Moxifloxacin Pharmacokinetics and Pleural Fluid Penetration in Patients with Pleural Effusion

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The aim of this study was to evaluate the pharmacokinetics and penetration of moxifloxacin (MXF) in patients with various types of pleural effusion. Twelve patients with empyema/parapneumonic effusion (PPE) and 12 patients with malignant pleural effusion were enrolled in the study. A single-dose pharmacokinetic study was performed after intravenous administration of 400 mg MXF. Serial plasma (PL) and pleural fluid (PF) samples were collected during a 24-h time interval after drug administration. The MXF concentration in PL and PF was determined by high-performance liquid chromatography, and main pharmacokinetic parameters were estimated. Penetration of MXF in PF was determined by the ratio of the area under the concentration-time curve from time zero to 24 h (AUC24) in PF (AUC24PF) to the AUC24 in PL. No statistically significant differences in the pharmacokinetics in PL were observed between the two groups, despite the large interindividual variability in the volume of distribution, clearance, and elimination half-life. The maximum concentration in PF (CmaxPF) in patients with empyema/PPE was 2.23 ± 1.31 mg/liter, and it was detected 7.50 ± 2.39 h after the initiation of the infusion. In patients with malignant effusion, CmaxPF was 2.96 ± 1.45 mg/liter, but it was observed significantly earlier, at 3.58 ± 1.38 h (P < 0.001). Both groups revealed similar values of AUC24PF (31.83 ± 23.52 versus 32.81 ± 12.66 mg · h/liter). Penetration of MXF into PF was similarly good in both patient groups (1.11 ± 0.74 versus 1.17 ± 0.39). Despite similar plasma pharmacokinetics, patients with empyema/parapneumonic effusion showed a significant delay in achievement of PF maximum MXF levels compared to those with malignant effusion. However, in both groups, the degree of PF penetration and the on-site drug exposure, expressed by AUC24PF, did not differ according to the type of pleural effusion.

The development of a pleural effusion is a common complication of pneumonia, occurring in up to 57% of cases. The majority of these effusions are clear, sterile exudates that frequently resolve with antimicrobial treatment and do not require drainage. In some cases, this initial effusion may progress to a complicated parapneumonic effusion (PPE), which is characterized by fibrin deposition and fluid infection. These effusions cannot resolve without drainage and usually require placement of a chest tube. Persistent pleural infection may result in the accumulation of pus in the pleural space, which is called “empyema” (1).

All patients with parapneumonic effusion or empyema should initially be treated with intravenous antibiotics. The initial selection of the agent and dose is usually based on whether the patient has community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP) and depends on the severity of the patient’s clinical condition (2). Respiratory fluoroquinolones, such as moxifloxacin (MXF) or levofloxacin, are recommended as initial empirical antibiotic therapy both for hospitalized patients with severe and nonsevere CAP (3) and for those with HAP or ventilator-associated pneumonia without known risk factors for multidrug-resistant pathogens and early onset (4).

MXF is widely used in the treatment of community-acquired pneumonia and pleural effusion due to its broad antimicrobial activity against Gram-positive and Gram-negative bacteria, including anaerobes (1). Although there are several studies (5–9) about ciprofloxacin (CIP) penetration in human pleural fluid (PF), data on MXF are scarce and are based on experimental pleural empyema in rabbits (10, 11). On the basis of these data, MXF penetrates well into infected rabbit pleural fluid. However, limitations, such as the different route and time of MXF administration, the difference in visceral pleura thickness between human and rabbit, and the turpentine-induced empyema, render the extrapolation of these results to human patients uncertain. To the best of our knowledge, despite its widespread use during the last 15 years, there are no studies investigating MXF penetration either in human empyema or in effusions due to other etiologies.

The aim of the present study was to determine the pharmacokinetics (PK) of MXF in plasma (PL) and human pleural fluid and to evaluate under actual clinical conditions its penetration into human exudative pleural fluid effusions of different etiologies, namely, empyemic/parapneumonic and malignant effusions.

MATERIALS AND METHODS

Study design. The study was designed as a prospective, open-label study and took place in the Pulmonary Department of the G. Papanikolaou Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece, from October 2012 to June 2013. The research was conducted in accordance with the Declaration of Helsinki as well as national and institutional standards. The study protocol was approved by the institutional review board of G. Papanikolaou Hospital (reference no. 12/25-10-2012), and written informed consent was obtained from all study participants.

Patient population. Patients were eligible for enrollment in the study if they were admitted to the Pulmonary Department for empyema/para-

Received 23 October 2013 Accepted 14 November 2013


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pneumonic effusion or exudative malignant pleural effusion and had in place a chest tube for continuous drainage. The documentation of the pleural effusion’s etiology was based on clinical manifestations, imaging studies, and pleural fluid biochemical analysis, microbiology, and cytology (12). Differentiation of transudates from exudates was performed according to the criteria of Light et al. (13).

A complete medical history and laboratory test results, including complete blood cell counts, erythrocyte sedimentation rate, serum glucose and electrolyte levels, liver function test results, total protein and albumin concentrations, serum creatinine levels, and results of urine analyses, were recorded prior to the commencement of the protocol. Pleural fluid underwent Gram’s staining, microbiology, and cytology studies upon clinical indication. Exclusion criteria were as follows: a history of allergy to fluoroquinolones, a prolonged Q-T interval, renal insufficiency, or malignancy. Differentiation of transudates from exudates was performed using the criteria of Light et al. (13).

MXF was prescribed empirically to the patients suffering from empyema or parapneumonic pleural effusion by their treating physician. MXF was given intravenously to these patients at a dosage of 400 mg every 24 h by infusion over 1 h via a peripheral venous line, and the study was conducted on the first day of treatment. Patients with malignant pleural effusion were administered a single intravenous dose of 400 mg MXF only for study purposes.

Specimen collection. Blood samples were obtained via a separate peripheral venous catheter just prior to the MXF administration (time zero) and at the following time points postdosing: 1 h (at the end of the infusion), 2 h, 3 h, 4 h, 6 h, 9 h, 12 h, and 24 h. Pleural fluid samples were obtained through a chest tube at the same time points. Plasma was separated from whole blood by centrifugation. All plasma and pleural fluid samples were stored at −20°C until analysis.

Moxifloxacin HPLC assay. MXF (Bayer AG, Leverkusen, Germany) concentrations in plasma and pleural fluid were determined using high-performance liquid chromatography (HPLC) with fluorescence detection according to the method previously described by Liang et al., with modifications (15).

Analytical separation was performed via a Nucleosil 100C18, 250- by 4.6-mm, 5-μm column (M-Z Analysentechnic, Mainz, Germany) protected by a guard column (20 by 4.6 mm; 5 μm) of the same composition. The detector was set at an excitation wavelength of 500 nm.

Coefficients of determination (r^2) for MXF and CIP over the standard curve concentrations of 0.05 to 10 mg/liter for plasma and pleural fluid were 0.999 for the entire study. Intraday and interday coefficients of variation were ≤5%. The rates of recovery of MXF and CIP in plasma and pleural fluid were greater than 100% and 99%, respectively.

Sample preparation and extraction procedure. Fifty microliters of an internal standard solution of 20 mg/liter and 300 μl of acetonitrile were added to 250 μl of plasma or pleural fluid, and the mixture was then vortexed for 30 s and centrifugated at 3,600 rpm for 10 min (Zentrifugen Micro 20; Hettich, Germany). The clear supernatant was then injected into the column via an autosampler and a 20-μl loop.

Pharmacokinetic analysis. PL and PF MXF concentrations were plotted against time, and the pharmacokinetic parameters were estimated by compartmental analysis using the WinNonlin software program (version 3.0; Pharsight Corporation, Mountain View, CA). A two-compartment model with first-order elimination and no lag time was used, and the goodness of fit of the model was determined by using the Akaike and Schwartz criteria, as well as the correlation between the observed and calculated concentrations. The peak (maximum) concentration in plasma (Cmax^pl) and the trough (minimum) concentration in plasma (Ctrough^pl) were observed at 24 h postdosing. The peak (maximum) concentration in pleural fluid (Cmax^pf) and the time to reach Cmax^pf (Tmax^pf) were obtained observationally from individual concentration-time data. All concentrations in both matrices were total drug concentrations. The area under the concentration-time curve from time zero to 24 h (AUC^24^pf) was determined by the trapezoidal rule. The penetration ratio for each patient was obtained by dividing the AUC^pf by the AUC^pl for plasma (AUC^pl). Calculation of the volume of distribution (V), total body clearance (CL), and elimination half-life (t_{1/2}) was performed by a compartmental method, as described above.

Statistical analysis. All data are expressed as means ± standard deviations unless otherwise noted. Biostatistical analysis was performed using SPSS for Windows, release 17.0.1 (standard version; SPSS Inc.). The normality of the distribution was assessed by the Shapiro-Wilk test. Pharmacokinetic parameters between empyemic/parapneumonic and malignant effusions were compared by an independent samples t test if the data were normally distributed. The nonparametric Kruskal-Wallis test was used if the data were not normally distributed. Linear regression analysis was performed to compare the drug concentrations in plasma and pleural fluid. The coefficients of determination (r^2) were calculated for plasma and pleural fluid concentrations of 0.05 to 10 mg/liter for plasma and pleural fluid. The rates of recovery of MXF and CIP in plasma and pleural fluid were greater than 100% and 99%, respectively.

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RESULTS

Twenty-four patients (19 males and 5 females) were included in the study. Twelve of these patients were admitted to the hospital due to complicated parapneumonic effusion (PPE) or empyema (group A), and the rest suffered from malignant pleural effusion (group B). Their demographics and pleural fluid characteristics are shown in Tables 1 and 2, respectively.

The pharmacokinetic parameters of MXF in plasma for both patient groups are summarized in Table 3. The mean peak concentrations in plasma were 4.64 ± 0.68 mg/liter for group A and 4.28 ± 0.69 mg/liter for group B, respectively, and were achieved by the end of drug infusion. The observed mean concentrations in plasma at 24 h (C_{trough,PL}) were 0.37 ± 0.13 mg/liter for group A and 0.39 ± 0.07 mg/liter for group B. A large variability in the pharmacokinetic data was observed for both groups, especially in V, which ranged from 82.66 to 310.95 liters, although their mean values were similar (165.12 liters for group A versus 155.22 liters for group B). Similarly, CL ranged from 6.82 to 19.10 liters/h, and t_{1/2} was as short as 3.84 h and as long as 36.20 h. In both groups, a similar AUC_{24,PL} was observed (28.39 ± 5.47 mg · h/liter for group A versus 28.06 ± 4.37 mg · h/liter for group B).

Regarding the pleural fluid, the mean C_{max,PF} in patients with empyema/PPE was 2.23 ± 1.31 mg/liter, and it was detected 7.50 ± 2.39 h after the initiation of the infusion. In patients with malignant effusion, the mean C_{max,PF} was 2.96 ± 0.74 mg/liter, and it was observed significantly earlier at 3.58 ± 1.38 h after the start of the infusion (P < 0.001). Both groups revealed a similar mean AUC_{24,PF} (31.83 ± 23.52 mg · h/liter for group A versus 32.81 ± 12.66 mg · h/liter for group B), but patients with empyema/PPE showed a remarkable interindividual variability (AUC_{24,PF} range, 51 to 96.11 mg · h/liter). The penetration of MXF into pleural fluid was similarly good in patients from both groups (1.11 ± 0.74 for group A versus 1.17 ± 0.39 for group B). The mean C_{trough,PF} was found to be 0.99 ± 0.84 mg/liter for group A and 0.73 ± 0.46 mg/liter for group B, with empyemic patients showing a slightly higher—but not statistically significant—trough concentration of moxifloxacin at the end of the 24-h interval. The equilibration of the MXF concentration between plasma and pleural fluid occurred at 5 h in patients with empyema/parapneumonic effusion, whereas it occurred at 3 h in those with malignant effusion. The pharmacokinetic parameters of MXF in pleural fluid for both patient groups are summarized in Table 4, while Fig. 1A and B represent the concentration-time curves of MXF in the plasma and pleural fluid of the two groups.

In order to overcome the age difference between the two groups, we assessed the PF pharmacokinetic data in two subgroups of the 10 older patients with empyema/PPE (mean age, 61.9 years) and compared them to the data for the eight younger patients with malignant effusion (mean age, 63.8 years). T_{max,PF} and C_{max,PF} maintained the same difference between the two groups (for T_{max,PF}, 7.50 versus 3.87 h for groups A and B, respectively; for C_{max,PF}, 3.13 versus 2.81 mg/liter for groups A and B, respectively), while AUC_{24,PF} and AUC_{24,PF}/AUC_{24,PL} remained equal (for AUC_{24,PF}, 31.49 mg · h/liter for group A versus 33.07 mg · h/liter for group B; for AUC_{24,PF}/AUC_{24,PL}, 1.12 for group A versus 1.15 for group B).
Antimicrobial agents may be increased (20). In the case of pleural space infection, the local environment (19). On the contrary, under circumstances of increased permeability of the thickened pleura and the more acidic serum antibiotic levels in patients with empyema, due to the degradation of fibrin on pleural membranes, and the formation of septations lead to a thick, nonelastic pleural peel (21). Regarding malignant effusions, which are predominantly exudates (22), the main mechanisms of fluid production include impaired drainage of the pleural space due to obstruction of blood vessels and lymphatics of the lung and pleura and increased formation of pleural fluid (23).

Therefore, it is important to evaluate the penetration of antibiotics into the pleural space, and careful consideration should be given to the underlying pathophysiology and the different mechanisms of fluid formation. In empyema, during the exudative stage, pleural fluid accumulates in the pleural space secondary to inflammation and the increased permeability of the visceral pleura. As the infection progresses, the bacterial invasion of the pleural space, the deposition of fibrin on pleural membranes, and the formation of septations lead to a thick, nonelastic pleural peel (21). Regarding malignant effusions, which are predominantly exudates (22), the main mechanisms of fluid production include impaired drainage of the pleural space due to obstruction of blood vessels and lymphatics of the lung and pleura and increased formation of pleural fluid (23).

### DISCUSSION

Antibiotic penetration into the site of infection is critical in order to achieve a favorable clinical outcome. The success of an antimicrobial agent in the treatment of pleural space infection depends on the achievement of sufficient drug concentrations in the pleura and, more specifically, in pleural fluid (16,17). For the first time in the literature, results from the present study indicate that MXF penetrates sufficiently into pleural fluid in patients with empyema with malignant effusion, though penetration is significantly slower in the empyemic patients.

In general, it is believed that antibiotic levels in pleural fluid are similar to those in serum, but most studies in humans involved patients with diseases other than empyema (18). Teixeira et al. have suggested that pleural fluid antibiotic levels are lower than serum antibiotic levels in patients with empyema, due to the decreased permeability of the thickened pleura and the more acidic local environment (19). On the contrary, under circumstances of acute infection, which involves inflammation, vasodilation, edema, and increased membrane permeability, the penetration of antimicrobial agents may be increased (20).

Therefore, it is important to evaluate the penetration of antibiotics into the pleural space, and careful consideration should be given to the underlying pathophysiology and the different mechanisms of fluid formation. In empyema, during the exudative stage, pleural fluid accumulates in the pleural space secondary to inflammation and the increased permeability of the visceral pleura. As the infection progresses, the bacterial invasion of the pleural space, the deposition of fibrin on pleural membranes, and the formation of septations lead to a thick, nonelastic pleural peel (21). Regarding malignant effusions, which are predominantly exudates (22), the main mechanisms of fluid production include impaired drainage of the pleural space due to obstruction of blood vessels and lymphatics of the lung and pleura and increased formation of pleural fluid (23).

Hence, it could be assumed that the penetration of antimicrobial agents into pleural effusions of a different etiology could vary according to the underlying pathophysiology. Indeed, in a rabbit model of empyema, penetration of antibiotics varied significantly (19). On the other hand, a previous study concluded that there is very little difference between chemically diverse antimicrobial agents in their degree of pleural penetration (18). Notably, none of these studies included fluoroquinolones, a class of antimicrobials able to achieve a large volume of distribution and extensive tissue penetration (24). There are indications that the antimicrobial activity of compounds like MXF, which is devoid of a piperazinyl ring at position 7, is not affected by acidic conditions (25). Therefore, it could be expected that newer fluoroquinolones, and specifically MXF, would be an attractive treatment option for infected or contaminated pleural effusions. The present data are in favor of this hypothesis.

Our results show that the interindividual variability of MXF’s pharmacokinetic parameters is considerable. This could be explained by the fact that all subjects were seriously ill, and therefore, pharmacokinetic parameters were subjected to a number of modifying factors, such as cardiac performance, the adequacy of tissue perfusion, coadministration of drugs, and competition for the same metabolic pathways (26). Moreover, it is known that the genetic variability of the metabolic pathways represents a major modifying factor (27). It is evident that the coexistence of more than one modifying factor in a given patient makes determination of the individual contribution practically impossible. Nevertheless, MXF revealed similar pharmacokinetic characteristics (e.g., Cmax, Ctrough, AUC24, and AUC24PF/AUC24PL) in both groups of patients, confirming its excellent ability to penetrate into tissue compartments independently of the degree of inflammation or pH reduction.

The main finding in our study is the statistically significant prolongation of TmaxPF in the group of patients with empyema/parapneumonic effusion and the slightly lower CmaxPF. Correspondingly, the same group of patients tended to achieve higher

### TABLE 4 Main pharmacokinetic parameters of moxifloxacin in PF

<table>
<thead>
<tr>
<th>Patient group</th>
<th>CmaxPF (mg/liter)</th>
<th>CtroughPF (mg/liter)</th>
<th>AUC24PF (mg · h/liter)</th>
<th>AUCPF/AUCPL</th>
<th>TmaxPF (h)</th>
</tr>
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<tbody>
<tr>
<td>Empyema/PPE</td>
<td>2.23 ± 1.31</td>
<td>0.99 ± 0.84</td>
<td>31.83 ± 25.32</td>
<td>1.11 ± 0.74</td>
<td>7.50 ± 2.39</td>
</tr>
<tr>
<td>Malignant effusion</td>
<td>2.96 ± 1.45</td>
<td>0.73 ± 0.46</td>
<td>32.81 ± 12.66</td>
<td>1.17 ± 0.39</td>
<td>3.58 ± 1.38</td>
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*P 0.001*
trough moxifloxacin levels in pleural fluid, although the difference did not reach statistical significance. It could be assumed that fibrin deposition on pleural surfaces, along with a degree of thickening, raises a barrier to prompt penetration into the pleural space. Notwithstanding, MXF was able to achieve AUCs in pleural fluid equal to or higher than those obtained in plasma in both groups of patients, indicating that microbial exposure to the drug’s antimicrobial action is not compromised by tissue factors or the degree of the inflammatory process. However, patients with empyema/PPE showed a remarkable variation in AUC24hPs indicating that in some patients, therapeutic drug monitoring and treatment individualization may be needed.

The main limitation of the present study was the age difference between the two groups. Although the possibility that this difference may interfere with MXF penetration into PF cannot be excluded, we do not believe that this is the case, for two reasons. First, both groups had similar plasma pharmacokinetic profiles, despite the age difference. Second, patients of similar ages from both groups maintained the same PF pharmacokinetic characteristics as the original groups. Therefore, it is reasonable to assume that the delay in TmaxPF in the case of empyema/parapneumonic effusions does not result from age-dependent differences in the MFX tissue distribution.

The results of the present study support the wide empirical use of MFX in the treatment of parapneumonic effusion and empyema, providing evidence for the first time under actual clinical conditions that MFX sufficiently penetrates into the pleural space and exhibits a favorable pharmacokinetic profile regardless of pleural fluid origin. The delay in the achievement of the maximum pleural fluid MFX concentration observed in patients with PPE/empyema may trigger further studies on the penetration of different antibiotics into the pleural space.

ACKNOWLEDGMENTS

We thank the staff of the Pulmonary Department of G. Papanikolaou Hospital for their assistance. No funding was received for this study. We have no competing interests to declare.

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