International Journal of Advances in Medicine
Prasad VGM et al. Int J Adv Med. 2022 Oct;9(10):1031-1038
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20222402

Original Research Article

A unique formulation of sodium bicarbonate buffered pantoprazole powder for oral suspension: perspectives from an active controlled cross-over bioequivalence study

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Received: 22 August 2022
Revised: 14 September 2022
Accepted: 15 September 2022

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ABSTRACT

Background: The aim was determining bioequivalence between pantoprazole buffered powder for oral suspension and pantoprazole enteric coated tablets under fasting conditions in healthy volunteers.
Methods: In randomized cross-over study, participants were administered a single oral dose of pantoprazole powder as suspension 40 mg (sodium bicarbonate as buffer) or one enteric coated tablet of pantoprazole 40 mg, with 240±2 ml of water as per the randomization schedule in each study period. Blood samples were collected at pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 12, 14, 16 and 24 hours post-dose. Plasma concentration of pantoprazole was determined with LC-MS and various pharmacokinetic parameters like C_{max}, AUC_{0-t}, AUC_{0-inf} were compared between test and reference groups.
Results: Amongst 41 subjects, C_{max} (3752.4±1084.6 vs. 3521.7±1099.5 ng/ml) was achieved higher in less T_{max} time (1 (0.28) vs. 2.3 (0.83) hrs) with test drug as compared to reference drug. The ratios of geometric least square mean and its 90% confidence interval on log transformed C_{max}, AUC_{0-t} and AUC_{0-inf} for pantoprazole fall within the acceptance criteria of 80% to 125%. No adverse events were observed.
Conclusions: Pantoprazole powder for oral suspension 40 mg (sodium bicarbonate as buffer) was well tolerated and bioequivalent with pantoprazole enteric coated tablets IP 40 mg in terms of rate and extent of absorption under fasting conditions. At same time, the shift in AUC to the left with reduction in T_{max} with the new formulation is suggestive of faster rate of absorption.

Keywords: Pantoprazole buffer powder, Peptic ulcer, New formulation, Bioequivalence, Pharmacokinetic

INTRODUCTION

Peptic ulcer disease is characterized by damage to gastric or duodenal mucosa due to hyperacidity and it is managed by various groups of drugs like H_2 blockers, proton pump inhibitors (PPIs), antacids, prostaglandin analogues, ulcer protective agents.[1] Among all these, PPIs are considered as the most effective group as they can mediate complete inhibition of acid secretion.[2]

PPIs inhibit the gastric acid secretion by specific inhibition of proton pump (H^+-K^+ ATPase) present on parietal cells which is the final step in gastric acid secretion.[3] PPIs are indicated for short-term treatment of peptic ulcer, erosive

esophagitis associated with gastroesophageal reflux disease (GERD), maintenance of healing of erosive esophagitis, and Zollinger Ellison syndrome.[3] They are also an integral part of *H. pylori* eradication regimens.[1]

Most of the PPIs are available as oral and parenteral formulations. Oral formulations are enteric coated as PPIs being the acid labile can be destroyed easily in low pH of stomach.[4] Though, PPIs are being the most effective group, there are few problems found with this group of drugs are slow onset of action due to delayed absorption in the intestine as a result of enteric coating; short half-lives; variable pharmacokinetics due to food-drug and drug-drug interaction; and difficult nocturnal acidity control. Some other challenges are difficulty in administration with this formulation in uncooperative, critically ill e.g., patients with stroke and esophageal strictures and geriatric patients.[4-7] Hence, there is a need of oral solution which can be designed in such a way that provide protection to PPI in acidic environment of stomach and is also as effective as the oral solid dosage form. The PPI formulation in combination of physiological buffer have been developed and available with omeprazole, esomeprazole, rabeprazole and pantoprazole in India as tablets.[8] Added buffer increases pH in stomach which can provide immediate pain relief due to acid neutralization and protects the PPI from degradation in acidic environment.[9] Moreover, the buffer stimulated gastrin release fulfil the requirement of activated proton pump for their inhibition by PPI.[10]

PPI in combination with buffer showed fast and sustained effect on gastric acid suppression as compared to conventional formulations.[9,11] In an animal study conducted by Bigoniya et al pantoprazole buffered tablet was found to have better, faster and prolonged bioavailability as compared to plain pantoprazole tablet.[12] Buffered pantoprazole also increased the gastric content pH; reduced free and total gastric acidity and improved ulcer grading more effectively.[12] Concentration of pantoprazole was found more in stomach content and stomach tissue homogenate with buffered formulation as compared to plain pantoprazole.[12]

Although all the buffered PPI formulations available thus far have various pharmacokinetic and pharmacodynamics advantages, they are not well accepted by the patients due to very large size of the formulation leading to difficulty and inconvenience in administration. To overcome the shortfalls of the available conventional PPI and the big size buffered pantoprazole tablets (leading to difficulty of swallowing in geriatric, uncooperative and critically ill patients), Alkem laboratories has developed a novel formulation of pantoprazole as powder, buffered with sodium bicarbonate to be used as oral suspension. In present study, bioavailability of pantoprazole powder for oral suspension 40 mg with sodium bicarbonate as buffer (Alkem Laboratories Ltd., India) was compared with conventional pantoprazole enteric coated tablets IP 40 mg.

METHODS

Study design and ethical consideration

It was a randomized, open label, balanced, two treatments, two period, two sequence, two way, cross-over, single oral dose, bioequivalence study conducted in healthy adult male human subjects under fasting conditions in March 2022 (period 1: 12 March 2022 to 14 March 2022; period 2: 22 March 2022 to 24 March 2022). The study was conducted at DCGI registered BA/BE study facility of Bio Scientific Research Laboratories (I) Pvt. Ltd. Mumbai, Maharashtra. The study was started after protocol and related documents were reviewed and approved by the Institutional Ethics Committee. The study was conducted according to the current version of the declaration of Helsinki (ethical principles for medical research involving human subjects, Brazil 2013), current ICH GCP guidelines, and relevant National Laws and Regulations, ICMR guidelines and New Drugs and Clinical Trials Rules 2019 (CDSCO guidelines). The informed consent form was issued to all the volunteers before the study conduction. The volunteers were explained about the study procedures, risks and discomforts associated with the study procedures, possible adverse events of the study drugs, the remuneration and duration of the study, number of the participants to be included, the voluntary participation and withdrawal from the study and the participant's confidentiality of his identity. All the participants voluntarily gave the written consent for participation in the study. The eligible participants were allotted a subject number to maintain the confidentiality of their identity.

Study COHORT

Non-smokers, non-alcoholics healthy adult human male participants within 18-45 years of age with body mass index (BMI) having range between 18.0 and 29.0 kg/m^2, no evidence of underlying disease, screening laboratory values were within normal limits, no history of drug abuse in the past one year, willing to follow instructions during study and willing to participate were included in the study. Participants with any known contra-indication to pantoprazole or related class of drugs; any significant medical disorder as determined by history, significant abnormal finding as determined by clinical examination including ECG and vital signs; difficulty in swallowing the suspension/tablets; difficulty in withdrawing the blood; found positive in urine test for drugs of abuse and alcohol; depot injections or implants within 6 months; positive screening test for any one: HIV, hepatitis B, hepatitis C and syphilis; consumption of xanthine/caffeine containing products, tobacco containing products, grapefruit juice and alcohol within 48 hours prior to dosing; refusal to abstain from food from at least 10 hours prior to study drug administration until at least 4 hours post-dose, in each study period; refusal to abstain from consumption of tobacco products 48 hours prior to dosing until the last blood sample collection of last study period; refusal to

abstain from fluid from at least 1 hour prior to study drug administration until at least 1 hour post-dose; requirement of any medication for chronic illness; consumption of any medication (prescribed or OTC) during 21 days prior to dosing and till the end of the study; participation in any clinical study during past 90 days; blood donation during 90 days prior to participation; clinically significant illness within 4 weeks before start of study and with any condition, which in the opinion of the investigators makes the participant unsuitable for inclusion were excluded from the study.

Study drugs

The test drug was the sodium bicarbonate buffered pantoprazole 40 mg powder for oral solution manufactured and provided by Alkem Laboratories Ltd., Mumbai, India. pantoprazole enteric coated tablet IP 40 mg was used as reference drug.

Study procedure

The study was conducted in two period as being the cross-over design. 7 days wash-out period was kept before crossing-over of the participants into different treatment arms. The study procedure was the same in each period.

Biometric identification and registration, obtaining consent, demographic data including BMI, clinical history, physical examination (vital signs and well-being), ECG, laboratory tests including haematology, biochemistry, serology (VDRL, HBsAg, HCV and HIV I and II), urine analysis were performed during the screening. Assessment of inclusion and exclusion criteria were done before check-in of each study period. The participants were confined within the study facility at least 11 hours prior to the dosing. All participants were on an overnight fast for at least 10 hours prior to and for 4 hours after the dose administration. On the day of dosing, they were administered a single oral dose of one sachet of test drug (T)-pantoprazole powder for oral suspension 40 mg (sodium bicarbonate as buffer) or one tablet of reference drug (R)-pantoprazole tablets IP 40 mg with 240±2 ml of water as per the randomization schedule at ambient temperature in sitting position in each study period. Drinking water was not allowed for 1 hour before and 1 hour after dose administration (except for the 240±2 ml of drinking water administered during dosing) and at all other times ad libitum were provided. No food was allowed 4 hours after dosing. A standardized meal was provided to all the participants during night of check in and at around 4, 9 and 13 (lunch, snacks and dinner) hours post-dose on day 1 within+30 minutes of scheduled time. Respective meal contents were identical for both periods. All participants were dosed at the fixed time and advised to remain in sitting position for the first 2 hours following drug administration except while going for blood sampling and/or vital signs or clinically indicated/for natural exigency. They were refrained from any strenuous activity during the confinement period at the testing facility and were instructed to abstain from consuming any xanthine/caffeine containing food or beverages (chocolates, tea, coffee or cola drinks), grapefruit juice and products, alcoholic products, cigarettes and tobacco products for 48 hours prior to first dosing until the last blood sample collection of last study period. Physical examination was done at the time of check in and check out of each study period. Vital signs (blood pressure, pulse rate, axillary temperature and respiratory rate) and well-being monitoring were assessed at the time of each period check in, pre-dose (within 3 hrs prior to drug administration in supine position) and check out. Vital signs (blood pressure, pulse rate) and well-being were assessed at 1, 3, 6 and 12 hrs post-dose, respectively. Post dose vital signs measurements and well-being were obtained in the supine position within±45 minutes of scheduled time.

Total of 25 blood samples (5 ml each) were collected from the participants in each study period. Blood samples were collected in pre-labelled vacutainers with K3EDTA as an anticoagulant at pre-dose (within 0.5 hour prior to dosing) to 24 hrs post dose within 2 minutes of the scheduled time 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 12, 14, 16 and 24 hours post-dose in each of the two periods. Samples were maintained in wet ice bath from collection to centrifugation. Samples were centrifuged to separate plasma, within 1 hour after collection. Blood samples were centrifuged at 3500 rpm for 05 minutes at around 5°C±3°C. After centrifugation, the separated plasma was divided into two aliquots in such a way that each aliquot was contained sufficient amount of plasma for analysis. Plasma samples were stored at -20°C±10°C in deep freezer of the sample processing room until transfer to deep freezer of the sample storage room. All plasma sample vials were stored upright at -20°C±10°C in self-seal bags in sample storage room. After completion of last period, both analysis and control plasma samples were transferred to the bio-analytical facility at Bio Scientific Research Laboratories (I) Pvt. Ltd where plasma concentration of pantoprazole was measured by detection was done by a validated LC-MS/MS detection method. The participants were instructed to report in case of any inconvenience or adverse events to the monitoring study personnel, during the study, wash out period and after check-out, as applicable for the study. As a precautionary measure, all activities where the drug may be exposed to light such as pharmacy activities (including acceptance, dispensing, reconciliation and retention), dose administration, blood sample collection, sample handling, processing and analysis were carried out under yellow monochromatic light.

Study variables

The pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} for pantoprazole were taken as primary pharmacokinetic variables for establishing the bioequivalence. The criteria for evaluating bioequivalence between the test product and reference product was to have 90% confidence interval

based on two one sided 't' test, for the test-to-reference ratio of geometric least square mean within the range of 80-125% for C_{max}, AUC_{0-t} and AUC_{0-inf} for pantoprazole. Time to reach peak plasma concentration (T_{max}), Elimination rate constant (Kel), elimination half-life (t1/2), percentage of AUC_{0-inf} due to extrapolation from last time point to infinity calculated ($AUC_{Extrapolated\%}$) were the secondary pharmacokinetic variables. Safety was evaluated by monitoring adverse events during each study period.

Data quality assurance

Dosing was done by the assigned study personnel responsible for the activity, under the observation of investigator and quality assurance (QA) personnel. While dosing, the assigned study personnel responsible for the activity confirmed subject number, study code, photograph and the subject registration number from the identity card provided to them during the study. Mouth check was performed immediately after drug administration to assess the compliance to this procedure. The labels identifying the study code, dosing date, period, subject no., randomization code (test T or reference R), dose, batch/lot no., expiry date and "for clinical trial use only" were affixed on the dosing record form, which was signed by the respectively assigned study personnel responsible for the activity. Analytical method used for plasma analysis of pantoprazole was calibrated and validated using internal control. Analyst was blind to the type of formulation administered to the participants. Quality audits were performed by quality assurance monitor for compliance to study protocol, standard operative procedure and applicable guidelines.

Sample size

The study was conducted on 48 healthy willing male subjects between 18 to 45 years (both inclusive) of age having BMI within 18.0 and 29.0 kg/m^2 (both inclusive) and having no medical history of significant diseases or clinically significant abnormal findings during the pre-study screening, physical examination and laboratory evaluations.

Statistical analysis

All the statistical analysis was performed using SAS® software 9.4 Version. The drug plasma concentrations at each sampling time point were planned to be tabulated for each participant and treatment, together with descriptive statistics for each treatment at each scheduled sampling time point. All the BLQ values were considered as zero for the computation of pharmacokinetic parameters and statistical calculations. Missing samples were considered as missing values for estimation of pharmacokinetic parameters and statistical calculations. The mean plasma concentration for all the participants versus time profiles for each product was presented graphically on both the scales, on the untransformed and log-transformed data. ANOVA was performed on untransformed and log transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} for pantoprazole at the α level of 0.05. The analysis of variance model includes sequences, subject nested within sequences, period and treatment as factors. The significance of the sequence effect was tested using the subject nested within sequences as the error term. All other main effects were tested against the residual error (mean square error) from the ANOVA model as the error term. Each analysis of variance also included calculation of least-square means, adjusted differences between formulation means and the standard error associated with these differences. 90% confidence intervals were constructed for the difference (test-reference) of least square means of the log-transformed C_{max}, AUC_{0-t} and AUC_{0-inf} for pantoprazole. The antilog (or exponential) of these limits gives the 90% confidence interval for the ratio of geometric least square means of the test and reference formulations. The geometric least square mean ratios of the test and reference product and their 90% confidence interval on the log transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} for pantoprazole were computed and bioequivalence was concluded if the confidence interval fell within the acceptable range of 80%-125% for log transformed C_{max}, AUC_{0-t} and AUC_{0-}inf for pantoprazole.

RESULTS

Total 48 normal, healthy, adult, human male participants were enrolled and of which three participants did not report for second period check in activity due to personal reasons. Thus, 45 subjects completed the clinical phases of the study successfully. Plasma samples of these 45 participants were analyzed of which four samples were further excluded as they showed C_{max} at first time point after dosing. The data of 41 participants were considered for pharmacokinetic and statistical analysis and to draw bioequivalence conclusion. Participants who completed the pharmacokinetic analysis in the study (n=41) had mean age 32.29±6.83 years, weight 65.05±9.61 kg, height 1.65±0.05 mts and BMI 23.74±3.06 kg/m^2.

Table 1: Mean pharmacokinetic parameters of pantoprazole.

Variables	Test drug (n=41)	Reference drug (n=41)
C_{max} (ng/ml)	3752.4±1084.6	3521.7±1099.5
AUC_{0-t} (ng.hr/ml)	12371.9±12311.7	11245.3±10368.0
AUC_{0-inf} (ng.hr/ml)	14797.1±17671.5	12282.1±12282.9
T_{max} (hrs)	1 (0.28)	2.3 (0.83)
Kel (hrs-1)	0.35±0.2	0.46±0.25
$T_{1/2}$ (hrs)	3.6±3.9	2.6±2.5
$AUC_{Extrapolated\%}$	8.2±7.7	5.5±3.9

Pharmacokinetic assessment

As shown in Table 1, all the pharmacokinetic parameters for test drugs were comparable to reference drug. C_{max} was achieved higher with test drug as compared to the reference drug [3752.4±1084.6 vs. 3521.7±1099.5 ng/ml] in less time [1 (0.28) vs. 2.3 (0.83) hrs] (Table 1) (Figure 1 and 2). Area under curve (AUC) was also higher for test drug as compared to reference drug (Table 1) (Figure 1 and 2). The ratios of geometric least square mean and its 90% confidence interval on the log transformed C_{max}, AUC_{0-t} and AUC_{0-inf} for pantoprazole fall within the acceptance criteria of 80% to 125%.

Safety assessment

Overall, both the formulations were safe and well tolerated by the participants under fasting condition.No adverse events and serious adverse events were observed during any of the study periods. There was no any significant change found in the laboratory values with single dose of both test and reference pantoprazole.

Table 2: Geometric means and 90% confidence interval for all the subjects' data of pantoprazole.

Variables	Geometric means*		% ratio	90% CI for log-transformed	
	Test group (n=41)	Reference group (n=41)	T/R	Lower limit	Upper limit
C_{max} (ng/ml)	3612.070	3384.010	106.74	100.06	113.87
AUC_{0-t} (ng.hr/ml)	8855.112	8365.376	105.85	98.26	114.03
AUC_{0-inf} (ng.hr/ml)	9691.159	8852.571	109.47	101.45	118.14

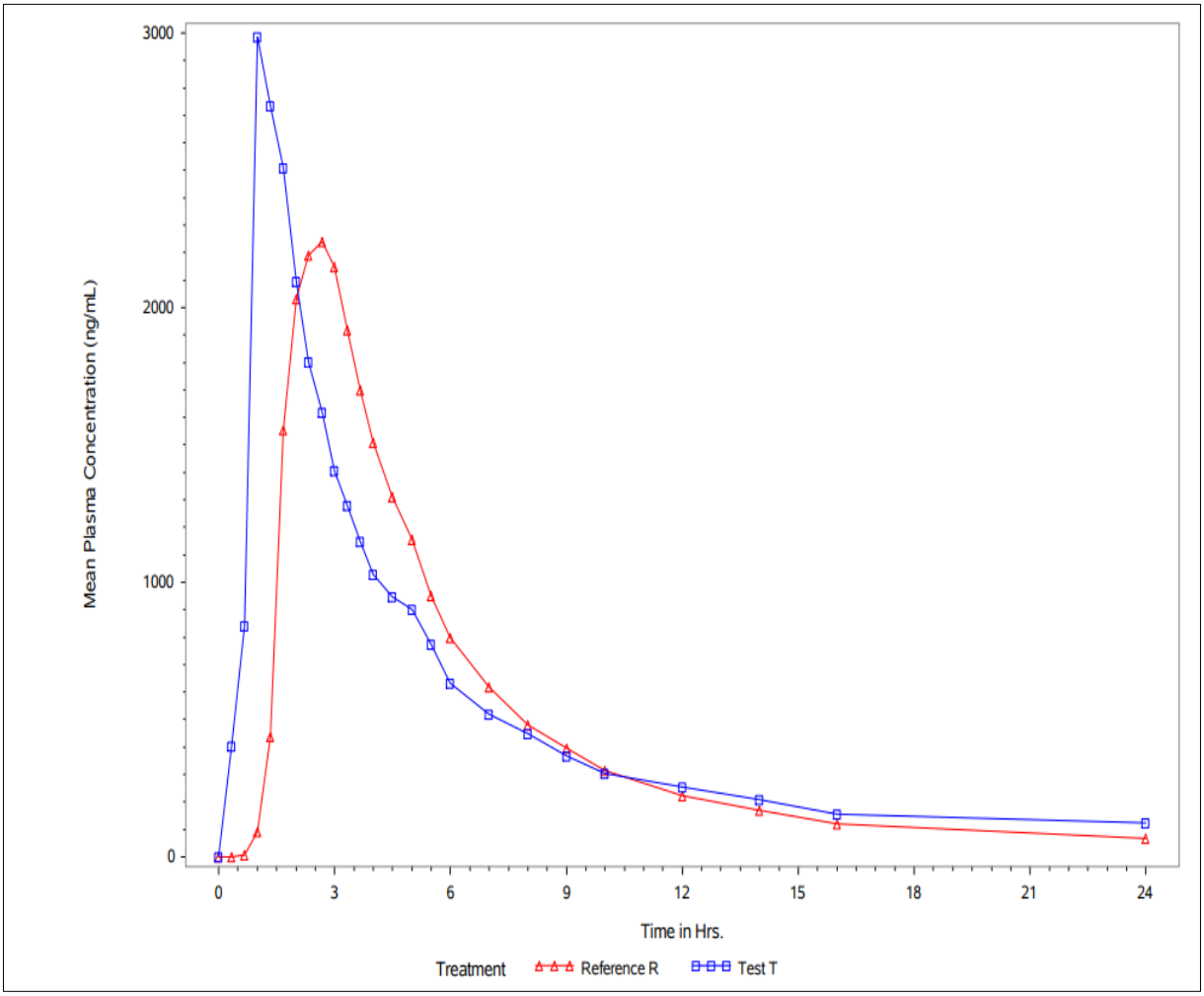

Figure 1: Mean plasma concentration versus time curve for reference (R) and test (T) product for pantoprazole (n=41).

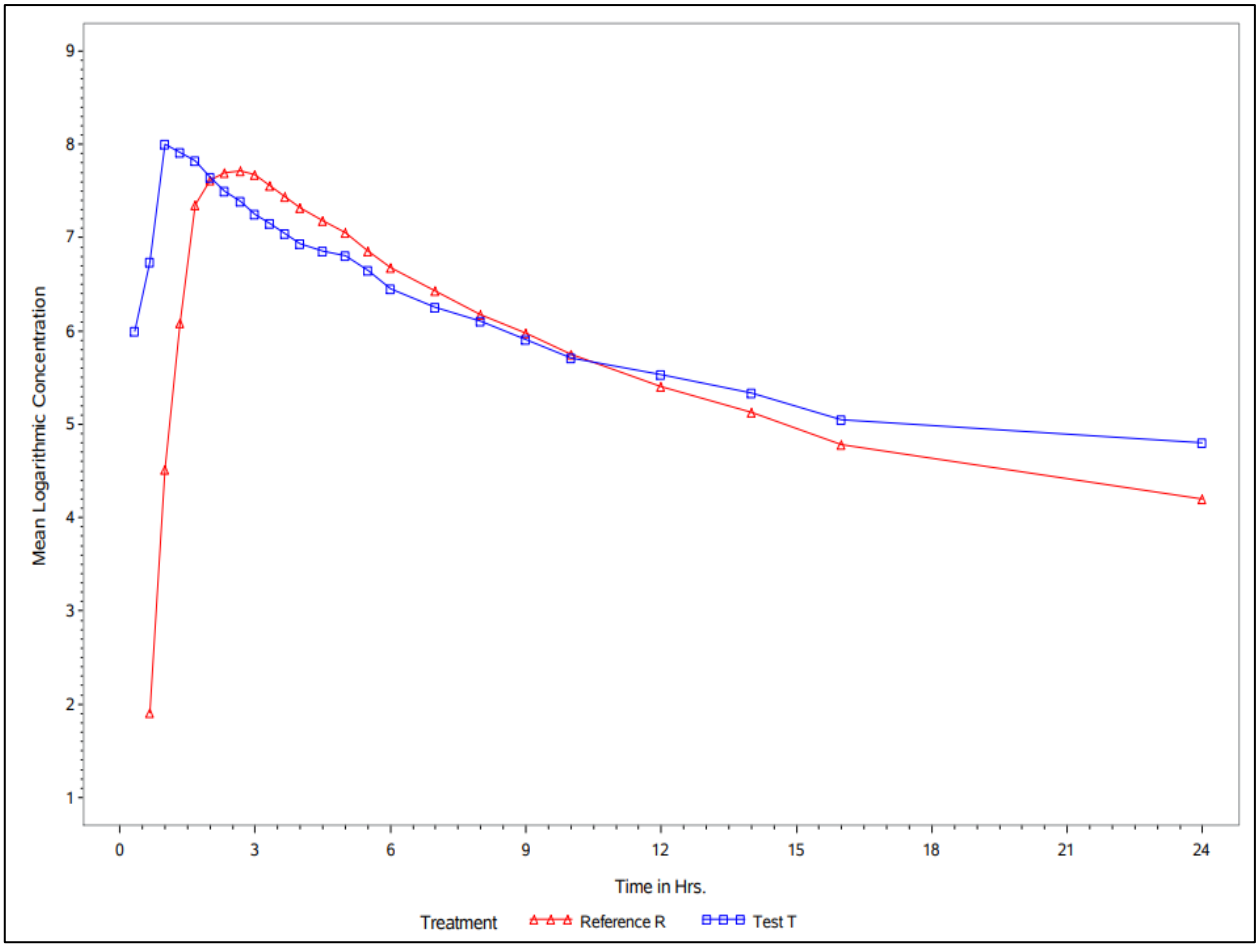

Figure 2: Log mean plasma concentration versus time curve for reference (R) and test (T) product for pantoprazole (n=41).

DISCUSSION

The present study showed bioequivalence of new test formulation, pantoprazole buffer powder 40 mg (sodium bicarbonate as buffer) as compared to reference pantoprazole 40 mg tablet as ratios of geometric least square mean and its 90% confidence interval on the log transformed C_{max}, AUC_{0-t} and AUC_{0-inf} for pantoprazole fall within the acceptance criteria of 80% to 125% (Table 2). The findings of the present study showed that pantoprazole was absorbed after oral administration with mean maximum plasma levels (C_{max}) of 3752.4 ng/ml and 3521.7 ng/ml at median time (T_{max}) of 1 hrs and 2.33 hrs for the test and reference formulations, respectively (Table 1) (Figure 1 and 2).

Thus, the buffered PPI formulation improved the pharmacokinetic properties (reduced T_{max}) of the PPI. The reduced T_{max} resulted in faster onset of action of pantoprazole-sodium bicarbonate powder for oral suspension as compared to pantoprazole enteric coated tablet. Moreover, being a powder for oral suspension, this new formulation will also have an ease of administration over enteric coated and buffered tablets in geriatric, uncooperative and critically ill patients.

Similar trend of improved pharmacokinetic properties has also been found with the US FDA approved omeprazole/sodium bicarbonate (Zegerid) when compared to conventional omeprazole (Prilosec) formulation.[13] In the comparative bioavailability study of Zegerid and Prilosec, C_{max}, AUC_t, and AUC_{inf} ratios for test to reference drug were found 220%, 117%, and 116%, respectively.[13] Thus, buffered PPI formulation improved the pharmacokinetic properties (reduced T_{max}, increased AUC) of the PPI. The reduced T_{max} along with the increased AUC is expected to result in faster onset of action of buffered PPI formulation as compared to conventional PPI formulation which is desirable for rapid and long pain relief, healing of ulcer and reduce gastro-esophageal reflux in critically ill patients of stroke and esophageal stricture. Faster and sustained effect of buffered PPI have been documented in various other studies. Esomeprazole/sodium bicarbonate can inhibit the secretion of gastric acid rapidly and continuously as compared to esomeprazole alone.[14] Once daily morning or bed time omeprazole/sodium bicarbonate was found effective in improving severe reflux esophagitis and GERD symptoms.[15] In another study by Gerson et al twice daily omeprazole/sodium bicarbonate showed nocturnal oesophageal reflux control in 100% of patients with

Barrett's oesophagus along with complete control of oesophageal pH during 97% of the 24-h recording periods.[16] Omeprazole-sodium bicarbonate was not found more effective than omeprazole in treatment of GERD however, it showed the more sustained relief and effect in systematic review by Higuera-de-la-Tijera.[17] Buffered omeprazole significantly caused gastric acid suppression with faster onset and duration as compared to delayed released lansoprazole in healthy volunteers.[18] In open-label, randomized, cross-over study conducted with patients of nocturnal GERD symptoms, buffered omeprazole was found superior in nocturnal acid control as compared to delayed release lansoprazole and comparable to esomeprazole.[19] Buffered omeprazole provided rapid control of nocturnal gastric pH and also reduced nocturnal acid breakthrough which is desirable effect for the patients of GERD.[19] In study by Banerjee et al oral buffered esomeprazole achieved intragastric pH of 6 within a minute of administration which was found superior to intravenous pantoprazole.[11] This can be very helpful in management of non-variceal bleed where sustained alkaline pH is desirable for better hemostasis. In present study, single dose pantoprazole/sodium bicarbonate powder for oral solution was well tolerated by study participants. Headache, dizziness, anxiety, constipation, flatulence, abdominal upset, nausea, vomiting are the various side effects reported with omeprazole/sodium bicarbonate and was comparable to conventional omeprazole formulation.[18,20] Further, various comparative clinical trials can provide more insight in regards to effectiveness and safety of buffered PPI formulations.

PPIs are available as either enteric coated tablet or sustained released capsules as a solid dosage form that can be difficult to administer pediatric, geriatric, uncooperative and critically ill-patients as crushing of tablet/capsule destroys the purpose of protecting PPI from degradation in gastric acidic medium. The test formulation is in powder form and with sodium-bicarbonate as a buffer. Sodium-bicarbonate provide immediate pain relief by increasing pH of stomach through acid neutralizing action and also protect pantoprazole from destruction in acidic pH. Being in powder form for oral solution it can overcome shortcomings of difficult administration to geriatric, uncooperative and critically ill-patients. Moreover, pharmacokinetic parameters derived in this study suggest fast and sustained effect may be obtained by administering the pantoprazole/sodium bicarbonate oral solution.

Limitation

This was a pharmacokinetic study and there were no clinical end points in the study. The inferences of this study about fast and sustained effect with pantoprazole/sodium bicarbonate oral solution are made from pharmacokinetic data. The hypothesis should be tested in larger clinical settings.

CONCLUSION

In conclusion, pantoprazole powder for oral suspension 40 mg (sodium bicarbonate as buffer) manufactured by Alkem Laboratories Ltd., India was well tolerated and bioequivalent with pantoprazole enteric coated tablets IP 40 mg in terms of rate and extent of absorption under fasting conditions. At same time, the shift in AUC to the left with reduction in T_{max} with the new formulation is suggestive of faster rate of absorption which can add value to initiate faster activity of inhibiting the proton pumps and thus acid suppression, along with an advantage of ease of administration across various patient population as being the powder formulation for oral suspension.

Funding: The study was funded by Alkem Laboratories Ltd., Mumbai
Conflict of interest: Second, third and fourth Authors work for Alkem Laboratories Ltd., Mumbai
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Prasad VGM, Chatterjee A, Vaddem R, Sharma AD. A unique formulation of sodium bicarbonate buffered pantoprazole powder for oral suspension: perspectives from an active controlled cross-over bioequivalence study. Int J Adv Med 2022;9:1031-8.