Opinion

Pharmacokinetic cross-over research in non-small cell lung cancer patients

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ABSTRACT

Afatinib is an oral epidermal growth factor receptor (EGFR) driver mutation metastatic non-small cell lung cancer (NSCLC) small molecule kinase inhibitor (SMKI). The majority of SMKIs have pH-dependent solubility, despite the convenience of oral administration. However, no human studies on the drug-drug interactions between afatinib and proton-pump inhibitors (PPIs) have been conducted. Therefore, we conducted a three-period, randomised cross-over research. There were no noticeable changes in toxicity. In conclusion, esomeprazole did not alter how much afatinib patients with NSCLC were exposed to. The coadministration of esomeprazole and afatinib is safe because there is no clinically significant drug-drug interaction. Due to the fact that other EGFR-SMKIs, such as erlotinib and gefitinib, do interact with acid suppressive drugs in clinically meaningful ways, this is crucial for clinical practise.

Key Words: *Bronchoscopy; Pleural disease; Interventional pulmonology.*

INTRODUCTION

An oral small-molecule kinase inhibitor (SMKI) called afatinib is primarily approved for the treatment of people with metastatic non-small cell lung cancer (NSCLC) that has an EGFR driver mutation. Afatinib clearly outperformed chemotherapy in terms of progression-free and overall survival. Afatinib is additionally used all over the world, where it has successfully treated a significant number of rare EGFR mutations. These mutations might cause progression during first- or second-line therapy with the third-generation EGFR-SMKI osimertinib, or they might develop spontaneously. Afatinib is the first-choice medication for this latter group of individuals. As a result, it continues to be a key component of the management of EGFRmutated NSCLC. The majority of SMKIs show pH-dependent solubility. Since SMKIs are typically weak bases, they can exist in both ionized and no ionized forms. This is dependent on the pH of the stomach and pharmacological properties like pKa, which is the pH level at which a balance between ionized and non-ionized drug molecules is achieved. An appropriate level of drug bioavailability requires a gastric pH below the pKa because ionized compounds often dissolve more readily. The equilibrium will change to the less soluble no ionized form, and as a result, its absorption will decline, if the gastric pH rises noticeably. Normal gastric pH is around, however when individuals use acid-suppressing medications (such proton-pump inhibitors), their pH will rise to. In terms of pH increase and continued effectiveness, the PPI esomeprazole is the strongest. However, the presence of a drug-drug interaction may not always be predicted by pKa. Esomeprazole and the SMKI regorafenib were thoroughly researched together. Regorafenib has a value of, hence a theoretical interaction was anticipated. Even when esomeprazole was administered at various times, regorafenib's bioavailability slightly reduced. Sunitinib is another instance, which has a pH-dependent solubility that diminishes as the pH range rises. PPI medication interactions have not been researched because it was anticipated that there would be no effect on drug absorption. Retrospective results, however, have demonstrated a reduced treatment efficacy when stomach acid suppressants and sunitinib are administered simultaneously. The same contradiction was observed with the oral formulation of capecitabine, which in theory shouldn't interact

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negatively with PPIs. However, the patients who were also on PPIs had noticeably worse survival rates. Afatinib is extremely soluble in solutions with a pH of and a pKa of. Afatinib and PPIs may not interact with each other, however, this has not been researched in humans. The impact of PPIs on afatinib bioavailability in patients cannot be exclusively anticipated based on in vitro evidence, comparable to sunitinib and capecitabine. Cancer patients utilize acid-reducing medications, therefore a potential drug-drug interaction would be extremely important for clinical practice. We, therefore, set out to research how afatinib and esomeprazole interact in people with NSCLC. A useful suggestion for everyday practice can be given to doctors and patients depending on the presence and scope of the encounter. Esomeprazole was the intervention in a three-period cross-over, randomized research that we carried out. In order to avoid dose modifications due to toxicity over the course of the research, patients were given afatinib at a constant dose for at least three weeks (loading phase). Each subject then underwent three two-week study periods in the order of the randomization. Afatinib was given without esomeprazole in period A, which functioned as the control period. For the final five days of period B, esomeprazole mg were given concurrently. For the final five days of the period, patients had to take esomeprazole mg three hours before taking afatinib. Afatinib was administered during the hospitalizations two hours following a light breakfast, which patients had to repeat each day of the admission. From four hours before to four hours after afatinib delivery, no other food or drink was allowed. Up to one hour before and one hour after taking afatinib, only free water consumption was permitted.

All blood samples were centrifuged as soon as they were drawn, and the blood plasma was then frozen below degrees Celsius since afatinib is unstable in the blood (not as a tablet) above degrees Celsius. Only ice was used to process the samples. A validated liquid chromatography-tandem mass spectrometric test was used to quantify afatinib, and all of the samples from each individual patient were examined in the same run. The primary goals were to compare the area under the curve of afatinib in patients with NSCLC to afatinib taken concurrently with esomeprazole and to afatinib used with esomeprazole three hours earlier. Other pharmacokinetic results were the secondary goals. To assess the frequency and seriousness of afatinib-related adverse events throughout the course of the three periods, the maximum concentration (Cmax) and time to Cmax (Tmax) were measured. For each trial period, participants were given a notebook to use to record the precise times and methods of afatinib and esomeprazole doses in order to ensure that they closely followed the study protocol. To further ensure drug responsibility, patients were also asked to return the empty esomeprazole and afatinib tablet packing. Additionally, patients were asked to describe any new or ongoing adverse events. The investigating physician also recorded adverse events at each of the three hospital admissions in compliance with the FDA's and the EMA's requirements that the confidence interval for the ratio of the test and reference products be confined within the acceptable range. It was crucial to keep in mind that there would be two main comparisons for which the Bonferroni correction would be used in the analyses when calculating the sample size. By dividing the nominal alpha by the total number of comparisons, this was calculated. Therefore, a two-sided alpha of is used to calculate the sample size. A total of evaluable patients were needed to detect a difference with sufficient precision, assuming the within-patient stan-

-dard deviation of afatinib trough concentrations. Using a non-compartmental analysis, AUCs were calculated. WinNonlin (Phoenix, Carrara, Princeton, NJ) (Phoenix, Certara, Princeton, NJ). In order to execute AUC0 and Cmax were converted to a logarithmic scale for statistical studies, assuming they have a log-normal distribution. Linear.

Mixed effect modeling was used to account for variations in AUC0 and Cmax, with the esomeprazole intervention, the sequence, and the duration acting as fixed effects and the subject within the sequence acting as a random effect Restrictive maximum likelihood (REML) techniques were employed to estimate the variance components, and the Ken ward-Roger approach was applied to determine the denominator's degrees of freedom. To calculate point estimates of the ratios of geometric means and their CIs, the mean differences in AUC0 and Cmax, along with their confidence intervals (CIs), were exponentiated (c.q. relative differences). The Wilcoxon signed-rank test was used to compare the Tmax between the periods. Each period's individual incidence and severity of adverse occurrences were documented. The results regarding the incidence and severity of adverse events were of a descriptive character because treatment time in each period was constrained and the trial was powered to detect a statistically significant difference for only the primary endpoint. Stata (StataCorp.) was used for all statistical analyses. The simultaneous administration of the PPI esomeprazole and the EGFR-SMKI afatinib in NSCLC patients is being investigated for the first time in this trial. The medicine combination can be used safely in clinical practice because there was no statistically significant drug-drug interaction. We examined the effects of esomeprazole when it was given concurrently with afatinib and three hours beforehand in this randomized, three-period cross-over pharmacokinetic research. Considering the high pKa of afatinib, we did not anticipate an interaction. The PPI with the greatest pH increase is esomeprazole. Drug-drug interaction between afatinib and esomeprazole can be ruled out because the combination was evaluated throughout two time periods with separate esomeprazole administration times. Since many patients use acid-reducing medications and other well-known EGFR-SMKIs exhibit clinically significant decreases in exposure when used concurrently with acid-reducing medications, this is a significant result for clinical practice. To be specific, when taken with esomeprazole or ranitidine, respectively, the exposure to erlotinib and gefitinib diminishes nearly immediately. As a result, afatinib may be an option for individuals who need to be treated with an EGFRSMKI but are PPI-dependent. We are cautious when applying these results to other PPIs and other acid-reducing medicines, despite the fact that most PPIs operate through a similar mechanism. The PPIs pantoprazole, omeprazole, and lansoprazole, for instance, all block the drug transporter ABCB1 (P-glycoprotein) that actively transports afatinib, in contrast to esomeprazole. This can result in further medication interactions. Similar interaction studies should be carried out before claiming that these other PPIs are secure when used with afatinib. In contrast to afatinib, other acid-reducing substances (such as antacids or H2-receptor antagonists) are less effective in raising gastric pH and are less likely to interact with it via drug transporters or cytochrome P450 enzymes. Theoretically, neither afatinib nor these acid-reducing medications will interact with one another. There was no discernible difference in toxicity between the two intervention periods and control period A. This result was anticipated because esomeprazole co-administration did not affect the bioavailability of

afatinib. Other than the potential toxicity of esomeprazole itself, chronic esomeprazole use is unlikely to affect the occurrence of events. The lack of intragastric pH measurements, which would have helped to further understand the interaction, could be a limitation of this work. However, pH monitoring is exceedingly invasive and uncomfortable for patients, making it difficult to execute and hence legitimate, and having little added value for clinical practice. Furthermore, a restricted amount of power may be indicated by the relatively high coefficient of variation in the research periods. However, it is not anticipated that an increase in patient volume will result in a statistically significant or clinically relevant difference given the relative variations. Another drawback of esomeprazole is that, like afatinib, it greatly reduces exposure when taken after a high-fat, high-calorie meal. In this investigation, esomeprazole, whether given concurrently or three hours before taking afatinib, had no effect on the exposure to the drug. It is safe to combine esomeprazole and afatinib in clinical practice because there is no clinically significant drug-drug interaction. We thank Mei Ho Lam and Peter de Bruijn for producing and evaluating all of the pharmacokinetic samples. Additionally, we thank Dr. Kees Kraaij for his assistance with patient enrollment. Additionally, we thank Yvonne van der He for conducting a linguistic evaluation of the entire manuscript.