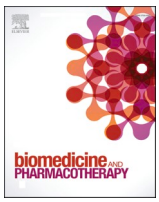
Biomedicine & Pharmacotherapy 155 (2022) 113695

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha



Influence of esomeprazole on the bioavailability of afatinib: A pharmacokinetic cross-over study in patients with non-small cell lung cancer

G.D. Marijn Veerman [a,*], Daan P. Hurkmans [a], Marthe S. Paats [b], Esther Oomen-de Hoop [a], Cor H. van der Leest [c], Eric R.E. van Thiel [d], Joachim G.J.V. Aerts [b], Roelof W. van Leeuwen [a,e], Anne-Marie C. Dingemans [b], Ron H.J. Mathijssen [a]

[a] Dept. of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands
[b] Dept. of Pulmonology, Erasmus MC, Rotterdam, the Netherlands
[c] Dept. of Pulmonology, Amphia Hospital, Breda, the Netherlands
[d] Dept. of Pulmonology, Albert Schweitzer Hospital, Dordrecht, the Netherlands
[e] Dept. of Hospital Pharmacy, Erasmus MC, Rotterdam, the Netherlands

ARTICLE INFO

Keywords:
Afatinib
Pharmacokinetics
Esomeprazole
Proton-pump inhibitor
Drug-interaction
Non-small cell lung cancer

ABSTRACT

Afatinib is an oral small-molecule kinase inhibitor (SMKI) approved for treatment of metastatic non-small cell lung cancer (NSCLC) with an epidermal growth factor receptor (EGFR) driver mutation. Although oral administration is convenient, most SMKIs experience pH-dependent solubility. A drug-drug interaction between afatinib and proton-pump inhibitors (PPIs) has, however, never been studied in humans. Hence, we performed a randomized, three-period cross-over study. Afatinib (30 mg or 40 mg) was administered without PPI (period A), concomitantly with esomeprazole (period B) and three hours after esomeprazole intake (period C). Primary objective was the area under the curve ($AUC_{0-24\ h}$) comparing period A to period B and period A to period C. Secondary objectives were other pharmacokinetic parameters and toxicity. Linear mixed effect modelling was performed for differences in $AUC_{0-24\ h}$ and C_{max} between periods A and B and periods A and C. In 18 evaluable NSCLC patients, concomitant use of 40 mg esomeprazole decreased the steady-state afatinib $AUC_{0-24\ h}$ with 10.2% (95% CI −29.2 to +14.0%; $p = 0.564$) compared to afatinib administration without PPI. Esomeprazole intake three hours prior to afatinib did not significantly influence afatinib $AUC_{0-24\ h}$ (−0.6%; 95% CI −14.9 to +16.1%; $p = 1.0$). No differences in toxicity were observed. To conclude, esomeprazole did not change the exposure to afatinib in patients with NSCLC. Since there is no clinically relevant drug-drug interaction, esomeprazole can safely be co-administered with afatinib. This is important for clinical practice, because other EGFR-SMKIs (*e.g.* erlotinib and gefitinib) do experience clinically relevant drug-drug interactions with acid-suppressive agents.

1. Introduction

Afatinib is an oral small-molecule kinase inhibitor (SMKI), primarily registered for treating patients with metastatic non-small cell lung cancer (NSCLC) with an epidermal growth factor receptor (EGFR) driver mutation [1,2]. Compared to chemotherapy, afatinib showed clear superiority in progression-free and overall survival [3]. Furthermore, afatinib is used world-wide, where it has been proven effective in vast numbers of uncommon EGFR mutations [4]. These mutations can occur spontaneously, or could be the driver mutation for progression under first- or second-line treatment with the third-generation EGFR-SMKI osimertinib [5,6]. For this latter group of patients, afatinib is the first-choice treatment. Therefore, it remains one of the pillars in treating EGFR-mutated NSCLC [7].

Most SMKIs exhibit pH-dependent solubility [8,9]. SMKIs are generally weak bases, hence they can be present in an ionized or

* Correspondence to: Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.
E-mail address: g.veerman@erasmusmc.nl (G.D.M. Veerman).

https://doi.org/10.1016/j.biopha.2022.113695
Received 28 July 2022; Received in revised form 8 September 2022; Accepted 9 September 2022
Available online 19 September 2022

non-ionized form. This depends on the gastric pH and drug characteristics such as pKa –the pH-value at which an equilibrium is reached between ionized and non-ionized drug molecules–. Because ionized molecules generally dissolve more easily, a gastric pH below the pKa is necessary to maintain adequate drug bioavailability. However, if the gastric pH increases significantly, the equilibrium will shift to the less soluble non-ionized form and its absorption will subsequently decrease [8,10]. Normal gastric pH is approximately 1–3, but it will rise to > 4 when patients use acid suppressive agents (*e.g.* proton-pump inhibitor; PPI). The PPI esomeprazole is the most potent in terms of pH increase and prolonged effectiveness compared to other PPIs [11]. For SMKIs with a pKa in this increased pH-range, a potential drug-drug interaction is likely to occur. For example, the exposure to erlotinib (pKa of 4.6) decreases by 47% when administered with esomeprazole a mere three days [12]. Since this decrease is highly clinically relevant, concomitant PPIs are advised to be avoided as it could diminish treatment effectiveness.

However, pKa may not always be predictive for the occurrence of a drug-drug interaction. In 2019, the SMKI regorafenib was thoroughly studied in combination with esomeprazole. Since regorafenib has a pKa-value around 2, an interaction was theoretically expected. However, regorafenib's bioavailability only decreased with 4%, even when esomeprazole was taken at different points in time [13]. Another example is sunitinib, that shows pH-dependent solubility that decreases when the pH increases in the range of 1.2–6.8. The drug-drug interactions with PPIs have not been studied, as no impact on drug absorption was expected. Nevertheless, retrospective data have shown that co-administration of gastric acid suppressants with sunitinib lead to decreased treatment efficacy [14]. The same discrepancy was seen with the oral 5-FU formulation capecitabine, which should theoretically not have a drug-drug interaction with PPIs due to absent pH-dependent solubility. The 42% of patients co-treated with PPIs had, however, significantly poorer survival outcomes [15].

Afatinib has a pKa of 8.8 [16,17] and is highly soluble in solutions with a pH < 6 [2]. A drug-drug interaction between afatinib and PPIs may therefore not be expected, but has never been studied in humans. Comparable to sunitinib and capecitabine, the effect of PPIs on afatinib bioavailability in patients cannot be solely predicted based on *in vitro* data. Since acid-reducing agents are used by 20–33% of cancer patients [18], a potential drug-drug interaction would be very relevant for clinical practise. Therefore, we aimed to study the interaction between afatinib and esomeprazole in patients with NSCLC. Depending on the presence and magnitude of the interaction, a practical recommendation for daily practice can be given to physicians and patients.

2. Materials and methods

2.1. Patient selection

Adult patients with World Health Organisation performance status 0 or 1 and adequate laboratory results (including full blood count, liver chemistry and kidney function, which had to be more than 1.5x the upper limit of normal) were eligible for inclusion, if they were treated with 20–40 mg afatinib QD for NSCLC and did not use, or could abstain from, acid-suppressive drugs or medication or supplements which could interact with esomeprazole or afatinib. Furthermore, pregnant patients or patients with possible impaired drug absorption (*e.g.* gastrectomy or achlorhydria) were not eligible. Written informed consent had to be provided prior to study initiation. The Erasmus University Medical Center Rotterdam ethics committee approved this study (MEC 17–251) and it was registered in the Dutch Trial Registry and International Clinical Trial Registry Platform (www.trialsearch.who.int; trial NL6336).

2.2. Study design

We performed a randomized, three-period cross-over pharmacokinetic study, in which esomeprazole was the intervention. The full study design is presented in Fig. 1. Patients received afatinib at a stable dose for at least three weeks to prevent dose adjustments because of toxicity during the study period (loading phase). Hereafter, following the randomization order, every patient underwent three study periods of two weeks each. In period A, afatinib was administered without esomeprazole, and served as control period. In period B, esomeprazole 40 milligrams was administered concomitantly for the last five days of the period. In period C, patients had to take esomeprazole 40 milligrams three hours before afatinib for the last five days of the period. This time slot was chosen, because esomeprazole reaches it maximum pH increase after 1–3.5 h after intake [11]. The last day of every study period –day 35, 49 and 63– was chosen as pharmacokinetic sampling day, for which each patient was admitted for 24 h. Pharmacokinetic sampling took place at $t = 0$ h (<5 min prior to afatinib intake), $t = 0.5$ h, $t = 1$ h, $t = 1.5$ h, $t = 2$ h, $t = 2.5$ h, $t = 3$ h, $t = 3.5$ h, $t = 4$ h, $t = 6$ h, $t = 8$ h, $t = 12$ h and $t = 24$ h. During the admissions, afatinib was taken two hours after a light breakfast, which patients had to repeat each admission day. Free intake of other food or beverages was prohibited from four hours prior until four hours after afatinib administration. Only free intake of water was allowed until one hour prior and one hour after afatinib intake.

Because afatinib is unstable in blood –not as tablet– at 37 degrees Celsius [19], all blood samples were centrifuged immediately after withdrawal and subsequent blood plasma was frozen below 70 degrees Celsius. Samples were solely processed on ice ($T = 0\ ^\circ C$). Afatinib quantification was performed with a validated liquid chromatography-tandem mass spectrometric assay (LC-MS/MS) [19], in which all the samples of every individual patient were analysed in the same run. Aliquots of 25 μL of plasma samples for the quantitation of afatinib were deproteinized by the addition of 100 μL of an internal standard solution (100 ng/mL afatinib-d6) in acetonitrile. After vigorously mixing for 5 s and centrifugation for 10 min at 18,000 *g, 50 μL of the clear supernatant was mixed with 100 μL water/formic acid/-ammonium formate (100:0.1:0.02, v/v/v), from which 5 μL was injected into the LC-MS/MS system. Peak area ratios of afatinib *versus* the Internal Standard were a linear function of the concentration from 1.00 to 100 ng/mL. The lower limit of quantitation (LOQ) was validated at 1.00 ng/mL. For afatinib, the within and between-run precisions at five tested concentrations, including the LOQ, were $\leq 9.71\%$ and $\leq 4.05\%$, respectively, while the average accuracy ranged from 96.0% to 101% [19].

2.3. Study end points

Primary objectives were to evaluate the area under the curve ($AUC_{0-24\ h}$) of afatinib compared to afatinib concomitantly used with esomeprazole (period A *versus* period B) and to afatinib used with esomeprazole three hours prior (period A *versus* period C) in patients with NSCLC. Secondary objectives were other pharmacokinetic outcomes (*c.q.* maximum concentration (C_{max}) and time to C_{max} (T_{max}) and to evaluate the incidence and severity of afatinib-related adverse events in the three periods.

2.4. Protocol compliance and adverse event monitoring

To aid participants in closely following the study protocol, they were given a diary for every study period in which the exact times and manner of the administrations of afatinib and esomeprazole had to be noted. Additionally, patients were asked to return the empty packaging of the esomeprazole and afatinib tablets, to further secure drug accountability. Patients were also asked to report any new or ongoing adverse events. Additionally, adverse events were scored at the three hospital admissions by the investigating physician in accordance with the Common

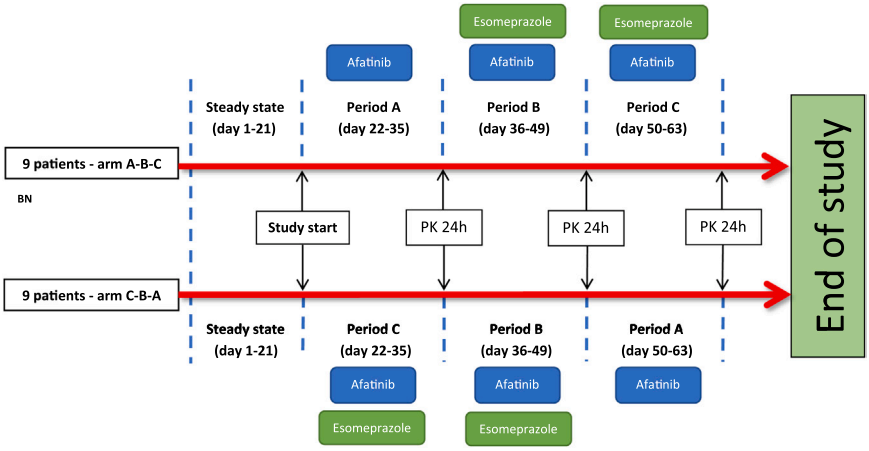


Fig. 1. Study design. After a loading period of three weeks, patients followed either arm A (study periods A-B-C) or arm B (study periods C-B-A). In period A, patients did not use esomeprazole. In period B, patients had to take esomeprazole 40 milligrams concomitantly for five days. In period C, patients had to take esomeprazole 40 milligrams three hours before afatinib for five days. The last day of every period –day 35, 49 and 63—was a pharmacokinetic sampling day, for which the patient was electively admitted for 24 h (PK 24 h).

Terminology Criteria for Adverse Events (CTCAE) grades version 5.0 [20].

2.5. Statistical analyses

Both U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) require the 90% confidence interval for ratio of the test and reference products to be contained within the acceptance interval of 80.00–125.00% [21,22]. For the sample size calculation it was important to consider that there would be two primary comparisons for which the Bonferroni correction was applied in the analyses. This was established by dividing the nominal alpha of 5% by the total number of comparisons. Hence, the sample size is calculated with a two-sided alpha of 2.5%. Assuming the within-patient standard deviation of afatinib trough concentrations to be 30% [23], a total of 18 evaluable patients was required to detect a 30% difference with 80% power [24].

AUCs were determined with a non-compartmental analysis using WinNonlin v.8.3 (Phoenix, Certara, Princeton, NJ). In order to perform statistical analyses, $AUC_{0-24\,h}$ and C_{max} were transformed to a logarithmic scale, presuming these are log-normally distributed [25]. Linear mixed effect modelling was performed for differences in $AUC_{0-24\,h}$ and C_{max} between periods A and B and periods A and C, using the intervention with esomeprazole, sequence, and the period as fixed effects, and the subject within the sequence as random effect [26]. Variance components were estimated by restricted maximum likelihood (REML) methods, and the Kenward-Roger method was used to compute the degrees of freedom of the denominator. The mean differences in $AUC_{0-24\,h}$ and C_{max} –including 97.5% confidence intervals (CIs) in which the Bonferroni correction was applied– were exponentiated to provide point estimates of the ratios of geometric means and their 97.5% CIs (*c.q.* relative differences). The periods' T_{max} were compared using the Wilcoxon signed rank test. The incidence and severity of adverse events were reported for each period separately. Since treatment time in every period was limited and the study was powered to detect a statistically significant difference for only the primary end point, the results in regard to incidence and severity of adverse events were of a descriptive nature. All statistical analyses were performed with Stata (StataCorp. 2017. Stata: Release 15.1. Statistical Software. College Station, TX: StataCorp LP).

3. Results

3.1. Patients

From August 2017 to December 2021, a total of 24 patients were included in the study of which 18 were evaluable for the primary endpoints. Six patients were not evaluable. Reasons why patients dropped-out were in four patients progression of disease occurred, one patient had conditional decline (which was probably due to disease progression), and one patient died of a COVID-19 infection. Hence, afatinib treatment and subsequent study participation were terminated prior to study completion for these patients. The evaluable 18 patients' demographics are presented in Table 1.

3.2. Pharmacokinetic effects of esomeprazole

In Fig. 2, the plasma concentration-time curves of the three different periods are shown. Esomeprazole did not result in a statistically significant difference in the exposure to afatinib (Table 2). Compared to afatinib administration alone, concomitant use of esomeprazole decreased the afatinib $AUC_{0-24\,h}$ with only 10.2% (95% CI −29.2 to +14.0%; p = 0.564). Also, exposure to afatinib was unchanged when esomeprazole was administered three hours prior to afatinib ($AUC_{0-24\,h}$ −0.6%; 95% CI −14.9 to +16.1%; p = 1.0). The coefficient of variability ranged from 49% in period B to 67% in period A. The other pharmacokinetic parameters C_{max} and T_{max} were also not statistically significantly changed by esomeprazole. Median T_{max} ranged from 3.5 to 4.0 h. All pharmacokinetic results are further specified in Table 2. When comparing the C_{max} and AUC ratios between phases A-B and A-C in

Table 1
Patient demographics.

Demographic	Total (*n* = 18)
Sex	11 (61%)
Male	7 (39%)
Female	
Age (years) median [IQR]	65 [53–71]
Body mass index kg/m^2 median [IQR]	23.2 [22.3 – 26.5]
WHO performance status	9 (50%)
0	9 (50%)
1	
Race	18 (100%)
Caucasian	
Prior therapy†	10 (56%)
None	6 (33%)
SMKI	4 (22%)
Chemotherapy	1 (6%)
Surgery	
Smoking status	9 (50%)
Never	9 (50%)
Former	
Afatinib dose	9 (50%)
40 milligrams QD	9 (50%)
30 milligrams QD	

Abbreviations: n = number of patients; IQR = interquartile range; WHO = World Health Organisation; † = two patients received both chemotherapy and SMKI sequentially; SMKI = small-molecule kinase inhibitor; QD = once daily.

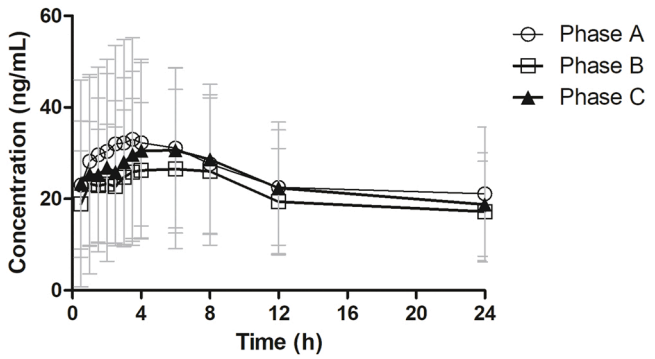


Fig. 2. Plasma concentration curves of afatinib for every study period. The lines represent the arithmetic mean concentrations of afatinib when taken in period A without esomeprazole, period B concomitant with esomeprazole, and period C three hours after esomeprazole. The grey error bars represent the standard deviation of each measurement.

patients treated with different doses of afatinib, neither Mann-Whitney U test nor T-test resulted in a statistically significant difference (all $p > 0.20$).

3.3. Toxicity

The incidence and CTCAE grades of the adverse events that patients experienced during the three study periods are depicted in Table 3. No eminent differences in adverse events were seen between the three study periods. Most frequent toxicity included grade 1 or 2 rash (in 61–67%), gastro-intestinal events (diarrhoea in approximately 40%, and stomatitis in 22%), and paronychia (in 28–35%). One patient experienced a serious adverse event (hospital admission after fall) that was not related to afatinib nor any study procedure. Considering all low-grade (grade 1 or 2) adverse events, the sum of events was equal. It appeared that more patients in period A compared to periods B and C had experienced grade 2 toxicity. However, this was because gastro-intestinal adverse events changed mildly during the study period.

4. Discussion

This is the first study to investigate the concomitant administration of the PPI esomeprazole and the EGFR-SMKI afatinib in patients with NSCLC. Since a statistically significant pharmacokinetic drug-drug interaction was absent, the drug combination can be used safely in clinical practise.

In this randomized, three-period cross-over pharmacokinetic study, we studied two different time points at which esomeprazole was administered: concomitantly, and three hours prior to afatinib intake. We did not expect an interaction because of afatinib's high pKa. Esomeprazole is the most potent PPI, with a maximum pH increase after 1–3.5 h [11]. Because we studied the combination in two periods with different points in time for esomeprazole administration, a drug-drug interaction between afatinib and esomeprazole can be ruled out. This is an important finding for clinical practice, since many patients use acid-reducing agents (*e.g.* PPIs) [18] and other well-known EGFR-SMKIs show clinically relevant decreases in exposure when taken

Table 2
Pharmacokinetic results per period.

Pharmacokinetic parameter	Period A without PPI ($n = 18$)	Period B concomitant PPI ($n = 18$)	Period C 3 h after PPI ($n = 18$)	GMR period B *versus* period A (97.5% CI)	*p*-value	GMR period C *versus* period A (97.5% CI)	*p*-value
Afatinib							
$AUC_{0-24\ h}$ (95% CI) geomean ng*h/mL	439.2 (324.7–594.1)	394.5 (313.3–496.7)	436.7 (339.5–561.8)	0.898 (0.708–1.140)	0.564	0.994 (0.851–1.161)	1.000
C_{max} (95% CI) geomean ng/mL	27.4 (20.0–37.6)	23.0 (18.3–28.8)	26.0 (20.1–33.7)	0.838 (0.606–1.159)	0.392	0.950 (0.773–1.167)	1.000
T_{max} (range) median hours	3.5 (1.0–6.1)	3.8 (1.0–8.1)	4.0 (0.6–24.0)	NA	0.214	NA	0.066

Abbreviations: $AUC_{0-24\ h}$ = area under the plasma concentration curve, time 0–24 h; CI = confidence interval; GMR = geometric mean ratio; C_{max}= maximum concentration; h = hours; n = number of patients; T_{max} = time until maximum concentration; NA = not applicable.

Table 3
Incidence and severity of adverse events.

	Period A ($n = 18$)		Period B ($n = 18$)		Period C ($n = 18$)	
Adverse event	Grade 1	Grade 2	Grade 1	Grade 2	Grade 1	Grade 2
All events	13 (72%)	6 (33%)	14 (78%)	5 (28%)	15 (83%)	4 (22%)
Rash	11 (61%)	–	11 (61%)	–	12 (67%)	–
Diarrhoea	5 (28%)	3 (17%)	6 (33%)	1 (6%)	6 (33%)	1 (6%)
Paronychia	4 (22%)	2 (11%)	3 (17%)	3 (17%)	3 (17%)	2 (11%)
Stomatitis	4 (22%)	–	4 (22%)	–	4 (22%)	–
Anorexia	1 (6%)	2 (11%)	1 (6%)	2 (11%)	2 (11%)	1 (6%)
Hypertrichosis	2 (11%)	–	2 (11%)	–	2 (11%)	–
Dry skin	–	1 (6%)	1 (6%)	1 (6%)	–	1 (6%)
Fatigue	1 (6%)	–	3 (17%)	–	1 (6%)	–
Nausea	–	1 (6%)	1 (6%)	–	–	–
Vomiting	–	1 (6%)	–	–	–	–
Alopecia	–	1 (6%)	–	1 (6%)	–	1 (6%)
Dyspnoea	1 (6%)	–	1 (6%)	–	1 (6%)	–
Hand-Foot syndrome	1 (6%)	–	–	–	1 (6%)	–
Elevated liver enzymes	1 (6%)	–	–	–	–	–
Pain	–	–	–	–	1 (6%)	–
Constipation	–	–	–	–	1 (6%)	–
Serious adverse event	1 (6%)		–		–	

Adverse events of all evaluable patients per period. Adverse events were scored by the Common Terminology Criteria for Adverse Events grades version 5.0 [20]. n = number of patients. Period A = afatinib intake without esomeprazole. Period B = afatinib intake for five days concomitant with esomeprazole. Period C = afatinib intake for five days three hours after esomeprazole.

concomitantly with acid-reducing agents. To be precise, the exposure to both erlotinib and gefitinib decreases with almost 50% when administered with esomeprazole and ranitidine respectively [9,12]. Hence, afatinib could be an alternative for patients who are PPI-dependent and should be treated with an EGFR-SMKI.

Even though most PPIs act through the similar mechanism, we are cautious in extrapolating these results to other PPIs and other acid-reducing agents. For example, in contrast to esomeprazole, the PPIs pantoprazole, omeprazole and lansoprazole all inhibit the drug transporter ABCB1 (P-glycoprotein) [27] that actively transports afatinib [1, 2]. This could cause other drug-drug interactions. To claim that these other PPIs are also safe in combination with afatinib, similar interaction studies should be performed. Other acid-reducing agents (*e.g.* antacids or H2-receptor antagonist) are less potent to increase gastric pH, and not likely to interact with afatinib through cytochrome P450-enzymes or drug transporters [28]. Theoretically, there will be no drug-drug interaction between afatinib and these acid-reducing agents either.

In neither of the two intervention periods (B or C), a clear difference in toxicity was found compared to control period A. Since esomeprazole co-administration did not change afatinib bioavailability, this finding was expected. Chronic esomeprazole use is not likely to influence the occurrence of adverse events, other than possible toxicity of esomeprazole itself.

A limitation of this study could be that no intragastric pH measurement was performed which might have helped to further interpret the interaction. However, a pH measurement is very invasive and patient unfriendly, its execution and thus validity is challenging [29] and its additional value for clinical practise would therefore be limited. Furthermore, the relatively high coefficient of variation in the study periods could point in the direction of limited power. Given the relative differences however, it is not expected that increasing the number of patients would lead to a statistical significant or clinically relevant difference. Another limitation is that, similar to afatinib, esomeprazole exposure significantly decreases when taken within 15 min of eating a high-fat, high-calorie meal [30]. This effect was smaller at day 5 compared to day 1. Nevertheless, esomeprazole is advised to be taken at least one hour before a meal [31]. In order to minimize this possible food-effect in period B of our study design, patients were asked to eat a light (low-fat) meal exactly two hours prior to esomeprazole and afatinib intake.

5. Conclusions

In this study esomeprazole did not change the exposure to afatinib, when either administered concomitantly, or three hours before afatinib intake. Since there is no clinically relevant drug-drug interaction, the co-administration of esomeprazole with afatinib is safe to be used in clinical practise.

Ethics approval

The study was approved by the local ethics committee (Erasmus University Medical Center Rotterdam; MEC 17–251) and was registered in the Dutch Trial Registry and International Clinical Trial Registry Platform (www.trialsearch.who.int; trial NL6336).

Funding

This study was financially supported by an unrestricted grant from Boehringer-Ingelheim (grant PO number 1200.290).

Consent to participate

All participating patients were asked to sign a written informed consent form prior to participation.

CRediT authorship contribution statement

GDMV, DPH, RWFvL, and RHJM designed the study. GDMV and DPH performed the research (*c.q.* screening and pharmacokinetic blood sampling). MSP, EREvT, JGJVA, and AMCD selected patients for screening. GDMV, EOdH, and RHJM analysed and interpreted the data. GDMV wrote the manuscript. All other authors critically reviewed the manuscript and gave final approval for publication.

Conflict of interest statement

G.D. Marijn Veerman reports grants from Eli Lilly, outside the submitted work, Roelof W.F. van Leeuwen reports grants from Bayer, Astellas, Pfizer, BMS and Roche, outside the submitted work (paid to institution), Ron H.J. Mathijssen reports an unrestricted grant from Boehringer-Ingelheim (paid to institution). Furthermore, Ron H.J. Mathijssen reports grants from Servier, Sanofi, Bayer, Astellas, Pamgene, Cristal Therapeutics, Pfizer, and Novartis, outside the submitted work (paid to institution), Joachim G.J.V Aerts reports grants from Boehringer-Ingelheim, outside the submitted work (paid to institution), Anne-Marie C. Dingemans reports grants from Boehringer-Ingelheim, outside the submitted work (paid to institution), All other authors declare no to have competing interests.

Data Availability

Access to the data generated during and/or analysed during the current study will be granted by the corresponding author on reasonable request.

Acknowledgements

We would like to acknowledge Mei Ho Lam and Peter de Bruijn for analysing all pharmacokinetic samples and for creation of Fig. 2. Furthermore, we would like to acknowledge dr. Kees Kraaij for assisting with the patient enrolment. We would also like to acknowledge Yvonne van der Hee for reviewing the entire manuscript from a linguistic point of view.

References

[1] US Food & Drug Administration label GILOTRIF (afatinib). January 2018. Reference ID 4207081.
[2] European Medicines Agency, Summary of Product Characteristics, GIOTRIF, July 25, 2013. Reference EMA/491185/2013.
[3] L.V. Sequist, J.C. Yang, N. Yamamoto, K. O'Byrne, V. Hirsh, T. Mok, S.L. Geater, S. Orlov, C.M. Tsai, M. Boyer, W.C. Su, J. Bennouna, T. Kato, V. Gorbunova, K. H. Lee, R. Shah, D. Massey, V. Zazulina, M. Shahidi, M. Schuler, Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations, J. Clin. Oncol. 31 (27) (2013) 3327–3334.
[4] J.C. Yang, M. Schuler, S. Popat, S. Miura, S. Heeke, K. Park, A. Märten, E.S. Kim, Afatinib for the treatment of NSCLC harboring uncommon EGFR mutations: a database of 693 cases, J. Thorac. Oncol. 15 (5) (2020) 803–815.
[5] A.J. Schoenfeld, H.A. Yu, The evolving landscape of resistance to Osimertinib, J. Thorac. Oncol. 15 (1) (2020) 18–21.
[6] W.M. Brückl, M. Reck, F. Griesinger, H. Schäfer, C. Kortsik, T. Gaska, J. Rawluk, S. Krüger, K. Kokowski, S. Budweiser, J.H. Ficker, C. Hoffmann, A. Schüler, E. Laack, Afatinib as first-line treatment in patients with EGFR-mutated non-small cell lung cancer in routine clinical practice, Ther. Adv. Med Oncol. 13 (2021), 17588359211012361, 17588359211012361.
[7] A. Leonetti, S. Sharma, R. Minari, P. Perego, E. Giovannetti, M. Tiseo, Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer, Br. J. Cancer 121 (9) (2019) 725–737.
[8] N.R. Budha, A. Frymoyer, G.S. Smelick, J.Y. Jin, M.R. Yago, M.J. Dresser, et al., Drug absorption interactions between oral targeted anticancer agents and PPIs: is pH-dependent solubility the Achilles heel of targeted therapy? Clin. Pharmacol. Ther. (2012) 203–213.
[9] K. Hussaarts, G.D.M. Veerman, F.G.A. Jansman, T. van Gelder, R.H.J. Mathijssen, R.W.F. van Leeuwen, Clinically relevant drug interactions with multikinase inhibitors: a review, Ther. Adv. Med Oncol. 11 (2019), 1758835918818347, 1758835918818347.

[10] R.W. van Leeuwen, T. van Gelder, R.H. Mathijssen, F.G. Jansman, Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective, Lancet Oncol. 15 (8) (2014) e315–e326.
[11] J.M. Shin, N. Kim, Pharmacokinetics and pharmacodynamics of the proton pump inhibitors, J. Neurogastroenterol. Motil. 19 (1) (2013) 25–35.
[12] G.D.M. Veerman, K. Hussaarts, R. Peric, E. Oomen-de Hoop, K.D. Landa, C.H. van der Leest, S.D. Broerse, H.B. Rutten, H. Belderbos, C. Steendam, M.S. Paats, S. Koolen, A.C. Dingemans, T. van Gelder, R. van Leeuwen, J. Aerts, R. Mathijssen, Influence of cow's milk and esomeprazole on the absorption of Erlotinib: a randomized, crossover pharmacokinetic study in lung cancer patients, Clin. Pharmacokinet. 60 (1) (2021) 69–77.
[13] F.M. de Man, K. Hussaarts, M. de With, E. Oomen-de Hoop, P. de Bruijn, H.K. van Halteren, N. van der Burg-de Graauw, F. Eskens, T. van Gelder, R. van Leeuwen, R. Mathijssen, Influence of the proton pump Inhibitor Esomeprazole on the bioavailability of regorafenib: a randomized crossover pharmacokinetic study, Clin. Pharm. Ther. 105 (6) (2019) 1456–1461.
[14] V.H. Ha, M. Ngo, M.P. Chu, S. Ghosh, M.B. Sawyer, C.R. Chambers, Does gastric acid suppression affect sunitinib efficacy in patients with advanced or metastatic renal cell cancer? J. Oncol. Pharm. Pr. 21 (3) (2015) 194–200.
[15] M.P. Chu, J.R. Hecht, D. Slamon, Z.A. Wainberg, Y.J. Bang, P.M. Hoff, A. Sobrero, S. Qin, K. Afenjar, V. Houe, K. King, S. Koski, K. Mulder, J.P. Hiller, A. Scarfe, J. Spratlin, Y.J. Huang, S. Khan-Wasti, N. Chua, M.B. Sawyer, Association of proton pump inhibitors and capecitabine efficacy in advanced gastroesophageal cancer: secondary analysis of the TRIO-013/LOGiC randomized clinical trial, JAMA Oncol. 3 (6) (2017) 767–773.
[16] DrugBank. Molecular characteristics of afatinib. 2022. ⟨https://go.drugbank.com/drugs/DB08916⟩.
[17] European Bioinformatics Institute. Molecular characteristics of afatinib, CHEMBL1946170. 2022. ⟨https://www.ebi.ac.uk/chembl/compound_report_card/CHEMBL1173655/⟩.
[18] G.S. Smelick, T.P. Heffron, L. Chu, B. Dean, D.A. West, S.L. Duvall, B.L. Lum, N. Budha, S.N. Holden, L.Z. Benet, A. Frymoyer, M.J. Dresser, J.A. Ware, Prevalence of acid-reducing agents (ARA) in cancer populations and ARA drug-drug interaction potential for molecular targeted agents in clinical development, Mol. Pharm. 10 (11) (2013) 4055–4062.
[19] G.D.M. Veerman, M.H. Lam, R.H.J. Mathijssen, S.L.W. Koolen, P. de Bruijn, Quantification of afatinib, alectinib, crizotinib and osimertinib in human plasma by liquid chromatography/triple-quadrupole mass spectrometry; focusing on the stability of osimertinib, J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 1113 (2019) 37–44.
[20] US Department of Health and Human Services (US National Institute of Health). Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. June 27, 2017.
[21] European Medicines Agency, Guideline on the investigation of drug interactions. June 21, 2012. ⟨https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf⟩.
[22] U.S. Department of Health and Human Services, Evaluation of Gastric pHDependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications draft-Guidance for Industry. November 2020. ⟨https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-gastric-ph-dependent-drug-interactions-acid-reducing-agents-study-design-data-analysis⟩.
[23] S. Wind, M. Schmid, J. Erhardt, R. Goeldner, P. Stopfer, Pharmacokinetics of Afatinib, a selective irreversible ErbB family blocker, in patients with advanced solid tumours, Clin. Pharm. 52 (12) (2013) 1101–1109.
[24] Schoenfeld D. Statistical considerations for a cross-over study where the outcome is a measurement: MGH Mallinckrodt General Clinical Research Center; 2018. ⟨http://hedwig.mgh.harvard.edu/sample_size/js/js_crossover_quant.html⟩.
[25] E.T. Hellriegel, T.D. Bjornsson, W.W. Hauck, Interpatient Variability in Bioavailability Is Related to the Extent of Absorption: Implications for Bioavailability and Bioequivalence Studies, Clin. Pharm. Ther. 60 (6) (1996) 601–607.
[26] B. Jones. Design and Analysis of Cross-over Trials, second ed.,, Chapman & Hall/CRC, United States, 2003.
[27] C. Pauli-Magnus, S. Rekersbrink, U. Klotz, M.F. Fromm, Interaction of omeprazole, lansoprazole and pantoprazole with P-glycoprotein, Naunyn Schmiede Arch. Pharm. 364 (6) (2001) 551–557.
[28] D. Patel, R. Bertz, S. Ren, D.W. Boulton, M. Någård, A systematic review of gastric acid-reducing agent-mediated drug-drug interactions with orally administered medications, Clin. Pharm. 59 (4) (2020) 447–462.
[29] C.G. Streets, T.R. DeMeester, Ambulatory 24-hour esophageal pH monitoring: why, when, and what to do, J. Clin. Gastroenterol. 37 (1) (2003) 14–22.
[30] M.B. Sostek, Y. Chen, T. Andersson, Effect of timing of dosing in relation to food intake on the pharmacokinetics of esomeprazole, Br. J. Clin. Pharm. 64 (3) (2007) 386–390.
[31] US Food & Drug Administration label NEXIUM (esomeprazole magnesium). December 2014. Reference ID 3675799.