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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

N. Carral[a], J.C. Lukas[a,b], I. Oteo[a], E. Suarez[a,*]

[a] Department of Pharmacology, Faculty of Medicine, University of Basque Country, 48940 Leioa, Spain
[b] Dynakin, S.L., PTB 801, 14890 Derio, Vizcaya, Spain

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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

* Corresponding author. Tel.: +34 94 601 5570; fax: +34 94 601 3220.
E-mail address: elena.suarez@ehu.es (E. Suarez).

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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

Table 2
Probability of target attainment (%PTA) of $fAUC_{0-24\,h}/MIC_{90}$ ratios for levofloxacin administered 500 mg every 12 h (q12 h), 500 mg every 24 h (q24 h) or 750 mg q24 h in control and delayed (1, 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 16, 19 and 24 h) dose ingestion scenarios.

Scenario	$fAUC_{0-24\,h}$ (mean ± S.D.)	*Streptococcus pneumoniae* (MIC_{90} = 1 mg/L) Target ratio ($fAUC_{0-24\,h}/MIC_{90}$) > 33.8	*Haemophilus influenzae* (MIC_{90} = 0.064 mg/L) Target ratio ($fAUC_{0-24\,h}/MIC_{90}$) > 100	*Moraxella catarrhalis* (MIC_{90} = 0.064 mg/L)
		%PTA	%PTA	%PTA
Levofloxacin 500 mg q24 h				
Control	32.05 ± 2.60	73	100	100
Delayed 1 h	31.66 ± 2.57	70	100	100
Delayed 2 h	30.62 ± 2.50	59	100	100
Delayed 3 h	30.17 ± 2.46	51	100	100
Delayed 4 h	29.69 ± 2.42	42	100	100
Delayed 6 h	28.62 ± 2.33	27	100	100
Levofloxacin 500 mg q12 h				
Control	64.10 ± 5.14	100	100	100
Delayed 4 h	61.80 ± 4.92	100	100	100
Delayed 8 h	59.50 ± 4.66	100	100	100
Delayed 12 h	36.84 ± 4.09	98	100	100
Delayed 16 h	32.46 ± 3.90	69	100	100
Delayed 19 h	28.04 ± 4.01	28	100	100
Delayed 24 h	16.68 ± 5.47	1	100	100
Levofloxacin 750 mg q24 h				
Control	48.07 ± 3.90	100	100	100
Delayed 4 h	44.54 ± 3.63	100	100	100
Delayed 8 h	41.04 ± 3.33	100	100	100
Delayed 10 h	38.84 ± 3.14	99	100	100
Delayed 11 h	37.60 ± 3.03	91	100	100
Delayed 12 h	36.05 ± 2.49	82	100	100
Delayed 13 h	34.82 ± 2.77	62	100	100
Delayed 14 h	33.06 ± 2.27	36	100	100
Delayed 16 h	29.56 ± 2.01	2	100	100

$fAUC_{0-24\,h}$, free-drug 24-h area under the plasma concentration–time curve; MIC_{90}, minimum inhibitory concentration that inhibits 90% of bacterial isolates.

control situation was 100% for *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. For LFX 500 mg q12 h, this probability was maintained although the patient can take the dose with a delay of up to 12 h for the three bacteria types. The probability is reduced to ≤69% for *S. pneumoniae* (but not for *H. influenzae* and *M. catarrhalis*, which remain covered at 100%) when the delay is longer than 12 h. Therefore, even skipping a dose of this LFX regimen allows maintaining the probability of efficacy of the antibiotic (Table 2). For LFX 750 mg q24 h, the probability of reaching the desired target for the three bacteria is maintained up to a 11 h delay. It drops to ≤82% for *S. pneumoniae* when the delay in dose ingestion is longer than 11 h.

With MOX 400 mg q24 h, the probability of achieving the target of $fAUC_{0-24\,h}/MIC_{90}$ in the control situation was 100% for *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. This success probability is maintained although the patient may have taken the dose up to 16 h later, especially for *S. pneumoniae* and *H. influenzae*. The probability falls to ≤85% at delays over 14 h for *M. catarrhalis* (Table 3).

4. Discussion

Dose omission and irregular timing of the dosing regimen are the most common types of non-adherence in outpatients receiving antibiotic therapy with dosing intervals of 12 h or 24 h, respectively. The consequences of these types of behaviour could produce unintended variability in drug exposure that can lead to loss of antimicrobial efficacy and thus increase the risk of appearance of resistance in causative micro-organisms.

To date, the majority of PK/PD discussions on antimicrobials have focused on PK/PD relationships evaluated at steady-state drug concentrations. However, assuming steady-state drug concentrations ignores events occurring while the pathogen is exposed to intermittent suboptimal systemic drug concentrations prior to attainment of a steady state. Suboptimal (inadequate) exposure can produce loss of efficacy and growth of resistant bacteria populations [3,13]. Therefore, random intermittent alterations

Table 3
Probability of target attainment (%PTA) of $fAUC_{0-24\,h}/MIC_{90}$ ratios for moxifloxacin administered at 400 mg every 24 h in control and delayed (8, 12, 14, 16 and 24 h) dose ingestion scenarios.

Scenario	$fAUC_{0-24\,h}$	*Streptococcus pneumoniae* (MIC_{90} = 0.25 mg/L) Target ratio ($fAUC_{0-24\,h}/MIC_{90}$) >33.8	*Haemophilus influenzae* (MIC_{90} = 0.064 mg/L) Target ratio ($fAUC_{0-24\,h}/MIC_{90}$) >100	*Moraxella catarrhalis* (MIC_{90} = 0.125 mg/L)
		%PTA	%PTA	%PTA
Control	22.69 ± 4.47	100	100	100
Delayed 8 h	19.39 ± 3.77	100	100	99
Delayed 12 h	17.31 ± 3.71	100	100	95
Delayed 14 h	16.02 ± 3.17	100	100	85
Delayed 16 h	15.97 ± 3.56	100	100	81
Delayed 24 h	5.74 ± 2.52	21	37	1

$fAUC_{0-24\,h}$, free-drug 24-h area under the plasma concentration–time curve; MIC_{90}, minimum inhibitory concentration that inhibits 90% of bacterial isolates.

in $fAUC_{0-24\,h}/MIC_{90}$, as occur in non-adherence, may significantly impact the expected clinical response and increase the possibility of resistance appearance.

Although missing (or delaying) a dose from the therapeutic regimen is a random process with no specific patterns, it is possible to assume some general representative scenarios for this situation that will allow formation of dosing recommendations in non-adherent patient behaviour. The difficulty in improving compliance through changes in patient behaviour has led to a focus on the drug and micro-organism itself, attempting to demonstrate which of the fluoroquinolones and dosing regimen shows most forgiveness with respect to loss of antimicrobial efficacy. Among the fluoroquinolones used to treat respiratory infections, not all have the some relationship between dose and concentration, and between concentration and antimicrobial effect, for respiratory micro-organisms [6].

Here PK/PD simulation has been used to evaluate the impact of patient adherence on fluoroquinolone efficacy against infections produced empirically by respiratory micro-organisms such as *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Data from previously reported population analyses for LFX [8] and MOX [9] have been extracted, so the present results concern similar populations and covariate relations. In the simulation, delays of 0 h (control) and up to 24 h, e.g. in 2-h increments and with respect to the standard protocol, on the fourth post-treatment day were assumed. The fourth post-treatment day was chosen because typically patients observe an improvement in their infectious process by the 4th day, leading to increased probability of delaying or skipping a dose in self-medication.

A PTA > 90% of reaching the PK/PD index ($fAUC_{0-24\,h}/MIC_{90}$ ratio) was the threshold for efficacious therapy [6,12]. The consequences of non-compliance to that threshold could vary depending on the fluoroquinolone and dosing regimen for the same lack of adherence.

The results show that LFX is a fluoroquinolone that guarantees antimicrobial efficacy in non-adherence episodes but with a dependence on the dosing regimen. With the 500 mg q12 h regimen, delays of $\leq$12 h, including skipping a dose entirely, continue to guarantee efficacy in >90% of cases for $fAUC_{0-24\,h}/MIC_{90}$ related to therapy for three major bacteria (*S. pneumoniae*, *H. influenza* and *M. catarrhalis*). When a 500 mg q24 h dose is given, the probability of efficacious therapy is low with any adherence, even full adherence. In countries (e.g. some European states) where the approved schedules are for 500 mg q24 h or 500 mg q12 h (within European Medicines Agency guidelines) [14], this can be problematic. In contrast, the higher dose of 750 mg q24 h guarantees reaching the PK/PD target with delays of up to 11 h, so, also considering its once-daily interval, this may be the optimal regimen for LFX in patients with irregular adherence to dose timing.

For MOX, when a 400 mg q24 h dose is administered, the probability to reach $fAUC_{0-24\,h}/MIC_{90}$ is >90% up to 16 h of delay, permitting comfortable margins in self-medication. But if the infectious process concerns *M. catarrhalis*, the probability is reduced significantly for delays $\geq$14 h.

The differential loss of efficacy for LFX and MOX in some of the combinations of regimen and non-adherence situations is related to the different PK and PD characteristics of LFX and MOX. The bioavailability (F) of both is elevated (99% for LFX and 86% for MOX) [7] and is nearly constant as it is not influenced by food intake. The parameter ranges in the studied population for the apparent systemic clearance (CL/F) were 8.69–13.32 L/h for LFX and 6.12–17.30 L/h for MOX. For LFX the variation in CL was linked to CL_{Cr} and age, whilst for MOX the dependence is on LBM.

The difference in free drug percent (52% for MOX and 69% for LFX) is related to the reduced $fAUC_{0-24\,h}$ of MOX. Protein binding may play an important role with these antibiotics. Assuming permeability of unbound drug into capillaries, therapeutic concentrations at the site of action may be more quickly achieved by agents with low protein binding [15]. Indeed, here the $fAUC_{0-24\,h}$ for LFX is higher than MOX after the respective dose. However, this is compensated by the pharmacodynamics [10,11]. The MIC_{90} for respiratory bacteria shows that MOX is more potent than LFX, which apparently compensates for differences in exposure due to the pharmacokinetics, and both drugs reach high $fAUC_{0-24\,h}/MIC_{90}$ ratios for *S. pneumoniae*, *H influenzae* and *M. catarrhalis*. The MIC_{90} against *S pneumoniae* is 1 mg/L for LFX and 0.25 mg/L for MOX. For *H. influenzae* and *M. catarrhalis*, the MIC_{90} is 0.064 mg/L for LFX and 0.064 mg/L and 0.125 mg/L, respectively, for MOX [10].

Importantly, the relationship between exposure intensity ($fAUC_{0-24\,h}/MIC_{90}$ ratio) and efficacy has a sigmoidal shape. At very low values of exposure intensity, there is no measurable effect, whereas at larger values, the greater the exposure intensity, the greater the bactericidal effect up to a maximum value. Therefore, in such antimicrobial treatments and risk of patients with irregular adherence to dose timing, it is imperative to seek a regimen that guarantees a high probability of maintaining elevated exposure in order to ensure efficacy. For patients with poor adherence to therapy, only the dose of 500 mg q24 h for LFX may not guarantee an elevated probability (>90%) of reaching efficacious $fAUC_{0-24}/MIC_{90}$.

Maintenance of steady state is another condition for efficacy as it also maximises efficacious exposure. In patients, lack of adherence to recommended dose continuity leads to a loss of the PK equilibrium steady-state that produces antimicrobial efficacy coverage. Since the half-lives of LFX and MOX differ (6.9 h vs. 12.1 h), missing a dose implies different times to equilibrium recovery.

In conclusion, both fluoroquinolones show forgiveness in situations with lack of adherence in dosing. The dose of 500 mg q24 h for LFX is the least robust treatment against *S. pneumoniae*, *H. influenzae and M. catarrhalis*, even under full compliance. A good choice is LFX 500 mg q12 h, but in order to maximally increase efficacy probability and increase the odds of adherence the once-daily regimens of LFX 750 mg q24 h or MOX 400 mg q24 h are clearly the best options.

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