International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Research Article **CODEN: IJPNL6**

PHARMACOKINETIC EVALUATION OF AMOXICILLIN ALONE AND SIMULTANEOUS ADMINISTRATION OF ANTACID

Anab Fatima[1], Syed Baqir Naqvi[1], Iyad Naeem Mohammed[2], Shaheen Perveen[3], Iqbal Nasiri[1] and Sheikh Abdul Khaliq[1]

[1]Faculty of Pharmacy, Hamdard University, Karachi, Pakistan
[2]Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, Karachi, Pakistan
[3]Department of Pharmaceutics, Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan

***Corresponding author e-mail:** anabfatima@gmail.com

ABSTRACT

Various antibiotics whenever given orally along with antacid show significant pharmacokinetic interactions. During the present single dose, cross over, randomized study pharmacokinetic interaction between oral combination of amino penicillin i.e. 250 mg amoxicillin with an antacid(10 ml) containing aluminium, magnesium hydroxide and simethicone were evaluated. The study was conducted on ten healthy male volunteers. The study was performed on Pakistani population and data obtained was used to compare pharmacokinetic parameters of amoxicillin alone and with simultaneous administration of antacid in an open one compartmental model. Initially Physico-chemical test were performed for amoxicillin to check the quality of product. Plasma concentrations of amoxicillin were determined by validated high performance liquid chromatography techniques and pharmacokinetic parameters were estimated for both treatments. The analysis showed significant difference($P < 0.05$,SPSS 16.0) when amoxicillin used along with antacid in various pharmacokinetic parameters. The values of mean Cmax of amoxicillin alone and with antacid found to be 8.88±0.09 and 7.84 ± 0.06 µg/ml at Tmax of 2 ±0.00 hrs and 3 ± 0.00 hrs with the values of AUC0-t(AUClast) and AUC 0-∞ were 33.33±0.70 and 37.89±0.70 alone and 36.25±0.43 and 41.64±1.15mg/ml.hr with antacid. Likewise significant difference in other pharmacokinetic parameters was observed between treatment groups (the values of Clearance(CL),Vd, absorption, distribution and elimination rate constants, MRT and AUMC).No serious adverse event observed during study period. The study demonstrated that oral absorption of amoxicillin may be affected by the presence of antacid therefore it must be recommended to avoid the combination of amoxicillin and antacid or to make a dose adjustment or close monitoring of patients.

Keywords: Pharmacokinetics, Antibiotics, Interactions, Antacid

INTRODUCTION

It can be said that with the advent of newly approved drugs our therapeutic armamentarium has been inflated but it also increase the potential for drug-drug interactions.These interactions could lead to a change in pharmacokinetic of drugs which can cause secondary amendment in pharmaco-dynamic of drugs. These drug-drug interactions depends on those factors which are related to drugs (like dosage of antibiotic, base line concentration of interacting drugs and its therapeutic index),patient (inter-individual variance) and administration(scheduling of other drug, duration of therapy with antibiotic). An inter-individual variability in the extent of metabolism resulting in a major alteration in the rate of elimination and plasma concentration time profile ultimately develop severe drug-drug interaction in some individuals [7] . It was estimated that incidences of adverse drug reactions(ADRs) increase and sometimes deaths are caused due to clinically significant drug interactions. One of the important

factor is that most of the enzymes involve in the metabolism of drugs are polymorphic i.e. they have more than one variants of genes although CYT isozymes have similar characteristics but due to polymorphism there will be variation in metabolism of drugs from population to population in efficacy, toxicity or side effects of different interacting drugs. These interactions generating so many problems in the current therapy. Various retrospective studies showed reduced bioavailability of flouroquinolones antibiotics by antacid [5,12] .The study conducted on doxycycline (teteracycline group antibiotics) revealed reduced G.I absorption of doxycycline (P less than 0.01) by antacid [2]. Amoxicillin is an oral product consisted of semisynthetic aminopenicillin and become analog of ampicillin derived from basic penicillin nucleus, 6-aminopenicillanic acid. Amoxicillin structurally be represented as:

Amoxicillin is a broad spectrum antibiotic and its bactericidal activity covered a broad range of Gram-positive and Gram-negative aerobic and anaerobic pathogens particularly against urinary and respiratory pathogens [1,3,11] .Mainly amoxicillin given orally to elderly outpatients.The oral absorption of antibiotic may be reduced by co-administration of antacid(containing polyvalent cations) with antibiotics and due to possibility of toxicity and altered efficacy,the prediction of such drug interactions are of clinical interest in drug therapy. Therefore the objective of the present study is to evaluate the effects of aluminum-magnesium-simithicone containing antacid on 250 mg amoxicillin administered as single dose to healthy Pakistani volunteers.

MATERIALS AND METHODS

Study design: The study was two treatment, two sequence, two way, single center, single dose, open label, randomized, cross over study. An equal number of volunteers were assigned to each sequence and become randomized to receive one of two treatment i.e.250 mg amoxicillin alone or 250 mg amoxicillin 10 minutes after administration of antacid. Both amoxicillin administrations were separated by a washout period of two weeks. The subjects were healthy males having normal physical evaluation(12-lead ECG and vital sign) age between 21-30yrs and laboratory evaluation(b/d hematology and chemistry),become non-smoker, capable of consent and able to swallow amoxicillin. All measurements carried out at Clinical laboratory of Imam hospital, Karachi. Pakistan. No any other medication except medication to treat adverse effect was allowed. One of the important exclusion criteria was a history of duodenal or stomach ulcer. The study design was approved by the National Bioethics Committee , Ministry of Health, Government of Pakistan.Islamabad after critical ethical review and a written informed consent duly signed by volunteers has been taken prior to study.

Drug administration: A single dose of amoxicillin (250 mg: Glaxo-smithkline.Pak) administered alone or simultaneously with antacid Mylanta which was supplied by Macter International Ltd. Karachi. Pakistan. It was administered as 10 ml suspension containing 400 mg aluminum hydroxide, 400 mg magnesium hydroxide and 30 mg simethicone.

During hospitalization any type of beverages, tea, coffee and chocolate were not allowed to volunteers 48 hours prior to study until last sample has been taken. Moreover volunteers were allowed to take food ten hours before during each of two trial period. For all volunteers in both trial periods the dietary regimen was kept similar.

The oral drug was administered in the morning after fasting period of 10 hours with 100 ml of mineral water. After one hour of administration first water intake and after two hour first food intake was allowed to volunteers. Adverse events were monitored through out study.

In the morning of each study period cannula was inserted into the subject forearm and remained there till the last sample drawn. A blood sample of 7-10 ml was drawn into EDTA-coated glass tubes at sampling schedule of 0,0.5hr,1hr,1.5hr,2hr,3hr,4hr,6hr and 8hours.The vital signs(b.p, pulse rate),physical examination and other clinical laboratory tests were carried out after washout phase and within seven days after last treatment period.

Analysis of plasma samples: After modification and validation a high performance liquid chromatography method was used for determination of amoxicillin in plasma. As Antacids not expected to be absorbed systemically and are locally acting agents therefore the plasma concentration of Mylanta was not determined [4] .The analysis of samples carried out in research laboratory of Department of Pharmaceutics. University of Karachi, Pakistan. The chromatographic condition consisted of HPLC isocratic pump with UV-VIS detector attached with RP 18e column (Hibar, 250 x 4.6cm) with mobile phase containing methanol(10 volume) and 0.02 M disodium hydrogen phosphate buffer(90 volume).The pH was adjusted to 3.0 by phosphoric acid. .The detector response was measured at 235nm and the calibration plots(concentration versus peak area) were obtained using the linear regression method. The linearity data showed linearity over a concentration range of 0.015-31.25 microgram/ml for amoxicillin. Repeatable and intermediate precision of method was determined and statistacical

parameters i.e. Mean, SDEV, RSD% and % DEV were also find out for amoxicillin. LLOQ and LOD were determined by injecting three samples of eleven dilutions for Amoxicillin i.e. 3.9, 1.95, 0.97, 0.48,0.24, 0.121, 0.06,0.03,0.015,0.0075,0.0037 µg/ml.

Pharmacokinetic analysis: The following pharmacokinetic parameters were determined using one compartmental model. The Cmax(maximum plasma concentration),Tmax(time to reach maximum plasma concentration),$AUC_{0-\alpha}$(area under the curve), t½(apparent terminal half life) and Vd(volume of distribution).The software Kinetica™ Ver 4.4.1.(Thermoelectron Corporation.USA) used to determine all parameters including both compartmental and non-compartmental analysis.

Statistical analysis: All pharmacokinetic parameters between two treatment groups(single dose versus combined administration) were statistically compared by analysis of variance. The independent t-test also applied for Cmax and AUC were analyzed by use of bio-equivalence criteria. The data analysis has been carried out for both non-transformed and logrithmly transformed form and P values <0.05 were considered significant. All statistical analysis such as one way ANOVA for all pharmacokinetic data and unpaired t-test for Cmax was performed by SPSS software (ver:16.0)

RESULTS

In this study ten healthy male subjects were enrolled. The subject had an average age of 23.8±2.9 years (range: 20-29 years) and an average body weight of 70.4±11.1 kg(range: 55-85 kg) as shown in table 1.The study was well tolerated by the subjects with out any detectable change in vital signs however some mild adverse events observed. One subject experienced headache which was treated with 500 mg acetaminophen, one subject complained about diarrhea.

The results of amoxicillin deviated from reported data when co-administered with antacid and present work showed significant variability in the values of pharmacokinetic parameters of Cmax, Tmax and AUC. In the absence and in the presence of antacid the mean Cmax values of amoxicillin alone were 2.98±0.27µg/ml and 7.84±0.06 µg/ml for amoxicillin plus antacid in non-compartmental analysis while calculated values were 3.17±0.32µg/ml and 6.76±0.05µg/ml in compartmental analysis. The mean serum concentration of amoxicillin alone and with antacid shown in Fig.2(a) and Fig.2(b).

The maximum concentration of amoxicillin was achieved in 1.85±0.01hr for amoxicillin alone and 2.36±0.02 with antacid in compartmental analysis but this Tmax value extended from 2hr to 3hr when administered with antacid in non-compartmental analysis and showed significant increase in Tmax. The mean AUC 0-α values calculated through compartmental analysis were 26.81±0.70µg.hr/ml for amoxicillin alone and 33.58±0.62µg.hr/ml with antacid The Cmax significantly increase with increasing lag time and AUC. Other pharmacokinetic parameters were also determined. The mean values of Clearance and Volume of central compartment for amoxicillin alone were 6.79±0.14 L/hr and 22.02±1.37 L. The mean apparent Volume of distribution during the terminal phase was 127.70±0.91 L for amoxicillin. Along with antacid the values of Clearance and Volume of central compartment for amoxicillin become 5.73±0.08L/hr and 19.14±0.7L with apparent volume od distribution of 127.37±0.46 L for amoxicillin which is not significantly different. All pharmacokinetic parameters listed in table 2.

DISCUSSION

The main objective of the present study was to determine pharmacokinetic parameters of amoxicillin antibiotic as single dose administration with or without antacid and to compare the pharmacokinetic data of the current study in local population with the previous reported data. Various reports of drug interactions with antacid has been documented. In a high performance liquid chromatography assay the effect of aluminum and magnesium hydroxide containing antacid on the pharmacokinetic profile of pefloxacin in ten healthy volunteers was investigated [15]. The suggested mechanism for such interaction was chelation and physical adsorption to aluminum hydroxide gel. Reduced oral bioavailability of rufloxacin due to effect of antacid containing magnesium hydroxide and aluminum hydroxide(30 ml) was also reported [8] . Other possible mechanism for such interaction may be due to reduction in the absorption of antibiotic by antacid due to alteration in G.I motility, alteration in G.I pH, involvement of any complexation mechanism or inhibition or induction of drug transport protein and pharmacogenetic differences. As amoxicillin is a widely used antibiotic, it is therefore obligatory to detect any interaction that might alter its efficacy.

In the present study we found that some pharmacokinetic parameters of amoxicillin affected by co-administration of Mylanta. In the absence and in the presence of antacid amoxicillin Cmax values were 3.17±0.32µg/ml and 6.76±0.05 µg/ml respectively; the AUC0-α values of amoxicillin were 26.81±0.70 µg/ml x hr and 33.58±0.62 µg/ml x hr respectively; and showed apparent terminal half lives

1.32±0.09 hr and 1.58±0.06 hr respectively which showed significant interaction. Both treatments were given under fasting conditions to all subjects. The values of pharmacokinetic parameters in this study for amoxicillin alone were comparable to Tom.B etal [14] and Burkhardt etal [10] .In the present study the results of amoxicillin deviated from reported data when co-administered with antacid and present work showed significant variability in the values of Cmax, Tmax and AUC with that of published data. Our study surprisingly showed accelerated absorption along with altered bio-availability of amoxicillin with increase in Cmax when administered with antacid(table 3).It could be postulated that this accelerated absorption might be due to increase in motility by osmotic effect of magnesium hydroxide component of antacid [2,9] .As the study didn't show any serious clinically significant adverse event, nor any drug related change in vital signs, urinalysis, hematology or clinical chemistry was found. It could be said that amoxicillin is well tolerated and very few adverse effects were reported [6,13] .In summary the study demonstrated that bioavailability of amoxicillin altered with simultaneous administration of antacid with increase in Cmax, Tmax and AUC. Therefore concomitant administration should be avoided or an interval of at least 2hours a part should be considered whenever prescribed.

ACKNOWLEDGEMENTS

The authors would like to thank the National Bioethics Committee, Ministry of Health, Government of Pakistan Islamabad. Pakistan for their critical review of study design, administrative and paramedic staff of Imam hospital for their humble co-operation during study and all volunteers who participated in this study.

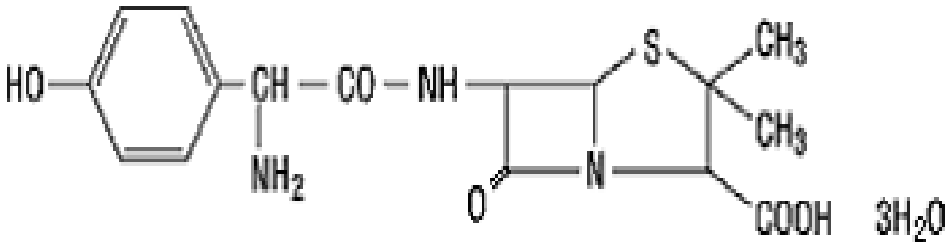

Figure 1: Structure of Amoxicillin

MEAN PLASMA CONCENTRATION TIME PROFILE OFAMOXICILLIN (250mg) TABLET ALONE IN 10 HEALTHY VOLUNTEERS

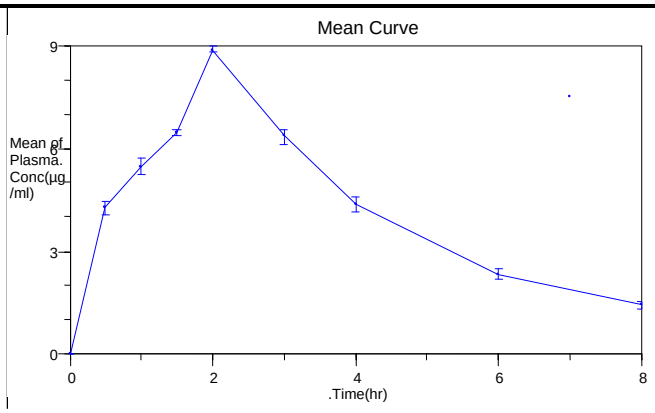

FIGURE 2(a): MEAN PLASMA CONCENTRATION TIME PROFILE OFAMOXICILLIN (250mg) TABLET ALONE

MEAN PLASMA CONCENTRATION TIME PROFILE OFAMOXICILLIN TABLET ALONE(250mg) +ANTACID(10ml) IN 10 HEALTHY VOLUNTEERS

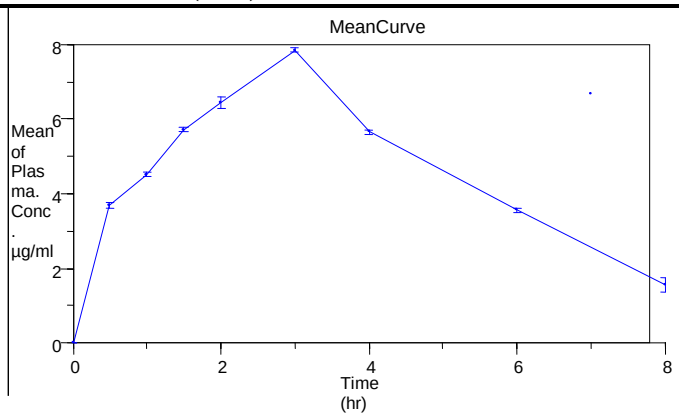

FIGURE 2(b): MEAN PLASMA CONCENTRATION TIME PROFILE OFAMOXICILLIN (250mg) TABLET plus antacid.

TABLE 1: Details of volunteers participated in comaparative study

DETAILS OF THE VOLUNTEERS PARTICIPATED IN PHARMACOKINETIC STUDIES								
S.No	Volunteer code	Sequence	Age (yrs)	Weight (Kg)	Height (ft.inch)	Blood Pressure (Phase I)	Blood Pressure (Phase II)	Pulse
1	V1	AB	22	71	5'10"	110/70	110/80	68
2	V2	BA	20	85	5'11"	120/80	120/70	60
3	V3	AB	21	72	6'	120/70	110/80	72
4	V4	BA	28	74	5'4"	120/80	100/70	60
5	V5	AB	28	56	5'7"	110/70	130/90	74
6	V6	BA	26	62	5'10"	130/80	110/80	88
7	V7	AB	23	55	5'7"	120/70	100/60	80
8	V8	BA	22	65	5'10"	110/80	120/80	64
9	V9	AB	26	81	5'10"	120/80	100/70	70
10	V10	BA	22	78	5'7"	130/70	120/80	72
Mean±S.D			23.8±2.9	70.4±11.1				

A= amoxicillin alone; B= amoxicillin+Antacid

TABLE 2: Comparison of Pharmacokinetic parameters of amoxicillin alone and along with antacid

PHARMACOKINETIC PARAMETERS OF AMOXICILLIN		
Subjects and Pharmacokinetic parameters	Amoxicillin (mean±SD)	Amoxicillin+antacid (mean±SD)
Subjects(n=10)		
Cmax(µg/ml)	3.17±0.32	6.76±0.05
AUC0-α(µg/mlxhr)	26.81±0.70	33.58±0.62
Tmax(hr)	1.85±0.01	2.36±0.02
T½(hr)	1.32±0.09	1.58±0.06
Varea(L)	127.70±0.91	127.37±0.46
Cl(L/hr)	6.79±0.14	5.73±0.08
MRT(hr)	1.93±0.08	4.55±0.18
Vcc(L)	22.02±1.37	19.14±0.7L

Antacid.Aluminum-magnesium hydroxide+simethicone(Mylanta)
One compartmental model
Pharmacokinetic parameters shown in mean±SD (P< 0.05)

TABLE 3: The comparative bio-availability of amoxicillin alone to that of along with antacid

% RELATIVE BIO-AVAILABILITY
The comparative bio-availability of amoxicillin alone to that of along with antacid :
% Relative bio-availability = Mean (AUC)b/ Mean(AUC) a x 100
Where a= amoxicillin alone
b= amoxicillin + antacid
% Relative bio-availability of Amoxicillin= 33.58/26.81 x 100= 125.2%

REFERENCES

1. Dinis PB, MonteiroMC etal.Sinus tissue pharmacokinetics after oral administration of amoxicillin/clavulanicacid.The Laryngoscope, 2000;110(6):1050-1055.
2. Deppermann,Lode, Höffken, Tschink,Kalz and Koeppe. Influence of ranitidine, pirenzepine, and aluminum magnesium hydroxide on the bioavailability of various antibiotics, including amoxicillin, cephalexin, doxycycline, and amoxicillin-clavulanicacid. Antimicrob Agents Chemother,1989;33(11): 1901-1907.
3. Ernie Riffer. Once Daily Clarithromycin Extended-Release Vs Twice-Daily Amoxicillin/Clavulanate in Patients With Acute Bacterial Sinusitis: a Randomized, clavulanicacid,Journal of Antimicrobial Chemotherapy,2005;16:763-771.
4. Gabriela Grunder, Yvonne Zysset-Aschmann, Florence Vollenweider,etal. Lack of Pharmacokinetic Interaction between Linezolid and Antacid in Healthy Volunteers,Antimicrob Agents Chemother,2006; 50(1): 68–72.
5. Hofken, G., K. Borner, P. D. Glatzel, P. Koeppe, and H. Lode.Reduced enteral absorption of ciprofloxacin in the presence of antacids. Eur. J. Clin. Microbiol,1986; 4:345-349.
6. LEVINE, LOUISE R.Quantitative comparison of adverse reactions to cefaclor vs. amoxicillin in a surveillance study. Pediatric Infectious Disease,1985; Volume 4 (6): 706.
7. Mastour S. Al-Ghamdi, Fikry El-Morsy and Zaki H. Al-Mustafa.Patterns of Resistance to antibiotics at king Fahd Hospital of the University.Journal of Family & Community Medicine,1999: 6(2);43-50.
8. M Lazzaroni, B P Imbimbo, S Bargiggia,etal.Effects of magnesium-aluminum hydroxide antacid on absorption of rufloxacin.Antimicrob Agents Chemother,1993; 37(10): 2212-2216.
9. Meyers, B. R., K. Kaplan, and L. Weinstein. Cephalexin:microbiological effects and pharmacologic parameters in man.Clin. Pharmacol. Ther,1969; 10:810-816.
10. Olaf Burkhardt, Klaus Borner, Nicolas von der Höh, Peter Köppe etal. Single- and multiple-dose pharmacokinetics of linezolid and co-amoxiclav in healthy human volunteers ,Journal of Antimicrobial Chemotherapy,2002; 50:707-712.
11. Paulo Borges Dinis, MariaConceição Monteiro,, Maria Luz Martins, etal. Sinus Tissue Pharmacokinetics After Oral Administration of Amoxicillin/ClavulanicAcid,TheLaryngoscope,2000; 110(6):1050 – 1055.
12. Parpia, S. H., D. E. Nix, L. G. Hejmanowski, H. R. Goldstein,J. H. Wilton, and J. J. Schentag. Sucralfate reduces the gastrointestinal absorption of norfloxacin. Antimicrob. Agents Chemother,1989; 33:99-102.
13. Sanz E, Boada J. Adverse drug reactions in paediatric outpatients. Int J Clin Pharmacol Res,1987;7(2):169-72.
14. Tom B. Vree, Erik Dammers and Peter S.Exler.Identical pattern of highly variable absorption of clavulanic acid from four different oral formulations of co-amoxiclav in healthy subjects,Journal of Antimicrobial Chemotherapy,2003; 51:373-378.
15. U Jaehde, F Sörgel, U Stephan and W Schunack.Effect of an antacid containing magnesium and aluminum on absorption, metabolism, and mechanism of renal elimination of pefloxacin in humans. Antimicrob Agents Chemother,1994; 38(5): 1129-1133.