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Evaluation of Pharmacokinetics and Pharmacodynamics of Levofloxacin in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Certain antimicrobial therapy should target not only clinical success but prevention of resistance in future. In modern antimicrobial therapy, in addition to a measure of the potency of the drug for the pathogen (Minimum Inhibitory Concentration-MIC), a measure of drug exposure of the individual patient (pharmacokinetic data) becomes essential component in rational dosage regime. The aim of the study was to assess thepharmaco-kinetic/pharmacodynamic (PK/PD) adequacy of levofloxacin in the treatment of acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Hospital-based analytical study was done in 20 patients with AECOPD admitted to three teaching hospitals. Serial blood collection was done to determine pharmacokinetics of oral and intravenous infusion levofloxacin in these patients. Culture and sensitivity of infecting pathogens were done and PK/PD indices were calculated by integrating pharmacokinetic data(C_{max} or AUC) with microbiological data (MIC). Pharmacokinetic para-meters were not significantly different between different routes indicating interchangeability of the route of administration of levofloxacin. Pathogens isolated were *Klebsiella* spp. (20%), *Escherichia coli* (10%), *Haemophilus influenzae* (10%), *Staphylococcus aureus* (5%), *Streptococcus pneumoniae* (5%) and *Pseudomonas* spp. (5%). Although the resulted PK/PD indices were found to be low to achieve the targeted PK/PD values (C_{max}/MIC of ≥8-10 and AUC/MIC of ≥87) in most patients, 90% (18/20) achieved clinical cure. The results indicated that although patients got clinical cure, microbiological eradication was uncertain and risk of emergence of resistance was high. This study highlighted the need of efficacy indices (PK/PD indices) for optimizing antimicrobial therapies in various infections for prevention and reduction of antimicrobial resistance problem in Myanmar.

Key words: Levofloxacin, PK/PD, COPD patients, Myanmar

INTRODUCTION

Lower respiratory tract infections (LRTIs) namely acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and pneumonia are the leading infectious causes of death in most countries. In Myanmar, pneumonia and acute lower respiratory tract infections are listed among the leading causes of morbidity and mortality.[1] Evolving drug resistance makes treating lower respiratory tract infections a major challenge.

In practice, most empirical LRTI therapy is clinically based and bacterial eradication is usually considered secondarily. Failure to kill or eradicate causative bacteria is most likely to result from sub-optimal therapy which predispose to resistance emergence. Spontaneous clinical recovery may mask differences in bacteriological effectiveness of antibiotics and allow suboptimal agents to continue to be prescribed.[2, 3] Successful

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antimicrobial therapy should target not only clinical success but prevention of resistance in future. In modern antimicrobial therapy, in addition to a measure of the potency of the drug for the pathogen (MIC), a measure of drug exposure of the individual patient (pharmacokinetic data) becomes essential component in rational dosage regime. Integration of MIC with pharmacokinetic (PK) parameter provides pharmacokinetic/ pharmacodynamic indices, which are valuable tools with which to predict clinical outcome, microbiologic outcomes and optimal drug dose.[4, 5] Animal and clinical data indicated that the development of resistance is correlated with dosing regimens that do not achieve sufficiently high PK/PD indices.[6] These indices include time above MIC (T>MIC); the ratio between peak serum concentration (C_{max}) and MIC (C_{max}/MIC) and relation between drug exposure i.e. area under the serum 24 hours concentration-time curve (AUC_{0-24}) and MIC (AUC_{0-24}/MIC).

Levofloxacin is a fluoroquinolone antibacterial agent characterized by a broad spectrum of antibacterial activity against aerobic microorganisms, both gram-negative and gram-positive, which may cover most of the aetiological agents frequently responsible for AECOPD. As levofloxacin has a good bioavailability, early and simple change of route from intravenous to oral treatment is possible. Moreover, because of being given without interference with other drugs, having fewer side effects and an excellent and rapid bactericidal activity, levofloxacin offers the clinician and patient an excellent therapy for AECOPD.

Studies on pharmacokinetics of quinolones like levofloxacin in correlation with MIC of commonly found pathogens (PK/PD indices) in Myanmar are urgently needed to assess whether the currently used regimens for LRTIs are really effective or not. Therefore, this study aimed to evaluate pharmacokinetic and pharmacodynamic indices of the standard regimen of levofloxacin 500 mg once daily, frequently used in routine clinical practice for the treatment of patients with AECOPD.

The most preferable treatments in AECOPD are those that are effective and minimize the amount of time that the patient spends in hospital. Oral or intravenous infusion levofloxacin has been prescribed frequently as either monotherapy or in combination therapy of AECOPD in Myanmar. There were some studies indicated that intravenous therapy incurred longer hospital stay, higher cost and more discomfort to patient than oral therapy.[7, 8]

Therefore, the second objective was to study pharmacokinetic profiles of oral and intravenous infusion levofloxacin to expedite a sequential timely conversion from intravenous to oral therapy, or replacing intravenous with oral treatment for enabling both a cost-effective treatment of infections and an early hospital discharge.

MATERIALS AND METHODS

The study was prospective, non-blinded pharmacokinetic-pharmacodynamic study. Patients were recruited from North Okkalapa, Thingangyun and Insein general and teaching hospitals. Twenty patients with AECOPD (10 in oral group and 10 in intravenous infusion group) admitted to study hospitals participated in the study. Laboratory tests, sputum culture and sensitivity test and assay for levofloxacin were carried out at Department of Medical Research. Adult patients admitted to medical ward of study hospitals who were ≥18 years of age, diagnosed as AECOPD by physician in charge, prescribed oral or intravenous infusion levofloxacin as part of their required medical care, were eligible for inclusion in this study and agreed to sign a written informed consent.

Patients receiving therapy with any drugs capable of causing pharmacocokinetic drug interactions with levofloxacin and quinolone antibacterials within two weeks were excluded.

Identifications of organisms and susceptibility testing for levofloxacin

The aetiological agents were assessed by cultures of sputum before administration of drug and, whenever isolated, *in vitro* susceptibility (by Modified Kirby-Bauer method) to levofloxacin were tested. The results were interpreted by comparing with standard zone size for each drug from zone size interpretation chart as resistant, intermediate or susceptible.

Pharmacokinetic study

The intravenous infusion and oral pharmacokinetic evaluations were carried out on 3rd day under steady-state conditions. From each patient, blood sample (3 ml) was taken from forearm vein through the cannula at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6 and 24 hours after dosing. Levofloxacin plasma concentrations were analyzed by means of a high performance liquid chromatography using the method of Wong *et al*.[9] with some modifications.

Analysis of pharmacokinetic parameters and PK/PD indices

Data entry and analysis were done using Microsoft Excel 2007 and SPSS version 22. Model dependent pharmacokinetic analysis was done for each patient. PK/PD indices were also analyzed by Microsoft Excel 2007. The level of statistical significance for all statistical tests was defined as a 'p' value less than 0.05.

Ethical consideration

This study was reviewed and approved by Ethics Review Committee of University of Medicine 2 (Yangon).

RESULTS

Patient characteristics

Mean age of the patients was 71.4±9.63 years and male to female ratio was 1:2.3. The average weight was 48.23±11.45 kg with the mean BMI and creatinine clearance of 0.44±4.64 kg/m^2 and 7.68±21.58 ml/min, respectively.

Bacteriological identification from sputum of AECOPD patients

Only 11 out of 20 patients (55%) had a microbiologically confirmed bacterial etiology. The infection was monomicrobial in all cases and 6 different species of microorganisms were isolated. The most common pathogen was *Klebsiella* spp. (n=4, 20%), followed by *Escherichia coli* (n=2, 10%), *Haemophilus influenzae* (n=2, 10%), *Staphylococcus aureus* (n=1, 5%), *Streptococcus pneumonia* (n=1, 5%) and *Pseudomonas* spp. (n=1, 5%).

More than 80% of isolates were shown to be sensitive *in vitro* to levofloxacin except one *Klebsiella* spp. and *Streptococcus pneumonia* (Fig. 1). As most of the organisms isolated were gram-negative ones, azithromycin was not sensitive in most cases. Ceftriaxone was found out to be resistant to one *Klebsiella* isolate, *Staphylococcus aureus, Streptococcus pneumoniae and Pseudomonas isolates* (resistance percent - 36.4%). Co-amoxiclav resistance was found in one *Klebsiella* spp., one *Haemophilus influenzae* isolate and *Pseudomonas* isolate (resistance percent - 27.3%) (Fig. 1).

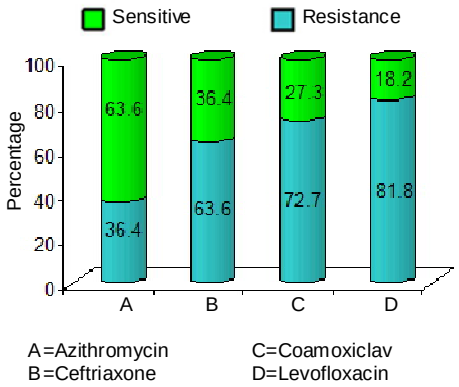

Fig. 1. Sensitivity pattern of microorganisms isolated from AECOPD patients

The mean plasma concentration-time profiles of oral and intravenous infusion levofloxacin in AECOPD patients are compared (Table 1 & Fig. 2). Plasma levofloxacin concentration rapidly rose within 1 hour and reached the peak at 1 hour in

both oral and intravenous infusion groups with the highest levels of 11.74±6.45 and 19.22±6.07 µg/ml, respectively.

Table 1. Comparison of pharmacokinetic parameters of oral and intravenous infusion levofloxacin in AECOPD patients

Parameters	Unit	Oral (n=10)		IV infusion (n=10)		P value
		Mean	SD	Mean	SD	
A	µg/ml	21.80	9.29	31.70	18.02	
B	µg/ml	10.42	6.18	8.98	2.88	
K_{ab}	h^{-1}	2.06	1.25	2.83	1.26	0.2
$t_{1/2ab}$	h	0.55	0.41	0.27	0.08	0.05
Alpha	h^{-1}	0.47	0.10	0.6	0.19	0.07
Beta	h^{-1}	0.06	0.02	0.05	0.02	0.3
$t_{1/2\alpha}$	h	2.04	0.72	1.62	0.79	0.2
$t_{1/2\beta}$	h	12.73	3.85	17.1	6.19	0.07
AUC	µg/ml.h	212.64	93.57	265.24	103.71	0.2
CL	L/h	2.79	1.2	3.58	1.36	0.2
V_d	L	51.27	25.73	50.88	19.37	0.9
C_{max}	µg/ml	11.74	6.45	19.22	6.07	0.02*
T_{max}	h	2.1	1.41	1.05	0.16	0.03*

A=Concentration at time "0" which was back extrapolated from distribution phase

B=Concentration at time "0" which was back extrapolated from elimination phase

Alpha=Distribution rate constant of two compartment model,

Beta=Elimination rate constant of two compartment model

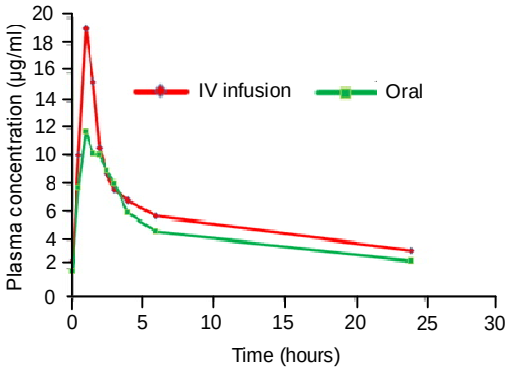

Fig. 2. Comparison of plasma concentration-time profiles of oral and intravenous levofloxacin in AECOPD patients

Plasma levofloxacin concentration then grdually decreased within 6 hours to 24 hours after administration in oral group but in intravenous infusion group, there was a steep fall within 1 hour and then a gradual fall up to 24 hours. Though the mean plasma concentrations of levofloxacin in intravenous infusion group of patients were higher than oral group at most time points, significant increase in concentration was seen only at 1 hour sample (peak) (Table 1 & Fig. 2).

Creatinine clearance (CL_{cr}) of the patients ranged from 12.2 to 90.1 ml/min with the mean of 39.69±18.78 ml/min. Correlation by linear regression analysis showed positive correlation between estimated creatinine clearance (CL_{cr}) and levofloxacin clearance (CL) of the COPD patients (r^2=0.8041, p<0.05) (Fig. 3).

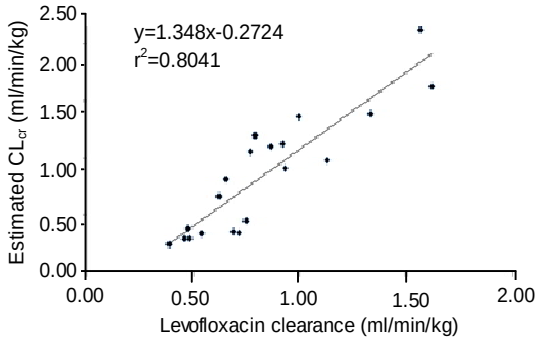

Fig. 3. Relationship between levofloxacin plasma clearance (CL) and estimated creatinine clearance (CL_{cr}) by means of the Cockcroft and Gault formula

Pharmacokinetic-pharmacodynamic target attainment in AECOPD patients

Infecting bacteria sensitive to levofloxacin were assumed to have MIC ≤2 µg/ml.[10] Studies have shown that both the C_{max}/MIC and AUC_{0-24}/MIC ratios are good predictors of fluoroquinolone efficacy. All patients achieved the desired C_{max}/MIC at MICs of ≤1 µg/ml. However, only 11.11% (1 out of 9) achieved desired C_{max}/MIC at 2 µg/ml. All patients achieved the desired AUC_{0-24}/MIC of ≥50 for treatment of infections caused by gram-positive pathogens with MICs of ≤1 µg/ml. For gram-negative organisms, only 66.67% of patients achieved desired AUC_{0-24}/MIC ratio of ≥87 at a MIC of 1 µg/ml. At MIC of 2 µg/ml, only 33.33% achieved lower threshold of targeted PK/PD index (AUC_{0-24}/MIC ≥50), 22.22% achieved PK/PD index of 87 and no patient achieved higher PK/PD index of 125 (Table 2).

Table 2. Percentage of AECOPD patients achieving targeted PK/PD indices with administration of levofloxacin 500 mg once daily dose

PK/PD indices	% of patients achieving target PK/PD indices at different MIC		
	0.25 µg/ml (Low)	1 µg/ml (Medium)	2 µg/ml (High)
C_{max}/MIC			
10	100.0	100.0	11.1
AUC_{0-24}/MIC			
50	100.0	100.0	33.3
87	100.0	66.7	22.2
125	100.0	22.2	0.0

For sensitive organism, MIC levels of 0.25, 1 and 2 µg/ml were used to evaluate achievement of target AUC_{0-24}/MIC and C_{max}/MIC indices for each patient. The targeted PK/PD indices for levofloxacin are C_{max}/MIC ratios of ≥10; AUC_{0-24}/MIC ratio of ≥87 to 125 for gram-negative bacterial infections; AUC_{0-24} /MIC ratio of ≥35 to 50 for gram-positive pathogens.[5, 11-13]

Outcome of therapy

Median length of hospital stay was 5 and 6 days for oral and IV treatment, respectively. In patients who responded, clinical symptoms subsided in 2.50±0.52 days. At the end of levofloxacin therapy, the overall clinical success rate was 90% since 18 out of 20 cases were cured.

DISCUSSION

In teaching hospitals where the present study was done, macrolides, second or third generation cephalosporins, co-amoxiclav and levofloxacin were found to be commonly used antibiotics either single or in combination therapy of AECOPD. In this study, sensitivity of pathogens to levofloxacin was the highest followed by co-amoxiclav and ceftriaxone (Fig. 1). The difference in sensitivity might be due to antibiotic usage pattern of the study hospitals.

Furlanut, *et al.*[14] reported that peak serum concentration of levofloxacin after oral and intravenous infusion were 7.93±3.44 µg/ml and 10.71±3.30 µg/ml, respectively and the values were lower than those found in Myanmar AECOPD patients. $AUC_{0-\alpha}$ was 74.97±29.29 µg.hr/ml and 85.60± 38.21 µg.hr/ml, respectively and these values were also lower than the present study. Lower clearance and longer elimination half-life were found in Myanmar AECOPD patients than other studies. The difference between Myanmar patients and other studies may be due to difference in weight (48.23±11.45 kg *vs.* 71±15 kg) and difference in renal function (creatinine clearance of 37.68±21.58 ml/min *vs.* 73.13±6.0 ml/min). The results showed that Myanmar patients had a larger drug exposure to the test drug (levofloxacin).

Most of the pharmacokinetic parameters were not different statistically between different routes of administration except higher C_{max} and shorter T_{max} in intravenous infusion group and the results of this study agreed with the study of Furlanut, *et al.*[14]

The differences may be because of food effect in oral group as patients had to be allowed to take levofloxacin whether they were fasted or not. This study also clearly demonstrates that great inter-patient variability is present and high degree of variability was observed to depend on difference in renal function which was described by creatinine clearance. Saito, *et al.*[15] and Kiser, *et al.*[8] also reported that inter-individual variation in levofloxacin pharmacokinetics was largely related to estimated creatinine clearance since the drug is excreted unchanged from kidney.

The results of present study showed that duration of hospital stay was 1 day shorter in oral group than intravenous group with no difference in pharmacokinetic parameters which determined the efficacy of levofloxacin (AUC, C_{max}) between the routes. Although intravenous levofloxacin should be considered the optimal route for initial empirical therapy in hospitalized patients with AECOPD, the oral route may represent both an effective and cost saving regimen in mild to moderate AECOPD outpatients or as a continuation therapy.

In this study, almost all patients achieved the PK/PD target for gram-positive organisms (AUC/MIC of 35-50) showing

that AECOPD patients in the study hospitals would be adequately treated with 500 mg of levofloxacin once daily regime. However, because of the high incidence of infections caused by gram-negative organisms in AECOPD patients, higher targeted AUC_{0-24}/MIC ratios (≥87) are necessary for effective empirical therapy. Higher doses of levofloxacin (i.e. greater than 500 mg/day) would be necessary to reliably achieve higher PK/PD indexes for treatment of infection caused by such organisms.

Use of levofloxacin as part of combination regimens would be the most appropriate clinical approach for the empirical treatment of severe systemic infections, especially gram-negative bacterial infections in this population. Some studies suggested the use of high dose, short course therapy (750 mg)[16] or twice daily regime of levofloxacin in the view of clinical and prevention of resistance.[17, 18]

Although some patients in this study got clinical cure despite their low PK/PD indices, further emergence of resistance in those patients was questionable. Most of the patients in this study were elderly with decreased clearance resulting in increased plasma concentration. Even if in these patients, microbiological eradication and emergence of resistance was doubtful, the treatment outcome in younger patients with severe LRTIs (e.g., community acquired pneumonia) may be questionable with 500 mg once daily regime.

Conclusion

This is the first study conducted in Myanmar regarding the pharmacokinetic disposition of levofloxacin in AECOPD patients. Despite several limitations, this study nevertheless provides the pharmacokinetic profiles of oral and intravenous routes of levofloxacin in Myanmar people. Moreover, this study will support to increase awareness in the medical community of the importance of PK/PD indices in optimal dosage regime and prevention of antibiotic resistance.

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