Effect of the Proton Pump Inhibitor Esomeprazole on the Systemic Exposure of Capecitabine: Results of A Randomized Crossover Trial

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Retrospective data suggest that gastric acid reduction by proton pump inhibitors (PPIs) impairs the dissolution and subsequent absorption of capecitabine, and thus potentially reduces the capecitabine exposure. Therefore, we examined prospectively the effect of esomeprazole on the pharmacokinetics of capecitabine. In this randomized crossover study, patients with cancer were assigned to 2 sequence groups, each consisting of 3 phases: capecitabine with esomeprazole administration 3 hours before (phase A), capecitabine alone (phase B), and capecitabine concomitant with cola and esomeprazole co-administration 3 hours before (phase C). The primary end point was the relative difference (RD) in exposure to capecitabine assessed by the area under the plasma concentration-time curve from zero to infinity ($AUC_{0\text{-}inf}$) and analyzed by a linear mixed effect model. Twenty-two evaluable patients were included in the analysis. After esomeprazole, there was a 18.9% increase in $AUC_{0\text{-}inf}$ of capecitabine (95% confidence interval (CI) −10.0% to 57.0%, $P = 0.36$). In addition, capecitabine half-life was significantly longer after esomeprazole (median 0.63 hours vs. 0.46 hours, $P = 0.005$). Concomitant cola did not completely reverse the effects observed after esomeprazole (RD 3.3% (95% CI −16.3 to 27.4%, $P = 1.00$). Capecitabine exposure is not negatively influenced by esomeprazole cotreatment. Therefore, altered capecitabine pharmacokinetics do not explain the assumed worse clinical outcome of PPI-cotreated patients with cancer.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Proton-pump inhibitor (PPI) use has been negatively associated with efficacy of capecitabine in previous retrospective analyses.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This is the first randomized pharmacokinetic (PK) crossover study investigating the effect of the PPI esomeprazole on capecitabine PKs.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ We found a higher capecitabine area under the plasma concentration-time curve (AUC) and longer capecitabine half-life after esomeprazole. Therefore, the proposed interaction between capecitabine and esomeprazole cannot be explained pharmacokinetically.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The evidence supporting an interaction between capecitabine and esomeprazole remains weak and of retrospective nature. Therefore, prospective studies are warranted to validate this hypothesis and—if validated—to elucidate the pharmacodynamic interaction.

Capecitabine, an oral prodrug of the active metabolite 5-fluorouracil (5-FU), is a frequently used antimetabolic agent in solid tumors, including breast cancer, gastroesophageal cancer, and colorectal cancer. It is most frequently administered in a 2 weeks-on, 1 week-off, schedule. After oral administration, capecitabine is rapidly and completely absorbed from the gastrointestinal tract as an intact molecule and is metabolized to 5-FU via a 3-step enzymatic cascade.[1] First to 5'-deoxy-5-fluorocytidine

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by carboxylesterase (primarily in the liver), then to 5'-deoxy-5-fluorouridine by cytidine deaminase (in tumor cells and liver), and finally to the active drug 5-FU by thymidine phosphorylase.[1]

A potential problem with orally administered agents is the variability in absorption due to various factors, such as food and/or comedication.[2–4] With capecitabine administered after food, a reduced exposure was demonstrated, however, with a minimal effect on the exposure to 5-FU.[4] In a study with the aluminium and magnesium containing antacid Maalox co-administered with capecitabine, an increased exposure to capecitabine was seen with minimal impact on the metabolite 5'-deoxy-5-fluorocytidine and no effect on other metabolites.[5] Hence, these specific interactions are not considered to be of clinical relevance.

Recent research has pointed toward a clinically relevant interaction between capecitabine and proton pomp inhibitors (PPIs). Capecitabine used concomitantly with several PPIs compared to the same regimens without PPIs resulted in a study of Chu et al. in patients with gastroesophageal cancer, in a significant reduction in median progression-free survival of 4.2 months vs. 5.7 months ($P = <$ 0.001) and median overall survival 9.2 months vs. 11.3 months, ($P = 0.04$). Sun et al. showed in patients with early stage colorectal cancer treated with capecitabine concomitant with PPI therapy a decrease in 5-year recurrence-free survival (74% vs. 83%, $P = 0.03$).[6,7]

The authors have speculated that changes in the stomach pH value following PPI administration reduce dissolution and absorption of capecitabine in the gastrointestinal tract.[6,7] These conclusions unfortunately were not supported by pharmacokinetic (PK) data of capecitabine or 5-FU. Given the potential impact of this specific interaction,[8] we prospectively assessed the systemic exposure to capecitabine and 5-FU with or without PPI (esomeprazole) co-administration. In addition, we investigated whether this potential PK interaction could be reversed by addition of the acidic beverage cola, as previously demonstrated by our group with the tyrosine kinase inhibitor erlotinib.[9]

METHODS

Trial design and outcome

This randomized two-armed, three-phase, crossover, interventional study was performed between February 2018 and December 2020 at the Erasmus MC Cancer Institute Rotterdam, The Netherlands. The study was approved by the local ethics committee of the Erasmus Medical Center (number MEC17-552) and competent authority. The study was registered at the European Clinical Trials Database (EudraCT 2017-004465-27) and the Dutch trial registry (www.trialregister.nl/ number NL6849).

In order to assess the effect of PPIs on the absorption of capecitabine, the primary outcome was to evaluate the area under the plasma concentration-time curve (AUC) of capecitabine alone as compared to capecitabine used with the PPI esomeprazole, and compared with capecitabine used with esomeprazole and cola. The secondary outcome was to study the maximum concentration (C_{max}) and time to C_{max} (T_{max}) of capecitabine, and to determine the AUC, C_{max}, and T_{max} of 5-FU.

Participants and treatment

Adult patients (aged ≥ 18 years) with a confirmed diagnosis of a solid tumor planned for capecitabine treatment according to standard of care (as monotherapy or in combination with oxaliplatin or bevacizumab) and an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, who provided written informed consent, were eligible to participate in the study. Prior treatment with capecitabine without a documented history of grade ≥ 3 toxicity was allowed. Patients actively treated for diabetes mellitus, patients who could not abstain from grapefruit juice, dietary supplements, or medication which could interact with capecitabine or esomeprazole (Nexium), and/or patients who could not interrupt gastric acid-suppressive therapy for a period of 8 days and, if necessary, were unwilling to switch to esomeprazole 40 mg once daily during the study period, were excluded.

Additionally, patients with a known impaired drug absorption (e.g., achlorhydria), a complete deficiency of dihydropyrimidine dehydrogenase activity, use of strong CYP 2C19/3A4 inducers and/or inhibitors, and pregnant and lactating women were also excluded.

Patients were treated with capecitabine twice daily for 2 weeks followed by a 1-week rest period in 3-week cycles[10] and were dosed between 2,000 mg and 3,500 mg daily[11] according to the physician's discretion. In addition, *DPYD* genotyping for variants *2A, c.2846A>T, c.1679T>G,

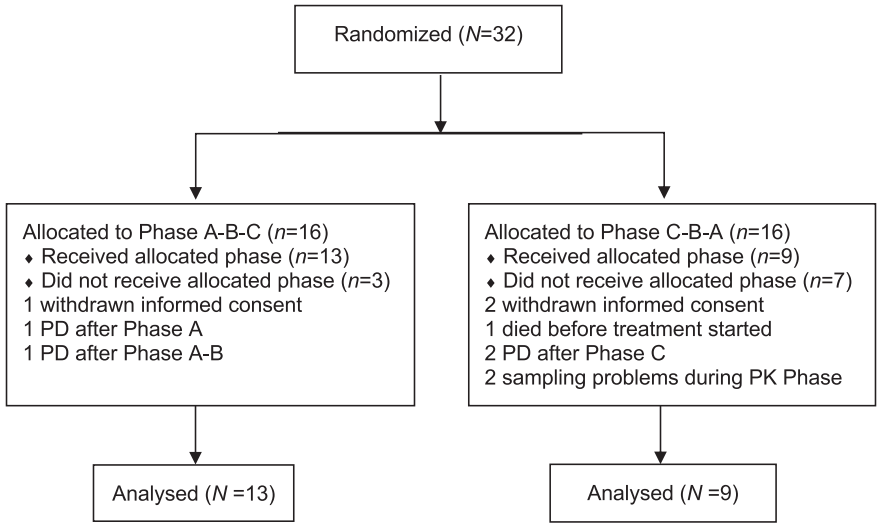

Figure 1 Consort flow diagram. Phase A: Capecitabine with esomeprazole, 3 hours before capecitabine intake for 4 days (days 5–8). Phase B: Capecitabine alone. Phase C: Capecitabine intake with 250 mL of cola and esomeprazole, 3 hours before capecitabine intake (days 5–8). PD, progressive disease; PK, pharmacokinetic.

and c.1236G>A was performed, which is considered standard practice in the Netherlands.[12] Because capecitabine has linear PKs[1] dose adjustments (e.g., due to toxicity) were allowed after the first 8 study days of a cycle and by the start of a new cycle.

Patients used the morning dose of capecitabine with esomeprazole (40 mg once daily) for 4 consecutive days (phases A and C) or capecitabine alone (phase B) within 30 minutes after a meal according to the package insert.[13] During phase A and phase C, the morning dose of capecitabine was administered 3 hours after esomeprazole intake, presuming a maximally elevated intragastric pH at the time of capecitabine intake.[14] During phase C, the capecitabine morning dose was administered concomitantly with 250 mL of cola (Coca Cola Classic), whereas in phases A and B, capecitabine was administrated with water. All patients were asked to fill in a diary to check for compliance and toxicities during each study period. Adverse events were classified based on the Common Terminology Criteria for Adverse Events, version 4.03.[15] The incidence of adverse events was obtained from electronic case records and patient diaries. Adverse events which were present at baseline were only registered if they worsened during treatment. To take possible sequence and time effects into account, patients were randomized into two sequence groups: sequence phase A-B-C or phase C-B-A.

Table 1 Patient characteristics

Characteristics	Phase A-B-C (*n* = 13)	Phase C-B-A (*n* = 9)	Total (*N* = 22)
Gender			
Female	2 (15%)	3 (33%)	5 (23%)
Male	11 (85%)	6 (66%)	17 (77%)
Age, years, median [IQR]	56 [51–63]	59 [53–61]	58 [52–63]
ECOG performance status			
0	1 (8%)	1 (11%)	2 (9%)
1	12 (92%)	8 (89%)	20 (91%)
Ethnic origin			
White	12 (92%)	9 (100%)	21 (95%)
Black	1 (8%)	0	1 (5%)
Tumor type			
Colorectal	10 (76%)	8 (89%)	18 (82%)
Esophagus/gastric	3 (23%)	0	3 (14%)
Parathyroid carcinoma	0	1 (11%)	1 (4%)
Metastatic disease	12 (92%)	8 (89%)	20 (90%)
Prior oncological surgery			
Hemicolectomy	7 (54%)	4 (44%)	11 (50%)
DPYD status based on 4 genotypes			
Normal metabolizer	13 (100%)	9 (100%)	22 (100%)
Type of treatment regimen			
Capecitabine - monotherapy	3 (23%)	2 (22%)	5 (23%)
Capecitabine - oxaliplatin	7 (54%)	5 (56%)	12 (54%)
Capecitabine - bevacizumab	3 (23%)	2 (22%)	5 (23%)
Capecitabine cumulative daily dosing			
4,000 mg	2 (15%)	2 (22%)	4 (18%)
3,500 mg	8 (62%)	5 (56%)	13 (59%)
3,000 mg	2 (15%)	1 (11%)	3 (14%)
2,000 mg	1 (8%)	1 (11%)	2 (9%)

Data were expressed as *N* %.
DPYD, gene encoding dihydropyrimidine dehydrogenase; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

Capecitabine pharmacokinetics

Patients were admitted to the hospital on day 8 of a course for a PK blood sampling day. Blood samples were collected at predefined time points just before capecitabine intake, and at 0.25 hours, 0.5 hours, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, and 8 hours (in total, 9 time points per PK day) after the first oral morning capecitabine dose during each of the study phases.

Details on the processing of the blood, the measurement of capecitabine, and 5-FU[16] are further outlined in the **Methods S1**. Predefined PK end points were the AUC from the pre-administration time point until infinity (AUC_{0-inf}), C_{max}, T_{max}, and the elimination terminal half-life at which AUC_{0-inf} and C_{max} were dose corrected to 1,500 mg capecitabine (PK parameter * (standard dose (1,500 mg)/administered dose). The parameters were determined using WinNonlin version 8.3 (Phoenix, Certara, Princeton, NJ, USA) for both capecitabine and 5-FU.

Statistical analysis

A difference in the systemic exposure to capecitabine of 25% was considered to be clinically relevant. It was assumed that the within-patient SD was 27%.[1] For capecitabine, the AUC of the 3 sampling days were compared "pair wisely" to each other. Therefore, the Bonferroni correction was applied to correct for multiple testing resulting in a 2-sided alpha of 0.0167. Given a power of 80%, the sample size calculation resulted in a required number of 22 evaluable patients.[17,18] Patients were considered evaluable when they completed all the three study phases. Analyses of AUC_{0-inf}, were performed on log-transformed values. Estimates for the mean differences in (log) AUC_{0-inf} were obtained using a linear mixed effect model with treatment, sequence, and period as fixed effects and patient within sequence as a random effect.[19] Variance components were estimated based on restricted maximum likelihood methods and the Kenward-Roger method of computing the denominator degrees of freedom was used.

The mean differences were exponentiated to provide point estimates of the ratio of geometric means and the Bonferroni-corrected 95% confidence intervals (CIs; i.e., 98.333% CIs were calculated) for these ratios, which can be interpreted as relative differences in percentages (RD = (geometric mean ratio-1)*100%). Because the aim was to show bioequivalence of the PK parameters of capecitabine alone and the combination of capecitabine, esomeprazole, and cola, a Bonferroni-corrected 90% CI (i.e., 96.667% CI) was determined for the comparison of these 2 phases. Bioequivalence is shown if this CI of the geometric mean ratio lies within 0.80 and 1.25.

The secondary PK outcomes C_{max} of capecitabine and the AUC and C_{max} of 5-FU were analyzed in a similar way as the AUC, whereas T_{max} and elimination terminal half-life were analyzed by means of the Wilcoxon signed rank test. Analyses were performed using Stata (StataCorp version 16.1, 2020. Statistical Software, College Station, TX, USA).

RESULTS

Participants

Between January 2018 and December 2020, 32 patients were enrolled into the study (**Figure 1**).

In total, 22 patients (phase A-B-C, $n = 13$; phase C-B-A, $n = 9$) completed all study phases and were evaluable for analysis. Patient characteristics are summarized in **Table 1**.

Effect of esomeprazole on the pharmacokinetics of capecitabine and 5-FU

The dose-corrected PK parameters AUC_{0-inf} and C_{max} of capecitabine and its active metabolite 5-FU are shown in **Figure 2** and summarized for all the study phases in **Table 2**.

After esomeprazole co-administration, the geometric mean AUC_{0-inf} and C_{max} of capecitabine increased with 18.9% (95% CI −10.0% to 57.0%, $P = 0.36$) and 9.9% (95% CI −33.0% to 80.1%, $P = 1.00$), respectively. Esomeprazole led to a delayed median T_{max} (2 hours vs. 1 hour, $P = 1.00$) and a longer median plasma half-life of capecitabine (0.63 hours vs. 0.46 hours, $P = 0.005$; **Figure 3**).

The differences in capecitabine PKs after esomeprazole were slightly reversed by concomitant cola use: the geometric mean ratio of AUC_{0-inf} of capecitabine + esomeprazole + cola vs. capecitabine alone was 1.04 with Bonferroni corrected 90% CI ranging from 0.84 to 1.28. No sequence nor period effects were seen for any of the comparisons of the AUC_{0-inf} and C_{max} (results not shown).

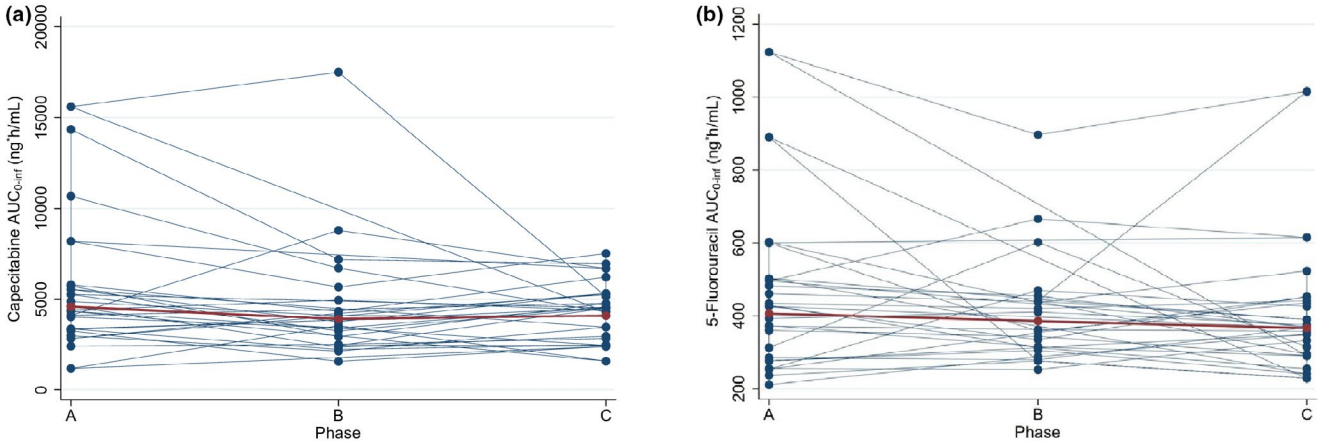

Figure 2 Scatter plots illustrating the AUC_{0-inf} of -capecitabine (**a**) and 5-FU (**b**) per subject for each study phase; AUC_{0-inf} was dose-corrected to 1,500 mg capecitabine. Phase A (capecitabine with esomeprazole, 3 hours prior), phase B (capecitabine alone) and phase C (capecitabine intake with concomitant 250 mL of cola and esomeprazole 3 hours prior capecitabine intake). The blue lines connect the values for each individual patient. The bold red line depicts the geometric means. The estimated parameters of patients were dose corrected to 1,500 mg capecitabine. 5-FU, 5-fluorouracil; AUC_{0-inf} = area under the curve from zero to infinity. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 2 Capecitabine and 5-FU pharmacokinetic results; AUC_{0-inf}. and C_{max} were dose-corrected to 1,500 mg capecitabine

PK parameter	Capecitabine + Esomeprazole 3 hours prior (phase A)	Capecitabine alone (phase B)	Capecitabine + cola concomitant + Esomeprazole 3 hours prior (phase C)	Relative difference phase A vs. phase B (95% CI)	*P* value	Relative difference phase C vs. phase B (90% CI)	*P* value
Capecitabine							
AUC_{0-inf}, ng*h/mL (CV%)	4601.6 (63.9)	3899.9 (58.5)	4098.5 (41.5)	18.9% (–10.0% to 57.0%)	0.36	3.3% (–16.3% to 27.4%)	1.00
C_{max}, ng/mL (CV%)	3040.6 (89.2)	2832.1 (79.0)	2731.2 (47.1)	9.9% (–33.0% to 80.1%)	1.00	–5.0% (–33.6% to 35.9%)	1.00
T_{max}, median hours (IQR)	2.0 (1.0–3.0)	1.0 (1.0–2.0)	1.0 (0.5–2.0)		1.00		1.00
$T_{1/2}$, median hours (IQR)	0.63 (0.52–0.84)	0.46 (0.36–0.55)	0.51 (0.44–0.67)		0.005		0.06
5 FU							
AUC_{0-inf}, ng*h/mL (CV%)	406.7 (43.4)	385.9 (32.5)	366.4 (35.6)	7.8% (–12.3% to 32.4%)	1.00	–5.3% (–15.8% to 6.5%)	0.90
C_{max}, ng/mL (CV%)	181.5 (58.0)	198.6 (45.8)	168.2 (38.1)	–4.33% (–27.6% to 26.4%)	1.00	–15.4% (–30.0% to 2.2%)	0.17
T_{max}, median hours (IQR)	2.0 (2.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–2.0)		1.00		1.00
$T_{1/2}$, median hours (IQR)	0.88 (0.71–1.02)	0.76 (0.70–0.79)	0.86 (0.75–1.01)		0.08		0.001

AUC_{0-inf}, area under the curve timepoint 0 hours to infinity (expressed as geometric mean ng*h/mL (CV)); CI, confidence interval; C_{max}, maximum concentration (expressed as geometric ng/mL (CV)); CV, coefficient of variation expressed in percentage; IQR, interquartile range; PK, pharmacokinetic; T_{max}, time until maximum concentration (expressed as median hours (IQR)); $T_{1/2}$, terminal half-life (expressed as median hours (IQR)).

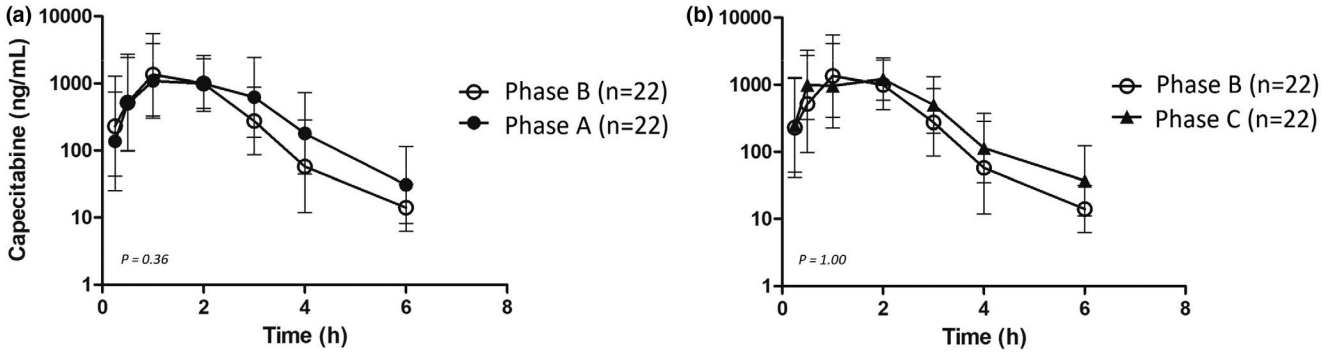

Figure 3 Concentration-time curves of capecitabine during each study phase. Capecitabine with esomeprazole, 3 hours prior (phase A, $n = 22$) compared to capecitabine alone (phase B, $n = 22$), and capecitabine intake with concomitant 250 mL of cola and esomeprazole 3 hours prior capecitabine intake (phase C, $n = 22$) compared to capecitabine alone (phase B). Data at t = 8 hours are not shown because capecitabine concentrations were below the limit of quantification for most patients. The estimated parameters of patients were dose corrected to 1,500 mg capecitabine. The difference in capecitabine AUC_{0-inf} between phase A and phase B was not statistically significant ($P = 0.36$). Median capecitabine half-life was longer in phase A (0.63 hours) than in phase B (0.46 hours, $P = 0.005$). AUC_{0-inf} = area under the curve from zero to infinity.

Adverse events

The most common all-grade capecitabine-related adverse events observed were fatigue (50%) and nausea (9%). Grade ≥ 3 adverse events were not observed. In phase A and phase C, there was a low grade (grade 1) headache ($n = 6$) as a possible side effect of esomeprazole.[20] All adverse events during the study periods are detailed in **Table S1**.

DISCUSSION

In this study, we prospectively assessed the role of esomeprazole co-administration on the systemic exposure of capecitabine and its active metabolite 5-FU and found a prolonged half-life of capecitabine following co-administration with esomeprazole. The addition of cola partly reversed the observed effects of esomeprazole co-administration on capecitabine PKs. We observed that the variability in capecitabine exposure was larger than was expected based on literature data,[1] which explains why an almost 19% increase in capecitabine exposure was not statistically significant. Nevertheless, the increase in capecitabine exposure after esomeprazole we found contradicts the theories that PPIs reduce capecitabine absorption and effect.[6,7]

These results might be caused by a prolonged absorption of capecitabine after cotreatment with PPIs and has previously also been observed after a single dose of capecitabine with concomitant Maalox.[5] As mentioned before, previous retrospective studies have shown a negative clinical impact on progression-free survival and overall survival of co-administration of a PPI with capecitabine.[6,7]

One of the assumed PK mechanisms to explain this observation is diminished intestinal absorption of capecitabine due to decreased dissolution in a less acidic environment. This potentially relevant interaction is included in widely used drug interaction databases, such as Micromedex and Lexicomp.[21] Given the higher, rather than lower, exposure to capecitabine after esomeprazole co-administration (i.e., the most potent gastric acid reducing PPI) observed in this study, we conclude that these observed differences in clinical outcome are not pharmacokinetically driven. Moreover, the likelihood of a drug interaction at absorption level has recently been challenged as the proposed dissociation constant of capecitabine is much higher than previously assumed.[22] This probably explains why a decrease in capecitabine absorption has not been observed in PK interaction studies with Maalox[5] and rabeprazole[23] or in patients with a previous gastrectomy.[24] It has been proposed that PPIs might reduce gastrointestinal motility, but evidence on this subject is conflicting and it remains questionable whether cola would reverse this effect.[25,26] As the metabolism of capecitabine and its metabolites is not mediated by CYP2C19, the CYP2C19 inhibiting PPIs are not expected to cause any changes in capecitabine metabolism.

In our study, the observed statistically significant prolonged half-life of capecitabine following esomeprazole co-administration does not seem to represent inhibition of capecitabine metabolism because the effect was not observed when cola was concomitantly administered. There is no evidence or rationale of esomeprazole inhibiting capecitabine metabolism, let alone of cola reversing that inhibition. If the prolonged half-life after esomeprazole represents a true biological effect, it would be at the absorption level where the acidity of cola would completely reverse the effects of prolonged absorption, but this does not comply with previous evidence that capecitabine does not exhibit flip-flop PKs.[24] Last, at the cellular level, we cannot exclude that PPIs reduce the intratumoral exposure to (or activation of) the active capecitabine metabolites.

In absence of an evident PK explanation, the negative association between PPIs and survival after capecitabine might be caused by pharmacodynamic effects. This might be a direct pharmacodynamic interaction at the cellular level, but this is not supported by previous *in vitro* studies,[23] as no effect of rabeprazole on the inhibitory effects of capecitabine metabolites on colon cancer cell line proliferation was found. Alternatively, indirect pharmacodynamic mechanisms might cause the interaction, as PPIs are known to inhibit the absorption of several vitamins and minerals, such as magnesium, which has been associated with adverse cancer outcome.[27]

Alternatively, and most relevantly, the potential drug interaction between capecitabine and PPIs has only been described in one retrospective and one *post hoc* analysis[6,7] and therefore needs to be

questioned. Moreover, in a recent third analysis from the phase III AXEPT trial in patients with colorectal cancer,[28] patients using PPIs did not have worse survival on capecitabine and irinotecan than those not on PPI cotreatment. In contrast, using PPIs was associated with better survival after a 5-FU containing regimen in that study. These conflicting results cause that no hard conclusions can be drawn on the existence of a true interaction between capecitabine and PPIs.

In conclusion, we have shown that capecitabine exposure is not negatively influenced by esomeprazole cotreatment. Therefore, altered capecitabine PKs do not explain the assumed worse clinical outcome of PPI cotreated patients with cancer. Because we cannot exclude a pharmacodynamic drug-drug interaction, prospective studies are warranted to truly confirm that there exists a drug-drug interaction between capecitabine and PPIs and, if present, to elucidate the mechanisms behind this interaction.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

L.vD., N.H., F.M.dM., P.dB., I.B., E.O.dH., F.A.L.M.E., A.vdG., R.H.J.M., and S.B. wrote the manuscript. L.vD., F.M.dM., P.dB., E.O.dH., R.H.J.M., and S.B. designed the research. L.vD., N.H., F.M.dM., P.dB., I.B., E.O.dH., R.H.J.M., and S.B. performed the research. L.vD., P.dB., E.O.dH., and S.B. analyzed the data.

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