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Effects of Diclofenac and Ibuprofen on Pharmacokinetics of Ciprofloxacin in Myanmar Healthy Volunteers

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The present study was done to explore the pharmacokinetics of ciprofloxacin that was altered by co-administration of either diclofenac or ibuprofen. The study was conducted on twelve Myanmar healthy volunteers and divided into three phases with a wash out period of one week in between phases. In phase, ciprofloxacin 500 mg was given to all volunteers, ciprofloxacin 500 mg with diclofenac 50 mg was given to same volunteers in phase 2 and ciprofloxacin 500 mg with ibuprofen 400 mg was given in phase 3. Blood samples were collected at 0, 0.5, 1, 2, 3, 4, 6 and 8 hours after drugs administration and ciprofloxacin concentrations in plasma samples were analyzed by HPLC with UV detection. It was found that mean clearance was reduced from 0.38±0.11 $Lhr^{-1}kg^{-1}$ in ciprofloxacin alone to 0.30±0.07 $Lhr^{-1}kg^{-1}$ and 0.28±0.09 $Lhr^{-1}kg^{-1}$ in ciprofloxacin with diclofenac and ciprofloxacin with ibuprofen (p=0.019). Similarly, the mean elimination rate constants (K_{el}) was significantly reduced from 0.24±0.03 hr^{-1} in ciprofloxacin alone to 0.18±0.024 hr^{-1} in ciprofloxacin with diclofenac and 0.12±0.03 hr^{-1} in ciprofloxacin with ibuprofen co-administration (p=0.000). Increase in AUC of ciprofloxacin was founded that AUC of ciprofloxacin alone was 13.51±1.91 μgml^{-1}.hr, ciprofloxacin with diclofenac was 17.36±2.67 μgml^{-1}.hr and with ibuprofen was 18.43±4.08 μgml^{-1}.hr, respectively (p=0.001). The mean elimination half-life ($T_{½el}$) of ciprofloxacin alone and ciprofloxacin with diclofenac or ciprofloxacin with ibuprofen were 2.85±0.46 hrs *vs.* 3.79±0.49 hrs and 2.85±0.46 hrs *vs.* 3.61±0.57 hrs, respectively (p=0.000). In comparison with ciprofloxacin alone study, the elimination parameters of the present study were altered significantly after diclofenac or ibuprofen co-administration. These findings suggested that it should be cautious in use of analgesics (diclofenac or ibuprofen) together with ciprofloxacin especially in elderly and renal function impaired patients in clinical practice. On the other hand, increased concentration (AUC) of ciprofloxacin may enhance bactericidal effect and can result better outcome in treating pathogenic organisms.

Key words: Pharmacokinetics, Ciprofloxacin, HPLC

INTRODUCTION

Some bacterial infections may cause inflammation of the affected organ system. When inflammation occurs, pain will follow since it is one of the symptoms of inflammation. Regarding the management of above process, antibiotics are used to cure the infections and analgesics are used for symptom control in clinical practice. Ciprofloxacin is one of the most commonly used broad spectrum antibiotics used for treatment of various bacterial infections and analgesics are usually prescribed together

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in the management of pain during the treatment of infections. Ciprofloxacin is commonly prescribed antibiotics and have potential for interaction with other drugs in multiple drug therapy. Ibuprofen co-administration with ciprofloxacin demonstrated that a significant increase in ciprofloxacin concentrations in the mandible and the tongue (maxillofacial tissues) following surgical trauma.[1] Some studies stated that concurrent administration of ciprofloxacin tablet with naproxen sodium tablet and concomitant administration of diclofenac with ciprofloxacin increased C_{max}, AUC, $t_{1/2}$ and decreased T_{max}, and total body clearance of ciprofloxacin.[2, 3]

Elevating blood concentration of ciprofloxacin was related with increased risk of side effects in animal study. Therefore, to get optimal therapeutic effect and to minimize the adverse effects, dosage adjustment will become mandatory when ciprofloxacin and NSAIDs are given together. On the other hand, increased concentration of ciprofloxacin may enhance bactericidal effect and can result better outcome in treating pathogenic organisms.

Therefore, co-administration of NSAIDs can cause increased concentration of ciprofloxacin which may be desired with regard to greater efficacy and undesired with regard to the higher incidence of adverse events in using ciprofloxacin in today's clinical practice. Since ciprofloxacin and NSAIDs are commonly used combination in orthopaedics and other clinical situations of today's practice, the findings of the present study would be useful in rational prescribing of antimicrobial therapy by providing helpful pharmacokinetic information.

MATERIALS AND METHOD

Methodology involved selection of eligible subjects according to inclusion criteria and the study was conducted on twelve healthy Myanmar volunteers of both sexes with age between 20 and 55 years. The study was laboratory-based longitudinal analytical study using the same subjects. Sample collection was carried out at Department of Pharmacology, University of Medicine 1 (Yangon) and laboratory investigations for all volunteers were done at the Pathology Department of Yangon General Hospital. Ciprofloxacin drug assays were carried out at Pharmaceutical Toxicology Research Division, Department of Medical Research (Lower Myanmar).

The present study was divided into three phases with a wash out period of one week in between phases. In the phase one of the study, each subject was administered a single oral dose of 500 mg ciprofloxacin. In the phase two, diclofenac 50 mg was given together with ciprofloxacin 500 mg to the same subjects. In the phase three of the study, ibuprofen 400 mg together with ciprofloxacin 500 mg was given to the same subjects after a wash out period of one week from the phase two. Blood samples were collected at 0, 0.5, 1, 2, 3, 4, 6, and 8 hours after dosing and stored at -20 ºC until analysis.

The plasma concentration of ciprofloxacin was determined by modified HPLC method.[4] The mobile phase composition was acetonitrile: N, N-dimethyl formamide: 0.01 M sodium dihydrogen phosphate dihydrate (13:5:82) and pH3.0 is adjusted by adding phosphoric acid (85%). The frozen plasma was allowed to thaw at room temperature just before the extraction procedure; it was then mixed and centrifuged at 3000 rpm for 10 minutes.

One milliliter of plasma sample was transferred into a test tube and to it, 1 ml of acetonitrile was added and the mixture was vortexed for 5 minutes; then the samples were centrifuged at 3000 rpm for 15 minutes. The supernatant solution was transferred to autosampler vials for chromatographic analysis, detection at 285 nm by using UV absorbance. Aliquots (20 µl) of ciprofloxacin reference standard, plasma spiked samples and unknown samples were injected to the HPLC system at 50°C with flow rate of 1 ml/min. Each

plasma concentrations were determined in duplicate and calculated from the standard curve obtained from the same day. Calculations of ciprofloxacin concentration in plasma samples were done by external standard method and method validation was done according to ICH guidelines Q2 (R1).[5, 6]

Concentration-time curves of ciprofloxacin alone, ciprofloxacin with diclofenac and ciprofloxacin with ibuprofen were plotted for each individual. From the concentration-time curve, the pharmacokinetic parameters were measured and calculated from plasma drug concentration-time curves by using Microsoft Office Excel program (2010) using one compartment model and statistical differences of these data were analyzed using SPSS statistical software version 16.0 (One-Way ANOVA, Turkey test). The difference between means for each parameter was considered significant for 95% confidence interval ($p<0.05$). Results are expressed as mean values ±SD.

Ethical consideration

This study was approved by Ethical and Research Committee of University of Medicine 1 (Yangon).

RESULTS

The standard curve for ciprofloxacin extracted from plasma was linear over the range of concentrations from 0.5 μgml^{-1} to 10 μgml^{-1}. The correlation coefficient, r^2 value is 0.9996. The average retention time for ciprofloxacin was 4.5 minutes. Intra-day assay of coefficient of variation of spiked samples were 3.02%, 2.29% and 1.59% and inter-day assay of coefficient of variations were 7.04%, 3.69% and 2.28% for 0.5 μgml^{-1}, 3 μgml^{-1} and 5 μgml^{-1}, respectively. These values demonstrated that the precision of the method was good over the range of the concentration studied and the values of precision were not exceeded 15%.

The limit of detection and lower limit of quantification of ciprofloxacin in plasma were 0.19 μgml^{-1} and 0.59 μgml^{-1}, respectively. The result of % RSD system suitability test for ciprofloxacin working solution 3 µg was 1.26 and thus, it was within the given theoretical limited range (<2%). The extraction recovery of ciprofloxacin from the plasma was 80.11%, 81.69% and 85.36%, respectively at the concentration range of 1, 3 and 7 μgml^{-1}. Those mean that extraction recovery of ciprofloxacin was within the acceptable level (80-120%).

Comparison of the mean plasma ciprofloxacin concentration-time curves and mean plasma ciprofloxacin concentrations at different times of ciprofloxacin alone, ciprofloxacin with diclofenac and ciprofloxacin with ibuprofen are shown in Fig. 1.

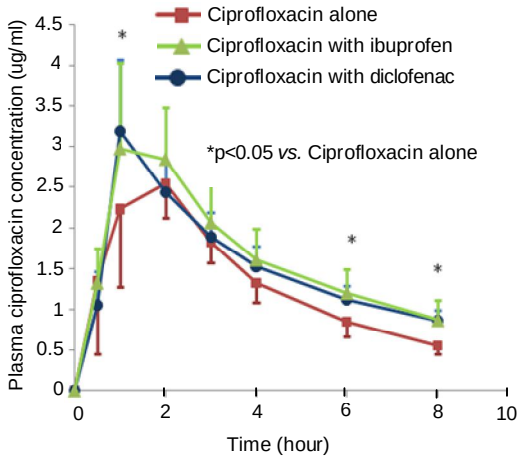

Fig. 1. Plasma ciprofloxacin concentration-time curves of ciprofloxacin alone, ciprofloxacin with diclofenac and ciprofloxacin with ibuprofen (n=12)

The results of the finding showed that there was significant increase in ciprofloxacin concentrations especially at 1-hour, 6-hour and 8-hour samples after co-administration of diclofenac. Similarly, comparison of plasma ciprofloxacin concentration-time profiles between ciprofloxacin alone and ciprofloxacin with ibuprofen showed significant increase in plasma concentration of ciprofloxacin after ibuprofen co-administration (at 6 hour and 8 hour). From the concentration-time curve, maximal plasma concentration (C_{max}), and time to reach maximal plasma concentration (T_{max}) were

determined and other pharmacokinetic parameters were calculated for each individual. The pharmacokinetic parameters of ciprofloxacin alone were compared with ciprofloxacin with diclofenac and ciprofloxacin with ibuprofen and shown in Table 1.

Table 1. Comparison of pharmacokinetic parameters of ciprofloxacin alone, ciprofloxacin with diclofenac/ ibuprofen (n=12)

Parameter	Cipro-floxacin alone	Cipro-floxacin with diclofenac	Cipro-floxacin with Ibuprofen	P value
T_{max}(hr)	1.4±0.51	1.33±0.49	1.5±0.52	0.728
C_{max} (μgml^{-1})	2.81±0.53	3.26±0.79	3.43±0.82	0.112
AUC_{0-} (μgml^{-1}.hr)	13.51±1.91	17.36±2.67	18.43±4.08	0.001
K_{ab}(hr^{-1})	2.01±0.96	2.98±1.01	2.39±1.09	0.078
$T_{1/2ab}$ (hr)	0.53±0.32	0.26±0.11	0.36±0.19	0.309
K_{el} (hr^{-1})	0.24±0.03	0.19±0.02	0.12±0.03	0.000
$T_{1/2el}$(hr)	2.85±0.46	3.79±0.49	3.61±0.57	0.000
CL ($Lhr^{-1}kg^{-1}$)	0.38±0.11	0.30±0.07	0.29±0.08	0.019
Vd (Lkg^{-1})	1.55±0.45	1.61±0.43	1.51± 0.33	0.822

Data are shown in Mean±SD

T_{max}=Time to reach maximum plasma concentration
C_{max}=Maximal plasma concentration
AUC_{0-}=Area under concentration time curve
K_{ab}=Absorption rate constant
$T_{1/2ab}$=Absorption half-life
K_{el} =Elimination rate constant
$T_{1/2el}$=Elimination half-life
CL=Clearance
Vd=Volume of distribution

The statistically significant changes were found in the pharmacokinetic parameters of ciprofloxacin after concurrent administration of diclofenac or ibuprofen. The mean clearance of ciprofloxacin alone was 0.38 ±0.11 $Lhr^{-1}kg^{-1}$, ciprofloxacin with diclofenac was 0.30±0.07 $Lhr^{-1}kg^{-1}$ and ciprofloxacin with ibuprofen was 0.28±0.09 $Lhr^{-1}kg^{-1}$. Clearance of ciprofloxacin was reduced significantly after diclofenac or ibuprofen co-administration (p=0.019). The mean AUC of ciprofloxacin alone was 13.51±1.91 μgml^{-1}.hr, ciprofloxacin with diclofenac was 17.36 ±2.67 μgml^{-1}.hr and with ibuprofen was 18.43±4.08 μgml^{-1}.hr, respectively. Therefore, the corresponding increase in AUC was significantly found after concomitant administration of ciprofloxacin with diclofenac or ibuprofen (p=0.001).

The mean elimination rate constants (K_{el}) were 0.24±0.03 hr^{-1} in ciprofloxacin alone, 0.19±0.02 hr^{-1} in ciprofloxacin with diclofenac and 0.12±0.03 hr^{-1} in ciprofloxacin with ibuprofen co-administration. The mean k_{el} was significantly decreased when diclofenac or ibuprofen were given together (p=0.000).

The mean elimination half-life ($T_{½el}$) of ciprofloxacin alone and ciprofloxacin with diclofenac or ciprofloxacin with ibuprofen were 2.85±0.46 hrs *vs.* 3.79±0.49 hrs and 2.85±0.46 hrs *vs.* 3.61±0.57 hrs, respectively. The differences were statistically significant (p=0.000).

Although statistically not significant, the mean peak plasma concentration (C_{max}) of ciprofloxacin was apparently increased from 2.81±0.52 μgml^{-1} in ciprofloxacin alone to 3.26±0.79 μgml^{-1} in ciprofloxacin with diclofenac and 3.43±0.82 μgml^{-1} in ciprofloxacin with ibuprofen. The mean $T_{½ab}$, K_{ab}, T_{max} and V_d were not altered significantly after concomitant administration of diclofenac or ibuprofen in comparison with ciprofloxacin alone. Moreover, pharmacokinetic parameters of ciprofloxacin with diclofenac were not different significantly from ciprofloxacin with ibuprofen.

DISCUSSION

The findings of the present study have shown that area under the concentration time curve ($AUC_{0-\alpha}$) and elimination half-life ($t_{1/2el}$) of ciprofloxacin were increased and elimination rate constants (K_{el}) and clearance (CL) of ciprofloxacin were reduced significantly when ciprofloxacin was taken concomitantly with diclofenac or ibuprofen. Since pharmacokinetic parameters of the present study were consistent with other studies,[7, 8] it may highlight that alteration of pharmacokinetic parameters of ciprofloxacin were affected by concurrent administration of diclofenac or ibuprofen.

Pharmacokinetic parameters of ciprofloxacin with diclofenac were not different significantly from ciprofloxacin with ibuprofen.

Therefore, it can be concluded that plasma levels of ciprofloxacin can be increased when most of NSAIDs that undergo renal elimination are concurrently administered.

Ciprofloxacin is a carboxylic acid-containing fluoroquinolone that undergoes renal and hepatic elimination. Renal elimination, including both glomerular filtration and tubular secretion accounts for approximately 66% of ciprofloxacin clearance. Metabolites of NSAIDs are eliminated by renal, frequently involving tubular secretion as organic acid metabolites. Thus, there was the possibility that NSAIDs may interact with ciprofloxacin at this site to competitively impair their mutual renal elimination.

Although exact mechanism is not known, increased concentration of ciprofloxacin by diclofenac or ibuprofen codministration can be explained by transport-mediated interactions. Ciprofloxacin is transported by several classes of membrane transporters: organic anion transporter, and efflux pumps such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).[9] Since NSAIDs is either substrate or inhibitor of OATs (organic anion transporters), concomitant administration of ciprofloxacin with diclofenac or ibuprofen may cause competition at renal tubular transport and blood and tissue levels of the ciprofloxacin may be therapeutic or higher than therapeutic.

Studies have shown that the fluoroquinolones are good substrates of multi-drug resistance protein (MRP) family of transporters, and that various MRP efflux transporters are inhibited by NSAIDs at therapeutically relevant concentrationsm,[10] thus may play important role in drug-drug interactions when these groups of drugs are concurrently administered.

Although ciprofloxacin has wide therapeutic range, increasing plasma concentration should be cautious in use of these drugs in renal impairment and elderly subjects in clinical practice. Ciprofloxacin disposition is affected by critical illness, particularly by the presence of organ failure and thus, dosage adjustment should be advised in patients with renal failure. Elimination half-life, C_{max} and AUC were significantly higher in renal failure patients, total body clearance was decreased by one-half to one-fourth in patients with creatinine clearance values ranging from 5 to 50 ml min^{-1}.[11]

Plasma concentrations of ciprofloxacin are higher in elderly subjects (>65 years) compared with young subjects.[12] Elevating blood concentration of ciprofloxacin was related with increased risk of side effects in animal study. There was high risk of arthrotoxicity with increased dose of ciprofloxacin and other concentration-related side effects were found.[13]

In the present study, there were increase in concentration, half-life and reduce in clearance of ciprofloxacin after diclofenac or ibuprofen co-administration. Since the magnitude of drug's effect is related to its plasma drug concentration, the findings of present study may lead to higher drug effects especially concentration related side effects when these drugs are used together in elderly and renal function impaired patients in clinical practice.

On the other hand, increased concentration of ciprofloxacin may enhance bactericidal effect and will result in better treatment outcome. Since ciprofloxacin exhibit concentration dependent killing of microorganisms, bactericidal activity of ciprofloxacin becomes more pronounced due to maximizing of AUC/MIC and the C_{max}/MIC ratios. The aim of certain antibiotic therapy should be not only clinical success but prevention of resistance of that antimicrobial in future. Higher AUC/MIC or C_{max}/MIC values are needed to prevent the emergence of resistance in a population of bacteria to achieve clinical efficacy.

By the above reasons, co-administration of NSAIDs with ciprofloxacin not only give symptomatic treatment of pain but also support curative effect of ciprofloxacin

in treating pathogenic organisms in the management of infection associated with pain. Therefore, the results of the present study can give valuable information to clinicians in rational prescribing of anti-microbial therapy in individual care.

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REFERENCES

1. Trichilis A, Saranteas T, Potamianou A, Mourouzis C & Tesseromatis C. Quinolone levels in serum and maxillofacial tissues under ibuprofen co-administration following surgical trauma. *Journal of Musculoskeletal and Neuronal Interactions* 2003; 3(2): 170-175.
2. Iqbal Z, Khan A, Naz A, Khan JA & Khan GS. Pharmacokinetic interaction of ciprofloxacin with diclofenac. *Clinical Drug Investigation* 2009a; 29(4): 275-281.
3. Iqbal Z, Khan A, Naz A, Khan JA, Khan GS, Saeed M & Khan TM. *In vivo* drug-drug interaction studies of ciprofloxacin with naproxen sodium in healthy human volunteers. *Folia Medica* 2009 b; 44 (2): 57-64.
4. Khan MK, Khan MF. Extraction and separation of ciprofloxacin by HPLC from human plasma *International Chemical and Pharmaceutical Medical* 2005; 2(2): 267-270.
5. European Medicine Agency. Guideline on bio-analytical method validation. Last updated on 21 July 2011. Available from: URL: http:// www.ema.europa.eu. accessed 21 April 2014.
6. Guidance for Industry, Bioanalytical Method Validation. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Veterinary Medicine, USA, 2001; 2-19.
7. Aye Soe. Effect of antacid on the pharmaco-kinetics of ciprofloxacin in Myanmar healthy volunteers. *Thesis*, M.Med.Sc. University of Medicine 1, Yangon, 2004.
8. Thummel KE, Shen DD & Isoherranen N. Design and optimization of dosage regimens; Pharmacokinetic data. In: *Goodman and Gilman's The Pharmacological Basic of Therapeutics*; Ed: Brunton LL, 12th ed, McGraw-Hill, Medical publishing division, New York, 2011; 1899-1991.
9. Vanwert AL, Srimaroeng C & Sweet DH. Organic anion transport oat3/Slc22a8 interacts with carboxyfluoroquinolones, and deletion increases systemic exposure to ciprofloxacin. *Molecular Pharmacology* 2008; 74: 122-31.
10. El-Sheikh AAK, Heuvel VD, Koenderink JB & Russel FM. Interaction of nonsteroidal anti-inflammatory drugs with multidrug resistance protein (MRP) 2/ABCC2 and MRP4/ABCC4-mediated methotrexate transport. *Journal of Pharmacology and Experimental Therapeutics* 2007; 320(1): 229-235.
11. Shah A, Lettieri J, Blum, Millikin S, Sica D & Heller AH. Pharmacokinetics of intravenous ciprofloxacin in normal and renally impaired subjects. *Journal of Antimicrobial Chemo-therapy* 1996; 38 (1): 103-106.
12. LeBel M, BarbeauG, Bergeron MG, Roy D & Vallée F. Pharmacokinetics of ciprofloxacin in elderly subjects. *Pharmacotherapy* 1986; 6(2): 87-91.
13. Keutz VE, Ruhl-Fehlert C, Drommer W & Rosenbruch M. Effects of ciprofloxacin in immature dogs immediately after dosing and after 5 month treatment-free period. *Archives of Toxicology* 2004; 78(7): 418-24.