Clinical Imaging and Case Reports (ISSN 2770-9205)

Pharmacokinetic and Pharmacodynamic Evaluation of a Sodium Bicarbonate Combination of Rabeprazole, a Proton-Pump Inhibitor, in Healthy Subjects

Yu Kyong Kim

Corresponding author

Yu Kyong Kim,
Department of Clinical Pharmacology and Therapeutics, Chungbuk National University College of Medicine and Hospital, Republic of Korea.

Received Date: July 14 2023
Accepted Date: July 16 2023
Published Date: August 16 2023

Abstract

Reason: Proton-pump inhibitors, including rabeprazole, are susceptible to stomach acid breakdown. The use of enteric-coated (EC) formulations reduces this issue, although their slower onset time is a drawback. A Fixed-Dose Combination (FDC) tablet containing rabeprazole and sodium bicarbonate, which was utilised to elevate the intragastric pH, was compared to a traditional extended-release (EC) tablet. Materials and procedures To assess PK and PD features, a 40-subject, randomised, open-label, multiple-dose, 2-treatment, 2-sequence, 2-period crossover research was conducted. During each period, eligible subjects were given either 20 mg rabeprazole EC tablets for 7 days or 20 mg rabeprazole plus 800 mg sodium bicarbonate FDC tablets. On days 1 and 7, serial blood samples were taken for up to 24 hours.The PK parameters for rabeprazole were calculated using non compartmental techniques. On days -1, 1 and 7, ambulatory pH monitoring was done to figure out the PD parameters. The criteria that the FDC-to-EC tablet ratio fell within the range of 0.80-1.25 allowed for a quantitative comparison based on the 90% Confidence Interval (90% CI) of the area under the concentration vs. time curve over the dosing interval (AUCtau,ss) and the percentage decrease from baseline in Integrated Gastric Acidity (% IGA) after 24 hours.

Results: After therapy with sodium bicarbonate FDC and EC tablets for 7 days, total rabeprazole exposures were comparable (90% CI of 1.0880-1.1731 for AUCtau,ss). The 90% confidence interval for the fall in percent IGA from baseline for the two formulations was 0.8937-1.0448.effect. All negative incidents were minor and brief.

Abbreviations

AUCtau is an acronym for Area Under the Curve During a Dosage Interval (Tau) Following a Single Dose and AUCtau,ss is an acronym for Area Under the Curve During Tau Following Several Doses. EDTA stands for ethylenediaminetetraacetic acid; IGA stands for integrated gastric acidity; MS/MS stands for tandem mass spectrometry; MRM stands for multiple reaction monitoring; PD stands for pharmacodynamic; PK stands for pharmacokinetic; Cmax stands for maximum plasma concentration after a single dose; Cmax,ss stands for maximum plasma concentration during tau after multiple doses; Terminal Half-Life: t1/2: Terminal Half-Life After Single Dose; Terminal Half-Life After Several Doses: t1/2,ss; Tmax,ss: Time to Reach Maximum Plasma Concentration After Drug Administration after Several Doses; Tmax: Time to Reach Maximum Plasma Concentration Following Drug Administration.

Introduction

Proton-Pump Inhibitors (PPIs) are a class of medications that are frequently used to treat and prevent early symptoms brought on by gastric acid in the stomach, duodenum, and oesophagus. They work by reducing the release of gastric acid [1]. The drug ingredient is supplied to the parietal cells via commonly used oral PPI formulations in the form of a prodrug, which then passes through the stomach and is absorbed into the systemic circulation from the upper duodenum and the small intestine [2,3]. After being transformed into an active state, the supplied prodrug binds permanently to the parietal cells' proton-pump, inhibiting H+ secretion into the stomach lumen [3]. Omeprazole and pantoprazole, two first-generation PPIs, are mostly metabolised by the Cytochrome p450 (CYP) 2C19 enzyme, leading to drug-drug interactions across several enzyme substrates or variations in pharmacokinetic properties because of genetic polymorphisms, which are still

unresolved [2,3]. Conversely, second-generation PPIs with less CYP2C19 dependence, such as In addition to making up for the drawbacks of the first-generation PPIs, esomeprazole and rabeprazole also produce equal to or better inhibitory effects [4–8]. Moreover, unlike other PPIs, rabeprazole exhibits nonenzymatic metabolic characteristics that include glutathione reductive cleavage, which mitigates the long-term negative effects [9]. Enteric-Coated (EC) versions of PPIs have been created to promote absorption in the intestine while minimising their breakdown owing to acid in the stomach because PPIs are weak bases with little stability in the acidic environment of the stomach [10–12]. These formulations have a slower rate of absorption than those for immediate release, which causes a slower onset time. PPIs have been used in conjunction with rescue antacids in the clinic.or H2 blockers in combination therapy to get around these onset time-related problems [13,14].It is common practise to create and employ Fixed-Dose Combination (FDC) formulations of two or more pharmacological components to increase medication adherence during combination therapy [15–18]. The FDC formulation can be used not only in combination treatment but also in augmentation treatment, which involves adding a drug to a commonly prescribed drug that is anticipated to have a positive impact on clinical outcomes (e.g., using thyroid supplementation in conjunction with an antidepressant to treat depression) [19]. PPI and sodium bicarbonate FDCs are being developed to prevent acid degradation of the PPI component by raising the intragastric pH and enabling absorption from the proximal duodenum, with the goal of maintaining the benefits of EC formulations, which demonstrate quicker absorption [20,21].

That is In a recent study, researchers compared the pharmacokinetic and pharmacodynamic properties of rabeprazole and sodium bicarbonate FDC tablets to those of the drug's EC tablet formulation in healthy volunteers. Intragastric pH was monitored using an ambulatory pH recording equipment (DigitrapperTM Recorder, MN, USA) for 24 hours or more. Prior to inserting each catheter, the recording device and the catheters were calibrated using standard buffer solutions (pH 4, pH 7, and distilled water). A calibrated pH catheter was put into the stomach through one of the nostrils for pH monitoring, and the procedure was repeated until the distal sensor's reading of the gastric pH dropped to about pH 2.5. The initial catheter insertion (continuous monitoring for baseline and Day 1) resulted in the measurement of the catheter's length in centimetres, which was then utilised to guide the placement of the second catheter (Day 7). The oesophagus pH was measured before the research medications were administered (proximal sensor), and (distal sensor) were kept at a pH range of 6-7 and 2.5, respectively. Throughout the pH monitoring period, which was carried out during the day, the individuals were kept upright.After multiple administrations of rabeprazole with and without the sodium bicarbonate combination in healthy subjects, all adverse events were transient and mild in severity, with no clinically significant findings in other tolerability parameters, such as the laboratory test results, vital signs, and physical examination. In this investigation, no concurrent medication was needed to manage adverse events (AEs).

Discussion

In this study, the corresponding features following repeated doses were compared with those of the traditional rabeprazole formulation in order to evaluate the pharmacokinetics and pharmacodynamics of rabeprazole FDC tablets with sodium bicarbonate. Only three out of 35 subjects had quantifiable plasma rabeprazole concentrations until the final blood sampling time on day seven, and two weeks of washout between each period was sufficient to allow rabeprazole to be eliminated to the lowest level of quantification as assessed during blood sampling prior to administration and in the following period in all subjects. The two formulations produced comparable exposure (AUCtau,ss) and IGA over a 24-hour period following seven days of repeated dosing; hence, comparable acid inhibiting effects can be anticipated. Furthermore, the When rabeprazole FDC tablet with sodium bicarbonate was administered, it took less time to obtain the appropriate mean intragastric pH than when rabeprazole EC tablet was administered. The proportion of time at which the pH was >4 was lower in those who got the FDC than in those who received the EC prior to the peak rabeprazole exposure and saturation of the decline of acidity. Nonetheless, the EC group's acidity variation was clinically identical to that observed after numerous FDC pill administrations. When administering the FDC pill to patients with acid-related disorders (such as GERD (gastroesophageal reflux disease), duodenal ulcers), a 4-week or longer regimen is recommended.Individuals with GERD should experience quick symptom relief and an identical treatment outcome in the clinical context. In addition to demonstrating its own benefits, such as the possibility for fewer drug interactions than with other PPIs, the bicarbonate FDC tablet also effectively demonstrates the advantages of FDCs that have already been commercialised. The cost-effective evaluation of the applicability of modified formulations and combination tablets was carried out by evaluating measurable PK and PD features in healthy volunteers. The symptom relief effect, however, cannot be generalised from healthy people since they have distinct pathophysiologies from GERD patients. For instance, the

location and sizes of the acid pockets that cause GERD as well as the potential for a hiatal hernia were not examined [30–32].A 20 mg rabeprazole daily dose is effective, even if the results came from healthy participants rather than the intended group of patients with symptoms of acid reflux. Similar acid-inhibiting effects between the new FDC and EC tablets are therefore anticipated to occur in patients. recognised to be sufficient to achieve a mean change in pH over 24 hours in GERD patients. More investigations will be necessary to establish the clinical result in people with GERD.

Conclusions

Without affecting the overall rabeprazole exposure or the intragastric acid suppression effect after numerous administrations, the maximal concentration of rabeprazole sodium was reached faster when sodium bicarbonate was added.

References

1. Hunt R, Armstrong D, Katelaris P, Afihene M, Bane A, Bhatia S, et al. World gastroenterology organisation global guidelines: GERD global perspective on gastroesophageal reflux disease. J Clin Gastroenterol. 2017;51(6):467-78.

2. Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. J Neurogastroenterol Motil. 2013;19(1):25-35.

3. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. Curr Gastroenterol Rep.2008;10(6):528-34.

4. Ishizaki T, Horai Y. Cytochrome P450 and the metabolism of proton pump inhibitors-Emphasis on rabeprazole. Aliment Pharmacol Ther. 1999;13 Suppl 3:27-36.

5. Liu MK, Wu IC, Lu CY, Kuo CH, Yu FJ, Liu CJ, et al. Randomized trial comparing rabeprazole--versus lansoprazole-based Helicobacter pylori eradication regimens. Kaohsiung J Med Sci. 2013;29(7):379-84.

6. Miner P, Delemos B, Xiang J, Lococo J, Ieni J. Effects of a single dose of rabeprazole 20 mg and pantoprazole 40 mg on 24-h intragastric acidity and oesophageal acid exposure: a randomized study in gastro-oesophageal reflux disease patients with a history of nocturnal heartburn. Aliment Pharmacol Ther. 2010;31(9):991-1000.

7. Wu J, Jia LT, Shao LM, Chen JM, Zhong DD, Xu S, et al. Drug-drug interaction of rabeprazole and clopidogrel in healthy Chinese volunteers. Eur J Clin Pharmacol. 2013;69(2):179-87.

8 Xia XM, Wang H. Gastroesophageal reflux disease relief in patients treated with rabeprazole 20 mg versus omeprazole 20 mg: a meta-analysis. Gastroenterol Res Pract. 2013;2013:327571.

9. Tang C, Chen Z, Dai X, Zhu W, Zhong D, Chen X. Mechanism of reductive metabolism and chiral inversion of proton pump inhibitors. Drug Metab Dispos. 2019;47(6):657-64.

10. Murali Krishna Goud C, Dhanalakshmi R, Ramesh P. Formulation, development and in-vitro evaluation of rabeprazole sodium delayed release enteric coated tablets. World J Pharm Pharm Sci. 2017;6(8):1121-34.

11. Tutunji MF, Qaisi AM, El-Eswed B, Tutunji LF. An in vitro investigation on acid catalyzed reactions of proton pump inhibitors in the absence of an electrophile. Int J Pharm. 2006;323(1-2):110-16.

12. Van Nguyen H, Baek N, Lee BJ. Enhanced gastric stability of esomeprazole by molecular interaction and modulation of microenvironmental pH with alkalizers in solid dispersion. Int J Pharm. 2017;523(1):189-202.

13. Leodolter A, Penagini R. On-demand therapy is a valid strategy in GERD patients:pros and cons. Dig Dis. 2007;25(3):175-8.

14. Lodrup A, Reimer C, Bytzer P. Use of antacids, alginates and proton pump inhibitors: a survey of the general Danish population using an internet panel. Scand J Gastroenterol. 2014;49(9):1044-50.

15. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med. 2007;120(8):713-9.

16. Bangalore S, Shahane A, Parkar S, Messerli FH. Compliance and fixed-dose combination therapy. Curr Hypertens Rep. 2007;9(3):184-9.

17. DiPette DJ, Skeete J, Ridley E, Campbell NRC, Lopez-Jaramillo P, Kishore SP, et al. Fixed-dose combination pharmacologic therapy to improve hypertension control worldwide: clinical perspective and policy implications. J Clin Hypertens (Greenwich). 2019;21(1):4-15.

18. Lee Y, Shin J, Kim Y, Kim DS. Consumption of single products versus fixed-dose combination medicines for hypertension and hyperlipidemia during 2015-2019 in South Korea. PLoS One. 2021;16(12):e0259467.

19. Fava M, Targum SD. Augmentation and combination strategies to treat the residual symptoms of major depressive disorder. Psychiatry (Edgmont). 2007;4(2):16-8.

20. Kim D, Park MS, Yoo BW, Hong T, Park SJ, Kim CO. The safety, pharmacodynamics,and pharmacokinetics of immediate-release formulation containing esomeprazole

21. mg/sodium bicarbonate 800 mg in healthy adult male. Drug Des Devel Ther.2019;13:3151-9.

22. Kim KN, Yang SW, Kim H, Kwak SS, Kim YS, Cho DY. Acid inhibitory effect of a combination of omeprazole and sodium bicarbonate (CDFR0209) compared with delayed-release omeprazole 40 mg alone in healthy adult male subjects. Clin Pharmacol Drug Dev. 2018;7(1):53-8.

23. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guideline for Good Clinical Practice E6 (R2). European Medicines Agency. 2016.

24. World Medical Association. World medical association declaration of helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4.

25. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drugs Evaluation Research. Guidance for Industry: Statistical Approaches to Establishing Bioequivalence. U.S. Maryland: FDA; 2001.

26. Gardner JD, Perdomo C, Sloan S, Hahne WF, Barth JA, Rodriguez-Stanley S, et al. Integrated acidity and rabeprazole pharmacology. Aliment Pharmacol Ther. 2002;16(3):455-64.

27. Kishore SP, Salam A, Rodgers A, Jaffe MG, Frieden T. Fixed-dose combinations for hypertension. Lancet. 2018;392(10150):819-20.

28. Lin CP, Tung YC, Hsiao FC, Yang CH, Kao YW, Lin YS, et al. Fixed-dose combination of amlodipine and atorvastatin improves clinical outcomes in patients with concomitant hypertension and dyslipidemia. J Clin Hypertens (Greenwich). 2020;22(10):1846-53.

29. Bae S, Kwon J, Lee SB, Jang IJ, Yu KS, Lee S. Comparative pharmacokinetics/ pharmacodynamics of fixed-dose combination of esomeprazole and calcium carbonate (AD-206) to the conventional esomeprazole. Drug Des Devel Ther. 2021;15:5099-108.

30. Howden CW. Review article: immediate-release proton-pump inhibitor therapy--Potential advantages. Aliment Pharmacol Ther. 2005;22 Suppl 3:25-30.

31. Beaumont H, Bennink RJ, De Jong J, Boeckxstaens GE. The position of the acid pocket as a major risk factor for acidic reflux in healthy subjects and patients with GORD. Gut. 2010;59(4):441-51.

32. Kirchheiner J, Glatt S, Fuhr U, Klotz U, Meineke I, Seufferlein T, et al. Relative potency of proton-pump inhibitors-comparison of effects on intragastric pH. Eur J Clin Pharmacol. 2009;65(1):19-31.

33. Rohof WO, Bennink RJ, De Ruigh AA, Hirsch DP, Zwinderman AH, Boeckxstaens GE. Effect of azithromycin on acid reflux, hiatus hernia and proximal acid pocket in the postprandial period. Gut. 2012;61(12):1670-7.