Moxifloxacin in Chronic Obstructive Pulmonary Disease: Pharmacokinetics and Penetration into Bronchial Secretions in Ward and Intensive Care Unit Patients

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ABSTRACT This study aimed to evaluate the pharmacokinetic profile of moxifloxacin (MXF) in serum and sputum/bronchial secretions of 22 patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) hospitalized in the ward and intensive care unit (ICU). The data showed that ICU patients had lower concentrations in secretions ($P = 0.01$). However, no other statistically significant differences were observed in pharmacokinetic parameters and penetration in secretions between ward and ICU patients. MXF showed a favorable pharmacokinetic profile, and the pharmacodynamic targets for common pathogens for AECOPD were achieved.

KEYWORDS COPD, ICU, bronchial secretions, moxifloxacin, pharmacokinetics

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are most often caused by Gram-positive (*Streptococcus pneumoniae*) and Gram-negative (*Haemophilus* spp., *Moraxella catarrhalis*) pathogens which are isolated in >50% of sputum cultures (1, 2). The empirical antibiotic therapy in AECOPD entails the use of quinolones (3–6). During the last decades, several studies focused on the pharmacokinetics (PK) of moxifloxacin (MXF) in the respiratory system (7–9), although data on its penetration in bronchial secretions and sputum in AECOPD are scarce.

The primary purpose of this study was to evaluate the PK profile of MXF, administered in doses of 400 mg once daily at steady state, in serum and sputum/bronchial secretions during AECOPD. The secondary purposes were assessment of the PK differences between ward and intensive care unit (ICU) patients and evaluation of the pharmacodynamic (PD) targets for the most common pathogens that cause AECOPD.

This was a prospective open-label study performed between May 2012 and June 2014 in the Department of Pulmonary Medicine and the Respiratory Failure Unit, Aristotle University of Thessaloniki, "G. Papanikolaou" Hospital, Greece. The study protocol was designed according to the declaration of Helsinki and national and institutional standards and was approved by the Institutional Review Board of the hospital (reference no. 350). The patients or their legal representatives gave informed consent. All patients were hospitalized with AECOPD according to Anthonisen criteria (10).

The criteria for exclusion were radiologic confirmation of pneumonia, hypersensitivity to quinolones, pregnancy or breast feeding, severe renal failure (11), hepatic insufficiency, a prolonged Q-T interval, history of convulsions after quinolone administration, epilepsy, hypokalemia, and use of theophylline or anti-arrhythmic medication. Patients with median forced expiratory volume in 1 s of <35% were also excluded, as the presence of *Pseudomonas aeruginosa* was considered possible.

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TABLE 1 Demographic characteristics of patients with AECOPD

Characteristic	Total	Ward	ICU
Age (yr, mean [SD])	70.68 (9.90)	70.90 (10.16)	70.45 (10.12)
Sex (F/M ^a) (n)	4/18	1/10	3/8
Weight (kg, mean [SD])	85.40 (18.03)	79.54 (8.23)	91.27 (23.22)
Smoking (pack-yr, mean [SD])	75 (32.03)	76.36 (31.07)	73.63 (34.43)

^aF, female; M, male.

A dose of 400 mg of MXF (Bayer AG, Leverkusen, Germany) was administered intravenously every 24 h by 1 h infusion, and the study was conducted at steady state (for at least 72 h after the first dose). Blood samples were collected from peripheral catheters (different from those used for MXF administration) at specific time points, i.e., just before MXF administration (time 0), after the 1-h administration ended (time 1), and 2, 3, 4, 6, 9, 12, and 24 h after initiation of the intravenous administration. The samples were centrifuged, and the supernatant plasma was stored at -20°C . Secretions were collected 0, 2, 4, 6, 9, 12, and 24 h after initiation of infusion, and they were homogenized and emulsified with ultrasonic processor for 1 min (VCX-130; Sonics and Materials, Inc., Newton, CT). The product was stored at -20°C . All specimens were processed using high-performance liquid chromatography (1100 series; Agilent Technologies, Inc., Santa Clara, CA) with fluorescence detection, as previously described (12).

Plasma and bronchial secretion concentrations were plotted against time, and the PK data were analyzed by a two-compartment model (WinNonlin v.3.0 PK software, Pharsight Corporation, Mountain View, CA). The goodness of fit of the model was evaluated by Akaike and Schwarz criteria (13), as was the correlation between observed and calculated concentrations. In bronchial secretions, maximum concentration of drug in serum ($C_{\max}$) and the time to reach $C_{\max}$ were obtained observationally by individual concentration-time data. The area under the concentration-time curve from time 0 to 24 h (AUC_{0-24}) was determined by the trapezoidal rule. To calculate the penetration ratio for each patient, the AUC_{0-24} for bronchial secretions was divided by the AUC_{0-24} for plasma.

$\text{AUC}_{0-24}/\text{MIC}$ ratio was also calculated and was contrasted with the PD target concerning the main pathogens related to AECOPD. The PD target for the fluoroquinolones was free (unbound) antibiotic AUC from time 0 to 24 h ($f\text{AUC}_{0-24}$)/MIC ≥ 30 and $\text{AUC}_{0-24}/\text{MIC} \geq 125$ for Gram-positive and Gram-negative microbes, respectively (14, 15). $f\text{AUC}$ was evaluated by multiplying the AUC_{0-24} by 0.6, which is the approximate free fraction of the drug (16). To adapt data to our hospital's bacterial resistance (for the period that the sampling took place), we calculated the AUC/MIC ratio using MIC_{90} (MIC at which 90% of strains are inhibited) of isolated bacteria in "G. Papanikolaou" Hospital. In this case, the MIC_{90} of *S. pneumoniae* was 0.25 mg/liter, and those of *H. influenzae* and *M. catarrhalis* were 0.06 mg/liter, respectively.

Statistical analysis was performed using IBM SPSS statistics 24 (SPSS, Inc., Chicago, IL). The normality was checked by the Shapiro-Wilk test and by the structure of P-P and Q-Q histograms. For statistical significance, Mann-Whitney and independent *t* tests were used.

Twenty-two patients (11 in ward and 11 in ICU) were included in the study. Demographic data are summarized in Table 1 and PK data in Table 2. Mean maximum concentration of MXF in plasma ($C_{\max\text{-pl}}$) at the end of administration was 5.9 ± 0.9 mg/liter. The respective concentration in secretions ($C_{\max\text{-sp}}$) was 4.5 ± 2.2 mg/liter and was reached 3.5 h after the beginning of administration. Mean total AUCs were 45.1 ± 10.1 and 40 ± 17.9 mg $\cdot$ h/liter in plasma and secretions, respectively. The mean penetration ratio in secretions was very good (0.9 ± 0.4). The total concentration profile in plasma and sputum/bronchial secretions is shown in Fig. 1.

In ward patients, $C_{\max\text{-pl}}$ was 6.2 ± 0.7 mg/liter, and $C_{\max\text{-sp}}$ was 5.6 ± 2.4 mg/liter. ICU patients had lower concentrations in blood and secretions, but the difference reached statistical significance only for bronchial secretions ($P = 0.01$) (Table 2). The penetration ratio did not differ significantly between the two groups. The concentration plots in plasma and secretions over time in the two subgroups are presented in Fig. 2.

TABLE 2 Pharmacokinetic parameters in plasma and sputum/bronchial secretions from ward and ICU patients with AECOPD

Parameter ^a	Total		Ward		ICU		P value
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	
$C_{\max\text{-pl}}$ (mg/liter)	5.96 (0.97)	3.87–7.52	6.25 (0.77)	5.16–7.52	5.68 (1.09)	3.87–7.28	0.170
$C_{\min\text{-pl}}$ (mg/liter)	0.56 (0.25)	0.22–1.32	0.564 (0.20)	0.25–1	0.56 (0.31)	0.22–1.32	0.987
$C_{\max\text{-sp}}$ (mg/liter)	4.51 (2.24)	1.41–9.66	5.69 (2.46)	1.41–9.66	3.33 (1.20)	1.56–5.25	0.01
$C_{\min\text{-sp}}$ (mg/liter)	0.34 (0.25)	0.05–1.08	0.41 (0.26)	0.11–0.96	0.38 (0.32)	0.05–1.08	0.848
$AUC_{0-24\text{-pl}}$ (mg · h/liter)	45.10 (10.13)	31.18–68.78	44.21 (3.29)	34.44–65.11	45.99 (12.04)	31.18–68.78	0.974
$AUC_{0-24\text{-sp}}$ (mg · h/liter)	40.02 (17.93)	9.18–71.39	44.14 (19.81)	12.28–71.39	35.89 (15.67)	9.18–53.99	0.292
Penetration ratio	0.90 (0.40)	0.17–1.53	0.99 (0.43)	0.33–1.53	0.80 (0.36)	0.17–1.37	0.263
CL (liter/h)	9.11 (2.18)	4.96–13.4	9.38 (1.75)	6.32–12.11	8.85 (2.60)	4.96–13.4	0.581
V_{ss} (liter)	119.02 (39.72)	59.01–216.83	122.2 (41.06)	59.01–211.9	115.77 (40.02)	67.87–216.83	0.622
V_1 (liter)	60.01 (18.16)	25.74–109.75	55.74 (12.35)	34.51–72.23	64.27 (22.36)	25.74–109.75	0.280
$t_{1/2}$ (h)	10.34 (4.68)	6.08–26.46	10.98 (5.57)	6.61–26.46	9.7 (3.74)	6.08–16.73	0.450
$t_{\max\text{-sp}}$ (h)	3.5 (median)	1–12	4 (median)	2–6	2 (median)	1–12	0.332

^a $C_{\max\text{-pl}}$, peak concentration in plasma; $C_{\min\text{-pl}}$, trough concentration in plasma; $C_{\max\text{-sp}}$, peak concentration in sputum; $C_{\min\text{-sp}}$, trough concentration in sputum; $AUC_{0-24\text{-pl}}$, area under the concentration–time curve from time zero to 24 h for plasma; $AUC_{0-24\text{-sp}}$, area under the concentration–time curve from time zero to 24 h for sputum; $t_{\max\text{-sp}}$, time to reach $C_{\max}$ in sputum; CL, total body clearance; V_{ss} , volume of distribution at steady state; V_1 , volume of the central compartment; $t_{1/2}$, elimination half-life; $t_{\max\text{-sp}}$, time to reach $C_{\max}$ in sputum.

As for PD parameters, the maximum MIC value to guarantee adequate exposure of MXF was calculated to be 0.9 mg/liter for the Gram-positive and 0.3 mg/liter for the Gram-negative strains. Based on local microbiological data, the PD target was accomplished for all patients for *S. pneumoniae* (mean $fAUC_{0-24}/MIC_{90}$, 108.2; range, 74.8 to 165.1). As for *M. catarrhalis* and *H. influenzae*, the PD target was also achieved for all patients (mean AUC_{0-24}/MIC_{90} , 751.6; range, 519 to 1,146.3).

Based on the present data, the MXF PK is in accordance with those of healthy volunteers (17), patients with lower respiratory tract infections (9), ICU patients with pneumonia (7), and model-estimated values for patients with community-acquired pneumonia (18), although plasma $C_{\max}$ and AUC values were generally higher in the present study. However, the concentrations in elderly patients with chronic bronchitis (19) and hemodialysis patients with pneumonia (20) were comparable to our results.

To our knowledge, this is the first study to assess possible differences in MXF PK in ward and ICU patients. Apart from the histological damage caused by mechanical ventilation (21), PK of antibiotics may be significantly different in ICU patients for various reasons (22–27). Despite these, PK was not generally different between ward and ICU patients in the present study. The only significant difference was observed in $C_{\max\text{-sp}}$. However, the small patient number does not allow for safe conclusions on this finding.

Penetration of MXF in the lung and pleura has been investigated (2, 28–31),

FIG 1 Mean $\pm$ standard deviation of moxifloxacin (MXF) concentration (C) versus time in plasma and sputum/bronchial secretions in AECOPD patients.

FIG 2 Mean $\pm$ standard deviation of moxifloxacin (MXF) concentration (C) versus time in plasma (a) and sputum/bronchial secretions (b) in AECOPD patients in ward and ICU.

although not in patients with AECOPD. A published review about the management of chronic bronchitis with MXF estimates penetration in saliva and bronchial mucosa to be between 0.75 to 1.3 and 1.7 to 2.1, respectively (2). Our ward data for sputum were within this range, but the ICU data were lower than the respective ratio for bronchial mucosa. In the study by Leone et al. (7), the $C_{\max}$ in bronchial secretions was very similar to ours (3.1 versus 3.33 mg/liter), and, although the AUCs in plasma and secretions were lower at steady state (27.2 and 24.2 mg $\cdot$ h/liter, respectively), the penetration was better.

Regarding PD parameters and bactericidal activity, the theoretical PD breakpoint of oral MXF was also 0.35 mg/liter in elderly patients with AECOPD (19). A similar conclusion was drawn from a recent study about patients with severe pneumonia and AECOPD, where it was found that the current MXF dose failed to achieve the desired outcome when the microbial MIC was ≥ 1 μ g/ml (32).

The main results of the present study are as follows: (i) MXF showed a favorable PK profile in plasma and good penetration in secretions in AECOPD; (ii) apart from the lower $C_{\max-sp}$ in ICU patients, no statistically significant differences were observed in PK parameters and penetration between the two groups of patients; and (iii) PD targets for the most common pathogens implicated in AECOPD were achieved.

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