Population pharmacokinetics of esomeprazole in patients with preterm preeclampsia

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Abstract

Esomeprazole is a proton pump inhibitor being investigated for treatment of preeclampsia. Esomeprazole pharmacokinetics during pregnancy is unknown. We used data from 10 pregnant patients with preterm preeclampsia, and 49 non-pregnant individuals to develop a population pharmacokinetic model of esomeprazole. A two-compartment model described the data well. In pregnant patients after single dose, clearance was 42.2% (14.9%– 61.6%) lower compared to non-pregnant, most likely due to downregulation of CYP2C19. In non-pregnant after repeated dosing, clearance was 54.9% (48.2% – 63.5%) lower in extensive metabolizers and bioavailability was 33% (10.0% – 52.0%) higher compared to single dosing, which could be due to autoinhibition of CYP2C19. Esomeprazole pharmacokinetics during pregnancy appears to be more dependent on CYP3A4.

Introduction

Esomeprazole is a proton pump inhibitor which is used for gastric acid-related disorders in all age groups, including in pregnancy.[1] Its pharmacokinetics is complex. After a single dose, two-thirds of esomeprazole is metabolized by cytochrome P450 (CYP) 2C19 to 5-hydroxy- and 5-O-desmethyl esomeprazole and one-third by CYP3A4 to esomeprazole sulphone.[2] CYP2C19 is a polymorphic enzyme, and, after a single dose esomeprazole exposure is at least three times higher in poor metabolizers compared to extensive metabolizers.[3,4] With repeated dosing, esomeprazole and esomeprazole sulphone inhibit CYP2C19, thus increasing exposure due to a lower clearance and higher bioavailability (caused by decreased first-pass effect).[5] This autoinhibition effect might be more apparent for extensive metabolizers than for poor metabolizers.[2]

Esomeprazole pharmacokinetics is unknown during pregnancy but could be altered due to metabolic changes. During pregnancy, CYP2C19 is downregulated, which is expected to reduce esomeprazole clearance, however, this might only be of relevance for extensive metabolizers. Moreover, CYP3A4 is upregulated during pregnancy, which could result in a larger proportion of the drug being metabolized by CYP3A4. Since CYP3A4 is present in the intestines as well as the liver, this could increase the first-pass effect, decreasing bioavailability and increasing clearance.[6]

Preeclampsia is a major complication of pregnancy, a multi-system disorder where placental dysfunction results in maternal hypertension and multi-system organ injury.[7] An estimated 60,000 maternal and 500,000 fetal deaths annually, of which more than 95% are in low-and-middle-income countries, are due to preeclampsia.[8,9] There is an urgent need to find treatment for preterm preeclampsia which slows disease

progression and prevents preterm delivery so that neonatal outcomes can be improved.[10] Esomeprazole has been identified as potential therapeutic for preeclampsia.[11]

Preclinical studies showed that esomeprazole lowers placental production of anti-angiogenic factors thought to play an important role in the pathogenesis of preeclampsia and improves endothelial dysfunction.[12] Given these findings, a clinical trial - the PIE trial - investigated the efficacy of a daily 40-mg oral esomeprazole dose in women with preterm preeclampsia.[13] The trial did not find a significant difference in clinical outcomes or circulating concentrations of anti-angiogenic factors among participants taking esomeprazole compared to those taking placebo. It was postulated that higher doses might be necessary for treating preeclampsia since concentrations in the pregnant patients were lower than concentrations which showed efficacy in the preclinical study.[13] The PIE trial generated pharmacokinetic data of oral esomeprazole in pregnant patients with preeclampsia, a population in whom esomeprazole pharmacokinetics has not been previously described.

The aim of this work is to describe the population pharmacokinetics of oral esomeprazole during pregnancy using data from pregnant women with pre-eclampsia and healthy, non-pregnant individuals.

Methods

Studies. Pharmacokinetic data were pooled from three studies where oral 40-mg esomeprazole was given. From PIE, day one concentrations were available from pregnant patients treated with esomeprazole capsules (Nexium brand).[13] Day one and day five concentrations obtained from healthy, non-pregnant individuals were included from two studies: those from Hunfeld *et al* . were treated with MUPS tablets while those from Helgadóttir *et al.*were treated with Actavis tablets.[14,15] Meal times differed between the studies: 2 hours post-dose for PIE and Helgadóttir*et al* . and 5 minutes post-dose for Hunfeld *et al* . CYP2C19 genotype information was available for the study by Hunfeld *et al* .[14] In all the studies, esomeprazole concentrations were quantified using validated LC-MS/MS. For Helgadóttir *et al.,*esomeprazole concentrations were determined at Actavis pharmaceutical company in Iceland. For Hunfeld *et al.* , the methods used for lab analysis of esomeprazole concentrations have been previously published,[16] and analysis was done at the laboratory of the Central Hospital Pharmacy, Netherlands. For PIE, esomeprazole concentrations were determined at the Tygerberg Hospital laboratory, the details of which have been included in the original publication.[13] The lower limit of quantifications (LLOQ) were 0.001, 0.0260 mg/l, and 0.00503, PIE, Hunfeld *et al* . and Helgadóttir *et al* ., respectively.[13–15]

Pharmacokinetic analysis. Population pharmacokinetic analysis was performed using non-linear mixed-effects software NONMEM (v7.4.3, Icon®), PsN v4.9.0, Pirana v2.9.8, and R v3.6.1 for data processing.[17] The first-order conditional estimation method with interaction was used for model runs. Concentrations below the limit of quantification were handled similarly to the M6 method by Beal, with additive error inflated by LLOQ/2.[18]

The clearance and bioavailability after a single dose in non-pregnant individuals were used as a reference to report the percentage change in pregnancy or repeated dosing. The pregnancy and the repeated-dosing effects were then tested as a categorical covariate on clearance and bioavailability for each genotype subgroup (CYP2C19 extensive and poor metabolizers). For individuals where genetic information was not available, a mixture model was used for imputation, as suggested by Keizer *et al* .[19] We used proportions fixed to 95% and 5%, for extensive and poor metabolisers, respectively, based on literature.[20] Study effects were also tested as covariates on all absorption parameters to account for differences in formulation and mealtimes between the studies.

A non-parametric bootstrap (n=500) was run on the final model to obtain 95% confidence intervals (CIs) for the parameter estimates.

Results

Fifty-nine participants were included from three studies: 10 pregnant women with preterm preeclampsia from the PIE trial and 49 non-pregnant individuals (55% female), 30 from Helgadóttir *et al* . and 19 from Hunfeld *et al* .[13–15] Median (range) age was 30 (21 – 43) years for pregnant patients and 24 (18 – 46) years

for the non-pregnant individuals while weight was 99 (56 – 126) kg for pregnant patients and 74 (54 – 107) kg for the non-pregnant individuals. Genotype information was available for the study by Hunfeld *et al* ., with 1 poor metabolizer and 18 extensive metabolizers. Participant characteristics are summarised in Table 1. A total of 1064 concentrations were obtained, of which 68 (6%) were BLQ. Ten (1%) samples from PIE were identified as outliers through goodness-of-fit and individual plots and were removed from the analysis.

Esomeprazole pharmacokinetics was best characterized by a two-compartment disposition model (ΔOFV=-225, $p < 0.0001$ compared with one-compartment) with first-order elimination and absorption with transit compartments. Allometric scaling with body weight improved the model fit (ΔOFV=-14.4). Final parameter estimates and precision are presented in Table 2. For a typical 70-kg individual, clearance in extensive metabolisers was more than 3 times faster than in slow metabolisers, 24.3 (20.5 – 29.3) versus 7.87 (6.04 – 9.75) L/h.

In pregnant women, clearance was 42.2% (14.9% - 61.6%) slower compared to non-pregnant after single dose ([?]OFV=-8.57, $p < 0.005$). Bioavailability was not found to be significantly different in pregnant women. In non-pregnant individuals, clearance was 54.9% (48.2% – 63.5%) slower in extensive metabolizers on day five compared to day one ([?]OFV=-142, $p << 0.0001$), and this effect could not be estimated for poor metabolizers. Bioavailability was 33.0% (10.0% - 52.0%) higher on day five ([?]OFV=-14.4, $p < 0.0001$), and this effect could not be isolated by genotype.

We found a fast absorption with large between-occasion variability of 485% (211% – 916%). Considering differences in formulation and mealtimes between the three studies (Table 1), study (dataset) was added as a covariate on absorption parameters. Absorption was slowest for individuals in the study by Helgadóttir *et al* ., with a mean transit time (MTT) of 1.74 h, compared to those in PIE and the study by Hunfeld *et al* . (0.491 h and 0.988 h, respectively). The visual predictive check (Figure 1) shows acceptable agreement between the model and the data.

Discussion

We developed a population pharmacokinetic model to describe the pharmacokinetics of esomeprazole in pregnant women with preeclampsia. To our knowledge, this is the first population pharmacokinetic model describing esomeprazole pharmacokinetics during pregnancy. We found that clearance was 42.2% (14.9% – 61.6%) lower in pregnant women with preterm preeclampsia after a single dose of esomeprazole compared to non-pregnant individuals. In non-pregnant individuals, clearance was 54.9% (48.2% – 63.5%) lower in extensive metabolizers and bioavailability was 33% (10.0% – 52.0%) higher after repeated dosing compared with single dose.

Increases in concentration of hormones such as oestrogen and progesterone during pregnancy could downregulate CYP2C19.[6,21] The lower clearance in the pregnant patients is likely to be due to this downregulation of CYP2C19. Previous studies reported that CYP3A4 is upregulated during pregnancy,[21,22] and since CYP3A4 is abundantly present in the gut one would expect a lower bioavailability. We did not find this effect in our model.

The lower clearance in extensive metabolizers in non-pregnant individuals with repeated esomeprazole dosing is likely to be due to auto-inhibition of CYP2C19 while the higher bioavailability could be because of a decreased first-pass effect associated with CYP2C19 auto-inhibition.[2,5] Moreover, it has previously been reported for omeprazole that a decrease in intragastric acidity with repeated doses could lower its degradation in the stomach, improving its absorption.[23] Hence, with repeated administration of esomeprazole, there could be improved bioavailability due to increase in pH and lower degradation in the stomach.

Esomeprazole disposition has mostly been described in literature with one-compartment kinetics for oral data and two-compartment kinetics for IV data.[24,25] Two-compartment disposition showed better fit in our model, similar to a model by Standing *et al* .[26] We estimated a typical clearance which was more than three times higher in extensive metabolizers compared to poor metabolizers This finding is consistent with previous reports that poor metabolizers have up to three times higher exposure than extensive metabolizers.[3,4] Our

estimate of clearance in poor metabolizers agrees with models by Nagase *et al* .[24] and Standing *et al* .[26]The typical central apparent volume of distribution of 14.9 L in our study is similar to that found in healthy individuals (˜16 L).[24,27] High variability in speed of absorption was observed in our model, likely due to differences in gastric acidity between-individuals and occasions.[24]

Our study shows that esomeprazole clearance is lower during pregnancy which is probably due to CYP2C19 downregulation. This has several implications: first, metabolism during pregnancy may be more dependent on CYP3A4, which could mean there is less need for CYP2C19 genotyping during pregnancy, which has previously been suggested for proton pump inhibitors due to genotype-dependent variations in exposure and therapeutic/adverse outcomes.[28] This could also mean less drug-drug interactions that involve CYP2C19. Second, the nonlinearity in esomeprazole pharmacokinetics with repeated dosing and with dose increases would be expected to be less in pregnancy. Specifically, the increase in exposure with repeated dosing, which is due to CYP2C19 autoinhibition, would not be expected to be as high as in non-pregnant. Esomeprazole exposure increases more than dose-dependently with dose increases above 20 mg, due to saturation of CYP2C19-based clearance and first pass effect.[5,29] We don't expect as high of a nonlinear increase in exposure during pregnancy since metabolism could be CYP3A4-dependent, which is generally considered linear.[5,24,29]

It was a limitation in our study that we couldn't isolate the actual effect of pregnancy and repeated dosing because there were other factors that were different between the studies, such as mealtimes and formulation, which could affect the absorption of esomeprazole. However, we believe that with the available data, our model can adequately describe changes during pregnancy and repeated dosing. Only single dose data was available for pregnant patients and effect of repeated dosing during pregnancy could not be investigated. Nevertheless, esomeprazole metabolism seems to be less dependent on CYP2C19 during pregnancy, and we expect pregnant patients to have similar exposure after repeated doses as after single dose.

We used the first oral esomeprazole data from pregnant patients generated by the PIE trial to describe esomeprazole pharmacokinetics in pregnancy. PIE had found similar esomeprazole exposure in pregnant women to non-pregnant. In our model, we identified a lower clearance in pregnant women, but no significant change in bioavailability. Richer data from pregnant patients including healthy, non-pregnant controls and with CYP2C19 genotyping are needed to further investigate this. PIE reported no clinical benefit of esomeprazole for preeclampsia. Preclinical studies are needed to identify the pharmacodynamic target for preeclampsia and how esomeprazole acts on this target. Further clinical trials are also needed to investigate whether the preclinical efficacy can translate into human efficacy and our model can help to inform the design of these studies as well as to establish the pharmacokinetic metric that relates with pharmacodynamic markers for preeclampsia.

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Conflict of interest:

There are no competing interests to declare.

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Data availability statement: The data that support the findings of this study are available from the corresponding authors of the original studies upon reasonable request.

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Tables

Table 1. Summary of study and participant characteristics, as median (range) when applicable.

	PIE[13] (n = 10)	Helgadóttir *et al.*[15] (n = 30)	Hunfeld *et al.*[14] (n = 19)
Formulation	Nexium capsules	Actavis tablets	MUPS tablets

	PIE[13] (n = 10)	Helgadóttir *et al.*[15] (n = 30)	Hunfeld *et al.*[14] (n = 19)
Mealtimes	2 h post-dose	2 h post-dose	5 min post-dose
Sampling times (h post-dose)	0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8, 10, and 24	Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, and 8	0.083, 1, 2, 3, 4, 5, 6, 7, and 8
Visit for sampling	Day one	Day one and day five	Day five
Number of samples	85	821	158
Excluded samples	10	0	0
LLOQ (mg/L)	0.001	0.00503	0.0260
Male, n (%) Female, n (%)	0 10 (100%)	15 (50%) 15 (50%)	7 (37%) 12 (63%)
Age (years)	30 (21-43)	24 (18-46)	21 (18-27)
Weight (kg)	99 (56-126)	76 (62-107)	69 (54-89)
CYP2C19 Genotype	NA	NA	9 homEM 9 hetEM 1 PM
Abbreviations: LLOQ = lower limit of quantification, homEM = homozygous extensive metabolisers, hetEM = heterozygous extensive metabolisers, PM = poor metabolisers	Abbreviations: LLOQ = lower limit of quantification, homEM = homozygous extensive metabolisers, hetEM = heterozygous extensive metabolisers, PM = poor metabolisers	Abbreviations: LLOQ = lower limit of quantification, homEM = homozygous extensive metabolisers, hetEM = heterozygous extensive metabolisers, PM = poor metabolisers	Abbreviations: LLOQ = lower limit of quantification, homEM = homozygous extensive metabolisers, hetEM = heterozygous extensive metabolisers, PM = poor metabolisers

Table 2. Parameter estimates for the final esomeprazole model.

Parameter	**Typical Value (95% CI)[a]**	**Parameter Variability, %CV[c]**
Clearance extensive metabolizers (L/h)[b]	24.3 (20.5, 29.3)	BSV: 23.1 (15.2, 32.9)
Clearance poor metabolizers (L/h)[b]	7.87 (6.04, 9.75)	BSV: 23.1 (15.2, 32.9)
Central volume of distribution (L)[b]	14.4 (8.70, 20.3)	
Intercompartmental clearance (L/h)[b]	6.47 (2.80, 11.3)	
Peripheral volume of distribution (L)[b]	7.71 (5.78, 10.5)	
Relative bioavailability ()	1 Fixed	BOV: 23.1 (15.2, 29.9)
Absorption rate constant (1/h)	4.80 (2.89, 6.39)	BOV: 485 (211, 916)
Mean transit time (h)	1.75 (1.54, 1.94)	BOV: 38.8 (29.1, 48.5)
Number of transit compartments	10 Fixed[d]	
Covariates[e]	**Covariates[e]**	**Covariates[e]**
Change in clearance on day five for non-pregnant extensive metabolizers (%)*	-54.9 (-63.5, -48.2)	

Parameter	Typical Value (95% CI)[a]	Parameter Variability, %CV[c]
Change in bioavailability on day five for non-pregnant (%)*	+33.0 (10.0, 52.0)	
Change in clearance on day one for pregnant (%)*	-42.2 (-61.6, -14.9)	
Change in mean transit time for PIE (%)*	-71.9 (-79.3, -58.2)	
Change in mean transit time for Hunfeld *et al.* (%)*	-43.1 (-68.7, -30.0)	
Residual unexplained variability	**Residual unexplained variability**	**Residual unexplained variability**
Proportional error (%)	36.7 (32.7, 40.5)	
Additive error (mg/L)	20% of LLOQ[f]	
[a]95% confidence intervals obtained by non-parametric bootstrap (n=500) [b]Allometric scaling with total body weight for a reference individual of 70 kg [c]Between-subject (BSV) and between-occasion variability (BOV) were obtained using the formula sqrt(exp $\left(OM^2\right) - 1$) and reported as approximate %CV [d]The number of transit compartments was fixed to 10 to make parameter estimates more stable [e]Study effect was tested on parameters with day one data from healthy, non-pregnant participants as reference group *Reference group is day one non-pregnant (non-pregnant group after single dose) [f]Lower limit of quantification (LLOQ) (mg/L) was study-specific: 0.001 for PIE, 0.0260 for Hunfeld *et al.*, and 0.00503 for Helgadóttir *et al.*	[a]95% confidence intervals obtained by non-parametric bootstrap (n=500) [b]Allometric scaling with total body weight for a reference individual of 70 kg [c]Between-subject (BSV) and between-occasion variability (BOV) were obtained using the formula sqrt(exp $\left(OM^2\right) - 1$) and reported as approximate %CV [d]The number of transit compartments was fixed to 10 to make parameter estimates more stable [e]Study effect was tested on parameters with day one data from healthy, non-pregnant participants as reference group *Reference group is day one non-pregnant (non-pregnant group after single dose) [f]Lower limit of quantification (LLOQ) (mg/L) was study-specific: 0.001 for PIE, 0.0260 for Hunfeld *et al.*, and 0.00503 for Helgadóttir *et al.*	[a]95% confidence intervals obtained by non-parametric bootstrap (n=500) [b]Allometric scaling with total body weight for a reference individual of 70 kg [c]Between-subject (BSV) and between-occasion variability (BOV) were obtained using the formula sqrt(exp $\left(OM^2\right) - 1$) and reported as approximate %CV [d]The number of transit compartments was fixed to 10 to make parameter estimates more stable [e]Study effect was tested on parameters with day one data from healthy, non-pregnant participants as reference group *Reference group is day one non-pregnant (non-pregnant group after single dose) [f]Lower limit of quantification (LLOQ) (mg/L) was study-specific: 0.001 for PIE, 0.0260 for Hunfeld *et al.*, and 0.00503 for Helgadóttir *et al.*

Figure legend

Figure 1. Visual predictive check of the final model. Blue circles represent observed plasma concentrations. The solid line in the middle represents the median observed concentration, while the dashed line below and above it represents the 5^{th} and 95^{th} percentiles of the observed concentrations, respectively. The shaded area around each line represents the 95% model-predicted confidence intervals for the same percentiles.