15) vs. 7 (IQR 4–11) ($p = .03$). In the study cohort, median gastrin levels rose from 10 (IQR 6–14) to 15 (IQR 13–20) ($p = .0002$). The serum levels for esomeprazole increased by an average of 299.8 ng/mL ($p < .001$) from day 1 to day 5. Comparison of the esomeprazole pharmacokinetic parameters between males and females revealed no significant sex-related differences. No significant correlation was found between the AUC and the gastrin level on day 5 ($p = .15$).

Conclusions: In healthy volunteers, serum gastrin increased significantly after a four-day PPI-therapy. There was also a significant increase in serum esomeprazole from day 1 to day 5. The increase in gastrin and esomeprazole concentration was not related to sex and no significant sex-related difference was found in terms of pharmacokinetic parameters. European Clinical Trial Database (2015-002230-41).

ARTICLE HISTORY
Received 20 August 2020
Revised 25 November 2020
Accepted 30 November 2020

KEYWORDS
Proton pump inhibitors; gastrin; pharmacokinetics; sex-related difference; pharmacology; area under the serum concentration curve

Introduction

Most patients on long-term PPI therapy exhibit some but very variable serum gastrin elevation due to the inhibition of gastric acid secretion [1]. A number of studies and meta-analyses have shown considerable inter- and intra-individual variation in PPI induced gastrin elevation [1–6]. The reasons why some develop hypergastrinemia and others show only moderate elevation are unclear. In a recent study, females on long-term PPI therapy had significantly higher fasting and postprandial gastrin levels than males [7,8]. The reason for this exaggerated gastrin response in females on PPI therapy is unknown. One hypothesis is that females have increased sensitivity to PPIs. The elimination of PPIs is mostly due to hepatic metabolic clearance, followed by renal and faecal excretion of metabolites [9]. Possible sex dependent differences have been demonstrated in both expression and activity of these two enzymes (CYP2C19 and CYP3A) mainly involved in the metabolism of PPIs [10,11]. There are few examples in the literature of sex-dependent differences in pharmacodynamics and/or pharmacokinetics although female sex has been shown to be a risk factor for clinically relevant adverse drug reactions [11,12]. The majority of data on gastrin elevation secondary to PPIs derive from medium- or long-term therapy [13,14] and little data are available on the effect of short-term therapy. PPI-induced gastrin elevation is believed to play a role in rebound hyperacidity when PPIs are discontinued [15], resulting in induced dyspeptic symptoms [16] that might attribute to re-institution of therapy and partly explain the increasing prevalence of long-term PPI therapy [17]. Many have raised concerns regarding potential side effects associated with long-term PPI therapy including [18]; increased risk of infections, osteoporotic fractures, malabsorption of vitamins and minerals, cardiovascular- and renal-disease [19] and possible development of gastric cancer have been postulated [20].

The present study was designed to compare serum concentration of esomeprazole between healthy males and

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*The authors confirm that the PI for this paper is Einar S. Björnsson and that he had direct clinical responsibility for patients.
Supplemental data for this article can be accessed here.

females in order to understand the sex-related difference in gastrin response to PPI therapy. The hypothesis was that serum concentration of esomeprazole might be associated with sex. The secondary objective of this work was to investigate the effect of four-day PPI treatment on fasting serum gastrin.

Materials and methods

Study population

Healthy volunteers were recruited by advertisements in the University Hospital of Iceland and the University of Iceland via email. Only adults (aged 20–50 years) without a history of gastrointestinal (GI) symptoms or use of acid suppressive therapy were invited to participate. During enrolment, all volunteers received a detailed description of the study design by investigators and information was obtained about prior medical and medication history. Individuals with obesity (BMI $>30\,kg/m^2$), chronic infectious diseases such as hepatitis, pregnant or taking known CYP inhibitors or inducers were excluded from the study. All participants were informed that they could cease participation at any time during the study period.

Study design

This study was a non-blind one-way trial consisting of a five-day study period. It took place between September 2015 and March 2017 at a single study site, The National University Hospital of Iceland. Participation included two visits to the hospital on the 1st and 5th investigation days after an overnight fasting. All participants who fulfilled the inclusion criteria were asked to undergo abstinence from alcohol three days prior to and during the study period. On the first investigation day, every participant underwent a short physical examination including measurements of blood pressure, weight (kg) and height (m). All essential clinical information including participants' demographics and questionnaires were recorded in REDCap [21], which is an electronic database managed by the hospital authority. An indwelling catheter was inserted into a peripheral vein for blood sampling and a fasting blood sample was obtained for gastrin measurement and biochemical tests to assess full blood count, creatinine and liver tests to screen for renal and hepatic impairment. The participants received a single oral dose of 40 mg tablet of esomeprazole (Esomeprazole Actavis®) with 250 mL glass of water. The blood samples for pharmacokinetic evaluation were obtained at 30-min intervals during the first 4-h and then hourly up to 8-h post-dose. Participants continued fasting over 2-h post-dose and then received a standard meal. The meal consisted of two slices of bread with cheese and butter and a cup of milk, about 677 kcal. The participants were then instructed to continue with 40 mg oral dose of esomeprazole administered once daily in the morning for five days. On the 5th investigation day and final visit participants underwent the same process and were financially compensated (equivalent to 75€ or 85$) for their participation. Information relating general caffeine consumption was not included in this study but participants did not get any coffee (or caffeine in any form) during the study sessions.

The study diagram is shown in Figure 1.

Study medication

The study drug was esomeprazole, the (S)-isomer of the first PPI omeprazole. Participants received commercially available 40 mg esomeprazole tablets (Esomeprazole Actavis; Actavis Group PTC ehf., Hafnarfjörður, Iceland) that were a gift from the pharmaceutical company Actavis (Hafnarfjörður, Iceland) and stored in the hospital pharmacy at the National

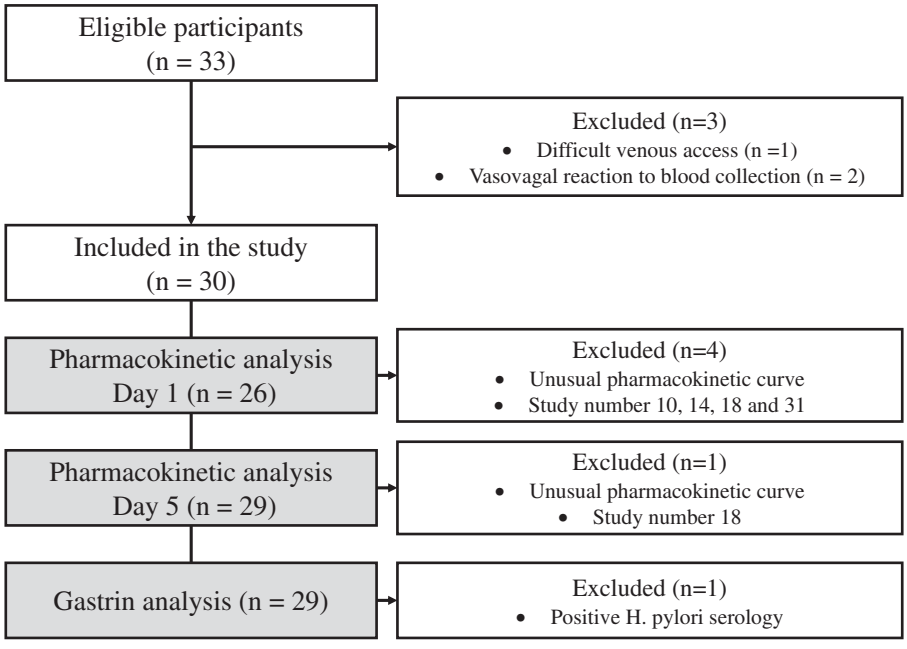

Figure 1. Flow diagram of the study enrolment and data analysis.

University hospital of Iceland. The dose of 40 mg esomeprazole is sufficient to induce maximal inhibition [22]. PPIs are acid-activated prodrugs that become active in the acidic environment of the canaliculi of active parietal cells. PPIs are most effective when the parietal cells are stimulated to secrete acid, as they are after a meal; as such, PPIs should be administered before a meal [23]. To ensure optimal inhibition of acid secretion participants were administered PPI dose in a fasting state before they received a test meal during the investigation.

Pharmacokinetics analysis

Blood samples for estimation of serum esomeprazole concentration were taken at 12 predetermined intervals throughout the 8 h of each visit (just before study drug administration (0 h) and at 30 min, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 5 h, 6 h, 7 h and 8 h post-dose). Blood samples were collected into evacuated tubes containing serum clot activator and left to coagulate for a minimum of 20 min. Serum was obtained by centrifugation at 2000 RCF for 10 min at 25 °C. Then serum was pipetted into 2 mL tubes which were stored at −80 °C until analysis in a verified laboratory operated by an Icelandic pharmaceutical company. Three participants had a single missing sample and one participant had a single sample not available for analysis of esomeprazole concentration (Supplementary Figure). Serum esomeprazole was quantified using liquid chromatography–mass spectrometry (LC–MS) with cc range = 5.027–4027.897 ng/mL. Esomeprazole concentration below limit of quantification (<5.027 ng/mL) was given the value of 0.1 in the analysis. The pharmacokinetic parameters were estimated using noncompartmental analysis on the serum esomeprazole concentration with time after administration of oral dose. Pharmacokinetic parameters included peak serum concentration (C_{max}, ng/mL); time at which C_{max} occurs (t_{max}, h); elimination rate constant (K_e, h^{-1}); elimination half-life ($t_{1/2}$, h), area under the serum concentration curve (AUC); apparent volume of distribution (Vd/F, L); apparent oral clearance (Cl/F, L/h) and absorption rate constant (K_a, h^{-1}).

K_a and K_e were estimated using slope of the least-square regression analysis of the log transformed concentration curve from first measurement to t_{max} and from t_{max} to 8 h, respectively. Elimination half-life was calculated from: $t_{1/2}$=0.693/K_e. Calculation of AUC from time zero to 8 h was performed using the Simpsons rule with RStudio. The apparent volume of distribution was found from: Vd/F =(dose×F)/C_{max} with bioavailability (F) being 64% on day 1 and 89% on day 5 [24]. The apparent clearance was calculated from: clearance = Vd/F×K_e. Participants with abnormal esomeprazole concentration curves were excluded from the final analysis. This was a post hoc exclusion of those who we were unable to calculate pharmacokinetic values by the equations given due to their unexpected curves. On day 1, this was true for four participants (number 10, 14, 18 and 31) and on day 5 only one participant (number 18) was excluded (Supplementary Figure).

Serum gastrin analysis

Serum gastrin samples were obtained in gel tubes just prior to dosing on day 1 and 5 for measurement of fasting gastrin concentration. Samples were kept frozen at −80 °C until analysis at the Department of Clinical and Molecular Medicine at the Norwegian University of Science and Technology. Gastrin concentration was determined by radioimmunoassay method (home-made gastrin-RIA) [25]. The normal range of fasting gastrin was <40 pM and values lower than 5 pM are inaccurate. Only five participants had gastrin <5 pM on investigation day 1 and were given the inaccurate number that the RIA calculated (2, 2, 4, 4 and 4 pM) in analysis.

Helicobacter pylori *testing*

The presence of *H. pylori* was determined for all participants with a serology test (Virion/Serion ELISA classic *H. pylori* IgG sets, REF: ESR118G; Virion, Wurzburg, Germany) [26] on day 1. Participants with a positive serology test were considered infected and excluded from gastrin analysis.

Gastrointestinal symptom assessment

During the initial visit a questionnaire to assess the presence of any GI symptoms was filled out. The Gastrointestinal Symptom Rating Scale (GSRS) was used, which includes 15 items combined into five symptom clusters depicting reflux, abdominal pain, indigestion, diarrhoea and constipation. The GRS has a Likert-type scale of 1–7, where 1 represents absence of symptoms and 7 represents very bothersome symptoms depending on how inconvenient it had been during the previous week. The sum of the scores for all 15 items is regarded as the GSRS total score, a higher score indicates greater severity of symptoms [27].

Statistical analysis

Statistical analysis was performed using RStudio Version 1.1.453 (RStudio, Inc., Boston, MA). Results are reported as median (25th percentile, 75th percentile) or percentage. For continuous variables, Student's t-test was used for unpaired values. When comparing groups with dichotomous variables the chi-squared test or Fisher's exact test was used, as appropriate. When comparing pharmacokinetic parameters between the first and fifth investigation day the Wilcoxon signed-rank test were performed for the majority of the variables. Shapiro–Wilk's test was used to test the normality and paired t-tests were performed only for elimination half-life ($t_{1/2}$) which was sufficiently normally distributed. In all cases, p <.05 was regarded as statistically significant. A mixed effects model was fitted to estimate the mean difference in esomeprazole concentrations after single dose and following repeated doses of esomeprazole with investigation day as a fixed effect and participants as a random effect.

The study was approved and registered with the European Clinical Trials Database (number 2015-002230-41) before initiation. Ethical approval for the conduct of this

study was obtained from The National Bioethics Committee of Iceland (number VSN-15-080). Informed consent was obtained from all individual participants included in the study.

Results

From the 33 healthy volunteers who met the inclusion criteria and gave informed consent, a total of 30 completed the study and three discontinued due to complications in blood collection before receiving the study drug (Figure 1). A summary of their baseline characteristics is shown in Table 1. Weight was the only significant difference between females and males with higher weight in males than females (Table 1). No participant met the definition of GERD, defined as weekly moderate symptoms of heartburn and/or acid regurgitation (GSRS score >4) [28]. Twenty-nine participants were included in the gastrin analysis (one male excluded due to positive *H. pylori* serology), 26 participants were included in the day 1 pharmacokinetic analysis and 29 participants were included in day 5 pharmacokinetic analysis (Supplementary Figure).

Gastrin

The gastrin concentration levels are shown in Table 2. Female participants had significantly higher baseline gastrin levels than males. Median fasting serum gastrin levels increased by approximately 50% during the treatment (p=.00015). The increase in gastrin was significant in both sexes, from a mean of 12.4–16.4 pM in females (p =.0017) and of 8.5–17.4 pM in males (p =.0058) (Figure 2). Despite the above described findings, there was not a significant difference between the sexes at the end of treatment (p =.89). Although the change in gastrin level from baseline was higher among males, mean 8.9 pM (105%), than females, mean 4 pM (32%), this difference did not reach a statistical significance (p =.11). Only one participant (male) had hypergastrinemia after four days of PPI therapy, with a value of 45 pM.

Pharmacokinetics: single dose vs. multiple doses

The mean value of esomeprazole serum concentrations increased by an average of 299.8 ng/mL (p <.001). The mean increase was 59.4 ng/mL lower in men than females (p =.49). The serum esomeprazole profiles after single dose and after daily administration for five days are shown in Figure 3(A,B), and the corresponding pharmacokinetic parameter estimates listed in Table 3.

After five days of treatment there was a significant increase in C_{max} and AUC following single and repeated doses (Table 3). Overall, the statistical analysis did not show any sex-related differences in pharmacokinetic parameters after single dose or after daily administration for five days (Table 3). The variable that was closest to a level of a significant p value for sex-related difference was absorption rate

Table 2. Gastrin levels among all, female and male volunteers with comparison of baseline levels and after only four days of PPI therapy[a].

Variable	Sex (n)	Gastrin (pM), median (IQR)	p Value[b]
Day 1	All (29)	10 (6–14)	–
	Females (15)	12 (10–15)	–
	Males (14)	7 (4–11)	–
Day 5	All (29)	15 (13–20)	.00015
	Females (15)	15 (14–19)	.0017
	Males (14)	15 (7–24)	.0058

IQR: interquartile range.
[a]Includes all participants with a negative *H. pylori* serology; n = 29.
[b]p Values calculated using paired t-test for day 0 vs. day 5.

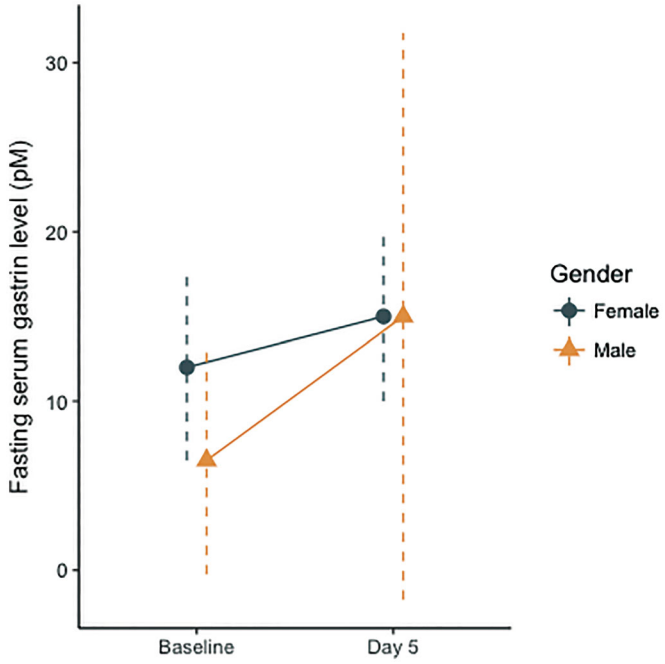

Figure 2. Median fasting gastrin levels at baseline and at the end of day 5 of treatment with 40 mg esomeprazole in healthy female (circle) and male (triangle) volunteers. The dotted lines show the 25th and 75th IQR.

Table 1. Baseline characteristics for all the volunteers and separately for female vs. male volunteers.

Variables Sex	All volunteers (n = 30)	Females (n = 15)	Males (n = 15)	p Value
Age, years	24 (20–46)	24 (22–46)	24 (20–42)	.5
Weight, kg	76 (62–107)	71 (62–96)	79 (70–107)	.01
BMI, kg/m^2	23 (19–33)	23 (20–33)	24 (19–31)	.5
H. pylori infection	1 (3)	0 (0)	1 (7)	1.0
Current smoking	4 (13)	2 (13)	2 (13)	1.0
GSRS heartburn score	1 (1–3)	1 (1–1)	1 (1–3)	.09
GSRS reflux score	1 (1–2)	1 (1–2)	1 (1–1)	.3

BMI: body mass index; GSRS: GI Symptom Rating Scale.
Categorical values are given as number (%) and continuous values as median (range).

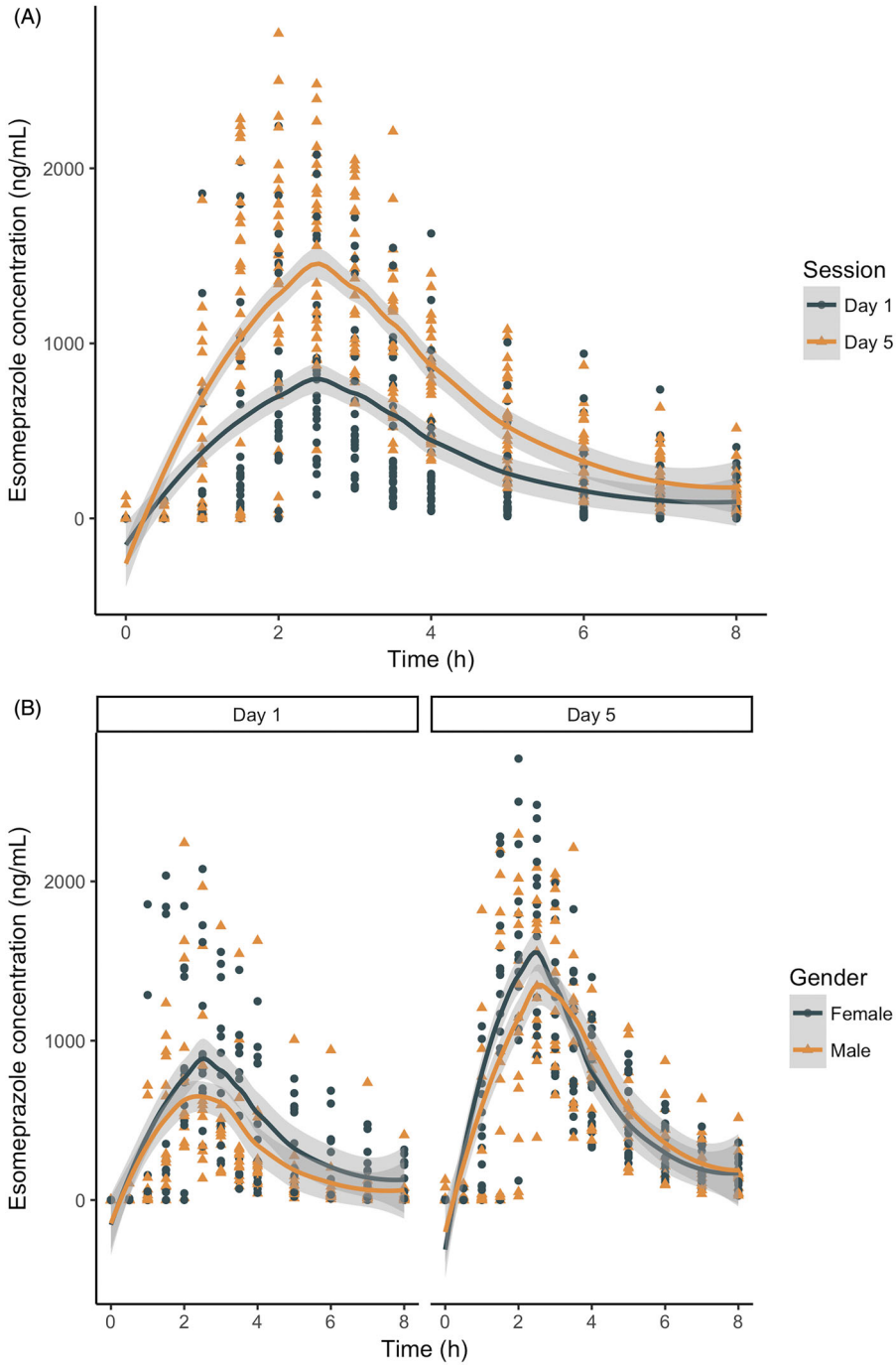

Figure 3. (A) Loess curves show the change in serum concentration vs. the time of esomeprazole following a single oral dose (circle) and following five days of repeated administration of 40 mg esomeprazole in tablet form (triangle) in 30 healthy participants. (B) Comparison of the change in serum esomeprazole concentration vs. time in healthy female (circle) and male (triangle) volunteers following 40 mg esomeprazole as a single dose (day 1) and after five days of oral dosing (day 5).

constant, with higher K_a in females than males ($p = .09$ on day 1 and $p = .05$ on day 5). The decrease observed in Vd/*F* and Cl/*F* on day 5 was generally similar for both sexes and a comparison of weight normalized Vd/*F* (L/kg) and Cl/*F* (L/h/kg) of esomeprazole between males and females on both days was non-significant (data not shown). Daily administration of esomeprazole for five days did not appear to affect the two disposition parameters, elimination rate constant and half-life in females but there was a significant change in males with an increase in half-life ($p = .01$) and decrease in rate constant ($p = .002$).

Area under the plasma concentration curve vs. gastrin

The comparison between the AUC values of esomeprazole between females and males revealed that AUC was higher in females than males, with 42% difference on day 1 ($p = .3$) and 5% on day 5 ($p = .7$). There was an increase in the AUC of esomeprazole from day 1 to day 5. AUC increased from 3150 to 5220 in females vs. 2219 to 4969 in males, this increase was more pronounced in males than females (122% vs. 66%). No significant association was found between the esomeprazole AUC and gastrin levels with a simple linear

Table 3. Pharmacokinetic parameter estimates for esomeprazole following administration of esomeprazole 40 mg in healthy volunteers.

Pharmaco-kinetic parameter	Day 1			Day 5		
	All ($n = 26$)	Females ($n = 13$)	Males ($n = 13$)	All ($n = 29$)	Females ($n = 15$)	Males ($n = 14$)
C_{max} (ng/mL)	872 (739–1599)	916 (793–1840)	768 (566–1008)	1799*** (1504–2123)	1975*** (1524–2339)	1776*** (1449–2002)
t_{max} (h)	2 (2–2.5)	2.5 (2–2.5)	2 (2–2.5)	2 (2–2.5)	2 (2–2.5)	2 (2–3)
AUC	1456 (1251–3808)	2338 (1322–5285)	1432 (1225–2101)	4507*** (3847–6259)	4818** (3866–6526)	4482*** (3873–5962)
K_a (h^{-1})	4.3 (2.8–5.5)	4.8 (4.3–5.8)	3.6 (2.8–4.3)	4.7 (3.2–6)	4.8 (4.6–6.2)	3.4 (2.5–5.7)
Vd/*F* (L)	29 (16–35)	28 (14–32)	33 (25–24)	20 (17–24)***	18 (15–23)*	20 (18–25)*
$t_{1/2}$ (h)	1.1 (0.9–1.9)	1.8 (0.9–2)	1 (0.9–1.2)	1.6 (1.3–1.8)**	1.6 (1.4–1.7)	1.5 (1.3–1.9)**
K_e (h^{-1})	0.6 (0.4–0.8)	0.4 (0.3–0.8)	0.7 (0.6–0.7)	0.4 (0.4–0.5)***	0.4 (0.4–0.5)	0.5 (0.4–0.5)***
Cl/*F* (L/h)	15 (5–24)	8.5 (5–24)	20 (13–23)	10 (6.5–12)***	10 (6–10)*	10 (7–12)**

AUC: area under the serum concentration-time curve; Cl/*F*: apparent oral clearance; C_{max}: peak serum concentration; K_a: absorption rate constant; K_e: elimination rate constant; t_{max}: time to reach peak serum concentration; $t_{1/2}$: elimination half-life; Vd/*F*: apparent volume of distribution.
Values are median and IQR (1st quantile–3rd quantile). *p* Values calculated using Wilcoxon's signed-rank test for day 1 vs. day 5 and paired *t*-test for $t_{1/2}$.
*$p<.05$.
**$p<.01$.
***$p<.001$.

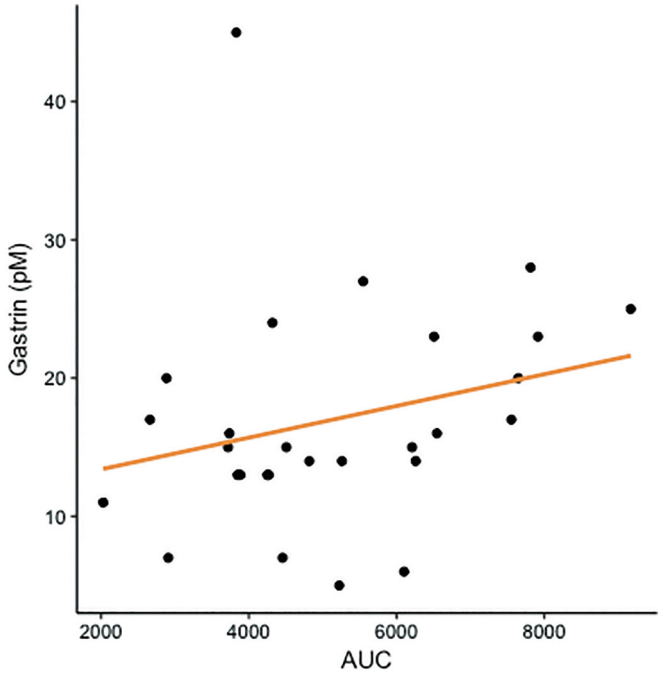

Figure 4. Relation between calculated area under the serum esomeprazole concentration curve (AUC) and measured gastrin in healthy volunteers after 5 days of 40 mg oral dosing. The correlation coefficient was 0.21 ($p=.15$).

regression ($p=.15$). Kendall's tau correlation coefficient was 0.21 (Figure 4).

Discussion

In the current study, a significant increase in serum esomeprazole levels from day 1 to day 5 was observed in healthy volunteers. However, no sex-related difference in the pharmacokinetic parameters was observed. Gastrin increased significantly after only a four day PPI course but the increase was not related to sex or the area under the esomeprazole concentration time curve.

The AUC increased threefold during repeated administration of esomeprazole, similar increase in AUC but to a lesser extent has previously been reported over the first week of treatment [24,29]. This dose-dependent increase during repeated administration in AUC of omeprazole and esomeprazole has been explained by: (1) decreased pre-absorption metabolism secondary to the profound decrease in intragastric acidity caused by the drug leading to reduced degradation of PPIs in the stomach [30] and (2) a combination of less first-pass hepatic metabolism and decreased systemic clearance [24] since esomeprazole and to a lesser extent omeprazole can inhibit their own metabolism [31].

Although the present study did not show a sex-related difference in the pharmacokinetics of esomeprazole females had higher peak serum concentration and AUC than males, but not statistically significant. These results are in line with a review of 12 pharmacokinetic studies that suggested a sex-related difference in the two pharmacokinetic parameters where AUC and C_{max} values were approximately 30% higher in females than in males after single dose, with less difference during repeated administration [32]. This might be due to the differences in CYP2C19 and CYP3A expression between the two sexes. It has previously been shown that females have a higher activity of CYP3A than males whereas the activity of CYP2C19 is lower [33]. Among Dutch whites, CYP2C19 activity was 40% greater in males than females [34]. Increased activity of CYP3A in women has been reported [11,35,36].

In the current study, no significant differences were found in weight normalized apparent volume of distribution or clearance between males and females. This is in contrast with a study on pharmacokinetics of omeprazole in an Iranian population where females had higher weight normalised volume of distribution and clearance [10].

The results of the present study demonstrated a high degree of variation among the healthy controls in the serum esomeprazole concentration time curves. It has previously been shown that poor metabolizers have higher AUC [37] and small percentage (3%) of whites do not express a functional form of CYP2C19 leading to several fold higher AUC [32]. Such outliers in AUC values were not observed in the present study but a few subjects showed relatively flat or obscure curves and these were excluded from the analysis. PPIs have a slow cumulative onset of effect with maximal effect and steady state reached after 4–5 days of daily dosing due to proton pump turnover [38]. In the current study, gastrin increased significantly in the first four days of the PPI course but the AUC was not associated with significant

gastrin elevation after a four-day PPI treatment. AUC has been shown to be the pharmacokinetic parameter that is best correlated to the gastric anti-secretory effect [39]. The gastrin elevation is however most likely representing the therapeutic gastric acid suppression as there is a well-known inverse relationship between the fasting serum gastrin concentrations and intragastric acidity [14,40].

Only a few studies have analysed the effects of short PPI therapy on gastrin stimulation. Despite the small study population and variable gastrin elevation, the present study had sufficient power to demonstrate a significant increase in gastrin after only four days of PPI therapy. A recent study demonstrated that gastrin was found to increase significantly after only five days of high dose PPI therapy ($n = 22$) [41]. Interestingly, the sharpest increase in gastrin took place from day 0 to day 5 whereas less increase in gastrin was evident between days 10 and 28 [41].

It could be argued that the current study should have included a longer treatment period, since most people who take PPIs take them for longer time periods. However, it is estimated that the daily dosing of PPIs reaches a steady state of inhibition after five days, and that state is the inhibition of about 66% of the maximal acid output [39]. Therefore, a short 5–7 day PPI course was considered to be enough to assess clinical response in GERD patients, representing the effect of PPIs on intragastric pH. There is need for randomized trials to support this hypothesis, but shorter PPI trials are likely to avert overutilization and minimize possible withdrawal symptoms in patients who do not benefit from PPI therapy.

In the current study, serum gastrin levels were found to be significantly higher in females than males at baseline before PPI therapy. In our previous study, gastrin at baseline and after a standard meal were similar in male and female controls but only females on long-term PPIs had significantly higher gastrin levels than males on PPIs [7]. Several other studies have investigated sex-related difference in gastrin among healthy subjects. Two studies have found young healthy females to have significantly higher basal and meal-stimulated gastrin compared with males [42,43], whereas two other studies in healthy subjects did not demonstrate any sex-related difference [44]. Despite the sex-related difference at baseline, we did not observe a sex-related difference in the gastrin increase following the first days of PPI therapy. This is in contrast to the hypothesis based on results from previous studies where females on long-term PPI therapy had significantly higher basal gastrin levels than males [7,8]. Likewise, studies on sex-related difference in gastrin among patients on PPI therapy have been conflicting [3,4,45,46]. The current study found no differences in metabolism of PPIs between sexes that could possibly explain the sex-related gastrin differences. Other possible alternatives that could contribute to the sex-related difference are; lower number of parietal cells in females [47], less sensitivity to gastrin effect on parietal cells [42], smaller stomach size and more postprandial distension [48,49]. Furthermore, it is conceivable that slower gastric emptying in females might affect gastrin secretion [50,51]. Whether these mechanisms can explain the registered sex-related differences in gastrin release remains to be established.T

The current study has several strengths. Study subjects were well characterized and we were able to collect necessary samples in the vast majority of subjects despite a demanding study protocol. The study has also some limitations. CYP2C19 genotyping of participants was not performed. The Cl/*F* and Vd/*F* are apparent clearance and volume of distribution, not Cl and Vd which can be calculated only with intravenous administration data. This omission is important because the bioavailability (*F*) can be vary between subjects and we used *F* from previously published data. Also, the males were significantly heavier than females, but similar BMI. In the current study, participants received a meal 2 h post dose, that is later than recommended (30–60 min before breakfast is the general recommendation) [19] but food intake can also affect the bioavailability by reducing systemic drug exposure [52]. Participants were recommended to take esomeprazole before breakfast between the visits and it is unlikely that this ~1 h delay in food intake decreased the antisecretory effect of the treatment and underestimated the gastrin elevation.

In summary, the results of the present study showed no sex-related difference in the pharmacokinetic parameters of esomeprazole. It is conceivable that other unknown factors than pharmacokinetics and the gastric anti-secretory effect of PPIs explain the high variability and potential sex-related difference observed in gastrin elevation following PPIs. Additional studies are needed to evaluate further which physiological factors are associated with PPI induced hypergastrinemia, particularly in patients with gastric acid related disorders.

Acknowledgements

We thank the Department of Clinical and Molecular Medicine at the Norwegian University of Science and Technology for the use of the home-made Gastin-Radioimmunoassay. We also thank the pharmaceutical company Actavis in Iceland for supplying the study medication and laboratory measurements of esomeprazole concentrations.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the University of Iceland Research Fund under Grant no. 140974-051 and funding from the Research Fund of the National University Hospital of Iceland was used in the preparation of this manuscript.

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Data availability statement

The original anonymous dataset is available on request from the corresponding author at einarsb@landspitali.is.

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