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Original Article

Effects of omeprazole and esomeprazole on the pharmacokinetics of erlotinib and its metabolite OSI-420 in rats

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Abstract: The purpose of this paper was to research the effect of long-term orally administered omeprazole and esomeprazole on the pharmacokinetics of erlotinib and its major active metabolite, desmethyl erlotinib (OSI-420) in rats. Eighteen healthy male Sprague-Dawley rats were divided into three groups at random: A group (control group, received normal saline for 7 days), B group (4 mg/kg omeprazole for 7 days) and C group (4 mg/kg esomeprazole for 7 days). All the rats were given a single dose of erlotinib (15 mg/kg) after the last administration. The plasma concentration of erlotinib and its major active metabolite, desmethyl erlotinib (OSI-420) were estimated using ultra performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) and different pharmacokinetic parameters were calculated by DAS 2.0 software. Compared to the control A group, omeprazole (B group) and esomeprazole (C group) significantly decreased the C_{max} and $AUC_{(0-\infty)}$ of erlotinib, but increased CL_z/F in rats. Moreover, the similar results were observed for the metabolite OSI-420 of erlotinib. These results revealed that omeprazole and esomeprazole have a significant reduction on the absorption of erlotinib. Therefore, it is recommended that the concomitant use of erlotinib with proton pump inhibitors should be avoided.

Keywords: Erlotinib, OSI-420, omeprazole, esomeprazole, UPLC-MS/MS, pharmacokinetics

Introduction

Erlotinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor; it is approved for the first-line treatment of non-small cell lung cancer (NSCLC) with mutated EGFR, second-line treatment of NSCLC and first-line treatment of advanced pancreatic adenocarcinoma [1, 2]. Erlotinib drug exposure may be altered by pharmacokinetic drug-drug interactions leading to high interpatient variability in plasma concentration [3]. It has been established that the magnitude of the pharmacological effect (tyrosine kinase inhibition) in vitro is concentration dependent. Moreover, in clinical studies though plasma concentrations of erlotinib and its major active metabolite, desmethyl erlotinib (OSI-420), seemed to correlate with treatment outcome [4, 5].

The large variability for both intrasubject and intersubject pharmacokinetics (PK) in oncology patients is increasingly recognized and often involves both intrinsic and extrinsic factors [6]. For oral medications, drug absorption can be affected by gastric acidity [7, 8]. During preclinical development, erlotinib was found to have pH-dependent solubility with a dissociation constant (pKa) of 5.4. This pH-dependent solubility is reflected in a study that compared erlotinib plasma concentrations in healthy volunteers who were or were not taking acid suppression (AS) therapy [8]. Subjects received a 7-day course of omeprazole, a proton pump inhibitor (PPI), along with a single dose of erlotinib. There was a median decrease of 54% in the area under the concentration-time curve (AUC) in PPI-treated subjects. Similarly, a study that investigated ranitidine, a histamine type-2 receptor antagonist (H2RA), showed that ranitidine decreased erlotinib's median AUC by 33% [9]. In contrast, a single patient report by Ter Heine and colleagues found that erlotinib levels were only significantly decreased during high dose intravenous administration of pantoprazole and returned to within the normal range

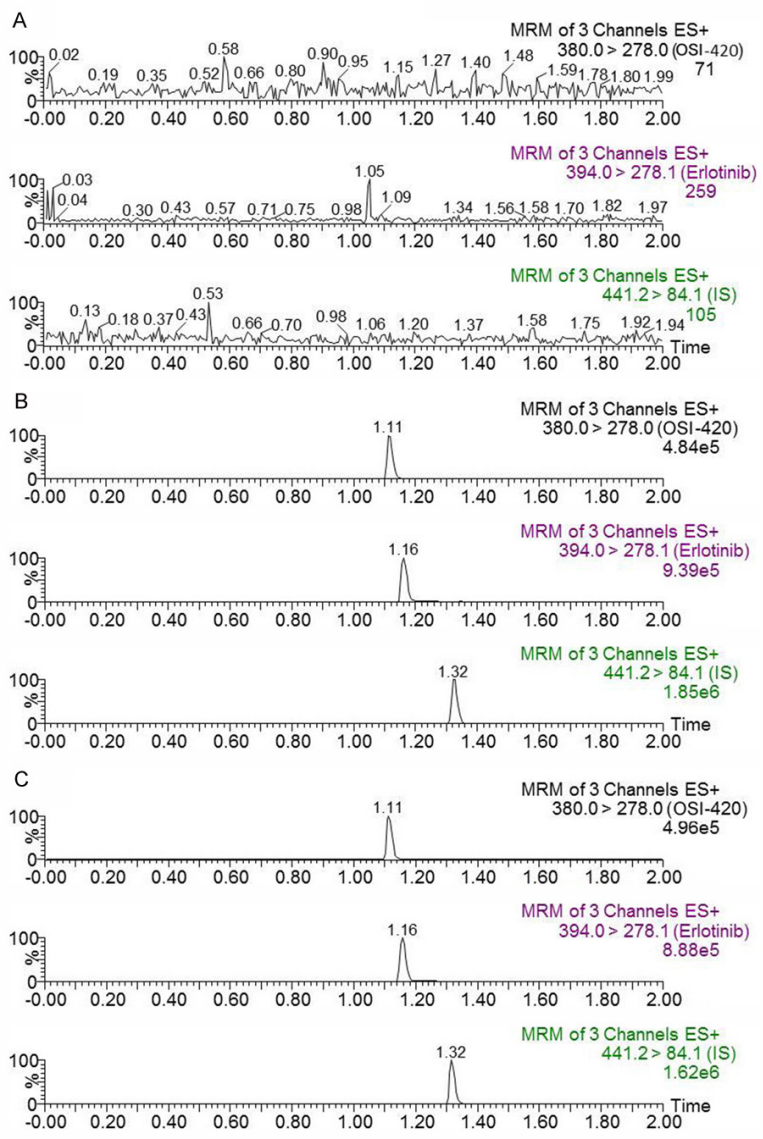

Figure 1. Representative chromatograms of blank plasma (A), blank plasma spiked with standard solution (B) and plasma sample obtained from oral administration of erlotinib in rats (C).

when switching to high dose oral administration [10]. Therefore, these results were not consistent. To date, it is still unclear whether PPIs lead to altered plasma levels of erlotinib generally [11, 12].

Among all therapeutic agents, PPIs are the most prevalent and most potent acid-reducing agents and with daily use produce a marked and sustained duration of acid suppression. A widely used PPIs, omeprazole and esomeprazole, were therefore chosen for the first study of erlotinib with acid-reducing agents. Therefore, in this study, we developed a high sensitive and rapid ultra-performance liquid chromatography-mass spectrometry (UPLC-MS/MS) method for the simultaneous determination of erlotinib and its major active metabolite, desmethyl erlotinib (OSI-420) in rat plasma and to investigate the effect of omeprazole and esomeprazole on the pharmacokinetics of erlotinib and OSI-420 in rats.

Materials and methods

Chemicals materials

Erlotinib (purity > 98%), OSI-420 (purity > 98%) and ibrutinib (purity > 98%, IS) were obtained from Sigma (St. Louis, MO, USA). Omeprazole and esomeprazole were purchased from Beijing Sun Flower Technology Development Co., Ltd. (Beijing, China). Acetonitrile and methanol were HPLC grade and purchased from Merck Company (Darmstadt, Germany). HPLC grade water was obtained using a Milli Q system (Millipore, Bedford, USA).

Animals

Male Sprague-Dawley rats with body weights of 220 ± 20 g were purchased from Henan University of Science and Technology. The rats were acclimatized for a week in laboratory conditions to minimize all efforts of any animal suffering before initiating the experiment. Necessary approval from the Institutional Animal Ethics Committee was obtained to carry out the experiments.

Study design

Eighteen Sprague-Dawley male rats were randomly divided into 3 groups: A group (the control group received normal saline for 7 days), B group (long-term administered with 4 mg/kg omeprazole for 7 days) and C group (long-term administered with 4 mg/kg esomeprazole for 7 days). After the last gavage administration, the

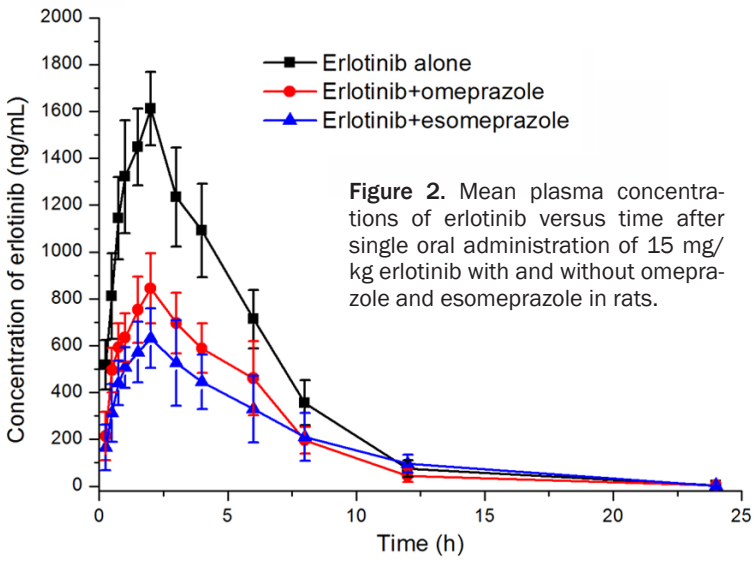

Figure 2. Mean plasma concentrations of erlotinib versus time after single oral administration of 15 mg/kg erlotinib with and without omeprazole and esomeprazole in rats.

rat in each group was given a single dose of 15 mg/kg erlotinib. Blood samples (0.3 mL) were collected from the tail vein into heparinized 1.5 mL polythene tubes at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h after oral administration. The samples were immediately centrifuged at 4000 × g for 8 min. The plasma obtained (100 μL) was stored at -20°C until analysis.

Sample preparation

Before analysis, frozen plasma sample was thawed to room temperature. In a 1.5 mL centrifuge tube, an aliquot of 200 μL of the internal standard working solution (100 ng/mL) was added to 0.1 mL of plasma sample. The tubes were vortex mixed for 1.0 min. After a 1.0 min ultrasound, the mixture was centrifuged for 10 min with 13,000 × g at 4°C. The protein-free supernatant (200 μL) was separated and a volume of 50 μL was pipetted into another 1.5 mL centrifuge tube, with addition of 50 μL ultrapure water. After vortex-mixing for 30 s, 6 μL of the solution was injected into UPLC-MS/MS system.

Plasma analysis for erlotinib and its metabolite

Erlotinib and OSI-420 plasma concentrations were determined by ultra high performance liquid chromatography-mass spectrometry method (UPLC-MS/MS). UPLC-MS/MS analyses were performed by an Acquity UPLC XEVO TQD triple quadrupole mass spectrometer (Waters Corp., Milford, MA, USA) equipped with an electrospray ion source. Chromatographic separation was performed using a Waters ACQUITY BEH C18 column (2.1 mm × 50 mm, 1.7 μm) thermostated at 40°C. The mobile phase was composed of acetonitrile (A) and 0.1% formic acid (B) with gradient as follows: 0-0.3 min (20-95% A), 0.3-1.9 min (95-95% A), 1.9-2.0 min (95-20% A), 2.0-3.0 min (20-20% A). And the flow rate was 0.4 mL/min. The total run time was 3.0 min. Erlotinib, OSI-420 and IS were detected in multiple reaction monitoring (MRM) scan mode with positive ion detection. The precursor-production pairs used for the MRM detection were *m/z* 394.0 → 278.1, *m/z* 380.0 → 278.0 and *m/z* 441.2 → 84.1 for erlotinib, OSI-420 and IS, respectively. The Masslynx 4.1 software (Waters Corp., Milford, MA, USA) was used for data acquisition and instrument control. The UPLC-MS/MS chromatograms of a blank plasma sample, blank plasma sample spiked with erlotinib, OSI-420 and IS, and a plasma sample are shown in **Figure 1**.

Statistical analysis

The results are given as mean and standard deviation (SD). The noncompartmental analysis was used to calculate the pharmacokinetic parameters by DAS (Drug and statistics) software (Version 2.0, Shanghai University of Traditional Chinese Medicine, China). The statistical analyses were evaluated by one-way ANOVA (SPSS 19.0, Chicago, IL). A value of $P < 0.05$ was considered to be statistically significant.

Results

Effect of omeprazole and esomeprazole on the pharmacokinetic study of erlotinib

Figure 2 shows the mean plasma concentration-time profiles of erlotinib after oral administration of erlotinib (15 mg/kg) in different treatment group, including the control, omeprazole and esomeprazole group. The corresponding pharmacokinetic parameters are shown in **Table 1**. As shown in **Table 1** and **Figure**

Table 1. The main pharmacokinetic parameters of erlotinib after single oral administration of 15 mg/kg erlotinib with and without omeprazole and esomeprazole in rats

Parameters	Erlotinib	Erlotinib + omeprazole	Erlotinib + esomeprazole
$t_{1/2}$ (h)	1.99 ± 0.42	1.87 ± 0.57	2.05 ± 0.51
T_{max} (h)	1.75 ± 0.42	1.92 ± 0.20	1.71 ± 0.51
CL_z/F (L/h/kg)	1.68 ± 0.17	3.07 ± 0.57**	3.69 ± 1.46**
C_{max} (ng/mL)	1667.19 ± 113.66	884.50 ± 114.01**	656.33 ± 98.22**
$AUC_{(0-t)}$ (ng·h/mL)	8979.29 ± 912.08	5024.36 ± 906.06**	4437.96 ± 806.54**
$AUC_{(0-\infty)}$ (ng·h/mL)	8985.00 ± 914.00	5027.82 ± 906.66**	4479.09 ± 815.72**

**Significantly different from the control group, P < 0.01.

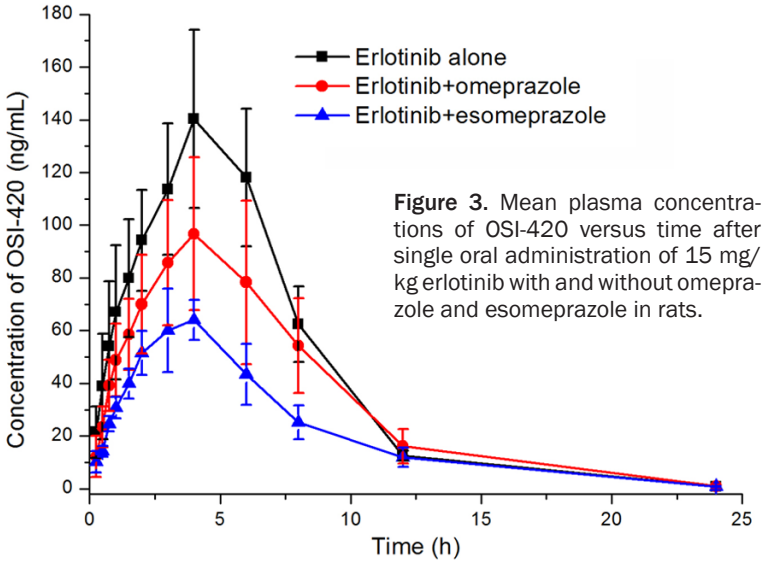

Figure 3. Mean plasma concentrations of OSI-420 versus time after single oral administration of 15 mg/kg erlotinib with and without omeprazole and esomeprazole in rats.

2, omeprazole and esomeprazole significantly altered the pharmacokinetic parameters of erlotinib. Compared with group A, the C_{max} of erlotinib was significantly decreased by 46.9% and 60.6%, respectively, by omeprazole and esomeprazole. Moreover, the $AUC_{(0-\infty)}$ of erlotinib was reduced by 44.0% and 50.1%, respectively. In addition, the CL_z/F of erlotinib with omeprazole and esomeprazole was increased by 82.7% and 119.6%, respectively. According to the data, it indicated that omeprazole and esomeprazole has significant effect on the absorption of erlotinib in rats.

Effect of omeprazole and esomeprazole on the pharmacokinetic study of OSI-420

Figure 3 shows the mean plasma concentration-time profiles of OSI-420 after oral administration of erlotinib (15 mg/kg) to rats in the presence or absence of omeprazole (4 mg/kg) and esomeprazole (4 mg/kg). **Table 2** shows the corresponding pharmacokinetic parameters. Although pharmacokinetic parameters were evaluable for erlotinib in all rats, there were insufficient data to reliably calculate the corresponding pharmacokinetic parameters of OSI-420. Therefore, the pharmacokinetic parameters of OSI-420 was utilized in the comparison of the impact of omeprazole and esomeprazole on this metabolite. Similarly to erlotinib, the C_{max} of OSI-420 was significantly reduced by 28.2% and 51.8%, respectively, by omeprazole and esomeprazole. Moreover, the $AUC_{(0-\infty)}$ of OSI-420 was decreased by 20.7% and 50.5%, respectively. In addition, the CLz/F of OSI-420 with omeprazole and esomeprazole was increased by 29.2% and 57.0%, respectively. Our results indicated that omeprazole and esomeprazole has effect on the production of OSI-420 in rats, which was consistent with the above results of erlotinib.

Discussion

The usage of PPIs is common; for example, it is estimated that in 2007-2008, 21.1% of Canadians were prescribed PPIs [13]. Based on previous analysis, it can be estimated that a similar proportion of participants with advanced NSCLC take PPIs. This possibly may lower the efficacy of erlotinib as AS medications have the potential to reduce the absorption of the medication. This potential interaction is not restricted to erlotinib [14]. For example, dasatinib AUC and C_{max} decreased by 61% and 63% respectively when co-administered with the PPI

Table 2. The main pharmacokinetic parameters of OSI-420 after single oral administration of 15 mg/kg erlotinib with and without omeprazole and esomeprazole in rats

Parameters	Erlotinib	Erlotinib + omeprazole	Erlotinib + esomeprazole
$t_{1/2}$ (h)	2.98 ± 0.41	2.73 ± 0.39	3.10 ± 0.25
T_{max} (h)	4.33 ± 0.51	4.50 ± 1.23	4.17 ± 0.98
CL_z/F (L/h/kg)	14.80 ± 1.20	19.12 ± 3.45*	30.24 ± 4.16**
C_{max} (ng/mL)	142.09 ± 33.77	102.03 ± 25.24*	68.49 ± 11.47**
$AUC_{(0-t)}$ (ng·h/mL)	1016.42 ± 79.91	804.54 ± 159.38*	500.48 ± 70.00**
$AUC_{(0-\infty)}$ (ng·h/mL)	1018.70 ± 80.96	808.32 ± 160.32*	504.07 ± 70.70**

*Significantly different from the control group, $P < 0.05$; **Significantly different from the control group, $P < 0.01$.

omeprazole [15], and the AUC and C_{max} for nilotinib decreased by 27-34% in the presence of the PPI esomeprazole [16]. This potential drug interaction poses a common clinical problem given the frequency of gastrointestinal disorders that may require AS for potential therapy.

Although it is clear that AS medications can affect the absorption of erlotinib, this effect was determined in tightly controlled single-dosing studies in healthy volunteers and it is uncertain whether these conclusions can be generalized when AS medications are prescribed for routine use. For example, Ter Heine and colleagues that erlotinib levels were only significantly reduced in their patient when the PPI pantoprazole was administered intravenously at high doses with a maintenance infusion; subsequently, when the patient was switched to oral administration of pantoprazole, erlotinib levels returned to baseline and were in the therapeutic range despite administering a higher dose than what would routinely be prescribed for gastroesophageal reflux disease (40 mg twice per day) [10].

In our study, we evaluated the potential impact of concurrent administration of PPIs on erlotinib pharmacokinetics in rats. Given the pH-dependent solubility profile of erlotinib, it was not a surprise that coadministration of the PPIs omeprazole and esomeprazole resulted in a substantial decrease in erlotinib plasma PK exposure. The absence of any impact on erlotinib $t_{1/2}$ or T_{max} supported that this observed decrease in PK exposure was due to reduced absorption and not a change in metabolism and elimination. Erlotinib metabolite (OSI-420) data were consistent with the reduced absorption of erlotinib; decreases in OSI-420 PK exposure when erlotinib was coadministered with omeprazole and esomeprazole were similar in extent to the erlotinib decrease.

In summary, by reducing the absorption of erlotinib, PPIs cause a reduction in drug exposure in rats. The impact of AS on erlotinib's pharmacokinetic parameters is higher with esomeprazole than omeprazole and is expected to be of similar significance with the remaining agents in the PPI class. In light of the current limited evidence, it is reasonable and prudent to avoid concomitant administration of erlotinib with PPIs if it is possible. Any clinical decision should be made by weighing the uncertain benefit of changing or discontinuing acid-reducing therapy against the potential negative impact that such actions may have on the patient.

Conclusion

Clinicians should be aware that administration of PPIs such as omeprazole and esomeprazole can decrease the absorption of erlotinib from the gastrointestinal tract, thereby resulting in a significant decrease in the plasma concentration of erlotinib. The combination of erlotinib and PPIs requires careful therapeutic drug monitoring of the erlotinib plasma concentration to ensure effective patient exposure to the drug.

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Disclosure of conflict of interest

None.

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