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Short Communication

Impact of poor compliance with levofloxacin and moxifloxacin on respiratory tract infection antimicrobial efficacy: A pharmacokinetic/pharmacodynamic simulation study

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ABSTRACT

The purpose of this report was to assess the impact of poor compliance on the efficacy of levofloxacin (LFX) and moxifloxacin (MOX), two fluoroquinolones with different pharmacokinetic (PK) and pharmacodynamic (PD) properties, in respiratory infections. The $fAUC_{0-24\,h}$ and $fAUC_{0-24\,h}/MIC_{90}$ ratio, a PK/PD index predictive of bacterial eradication, were extracted from previously described population PK models for LFX and MOX. The MIC_{90} was according to EUCAST. Monte Carlo simulations were used with LFX 500 mg every 24 h (q24 h) or every 12 h (q12 h), LFX 750 mg q24 h and MOX 400 mg q24 h in non-compliance scenarios to derive the proportion of patients achieving target ratios of $fAUC_{0-24\,h}/MIC_{90} > 33.8$ for *Streptococcus pneumoniae* and >100 for *Haemophilus influenzae* and *Moraxella catarrhalis* (PTA > 90%). In non-adherent dosing scenarios, LFX 500 mg q24 h was not able to reach the PK/PD index guaranteeing clinical efficacy. With LFX 500 mg q12 h or 750 mg q24 h, this probability was maintained although patients can take the dose with delays of up to 12 h and 11 h, respectively, for the three bacterial types. With MOX 400 mg q24 h, the probability of achieving this PK/PD index is maintained with delay in dosing up to 16 h. In conclusion, LFX 500 mg q24 h is the least robust treatment against *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* in a non-adherence situation. A good choice is LFX 500 mg q12 h, but in order to favour patient adherence, LFX 750 mg q24 h or MOX 400 mg q24 h appears as more appropriate.

1. Introduction

A major problem in antimicrobial therapy is non-compliance with the treatment regimen [1]. Neglecting to take medication as prescribed is a major cause of variability in drug exposure and has been associated with the failure of many treatments. Efforts to improve patient adherence to medication regimens would include multidisciplinary patient interventions. Dimensions such as patient-related factors and therapy-related factors need to be considered [2].

The diversity of the pattern of poor compliance and the difficulty in improving compliance via changing patients' behaviour have led to an increased focus on the drug itself. In relation to therapy-related factors, antimicrobial drugs need to be taken on a relatively rigid dosage schedule in order to maintain plasma concentrations achieving drug exposure relative to the minimum inhibitory concentration (MIC) for the pathogen that guarantees not only eradicating the dominant bacterial population, but also achieving an exposure preventing as much as possible the growth of resistant subpopulations [3].

Several authorities, including the European Society for Clinical Microbiology [4] and the Infectious Diseases Society of America/American Thoracic Society [5], recommended empirical therapy with fluoroquinolones, such as levofloxacin (LFX) and moxifloxacin (MOX), for the treatment of patients with lower respiratory tract infections, such as acute exacerbations of chronic bronchitis and mild-to-moderate community-acquired pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, especially when there are clinically relevant bacterial resistance rates.

However, it is not known which dosing regimen is most unaffected in its own right by lack of adherence. Different pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of these alternative antimicrobial agents [6] could condition their potential that delayed or missing doses will not have any consequence on their expected efficacy [2,7]. It could be of importance for a prescriber to know whether they could authorise or should restrict variability in the time interval between two consecutive

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Table 1
Interindividual variability of pharmacokinetic parameters for levofloxacin (LFX) and moxifloxacin (MOX), and $fAUC_{0-24\,h}$ estimated for various drug dosing regimens in simulated patients.

Parameter	LFX		MOX	
	Mean (S.D.)	Range	Mean (S.D.)	Range
CL (L/h)	10.91 (0.86)	8.69–13.32	10.08 (1.93)	6.12–17.30
V_c (L)	77.01 (15.41)	49.70–129.80	141.0 (19.70)	85.40–213.0
K_a (h^{-1})	2.38 (fixed)		5.97 (fixed)	
K_{cp} (h^{-1})	0.40 (0.08)	0.23–0.58		
K_{pc} (h^{-1})	0.55 (0.12)	0.35–0.93		
Q (L/h)			4.77 (2.15)	0.84–9.62
F (%)	99 (fixed)		86 (fixed)	
f_u	0.69 (fixed)		0.52 (fixed)	
$AUC_{0-24\,h}$ (mg h/L)				
LFX 500 mg q24 h	45.78 (3.72)	37.21–57.13		
LFX 750 mg q24 h	68.68 (5.58)	55.82–85.69		
LFX 500 mg q12 h	91.57 (7.34)	77.66–115.48		
MOX 400 mg q24 h			43.63 (8.60)	26.43–72.20
$fAUC_{0-24\,h}$ (mg h/L)				
LFX 500 mg q24 h	32.05 (2.60)	26.04–39.99		
LFX 750 mg q24 h	48.07 (3.90)	39.07–59.99		
LFX 500 mg q12 h	64.10 (5.14)	54.36–80.84		

$fAUC_{0-24\,h}$, free-drug 24-h area under the plasma concentration–time curve; S.D., standard deviation; CL, total clearance; V_c, central volume of distribution; K_a, absorption rate constant; K_{cp}, rate constant from the central compartment to the peripheral compartment; K_{pc}, rate constant from the peripheral compartment to the central compartment; Q, intercompartmental clearance; F, bioavailability; f_u, free drug fraction; $AUC_{0-24\,h}$, 24-h AUC; q24 h, every 24 h; q12 h, every 12 h.

administrations, and dosage errors that should not be exceeded for a specific drug.

Because of the consequences of non-compliance to therapeutic regimens, it is unethical to investigate this non-compliance in properly designed trials. Therefore, the aim of the present analysis was to evaluate the consequences of different types of poor adherence (irregular patient adherence to dose timing) for new fluoroquinolone efficacy, using simulation pharmacokinetic/pharmacodynamic (PK/PD) methods.

2. Methods

2.1. Scenarios of patients and dosing regimens

Demographic variables for the virtual patients were extracted from a population similar to that described by Preston et al. [8]. The population was of younger age (<65 years), male, Caucasian patients with a mean weight of 70 kg, mean lean body mass (LBM) of 54 kg and mean creatinine clearance (CL_{Cr}) rate of 100 mL/min. The approximate interindividual variability for the demographic and physiological parameters used in the simulation was 20%.

The oral drug dosing regimens applied in the simulation over 7 days were: (i) 500 mg of LFX every 24 h (q24 h); (ii) 500 mg of LFX every 12 h (q12 h); (iii) 750 mg of LFX q24 h; and (iv) 400 mg of MOX q24 h.

For each of the LFX and MOX dosing protocols, simulation scenarios included irregular patient adherence to dose timing so that the dose for the fourth day of treatment was taken with delays of either 0 h (control), then, 1, 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 16, 19 and 24 h.

2.2. Pharmacokinetic/pharmacodynamic simulation

Previously reported population PK models for LFX [8] and MOX [9] were used to simulate drug pharmacokinetics after dosing in patients similar to those populations. For LFX, the plasma concentration at steady-state was simulated by extracting from the population PK parameters using a two-compartment model with first-order absorption. Demographic and physiological variables (age, CL_{Cr} and weight) were included as predictors in the model [8]. For MOX, a similar two-compartmental model was used where clearance (CL) and central volume of distribution (V) were a function of the patient's LBM [9].

Because the area under the plasma concentration–time curve (AUC) to MIC ratio (AUC/MIC) has been reported to have the strongest correlation with clinical outcomes and the development of resistance to fluoroquinolones, it was chosen as a criterion to evaluate treatment efficacy in this study [3,6]. This PK/PD index was calculated for each patient with the simulated drug concentrations and corresponding MICs. Micro-organism MIC_{90} values (MIC that inhibits 90% of bacterial isolates) from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [10] were obtained for *S. pneumoniae*, *M. catarrhalis* and *H. influenzae*, the most frequent micro-organisms associated with lower respiratory tract infections.

In total, 1000 virtual patients were extracted by Monte Carlo simulation to determine the probability of attaining a target free-drug 24-h AUC to MIC ratio ($fAUC_{0-24\,h}/MIC_{90}$) of 33.8 to assess bacterial eradication of *S. pneumoniae* and of 100 for *H. influenzae* and *M. catarrhalis* for all dosing schemes [6,11]. The probability of target attainment (PTA) (i.e. the probability of reaching the threshold ratio) must be >90% to assure clinical efficacy [6,11,12]. The $fAUC_{0-24\,h}/MIC_{90}$ was determined by dividing the free-drug $AUC_{0-24\,h}$ for each patient by the MIC_{90} of each bacterium. Monte Carlo simulation [12] was performed using NONMEM v.7 (Icon plc., Dublin, Ireland).

3. Results

PK parameters and complete PK profiles for LFX and MOX obtained via Monte Carlo simulation as well as the corresponding mean simulated $fAUC_{0-24\,h}$ for each regimen are listed in Table 1. The $fAUC_{0-24\,h}/MIC_{90}$ was calculated for the alternative dosing protocols across degrees of loss of adherence. Finally, the PTA against *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* was calculated (Tables 2 and 3).

Simulation of the LFX 500 mg q24 h regimen yielded probabilities of achieving $fAUC_{0-24\,h}/MIC_{90}$ in the control situation only for 73% of patients for *S. pneumoniae* but 100% for *H. influenzae* and *M. catarrhalis*. In the non-adherent dosing scenarios, this regimen was not capable of reaching the minimum PTA of the PK/PD index guaranteeing clinical efficacy (>90%), particularly for *S. pneumoniae*.

With the LFX 500 mg q12 h and 750 mg q24 h regimens, the probability of achieving the target of $fAUC_{0-24\,h}/MIC_{90}$ in the