Evaluation of gastric pH-dependent drug interaction between famitinib and the commonly used proton pump inhibitor omeprazole in healthy subjects

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Abstract

Aims: To evaluate the potential gastric pH-dependent drug-drug interaction (DDI), safety and tolerability of famitinib co-administered with omeprazole in healthy subjects. Methods: Twenty healthy subjects were enrolled in a single-center, single-arm, open-label, fixed-sequence study. Famitinib was administered as a single oral 25 mg under a fasting condition on day 1, omeprazole (40 mg once daily) was given on days 10–14, concomitantly with famitinib on day 15, and for the follow-up 7 additional days (days 16–22). Blood samples were collected at predetermined timepoints for the pharmacokinetic analysis of both famitinib and its metabolite SHR116637 following each famitinib dose. Safety and tolerability were assessed during the whole progress via clinical laboratory tests. Results: The least-squares geometric mean ratios (GMRs) (90% CI) of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}[?]}$ for famitinib combined with omeprazole to famitinib alone were 0.989 (0.953, 1.027), 0.956 (0.907, 1.007) and 0.953(0.905, 1.005) respectively. For the metabolite SHR116637, their GMRs (90% CI) of the above parameters were 0.851 (0.786, 0.920), 0.890 (0.838, 0.946)and 0.887 (0.835, 0.943), indicating the absence of significant differences in the parameters respectively. During the treatment period, 9(45%) subjects reported 16 treatment emergent adverse events (TEAE), among which 6 subjects (30%) reported 9 TEAEs and 1 subject (5%) reported 1 TEAE during famitinib or omeprazole administered alone respectively, 5 subjects (25.0 %) reported 6 TEAEs during in the combined administration phase. Conclusion: The PPI omeprazole did not have a significant influence on the pharmacokinetics (PK) of famitinib and SHR116637, and the safety profile was good upon co-administration.

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What is already known about this subject?

1. Absorption of an orally administered drug with pH-dependent solubility may be altered when it is co-administered with a gastric acid reducing agent (ARA).

2. Famitinib is a multi-targeted tyrosine kinase receptor inhibitor which is effective in a wide variety of solid and hematologic malignancies.

3. Famitinib is a BCS class IV drug, exhibiting pH-dependent solubility.

What this study adds

1. The proton pump inhibitor omeprazole does not have large effects on the PK behavior of famitinib and its metabolite SHR116637.

2. The safety profile was generally good upon coadministration.

3. Prescribers and patients may not have to be concerned about altered effectiveness or safety when using famitinib with ARAs.

Abstract

Aims: To evaluate the potential gastric pH-dependent drug-drug interaction (DDI), safety and tolerability of famitinib co-administered with omeprazole in healthy subjects.

Methods: Twenty healthy subjects were enrolled in a single-center, single-arm, open-label, fixed-sequence study. Famitinib was administered as a single oral 25 mg under a fasting condition on day 1, omeprazole (40 mg once daily) was given on days 10–14, concomitantly with famitinib on day 15, and for the follow-up 7 additional days (days 16–22). Blood samples were collected for the pharmacokinetic analysis of both famitinib and its metabolite SHR116637 following each famitinib dose. Safety and tolerability were assessed during the whole progress via clinical laboratory tests.

Results: The least-squares geometric mean ratios (GMRs) (90% CI) of$C_{\max}$, $AUC_{0\text{-t}}$ and$AUC_{0\text{-}[?]}$ for famitinib combined with omeprazole to famitinib alone were 0.989 (0.953, 1.027), 0.956 (0.907, 1.007) and 0.953(0.905, 1.005) respectively. For the metabolite SHR116637, their GMRs (90% CI) of the above parameters were 0.851 (0.786, 0.920), 0.890 (0.838, 0.946)and 0.887 (0.835, 0.943), indicating the absence of significant differences in the parameters respectively. During the treatment period, 9(45%) subjects reported 16 treatment emergent adverse events (TEAE), among which 6 subjects (30%) reported 9 TEAEs and 1 subject (5%) reported 1 TEAE during famitinib or omeprazole administered alone respectively, 5 subjects (25.0 %) reported 6 TEAEs during in the combined administration phase.

Conclusion: Omeprazole did not have a significant influence on the pharmacokinetics (PK) of famitinib and SHR116637, and the safety profile was good upon co-administration.

Keywords

Gastric pH-dependent drug interactions, omeprazole, pharmacokinetics, famitinib

1 Introduction

Multi-kinase inhibitors (MKIs), particularly tyrosine kinase inhibitors (TKIs) have rapidly become an established factor in oncology, and have been shown to be effective in a wide variety of solid and hematologic malignancies[1-3]. The oral administration route of TKIs offers logistic flexibility and is convenient for the patients, however, despite these advantages, it also causes a highly relevant new problem. Of recently approved orally administered cancer therapeutics, >50% are characterized as having pH-dependent solubility[4-6]. The poor and variable pH-dependent solubility, together with other variable pharmacokinetic factors, contribute to a significant patient variability in plasma levels and exposure. Next to other factors, TKI therapy is associated with a higher risk for gastrointestinal disorders. A majority of cancer patients frequently take

acid–reducing agent (ARA) to alleviate gastroesophageal symptoms, thereby raising the potential for a gastric pH-dependent drug interaction[4]. This type of DDI may have detrimental effects on the efficacy of TKIs, with major clinical impacts described for some orally administrated targeted therapies (erlotinib, gefitinib, pazopanib, palbociclib), and conflicting results with many others, including nilotinib or dasatinib[4,7,8]. Long-term suppression of gastric acidity could decrease the absorption of certain major oral anticancer drugs with pH-dependent solubility and result in subsequent failure of therapy. To address this, guidelines are provided by the FDA and the European Medicines Agency (EMA) that recommend studying the DDI between pH-dependent drugs and ARAs.

Famitinib (famitinib-malate, SHR1020) is a novel and potent multi-targeted receptor TKI that targets at c-kit, vascular endothelial growth factor receptor 2 and 3 (VEGFR-2 and 3), platelet-derived growth factor receptor (PD-GFR), FMS-like tyrosine kinase-3 receptor (FLT3) and protooncogene tyrosine kinase receptor (RET)[9,10]. Famitinib is a structural analog of sunitinib with improved cell inhibitory activity. Due to its anti-angiogenic effect, it was effective against metastatic renal cell carcinoma, non-small cell lung cancer and metastatic breast cancer[11-13]. Clinical trials of famitinib in combination with the concurrent medication or chemoradiotherapy also showed its good antitumor abilities against other solid tumors such as metastatic urothelial carcinoma, advanced immunomodulatory triple-negative breast cancer, advanced nasopharyngeal carcinoma, platinum-resistant recurrent ovarian cancer, advanced colorectal cancer and gastric cancer[9,14-20]. A phase I study showed that famitinib had favorable PK characteristics and was generally well-tolerated. After a single oral administration of famitinib, it was well absorbed and extensively metabolized. The major circulating metabolite SHR116637 was the formation of N-desethyl famitinib, which is pharmacodynamically active but exhibits a lower potency than the parent drug[21]. Within the dosing range of 4–27 mg, the increase in $C_{\max}$and $AUC_{0\text{–}24h}$ for famitinib and SHR116637 were proportional to the increase in dose level, $T_{\max}$of the parent drug and the major metabolite SHR116637 in cancer patients occurred within 3.3–5.3 and 4.0–6.2 h, respectively. The plasma level of SHR116637 is approximately equivalent to 3.6 % of that of the parent drug, and both famitinib and SHR116637 were slowly removed from circulation[9]. After administration for 28 days, the degrees of famitinib accumulation in vivo were significantly lower than sunitinib and the major side effects were noted in terms of neutrocytopenia, thrombocytopenia, diarrhea, fatigue and peripheral edema, with particularly less severe fatigue and thrombocytopenia[9]. These toxicities had no significant accumulation while treatment proceeded, however, the common adverse events (AEs) of gastrointestinal reactions, such as nausea and diarrhea, needed ARAs and gastric mucosal protective to alleviate these adverse events.

Although ARAs are extensively used during anticancer treatment, there is still much controversy on how to manage drug–drug interactions (DDIs) between TKIs and ARAs[22]. Early assessment of pH-dependent DDIs for TKI of poorly soluble and weakly acidic compounds offers various advantages for patient safety. Famitinib has been classified as a BCS class IV drug (low solubility, low permeability) by the FDA. The results of in vitro solubility test showed that the solubility of famitinib was 85, 140 and 8 μg/mL in the medium system of pH 1.0, 4.5, 6.8 respectively. The magnitude of solubility change with increasing pH occurs at a pH of 6.0-6.8. According to the FDA guidance's decision tree on the evaluation of gastric pH-dependent drug interactions, DDI studies with ARAs are required if the drug dissolution is too low to determine the effect of pH on drug solubility or the solubility of the drug at pH 6.0–6.8 is less than dose divided by 250 mL[5]. Famitinib fits both of these criteria, so it is necessary to explore the effects of pH on the PK of famitinib, including maximum plasma concentration ($C_{\max}$), area under the curve (AUC), and other PK parameters. Among all therapeutic agents, PPIs are the most prevalent and most potent ARAs and with daily use produce a marked and sustained duration of acid suppression[4,5]. A prospective study in four French Comprehensive Cancer Centers, more than a quarter of cancer patients used PPIs, mostly on a daily basis and in the long term[23]. As PPIs generally have a longer duration of suppression effect on gastric acid secretion than H_2 blockers and antacids do, they are expected to interfere with the intestinal absorption of TKIs to a greater extent. In this paper, omeprazole, was therefore chosen for the study of famitinib with an ARA. We aim to update the potential gastric pH-dependent drug interactions between omeprazole and famitinib in healthy subjects, as well as to ascertain the safety of co-administration of famitinib and omeprazole.

2 Method

2.1 Ethical approval of the study protocol

The study protocol was approved (approval number, 2021ZDSYLL195-P01) by the Ethics Committee of the Zhongda Hospital, Medical School, Southeast University (Nanjing, China). The study was conducted in accordance with the tenets of the Declaration of Helsinki 1964 and its later amendments and Good Clinical Practice guidelines. All participants provided written. The study was registered with the Clinical Trials Registry on 26 August 2020 (NCT 05041920).

2.2 Participants

Inclusion Criteria:

Informed consent was signed before the trial, healthy male and female subjects aged between 18 and 45 (inclusive) at the time of signing the informed consent, of which no less than 1/3 are female subjects. Subjects have no childbirth plans and agree to take effective contraceptive measures within 6 months of the last medication, the blood pregnancy test for women of child bearing age must be negative before taking the study drug; The serum HCG test of fertile women must be negative before screening. the bodyweight of male subjects was [?]50 kg, and that of females was[?]45 kg; The body mass index should range between 19–28 kg/m^2, the bodyweight of male subjects was [?]50 kg, and that of females was[?]45 kg; the body mass index should range between 19–24 kg/m^2((inclusive); Creatinine clearance (CLCr) [?]80 mL/min, and creatinine is less than or equal to the upper limit of normal value.

Exclusion Criteria:

Those who donated blood or suffered blood loss [?]400 mL within 3 months prior to Screening, donated blood or suffered blood loss [?]200 mL within 1 month prior to screening, or received blood transfusion; Allergic constitution, including a history of severe drug/food allergy; Any history of allergy to famitinib malate capsules or omeprazole magnesium enteric-coated tablets; Any history of drug abuse, positive results for alcohol, nicotine or drugs at Screening; Those who have heavy smokers and alcoholic will not be able to prohibit smoking and alcohol during the trial; Any history of dysphagia or any gastrointestinal disease that affects drug absorption; Those who have any uncontrolled peptic ulcer, colitis, pancreatitis, etc.; Those who have received any operation within 6 months before Screening; Previous surgery affecting gastrointestinal absorption (including gastrectomy, intestinal resection, gastric contraction surgery, etc.);Subjects with any clinically significant acute disease occurring within 1 month prior to Screening; QTcF>470 msec for women or >450 msec for men; Any pre-existing chronic or severe medical history of nervous system, cardiovascular system, urinary system, digestive system, respiratory system, metabolism, and musculoskeletal system; Participation in any clinical trial within 3 months before Screening; Those who took any other drugs that affect liver metabolism within 28 days prior to taking the investigational drug; Those who took any prescription or non-prescription drugs, any vitamin products or herbal medicine within 14 days prior to receiving the investigational drug; Abnormal vital signs at Screening; Clinical laboratory tests, infectious disease screening, 12-lead electrocardiogram, abdominal B ultrasound, X-ray or CT examination with abnormalities and clinical significance; Consumption of grapefruit or grapefruit products, caffeine, or xanthine foods or beverages within 48 hours prior to taking the investigational drug; Strenuous exercise, or other factors affecting drug absorption, distribution, metabolism, excretion, etc.; Lactating women; History of injection needle or blood fainting, those who have difficulty in blood collection or cannot tolerate venipuncture blood collection; Those who cannot accept a uniform diet; Subjects with other factors unsuitable to participate in the study considered by the researcher or subjects withdraw from the study due to their own reasons.

2.3 Formulations

Jiangsu Hengrui Pharmaceuticals produced and supplied famitinib capsules (specification: 25 mg/capsule, Lot: 200906NS). Omeprazole magnesium enteric-coated tablets (specification: 20 mg/tablet, Lot: SAMU) were also provided by Jiangsu Hengrui Pharmaceuticals.

2.4 Study Design and regimen

The screening was performed from day-7 to day-1. Eligible subjects were admitted to the Phase I clinical trial ward on day-1, provided a light diet in the evening, and then fasted for 10 hours. On day 1, each subject was administered famitinib as a single oral 25 mg dose. Blood samples were collected before administration (within 1 h), 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 144 and 192 hours after dosing. On day 10 through 22, subjects were orally daily administered 40 mg of omeprazole at least 0.5 hours before breakfast, with the exception of day 15. On day 15, famitinib (25 mg) was administered concomitantly with omeprazole (40 mg), and the collection of the blood samples was the same as that on day 1. During the study period, all drugs were administered with approximately 240 mL water under a fasting condition, on day 1 and day 15, water was forbidden within 1 hour before and after the study drug administration, and food was to be avoided within 4 hours after administration. On day 23, all subjects were discharged after examination in the morning. Subjects returned to the research center for follow-up or telephone follow-up from day 28 to day 30. A safety assessment was performed during the entire test period. A flowchart of this study is presented in Figure 1.

2.5 PK assessment

Approximately 3 mL blood was collected into heparin lithium anticoagulant tubes, gently reversed, and mixed 6–10 times. The plasma concentration of famitinib and SHR116637 was determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) at the Frontage Holdings Corporation (Shanghai). The analytical method was developed and validated to meet the standard operating procedure established by the sponsor. Plasma samples were stored at -80°C, and the detection was completed within the storage time limit (long-term stability period was 160 days). The concentration range of calibration standards for famitinib and SHR116637 was both 0.05-100 ng/mL. In each analytical batch, the number of quality control samples (QC) accounts for more than 5% of the total number of samples, and at least two samples at each concentration level per time. For famitinib, the inter-run precision was 2.9–4.1%,while the inter-run accuracy ranged between 1.3-3.1%. For the metabolite SHR116637, the inter-run precision and accuracy were 1.6-3.4% and -2.7-1.1%, respectively.

2.6 Safety assessment

All subjects were assessed for tolerability and safety parameters during the entire study. Safety was monitored by measurements of vital signs (blood pressure, heart rate and temperature), physical examination clinical laboratory tests and 12-lead electrocardiogram. Tolerability was assessed by recording adverse events (AEs). Details of any AEs were recorded, including the AEs types, incidence, severity (graded according to NCI-CTCAE5.0), onset and end time, serious AEs, correlation with the test drug, and outcomes.

2.7Pharmacokinetic and Statistical Analysis

The concentration of the famitinib and the metabolite SHR116637 was determined by LC-MS/MS. The PK parameters of above analytes were calculated using a standard noncompartmental analysis method (NCA) by Phoenix WinNonlin (Pharsight Corporation 8.3 or higher). The main evaluation indices were $C_{\max}$ (maximum plasma concentration), the area under the curve of plasma concentration-time from zero to the last measurable concentration calculated by the linear trapezoid method (AUC_{0-t}), and the area under the curve of blood concentration from zero to infinity ($AUC_{0-[?]}$). The secondary evaluation indices were $T_{\max}$, elimination half life ($t_{1/2}$), apparent clearance rate (CL/F), and apparent volume of distribution (Vz/F). In addition, CL/F and Vz/F were not applicable to the metabolite SHR116637.

Statistical analysis was carried out using SAS v 9.4 (SAS Institute, Cary, NC, USA). Descriptive statistics and lists of PK parameters of the analyte were conducted and mean concentration–time curves were plotted. After natural log transformation, a mixed-effect model was used to fit PK parameters. Based on this model, the drugs were considered as fixed effects and the volunteers as random effects. The GMRs (co-administration of famitinib and omeprazole, and administration of famitinib alone) and their 90% CIs were estimated.

3 Results

3.1 Subject demographics

Among the 20 Chinese subjects, there were 13 males and 7 females; 18 were of Han nationality and 2 were of other nationalities. The median age was 24.5 years (range 19–37 y), and the average height (+- SD) was 168.38 +- 8.291 cm. The average body weight (+- SD) was 69.09+-10.337 kg, and the average body mass index (+- SD) was 24.26 +-2.333 kg/m^2.

3.2 PK analysis

The main PK parameters of famitinib and its metabolite SHR116637 between famitinib alone and co-administration with omeprazole were showed in Tabel 1. No clinically significant difference was observed in the$C_{\max}$, $AUC_{0\text{-t}}$ and$AUC_{0\text{-}[?]}$ of famitinib between alone monotherapy and co-administration with omeprazole. The GMRs of$C_{\max}$, $AUC_{0\text{-t}}$ and$AUC_{0\text{-}[?]}$ of famitinib were 98.9%, 95.6% and 95.3%, respectively. The exposure of the metabolite SHR116637 was slightly decreased when famitinib was co-administered with omeprazole, with the $C_{\max}$, $AUC_{0\text{-t}}$ and$AUC_{0\text{-}[?]}$ of SHR116637 decreased by 14.9%, 11.0% and 11.3% upon co-administration. The GMRs of$C_{\max}$, $AUC_{0\text{-t}}$ and$AUC_{0\text{-}[?]}$ for SHR116637 were 85.1%, 89.0% and 88.7%, respectively. Evaluation of drug interactions between famitinib and omeprazole was shown in Table 2. The mean plasma concentration–time curve is shown as Figure 2. The plasma concentrations of famitinib were similar over time, and there was no significant change in PK parameters between administration of famitinib alone and co-administration with omeprazole.

3.3 Safety analysis

All the 20 subjects enrolled in this study completed 2 times of famitinib and 13 times of omeprazole administration as planned. A total of 9 (45.0%) subjects had 16 AEs, all of which were treatment-emergent adverse events (TEAEs) at grade 1 severity according to the Common Terminology Criteria for Adverse Events (CTCAE) guidelines. No adverse events of grade 2 or above were reported. Among the total 16 AEs, 9 TEAEs occurred in 6 subjects (30.0%) in the single administration phase of famitinib; 1 subject (5.0%) had 1 TEAE in the single administration phase of omeprazole; At the stage of famitinib combined with omeprazole, 5 subjects (25.0%) had 6 TEAEs. Famitinib was generally well tolerated when administered either alone or in combination with omeprazole.

A summary of the above TEAEs was shown in Table 3. 5 (25.0%) subjects had 10 TEAEs related to famitinib including alanine aminotransferase increased (10%), blood triglycerides increased (10%), gamma-glutamyl transferase increased (5%), basophil count increased (5%), white blood cells urine positive (5%), glucose urine present (5%), and blood glucose increased (5%). 2 (10.0%) subjects had 2 TEAEs related to omeprazole including gamma-glutamyl transferase increased (5%) and increased heart rate. All adverse events occurred during the study period were recovered / resolved at the end of the study.

4.Disscusion

Since the usage of PPI is associated with decreased TKI efficacy, prescribers are posed with a great dilemma whether or not to continue the combined treatment. To our knowledge, this is the first study to assess the PK and safety effects of omeprazole on the potent MKI famitinib as well as its major metabolite SHR116637 in healthy subjects. Our findings suggested that omeprazole did not significantly impact the PK properties of both famitinib and SHR116637, demonstrating good safety on co-administration.

Key factors in the design of a pH-dependent DDI study include study population, selection of ARAs, type of crossover design (randomized or single-sequence), and the dose/dosing regimen etc[5]. Previous clinical trials have demonstrated that famitinib showed linear dose-related pharmacokinetic characteristics in the dosing range of 4-27 mg. The recommended dose for phase II clinical trials is 25 mg. Hence, for the safety evaluation, the dose of famitinib was selected to be 25 mg. The main PK parameters were similar in terms of $C_{\max}$,AUC and $t_{1/2}$ between the patients with advanced solid cancer and healthy subjects. Food intake was unlikely to impact on the PK of famitinib[9]. Ideally, the DDI results obtained in this study under fasting condition can help guide cancer patients' treatment. Furthermore, Multiple enzymes, mainly CYP3A4/5 and CYP1A1/2, are involved in famitinib metabolic clearance. And it is also a weak inhibitor of CYP3A4, *in vitro* study, however, it's unlikely to affect CYP3A4 due to a single dose of famitinib at 25 mg. As a

result, omeprazole was chosen for the DDI study, it gives its high affinity for CYP2C19 and moderate affinity for CYP3A, which could show little influence to the systemic exposure of famitinib and SHR116637. And a self-control study was also used to overcome the influence of enzyme differences between individuals.

Compared with famitinib single-dose administration, the geometric mean of $AUC_{0\text{-}[?]}$ was slightly reduced when famitinib was co-administered with omeprazole (1417.927 vs. 1351.939 h*ng/mL, decreased by approximately 4.7%), along with theC_{max}, T_{max},$t_{1/2}$, CL/F and Vz/F did not significantly differ between the two phases. The least squares GMRs ofC_{max}, $AUC_{0\text{-}t}$ and$AUC_{0\text{-}[?]}$ (90% CIs) of famitinib combined with omeprazole to famitinib alone were 0.989 (0.953, 1.027), 0.956 (0.907, 1.007) and 0.953 (0.905, 1.005) respectively, indicating the absence of significant differences in$AUC_{0\text{-}t}$, $AUC_{0\text{-}[?]}$ andC_{max} of famitinib when compared with famitinib alone. The metabolite SHR116637 data was consistent with the reduced absorption famitinib, and the metabolic ratio remained similarly small for both treatment arms with 0.075 versus 0.081 for famitinib and famitinib plus omeprazole, respectively. The median T_{max} of famitinib metabolite SHR116637 was 5.00 h and 6.50 h, indicating that the peak time of famitinib metabolite SHR116637 was slightly prolonged after omeprazole combined with famitinib. The C_{max},$AUC_{0\text{-}t}$ and $AUC_{0\text{-}[?]}$decreased by 14.9%, 11.0% and 11.3% for famitinib and famitinib plus omeprazole, respectively. The least squares GMRs ofC_{max}, $AUC_{0\text{-}t}$ and$AUC_{0\text{-}[?]}$ (90% CIs) of SHR116637 between coadministration group and alone group were 0.851 (0.786, 0.920), 0.890 (0.838, 0.946)and 0.887 (0.835, 0.943) respectively. Except the lower limit for the SHR116637 GMR of C_{max} (90% CIs) is 78.6%, the least squares GMRs of $AUC_{0\text{-}t}$,$AUC_{0\text{-}[?]}$ and C_{max} (90% CIs) of both famitinib and SHR116637 are all in the range of 80%-125%. Compared the "no concomitant PPIs" versus "concomitant PPIs" based on their clinical characteristics, the exposure of metabolite SHR116637 is approximately equivalent to 9.47% and 8.72% of that of the parent drug, so it has little effect on the PK of famitinib. In general, there was no significant difference in the exposure, absorption, distribution or elimination of famitinib, indicating that omeprazole did not have a significant influence upon the PK parameters of famitinib.

According to one completed phase-I clinical trial, the most common AEs of famitinib included neutrocytopenia, thrombocytopenia, diarrhea, fatigue and peripheral edema. In some cases, it can also result in elevation of blood lipids and glucose[9,21]. In our study, we also assessed the safety profile of combination therapy in the present study, compared with the above AEs, most AEs observed in the present study was mild or moderate, such as increased gamma-glutamyl transferase, increased basophil count, increased heart rate, alanine aminotransferase, blood glucose increased, blood triglycerides elevated, the positive urine test for leukocyte-esterase and sugar. During the treatment period, a total of 6 (30.0%) subjects had 9 AEs during famitinib alone, and 1 (5.0%) subject had 1 AE during the mutiple dose of omeprazole, while 5 (25.0%) subjects had 6 AEs during famitinib combined with omeprazole. Less severe and less frequent side effects were noted after the co-administration of omeprazole and famitinib compared with the single phase of famitinib, revealing the safety and tolerability of famitinib and omeprazole coadministration in clinical settings. Co-administration of famitinib and omeprazole was associated with good safety.

In this single-center, open, single-dose and self-control study, use of a PPI may be considered a worst-case scenario in the *in vivo*evaluation of the pH effect. If a PPI does not result in any clinically relevant effect on the absorption of a weak base drug, further dedicated DDI studies with other classes of ARAs may not be necessary. The common dose of omeprazole is 20 mg qd, which can achieve maximum suppression of gastric acid within ˜ 4 days, and the expected effect of a 40-mg dose follows a similar time-course[24]. Therefore, 40 mg of omeprazole was administered for 5 consecutive days in our study, and a second dose of famitinib was administered 5 days after omeprazole administration to ensure that subjects achieved maximum inhibition of gastric-acid secretion.

5 Conclusion

To conclude, the effect of PPIs on the efficacy of certain anticancer agents, particularly TKIs, is a major issue in daily practice. In this opinion paper, although the famitinib has pH-dependent solubility in vitro, the PPI omeprazole had minimal effect on the PK of famitinib and SHR116637 in healthy subjects. Therefore, famitinib as a formulated tablet can be administered with or without ARAs such as PPIs, antacids, and H_2

blockers. In addition, interactions caused by other factors involved in absorption, apart from the pH effect, need to be considered during drug development on a case-by-case basis.

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Conflict of interest statement.

The authors declare no conflicts of interest.

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Tables :

Table 1 Summary of pharmacokinetic parameter analysis of famitinib and SHR116637

Administration mode	**Pharmacokinetic parameters(unit)**	**Famitinib**	**Famitinib**	**Famitinib**	**SHR116637**	**SHR116637**	**SHR116637**
		Mean ± SD	**Geometric Mean (CV%)**	**Median (minimum-maximum)**	**Mean ± SD**	**Geometric Mean (CV%)**	**Median (minimum-maximum)**
Famitinib	T_{max}* (h)	5.65 ± 0.875	-	6.00 (3.00, 7.00)	5.8 ± 1.64	-	5.00 (5.00, 12.00)
	C_{max} (ng/mL)	43.2 ± 7.8	42.5 (19.6)	43.8 (25.7, 55.3)	1.9 ± 0.5	1.8 (28.9)	1.9 (1.2, 3.1)
	AUC_{0-t} (h·ng/mL)	1425.5 ± 296.3	1395.0 (22.1)	1391.2 (778.0, 2052.3)	115.8 ± 44.6	108.2 (39.4)	108 (46.0, 201.4)

Administration mode	Pharmacokinetic parameters(unit)	Famitinib	Famitinib	Famitinib	SHR116637	SHR116637	SHR116637
	$AUC_{0\text{-}[?]}$ (h·ng/mL)	1450.8 ± 312.0	1417.9 (22.7)	1407.1 (787.6, 2125.6)	128.0 ± 52.2	118.9 (41.0)	119.3 (50.8, 233.6)
	$t_{1/2}$ (h)	32.5 ± 5.6	32.1 (17.0)	31.3 (24.6, 45.5)	53.2 ± 9.4	52.4 (17.3)	51.7 (40.0, 76.3)
	CL/F (L/h)	18.1 ± 4.4	17.6 (22.7)	17.8 (11.8, 31.7)	-	-	-
	Vz/F (L)	837.7 ± 221.2	815.3 (23.3)	794.9 (529.6, 1606.4)	-	-	-
Famitinib + Omeprazole	$T_{\max}$* (h)	6.7 ± 1.03		6.50 (5.00, 8.00)	6.9 ± 2.07		6.50 (5.0, 12.0)
	$C_{\max}$ (ng/mL)	42.7 ± 7.3	42.0 (18.2)	42.4 (28.0, 57.6)	1.6 ± 0.5	1.5 (33.5)	1.5 (0.9, 2.8)
	$AUC_{0\text{-t}}$ (h·ng/mL)	1355.0 ± 247.1	1333.2 (18.8)	1312.7 (885.1, 1875.5)	101.7 ± 34.6	96.3 (35.4)	97.1 (53.9, 185.4)
	$AUC_{0\text{-}[?]}$ (h·ng/mL)	1375.1 ± 257.0	1351.9 (19.3)	1321.8 (895.1, 1915.0)	111.7 ± 38.8	105.5 (36.1)	106.9 (58.1, 203.3)
	$t_{1/2}$ (h)	32.0 ± 4.7	31.7 (14.0)	30.7 (26.3, 44.5)	52.8 ± 9.2	52.2 (16.3)	51.6 (40.1, 81.5)
	CL/F (L/h)	18.8 ± 3.7	18.5 (19.3)	18.9 (13.1, 27.9)	-	-	-
	Vz/F (L)	859.7 ± 161.7	846.0 (18.4)	825.6 (618.8, 1272.6)	-	-	-

*: $T_{\max}$ expressed in median (minimum, maximum), the other parameters were expressed as Mean ± SD and Geometric Mean(CV%);

Table 2 Statistical analysis of pharmacokinetic parameters of famitinib and SHR116637

Agent	Pharmacokinetic parameters(unit)	Geometric Mean	Geometric Mean	Ratios (90
		Famitinib + Omeprazole	**Famitinib**	
Famitinib	$C_{\max}$ (ng/mL)	42.0	42.5	0.989(0.953,
	$AUC_{0\text{-t}}$ (h·ng/mL)	1333.2	1395.0	0.956(0.907,
	$AUC_{0\text{-}[?]}$ (h·ng/mL)	1351.9	1417.9	0.953(0.905,
SHR116637	$C_{\max}$ (ng/mL)	1.5	1.9	0.851(0.786,
	$AUC_{0\text{-t}}$ (h·ng/mL)	96.3	108.2	0.890(0.838,
	$AUC_{0\text{-}[?]}$ (h·ng/mL)	105.5	118.9	0.887(0.835,

Table 3 Summary of treatment emergent adverse events

Adverse event	**Famitinib**	**Famitinib**	**Omeprazole**	**Omeprazole**	**Famitinib + Omepr**
	N=20	**N=20**	**N=20**	**N=20**	**N=20**
	n(%)	**Incidence**	**n(%)**	**Incidence**	**n(%)**
Any treatment-emergent adverse event	6 (30.0%)	9	1 (5.0%)	1	5 (25.0%)
Gamma-glutamyl transferase increased	0	0	0	0	1 (5.0%)
Alanine aminotransferase increased	2 (10.0%)	2	0	0	0
White blood cells urine positive	1 (5.0%)	1	0	0	0
Glucose urine present	1 (5.0%)	1	0	0	0
Basophil Count increased	1 (5.0%)	1	0	0	1 (5.0%)
Heart rate increased	1 (5.0%)	1	0	0	1 (5.0%)
Blood triglycerides increased	2 (10.0%)	2	0	0	0
Blood glucose increased	1 (5.0%)	1	0	0	0
Blood pressure decreased	0	0	1 (5.0%)	1	2 (10.0%)