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PHARMACOKINETIC INTERACTION BETWEEN ANTACID AND COMMONLY PRESCRIBED MEDICATIONS - METFORMIN, DICLOFENAC, AMOXICILLIN

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ABSTRACT

Introduction: The self-prescribed use of antacids by ambulant patients may be ever increasing, because they are freely available over-the-counter and may commonly be taken along with various prescribed medications owing to the nature of comorbidities. It is important to understand their influence on pharmacokinetics of drugs. The influence may result in extreme clinical outcomes, ranging from treatment failure to toxicity. This study was, thus, conceived intending to study effect of antacids on pharmacokinetics of three commonly prescribed drugs. **Methods:** 18 consenting healthy human volunteers were recruited for study, 6 each to evaluate antacid's effect on Amoxicillin, Diclofenac, Metformin, as per random in each treatment period. Clinical confinement and blood sampling was done as per ethics committee approved protocol following good clinical practice principles. The plasma samples were analyzed using validated LC-MS/MS bioanalytical method to quantify Amoxicillin, Diclofenac and Metformin in line with good laboratory practice principles. Pharmacokinetic and statistical evaluation of the results was conducted using WinNonlin. **Results:** The results showed variation in all pharmacokinetic parameters. It was observed that C_{max} and AUC were reduced for all the three drugs when administered with antacid. The ANOVA results confirmed that bioavailability was incomparable, as the 90% CI for all three drugs did not fall within acceptable range of 80%-125%. **Conclusion:** It is observed that antacids influence pharmacokinetics of Amoxicillin, Diclofenac and Metformin by reducing their bioavailability. Further investigation is required to find clinical implications of these pharmacokinetic changes and to specifically understand influence of antacid on excipients used in drug products.

KEYWORDS: Pharmacokinetic, Antacid, Diclofenac, Amoxicillin, Metformin, Bioavailability.

INTRODUCTION

Antacids are weak bases, available tablet, chewable tablet, suspension and gel. They are salts of calcium, magnesium and aluminium in various compounds or combinations. Antacids are available as over-the-counter medications and are commonly used self-prescribed medications.[1] The effect of antacids on stomach is due to partial neutralisation of gastric hydrochloric acid and inhibition of the proteolytic enzyme, pepsin.[1] Generally, they are indicated for mild acid peptic or acid releated disease which is a spectrum of acid peptic diseases [1,2] However, use of antacid is controversial in management of non-ulcer dyspepsia or non-steroidal anti-inflammatory drug related upper gastrointestinal mucosal damage.[3]

The role of antacids has been drastically reduced over the years. But they continue to hold one of the top positions in the list of over-the-counter medications used for a number of years now. In India, ~24% of the total population indulge in self- medication with over-the-counter available anatcids.[4]

The rationale behind the increase in use of antacids could be contributed to increased prevalence of GERD worldwide and the disease burden may be increasing.

Among non-communicable diseases, Diabetes mellitus is a leading cause of death and disability worldwide.[5, 6] Type II diabetic patients have significantly higher risk of PUD.[7] Many complications of diabetic neuropathy are esophageal manifestations including abnormal peristalsis, spontaneous contractions, and impaired lower esophageal sphincter tone, all resulting in heartburn and dysphagia.[8, 9]

The most common anti-diabetic agent prescribed for treatment of diabetes mellitus type 2 is Metformin, as it remains the optimal drug for mono-therapy as reported by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

in 2012.[10, 11] Its low cost, proven safety record, weight neutrality, and possible benefits on cardiovascular outcomes have secured its place as the favored initial drug choice, also in India.[12, 13, 14] Moreover, frequently reported side effects of Metformin are abdominal pain, distension, flatulence, dyspepsia and heartburn.

NSAIDs are one among the most frequently prescribed drugs worldwide.[15, 16] Over-the-counter (OTC) NSAID use is also widespread.[17] The prevalence of upper GI symptoms in users of prescribed NSAIDs varies widely from 5% to 50%.[16, 18] NSAIDs are popularly prescribed for arthritis, a degenerative condition, and thus are given on a chronic basis. Thus, to prevent these adverse effects, antacids and other acid-suppressing agents are co-prescribed for such patients. And as studied by Paul and Chauhan [19] and Singh V in 2014, [20] Diclofenac is one of the most commonly prescribed monotherapy NSAID in India and also world-wide.[21, 22]

The treatment of H. pylori infection, one of major causes of chronic gastritis, utilizes combination drug therapy regimens [23] comprising of a proton pump inhibitor and two antibiotics (clarithromyin/tetracycline plus amoxcillin/metronidazole). It is estimated that approximately 50% of the world's population is infected.[24] The infected individuals tend to use antacids along with these drugs for acute relief of symptoms of gastritis. Thus, Amoxicillin, being a broad spectrum penicillin antibiotic and one of the ten most prescribed drugs [25] was chosen as one of the treatments for the study.

Antacid drug interactions are well known, but can be avoided by rescheduling medication administration times. However, multiple dosing times for different drugs can be inconvenient to the patients and discourage compliance.[1] All antacids can produce drug interactions by changing gastric pH, thus altering drug dissolution of dosage forms, reduction of gastric acid hydrolysis of drugs, or alter drug elimination by changing urinary ph. Most antacids, except sodium bicarbonate, which is given systemically, may decrease drug absorption by adsorption or chelation of other drugs.[1, 26] Antacids consisting of weak basic substances coupled with polyvalent cations may alter rate and/or extent of absorption of concomitantly administered drugs via different mechanisms.[27]

One may consider that drug-drug interactions (DDIs) associated with antacids is an obsolete topic because they are prescribed less frequently by medical professionals due to advent of drugs that more effectively suppress gastric acidity (i.e. H2RAs and PPIs). Nevertheless, antacid use by ambulant patients may be ever increasing, because they are freely available over-the-counter.[27]

Though the health care personnel educate and encourage the patients on prevention of complications and strive to reduce the adverse effects of various drugs, the individuals indulge in self-medication with OTC drugs owing to lack of knowledge regarding the possibilities of drug-drug interactions and in search for acute symptomatic relief.

In India, many drugs are available as OTC due to lack of stringent regulatory measures for drug dispensing.

Such antacid drugs may commonly be taken along with various prescribed medications owing to the nature of comorbidities and it is important to understand their influence in pharmacokinetics of such drugs. The influence on pharmacokinetics of a drug can have extreme clinical outcomes, ranging from treatment failure to toxicity.

This study was thus conceived with an intention to obtain information on the effect of antacids on the pharmacokinetics of a few commonly prescribed drugs.

AIMS AND OBJECTIVES

Primarily, to investigate the impact of antacid on the pharmacokinetic parameters of commonly prescribed medications, Amoxicillin, Diclofenac and Metformin, in adult male population following oral administration under fasting conditions. Secondarily**,** to ensure safety and well being of the study participants during the course of the study.

SUBJECTS AND METHODS

The study was reviewed and approved by Institutional Human Ethics Committee of Chettinad Hospital and Research Institute on 12-MAY-2015.

The study was conducted as per ICMR Ethical Guidelines for Biomedical Research on Human Subjects (2006), ICH GCP, Schedule Y CDSCO, 'Good Clinical Practices for Clinical Research in India' Guidelines and Declaration of Helsinki in Azidus Laboratories Ltd.

The study was as an open label, three treatment, two period, three sequence, single dose, cross over, oral pharmacokinetic study in 18 healthy male subjects under fasting conditions. Wash out was 3 days between periods.

Pharmacokinetic interaction was determined by statistical comparison of log-transformed data of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for the test and reference products.

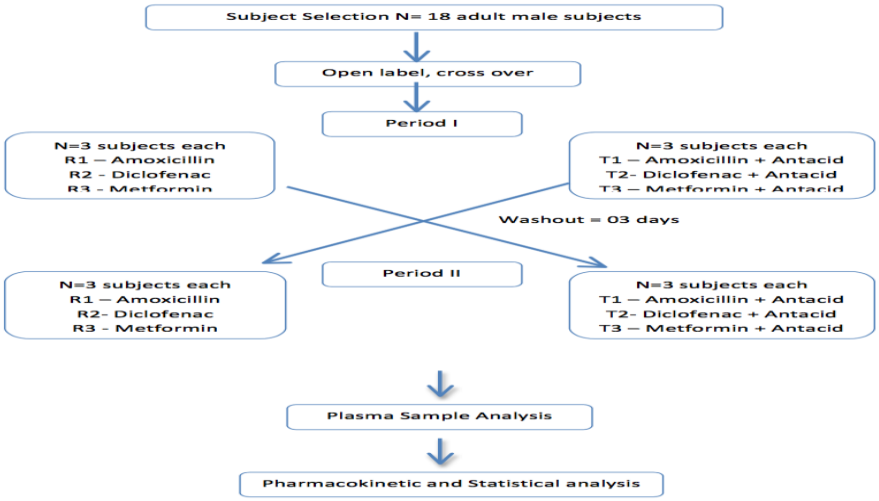

Figure I: Study design

Written informed consent was obtained from each volunteer prior to screening and enrollment in study. Subjects were given ample amount of time to read the ICFs and presentation about the study was made by investigator to resolve any queries.

All subjects underwent a screening procedure prior to the study - demography, medical history, systemic examination, vitals measurement, lab investigations - ECG, hematological, biochemical, serological & urinary analysis. Further, subjects were selected on basis of following inclusion and exclusion criteria.

Inclusion criteria: Volunteers meeting all of the following criteria were considered for enrollment in study

- Healthy male volunteers of 20 to 45 years (both the years inclusive)
- Willing to give informed written consent and comply with study requirements.
- Able to communicate effectively
- BMI 18.50 – 24.99 Kg/m^2 and body weight > 50 kg
- Vital parameters: BP of 100 – 139 mmHg systolic; 60 – 89 mmHg diastolic. PR within 60 – 100 / min. Oral temperature 97.8˚ F to 99.0˚ F. Respiratory rate 14-18/min.
- Normal bio-chemical, hematological and urinary parameters, Chest X-ray and 12 lead ECG
- Negative for HIV 1 & 2, Hepatitis B, Hepatitis C, and Syphilis tests, alcohol breath analysis

Exclusion criteria: Subjects meeting this any of these criteria were not considered for the study

- Any major surgical procedure in past 3 months
- Clinical history suggestive of cardiac, gastrointestinal, respiratory, hepatic, renal, endocrine, neurological, metabolic, psychiatric, hematological systems or glaucoma judged to be clinically significant
- Chronic alcoholism, smoking > 9 cigarettes / beedies per day and / or inability to withhold smoking / consumption of tobacco containing products during study.
- Any drug abuse in past 12 months, habituation to coffee, tea or other xanthine containing products and inability to withhold the intake during the in-house stay
- Hypersensitivity to study drugs / related drugs / excipients, allergy to food substances
- Intake of drugs within 7 days prior to study and / or intake of any drug in the past which potentially modify kinetics / dynamics of Amoxicillin/ Diclofenac / Metformin/ Antacid or any other medication judged to be clinically significant by the investigator
- Subject who had participated in any other clinical study/ donated blood during the last 3 months

Withdrawal of Subjects: The following criteria were followed as withdrawal criteria for subjects

- Subject withdraws consent
- Development of intolerable adverse event due to study participation
- Subjects who experience emesis at any time during the study and/or significant diarrhea.
- Development of inter-current illness or condition requiring concomitant medications that interfere with kinetics of study medication
- Discovery that subject entered study in violation of the protocol or occurrence of a significant protocol violation during the study
- The investigator feels that in the best interest of the subject's health, the subject is to be withdrawn from trial
- Data not known before starting trial become available and raise concern about the safety of the study drug so that continuation would pose potential risk to any particular subject
- If the subject is non-cooperative and / or un-disciplined

The eligible subjects, who fulfilled inclusion and not exclusion criteria for the study, were enrolled and randomly assigned to one of the possible sequences of test (T) and reference product (R).

Disposition of Subjects

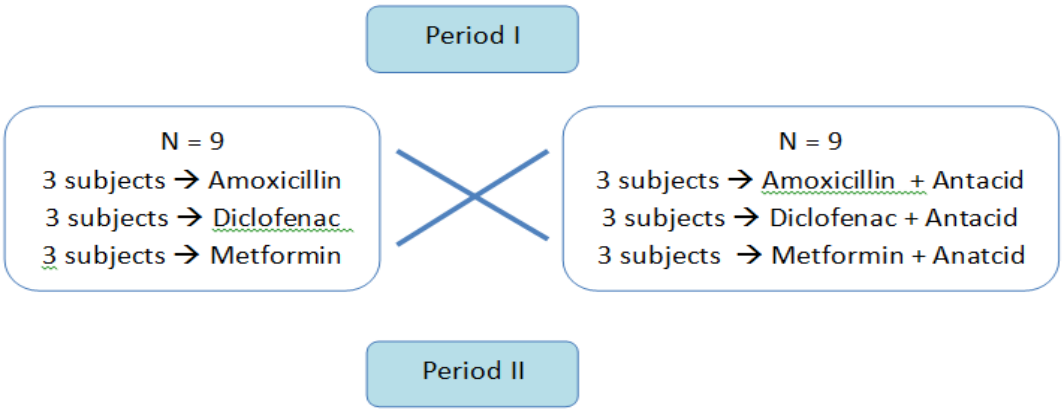

Figure II: Randomization of subjects

Table I: Formulations

Reference	Test
Amoxicillin (R1) Novamox 500 mg	Amoxicillin + Antacid (T1)
Diclofenac (R2) Voveron 100 mg XR	Diclofenac + Antacid (T2)
Metformin (R3) Gliciphage 500 mg XR	Metformin + Antacid (T3)

Antacid – Happicid 15 mL (Aluminium hydroxide 600 mg, Magnesium hydroxide 300 mg, Simethicone 25 mg, Oxetacaine 10 mg)

All the selected subjects were housed in the clinical facility minimum 12 hours prior to drug administration and until 24.00 hours post dose in each period. After check-in, subjects received standard dinner after which they were required to fast overnight for at least 10 hours. They received standard food at 04.00, 08.00, 12.00 hrs post-dose. Drinking water was not permitted 1 hour before and after dosing, at all other times drinking water was permitted ad libitum. Subjects were not provided any other xanthine containing food or drinks and carbonated drinks during stay. They were instructed not to consume juice / food containing citrus fruits during study.

A single oral dose of investigational drug was administered to subjects with 240 mL of water at ambient temperature in sitting posture at fixed time points followed by mouth check to assess the compliance. Subjects were dosed sequentially at fixed time intervals. Antacid was administered 15 mins prior to dosing. Subjects had to be seated for 4 hrs after dosing. No exercise or strenuous physical activities were permitted.

21 blood samples of 2mL each were collected at 00.00 hour (pre-dose), 00.25, 00.50, 00.75, 01.00, 01.25, 01.50, 01.75, 02.00, 02.25, 02.50, 02.75, 03.00, 03.50, 04.00, 05.00, 06.00, 08.00, 12.00, 20.00 and 24.00 hrs post dose in-house through indwelling cannula using pre-labeled K_3EDTA vacutainers. Pre-dose samples were collected within 1 hour prior to drug dosing and post-dose samples within 2 minutes of scheduled times. Vacutainers were placed in ice bath till centrifugion at 4000 rpm for 10 minutes at 4°C. Plasma samples were separated into two aliquots and stored at -70°C till analysis. The total volume of blood draw from each subject was 121 mL.

Subjects were monitored and wellbeing was investigated by physical examination and vital signs measurements were done before check-in, check out of each period, and at 00.00, 02.00, 04.00, 12.00, 24.00 hours.

There were no events of adverse effects or deviations in the study.

Bio-analytical Methodology

Estimation of Amoxicillin, Diclofenac and Metformin in plasma was done using validated Liquid chromatography – Mass spectometry (LC- MS/MS) bioanalytical method.

Method validation includes the following parameters

- Specificity – Specificity was performed on at least six independent sources of same matrix.

- Sensitivity – Sensitivity was performed at LLOQ concentration.

- Precision and Accuracy- Three precision and accuracy batches were checked. The between batch precision for low, medium and high QC samples should be ≤ 15%, whereas for LLOQQC ≤20%. Between batch mean accuracy should be within ±15% of nominal value at

low, medium and high QC concentrations, whereas for LLOQQC it should be ±20%.

• Stability – Freeze-thaw, bench top, in-injector, long term stability and stock solution stability were performed.

• Recovery – For analyte and internal standard from biological matrix
• Dilution Integrity

The plasma samples were transferred to bio-analytical facility where they were stored at below -70 ± 15°C.

Table II: Quantification limits

Analyte	LLOQ (ng/mL)	ULOQ (ng/mL)
Amoxicillin	0.484	30.502
Diclofenac	5.283	5153.458
Metformin	25.597	4702.480

The analytes were selectively isolated from 100 µL Plasma by Liquid–Liquid extraction and estimation was done by MS detection on Symmetry C18 (4.6 x 50mm) 5µm column.

A batch consisted of aqueous MQC, Reconstitution Solution, K3EDTA human blank plasma (standard blank), K3EDTA human Blank plasma containing IS (standard zero), calibration curve standards, two sets of Quality control samples at LQC, MMQC, MQC and HQC interspersed among subject samples. All samples originating from a subject were analysed in same batch.

Pharmacokinetic and Statistical analysis

Samples from all 18 subjects were analyzed. Pharmacokinetic parameters were calculated using WinNonlin® (v5.3). The mean, standard deviation, geometric mean, coefficient of variation (CV%), minimum, median, maximum and range were calculated.

Statistical Analysis

Analysis of variance (ANOVA) was performed on Ln-transformed data of Cmax, AUC0-t and AUC0-∞ using GLM procedure of SAS® (v9.2). The sequence effect was tested at 0.10 level of significance and other effects at 0.05 level of significance using the subjects nested within sequence mean square from ANOVA as error term. Based on comparisons of test and reference products for Ln-transformed Cmax, AUC0-t and AUC0-∞ data, the ratio of least square mean and 90% confidence intervals were calculated.

RESULTS

The Ln- transformed data of Cmax, AUC0-t and AUC0-∞ was analyzed using GLM procedure of SAS® (v9.2) for each of Test treatments comparing it to the respective Reference treatments. The statistical output results are described below;

Results of (Amoxicillin + Antacid) T1 *vs.* Amoxicillin R1

Table III: 90 % Confidence Interval Output - PK of Amoxicillin administered with Antacid (T1) compared with Amoxicillin PK (R1)

Dependent	Ratio [%Ref]	CI_90_Lower	CI_90_Upper	ISCV
Ln (Cmax)	78.25	73.67	83.11	0.049
Ln (AUClast)	82.68	73.99	92.38	0.090
Ln (AUCINF_obs)	83.2	73.91	93.67	0.096

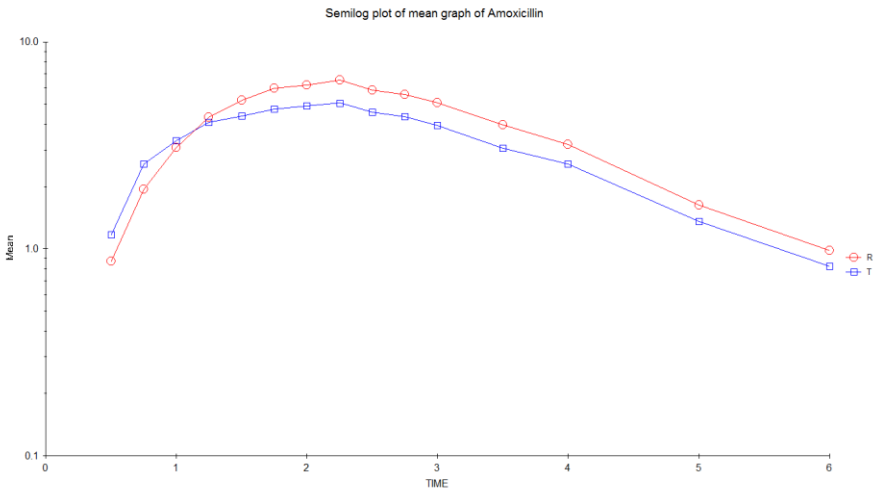

Figure III: Mean semilog plot comparing PK of Amoxicillin administered with Antacid (T1) with Amoxicillin PK (R1)

Results of (Diclofenac SR + Antacid) T2 *vs* Diclofenac SR R2

Table IV: 90 % Confidence Interval Output - PK of Diclofenac administered with Antacid (T2) compared with Diclofenac PK (R2)

Dependent	Ratio [%Ref]	CI_90_Lower	CI_90_Upper	ISCV
Ln (Cmax)	73.63	59.72	90.79	0.17
Ln (AUClast)	69.41	51.12	94.24	0.25
Ln (AUCINF_obs)	70.93	50.99	98.66	0.27

Figure IV: Mean semilog plot comparing PK of Diclofenac administered with Antacid (T2) with Diclofenac PK (R2)

Results of (Metformin XR + Antacid) T3 vs. Metformin XR R3

Table V: 90 % Confidence interval output - PK of Metformin administered with Antacid (T3) compared with Metformin PK (R3):

Dependent	Ratio [%Ref]	CI_90_Lower	CI_90_Upper	ISCV
Ln (Cmax)	76.90	56.70	104.31	0.25
Ln (AUClast)	81.96	50.47	133.08	0.41
Ln (AUCINF_obs)	88.92	53.35	148.19	0.43

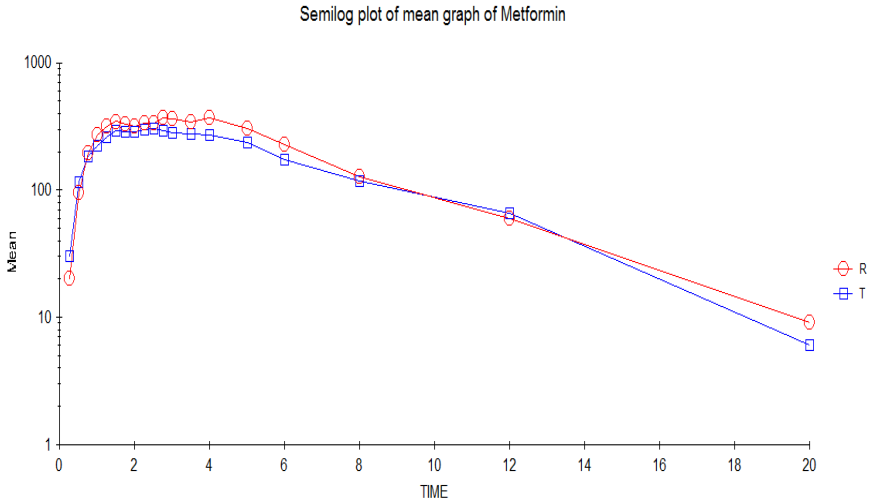

Figure V: Mean Semilog plot comparing PK of Metformin administered with Antacid (T3) with Metformin PK (R3)

DISCUSSION

Pharmacokinetics Parameters

Antacids can affect drug absorption and all pharmacokinetic parameters by changes in pH, gastric emptying and also by chelation which maybe specific to each drug.[28]

Based on the results obtained, it is clearly observed that there are significant variations in all pharmacokinetic parameters when a drug is administered with an antacid.

All test groups, which were administered antacid with respective drug (Amoxicillin, Diclofenac and Metformin) show a decrease in bioavailability, indicated by decreased Cmax and AUC ratios.

The 90% CI output comparing the effect of antacid administration on PK of Amoxicillin, Diclofenac and Metformin also indicate a decrease in bioavailabilty, reflected in all the compared parameters outside the recommended limits of 80%-125 % for bioequivalence.

Significant changes are observed in the pharmacokinetic parameters of all the three drugs upon administration of an antacid. Owing to the variations observed, within subject variability also does not correlate with literature reported values for the respective drugs. The bioavailability of the same drug within the same set of subjects (cross over design) was not comparable when administered with an antacid.

Antacids and Decrease in Drug Bioavailability

Various mechanisms have been postulated for antacids decreasing bioavailability of drugs absorbed from gastrointestinal tract, which include transient elevation of gastrointestinal pH, alteration of gastric transit time including reduced gastric emptying time, opportunity for intra-luminal binding and/or chelation of the drug. In particular, antacid effects may be further compounded if a drug shows certain other attributes such as sparse solubility, poor permeability, instability at alkaline pH conditions and existing in a high state of ionization.[29]

The interaction of antacids with several NSAIDs, including diclofenac, ibuprofen and ketoprofen have been studied [30] and reported that absorption can be specifically affected, where magnesium hydroxide could possibly increase absorption of NSAIDs and aluminium hydroxide could reduce absorption in contrast. However, there is limited information on effect of such antacid preparations in modified release NSAIDs. Researchers have reported increased absorption of ibuprofen and other NSAIDs in presence of magnesium hydroxide antacids, and that aluminum hydroxide in antacids could possibly retard absorption due to chelation.[30] In this study, Diclofenac sustained release demonstrates decreased bioavailability in presence of antacid preparation. This may be due to the fact that antacids increase gastric pH, which in turn may reduce absorption of diclofenac, an acidic drug. Also, this is in agreement with previous findings that antacids can increase urine pH and thereby cause increased elimination of acidic drugs by ionization.[31] The decreased absorption and increased elimination of diclofenac could possibly be a contributing factor for the decreased bioavailability when administered with antacid. The chelation of diclofenac by aluminium ions in addition could in turn decrease absorption of antacid and thus, the bioavailability of diclofenac, which is observed.

Similarly, it is observed that bioavailability of amoxicillin and metformin have also been decreased in the respective test groups, which maybe due to contrasting mechanism of antacids that can reduce absorption of drugs as described above. This is in alignment with findings reported by Depperman et al., that decrease in bioavailability of amoxicillin when administered with antacids due to possible chelation.[32] Limited information is available on in vivo interaction of antacids with metformin. In vitro research suggests that absorption of metformin could be reduced due to adsorption with magnesium and calcium salts.[33] In vivo data obtained from the current study suggests similar influence of antacid on absorption, which is possibly reflected as a decrease in bioavailability.

The influence of simethicone and oxetacaine on pharmacokinetic parameters of drugs administered is also not well reported in available literature. It is possible that the local surfactant action of simethicone could influence absorption of these drugs.

The interaction of antacids with excipients in the studied drug products and possible influence of the same on absorption of drugs are unclear.

Safety Evaluation

Safety was evaluated throughout the study and there was no adverse event(s) reported during the study. Hence, it can be concluded that both test and reference products when given together are safe and well tolerated at the selected dose level. Post study assessment was performed for subjects as per protocol and there were no significant deviations observed. The administration of antacid with Amoxicillin, Diclofenac and Metformin does not seem to influence the safety profile of the respective drugs.

CONCLUSION

The present study has only evaluated the influence of antacids on the pharmacokinetics of Amoxicillin, Diclofenac and Metformin drug products. It does not clearly demonstrate if antacids affect the pharmacokinetics of the active drug directly or the excipeints in the drug product.

The study demonstrates the decrease in bioavailability of all three drugs when administered with antacids, and further investigation is required to evaluate the effect of

reduced bioavailablity on clinical treatment in a larger population.

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REFERENCES

1. Maton P, Burton M. Antacids Revisited. Drugs. 1999; 57(6): 855-870.
2. Mejia A, Kraft W. Acid peptic diseases: pharmacological approach to treatment. Expert Review of Clinical Pharmacology. 2009; 2(3): 295-314.
3. Ching C, Lam S. Antacids. Drugs. 1994; 47(2): 305-317.
4. An analysis of wrong practices among pharmacies and pharmacists in India. Health and Medicine. 2015
5. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012; 380(9859): 2095-2128.
6. Murray C, Vos T, Lozano R, Naghavi M, Flaxman A, Michaud C et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012; 380(9859): 2197-2223.
7. Peng Y, Leu H, Luo J, Huang C, Hou M, Lin H et al. Diabetes is an independent risk factor for peptic ulcer bleeding: A nationwide population- based cohort study. J Gastroenterol Hepatol. 2013; 28(8): 1295-1299.
8. Rayner C, Samsom M, Jones K, Horowitz M. Relationships of Upper Gastrointestinal Motor and Sensory Function With Glycemic Control. Diabetes Care. 2001; 24(2): 371-381.
9. Ebert E. Gastrointestinal Complications of Diabetes Mellitus. Disease-a- Month. 2005; 51(12):620-663.
10. Inzucchi S, Bergenstal R, Buse J, Diamant M, Ferrannini E, Nauck M et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach: Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012; 35(6): 1364-1379.
11. Inzucchi S, Bergenstal R, Buse J, Diamant M, Ferrannini E, Nauck M et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012; 55(6): 1577-1596.
12. Agarwal A, Jadhav P, Deshmukh Y. Prescribing pattern and efficacy of anti- diabetic drugs in maintaining optimal glycemic levels in diabetic patients. J Basic Clin Pharma. 2014; 5(3): 79.
13. Churi S, Ravi Kumar Y, Abdi S. Study of drug utilization pattern of antihyperglycemic agents in a South Indian tertiary care teaching hospital. Indian Journal of Pharmacology. 2012; 44(2): 210.
14. Kamrai D, Sachdeva P. 19. Prescribing Trends Of Antidiabetics In Diabetic Patients And Hypertensive Diabetic Patients In An Urban Secondary Care Hospital. International Journal of Pharmaceutical & Biological Archives. 2010; 1(2): 249-55.
15. Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high- risk patient. Gastroenterology. 2001; 120(3): 594-606.
16. Singh G. Gastrointestinal Complications of Prescription and Over-the-Counter Nonsteroidal Anti-inflammatory Drugs. American Journal of Therapeutics. 2000;7(2):115-122.
17. Motola D, Vaccheri A, Silvani M, Poluzzi E, Bottoni A, De Ponti F et al. Pattern of NSAID use in the Italian general population: a questionnaire-based survey. European Journal of Clinical Pharmacology. 2004; 60(10): 731-738.
18. Drug Topics. 2010 Top 200 generic drugs by total prescriptions [Internet]. 2011. Available from: http://drugtopics.modernmedicine.com/drug-topics/news/modernmedicine/modern-medicine-news/2010-top-200-generic- drugs-total-prescriptions?page=full

19. Study of usage pattern of nonsteroidal anti-inflammatory drugs (NSAIDs) among different practice categories in Indian clinical setting. Eur J Clin Pharmacol. 2005; 60(12): 889-92.
20. CURRENT TRENDS OF PRESCRIBING PATTERNS OF NSAIDS IN AN ORTHOPAEDIC OPD IN A TEACHING HOSPITAL. Int J Pharm Bio Sci. 2014; April 5(2): 486-91.
21. McGettigan P, Henry D. Use of Non-Steroidal Anti-Inflammatory Drugs That Elevate Cardiovascular Risk: An Examination of Sales and Essential Medicines Lists in Low-, Middle-, and High-Income Countries. PLoS Med. 2013; 10(2): e1001388.
22. Conaghan P. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. Rheumatol Int. 2011; 32(6): 1491-1502.
23. Chey W, Wong B. American College of Gastroenterology Guideline on the Management of Helicobacter pylori Infection. The American Journal of Gastroenterology. 2007; 102(8): 1808-1825.
24. Brown L. Helicobacter Pylori: Epidemiology and Routes of Transmission. Epidemiologic Reviews. 2000; 22(2): 283-297.
25. DeNoon D. The 10 Most Prescribed Drugs [Internet]. WebMD. 2015 [cited 20 October 2015]. Available from: http://www.webmd.com/news/20110420/the-10-most-prescribed-drugs
26. Sadowski D. Drug Interactions with Antacids. Drug Safety. 1994; 11(6): 395- 407.
27. Clinically significant drug interactions with antacids: an update. Drugs. 2011; 71(14): 1839-64.
28. Romankiewicz JA. Effects of antacids on gastrointestinal absorption of drugs. 1976 Sep; 3(3): 537-50.
29. Srinivas N. Antacid Use and Reduced Bioavailability of Oral Drugs. Arzneimittelforschung. 2009; 59(07): 327-334.
30. Neuvonen P. The effect of magnesium hydroxide on the oral absorption of ibuprofen, ketoprofen and diclofenac. British Journal of Clinical Pharmacology. 1991; 31(3): 263-266.
31. Hurwitz A. Antacid Therapy and Drug Kinetics1. Clinical Pharmacokinetics. 1977; 2(4): 269-280
32. Deppermann K, Lode H, Hoffken G, Tschink G, Kalz C, Koeppe P. Influence of ranitidine, pirenzepine, and aluminum magnesium hydroxide on the bioavailability of various antibiotics, including amoxicillin, cephalexin, doxycycline, and amoxicillin-clavulanic acid. Antimicrobial Agents and Chemotherapy. 1989; 33(11): 1901-1907.
33. Khalil S, Naggar V, Zaghloul I, Ismail A. In vitro anticoagulant-antacid interactions. International Journal of Pharmaceutics. 1984; 19(3): 307-321.