Moxifloxacin pharmacokinetics and pleural fluid penetration in patients with pleural effusion

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ABSTRACT

Objectives: The aim of this study was to evaluate the pharmacokinetics and penetration of moxifloxacin (MXF) in patients with various types of pleural effusion.

Patients and methods: Twelve patients with empyema/parapneumonic effusion and twelve patients with malignant pleural effusion were enrolled 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 24h time interval after drug administration. MXF concentration in (PL) and (PF) was determined by HPLC and main pharmacokinetic parameters were estimated. Penetration of MXF in PF was determined by the AUC_{24 PF/PL} ratio.

Results: No statistically significant differences were observed between two groups in PL pharmacokinetics despite large interindividual variability in volume of distribution, clearance and elimination half-life. In PF, Cmax_{PF} in patients with empyema/PPE was 2.23±1.31 mg/L, and it was detected 7.50±2.39 h after the initiation of the infusion. In patients with malignant effusion, Cmax_{PF} was 2.96±1.45 mg/L, but it was observed significantly earlier at 3.58±1.38 h (p<0.001). Both groups revealed a similar AUC_{24PF} (31.83±23.52 vs 32.81±12.66 mg/L*h). Penetration of MXF into PF was similarly good in both patient groups (1.11±0.74 vs 1.17±0.39).

Conclusions: 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 MXF PF penetration and the on-site drug exposure as expressed by the AUC\textsubscript{24PF}, did not differ according to the type of pleural effusion.

Keywords: Moxifloxacin, pharmacokinetics, pleural fluid penetration, pleural effusion
INTRODUCTION

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 exudatives that frequently resolve with antimicrobial treatment and do not require drainage. In some cases this initial effusion may progress to a “complicated parapneumonic effusion”, which is characterized by fibrin deposition and fluid infection. These effusions can’t resolve without drainage and usually require a chest tube placement. Persistent pleural infection may result in the accumulation of pus in the pleural space that is called “empyema”.¹

All patients with parapneumonic effusion or empyema should be initially treated with intravenous antibiotics. The initial selection of agent and dose, is usually based on whether the pneumonia is community-acquired (CAP) or hospital acquired (HAP) and depends on the severity of patient’s clinical condition.² Respiratory fluoroquinolones such as moxifloxacin or levofloxacin are recommended as initial empiric antibiotic therapy both for hospitalized patients with severe and non-severe CAP³ and for those with HAP or ventilator-associated pneumonia without known risk factors for multidrug-resistant pathogens and early onset.⁴

Moxifloxacin (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 penetration in human pleural fluid, data on MXF are scarce and are based on experimental pleural empyema in rabbits.¹⁰⁻¹¹ Based on 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 fifteen years, there are no studies investigating the MXF penetration neither in human empyema, nor in effusions due to other etiologies.

The aim of the present study was to determine the pharmacokinetics of MXF in plasma and human pleural fluid and to evaluate in 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 Aristotle University of Thessaloniki, in G. Papanikolaou Hospital, 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 in the Pulmonary Department for empyema/parapneumonic effusion or exudative malignant pleural effusion and had in place a chest tube for continuous drainage. The documentation of pleural effusion's etiology was based on clinical manifestations, imaging studies, and pleural fluid biochemical analysis, microbiology and cytology. Differentiation of transudates versus exudates, was performed according to Light's criteria.

A complete medical history and laboratory test results, including complete blood cell counts, erythrocyte sedimentation rate, serum glucose and electrolytes, liver function tests, total proteins and albumin, serum creatinine and urine analyses, were recorded prior to the commencement of the protocol. Pleural fluid specimens were examined for glucose, pH, LDH and protein levels, total white blood cell count and differential. Samples of 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 [defined as a creatinine clearance (CLCR) of 30 ml/min or less, as calculated by the Cockroft-Gault equation], hepatic impairment (defined as a Child-Pugh score of B or C), a history of convulsions and concomitant therapy with cytostatic agents.

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 post-dosing: 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 by centrifugation from whole blood. 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 H. Liang et al. with modifications.15

Analytical separation was performed via a Nucleosil 100C18, 250 X 4.6 mm, 5 μm column (M-Z Analysentechnic, Mainz, Germany) protected by a similar composition guard column (20 X4.6 mm, 5 μm). The detector was set at an excitation wavelength of 293 nm and at an emission wavelength of 500 nm. The mobile phase consisted of 10 mM sodium
dodecyl sulphate, 25 mM citric acid, 10 mM tetrabutylammonium hydrogen sulfate with 43% (vol/vol) acetonitrile at pH 3.5 adjusted with NaOH 1N. Ciprofloxacin (CIP), (Elpen Pharmaceuticals, Athens, Greece) was used as internal standard. The isocratic flow rate was 1 ml/min, the column temperature was set at 37°C, the total run time was 7 min and the retention time of CIP and MXF was 4.4 and 6.1 min respectively.

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

**Sample preparation and extraction procedure**

A 50 μl of internal standard solution of 20 mg/L and 500 μl of acetonitrile were added to 250 μl of plasma or pleural fluid and then being vortexed for 30 seconds and centrifuged at 3600 rpm for 10 min (Zentrifugen Micro 20, Hettich, Germany). The clear supernatant was then injected into column via an autosampler and a 20 μl loop.

**Pharmacokinetic analysis**

Plasma (PL) and pleural fluid (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 the calculated concentrations. The
peak (maximum) concentration (Cmax<sub>PL</sub>) in plasma was at the end of the infusion, and
the trough (minimum) concentration (C<sub>trough</sub><sub>PL</sub>) in plasma was observed at 24 hours
post-dosing. In pleural fluid, Cmax<sub>PF</sub> and the time to reach Cmax (T<sub>max</sub><sub>PF</sub>), were obtained
observationally from individual concentration-time data. All concentrations in both
matrices were total drug concentrations. The area under the curve from 0 to 24 h (AUC<sub>24</sub>)
was determined by the trapezoidal rule. The penetration ratio for each patient was
obtained by dividing the AUC<sub>24</sub> for pleural fluid by the AUC<sub>24</sub> for plasma. Calculation of
Vd, CL, and t1/2 was performed by a compartmental method, as it was previously
described.

Statistical analysis

All data are expressed as mean± standard deviations unless otherwise noted.
Biostatistical analysis was performed using SPSS for Windows release 17.0.1 (Standard
version, SPSS Inc). The normality of distribution was assessed by the Shapiro-Wilk test.
Pharmacokinetic parameters between empyemic/parapneumonic and malignant effusions
were compared by independent samples t-test if normally distributed and by Mann-
Whitney test if nonnormally distributed.
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.

The pharmacokinetic parameters of MXF in plasma for both patients groups are summarized in Table 3. The mean peak concentrations in plasma were 4.64±0.68 for group A and 4.28±0.69 mg/L for group B, respectively and were achieved by the end of drug infusion. The observed mean concentrations in plasma at 24 hours (C_{trough_{PL}}) were 0.37±0.13 for group A and 0.39±0.07 mg/L for group B. A large variability was observed in the pharmacokinetic data, for both groups, especially in the volume of distribution (Vd), which ranged from 82.66 to 310.95 L, although their mean value was similar (165.12 for group A vs 155.22 L for group B). Similarly, clearance (CL) ranged from 6.82 to 19.10 L/h, and the elimination half-life (t_{1/2}) was as short as 3.84 h and as long as 36.20 h. In both groups a similar AUC_{24PL} was observed (28.39±5.47 for group A vs. 28.06±4.37 mg/L*h for group B).

Regarding the pleural fluid, mean C_{max_{PF}} in patients with empyema/PPE was 2.23±1.31 mg/L, and it was detected 7.50±2.39 h after the initiation of the infusion. In patients with malignant effusion the mean C_{max} was 2.96±1.45 mg/L, 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_{24PF} in pleural fluid (31.83±23.52 for group A vs
32.81±12.66 mg/L*H for group B), but patients with empyema/PPE showed a remarkable interindividual variability (AUC_{24PF} ranged from 8.51 to 96.11 mg/L*h). Penetration of MXF into pleural fluid was similarly good in patients from both groups (1.11±0.74 for group A vs. 1.17±0.39 for group B). Mean C_{trough,PF} was found to be 0.99±0.84 for group A and 0.73±0.46 mg/L for group B, with empyemic patients showing a slightly higher-but not statistically significant- trough concentration of moxifloxacin, at the end of 24 hour interval. The equilibration of MXF concentration between plasma and pleural fluid occured at 5 hours in patients with empyema/parapneumonic effusion, versus 3 hours in those with malignant effusion. The pharmacokinetic parameters of MXF in pleural fluid for both patients groups are summarized in Table 4, while Figures 1A and 1B represent the concentration-time curves of MXF in 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 ten older patients with PPE/empyema (mean age 61.9 years) compared to the eight younger patients with malignant effusion (mean age 63.8 years), T_{max,PF} and C_{max,PF} maintained the same difference between two groups (7.50 vs 3.87h for group A and 3.13 vs 2.81mg/L for group B), while AUC_{24PF} and AUC_{24PF,PL} remained equal (31.49 for group A vs 33.07 mg/L*h for group B) and (1.12 group A vs 1.15 for group B) respectively.

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 pleura and, more specifically, in pleural fluid. For the first time in the literature, results from the present study indicate that MXF penetrates sufficiently into pleural fluid in patients with empyema and those 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. Texeira et al have suggested that pleural antibiotic levels are lower than serum levels in patients with empyema, due to the decreased permeability of the thickened pleura and the more acidic local environment. On the contrary, under circumstances of acute infection, which involves inflammation, vasodilation, oedema and increased membrane permeability, the penetration of antimicrobial agents may be increased.

Therefore, it is important to evaluate the penetration of antibiotics into pleural space, with careful consideration to the underlying pathophysiology and the different mechanisms of fluid formation. In empyema, during the exudative stage, pleural fluid accumulates in pleural space secondary to inflammation and increased permeability of the visceral pleura. As the infection progresses, the bacterial invasion of pleural space, the deposition of fibrin on pleural membranes and the formation of septations, lead to a thick, non-elastic pleural peel. Regarding malignant effusions which are predominantly exudates, 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.
Hence, it could be assumed that penetration of antimicrobial agents into pleural effusions of different etiology could vary according to the underlying pathophysiology. Indeed, in a rabbit model of empyema, penetration of antibiotics varied significantly. 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. Notably, none of these studies included fluoroquinolones, a class of antimicrobials being able to achieve large volume of distribution and extensive tissue penetration. There are indications that antimicrobial activity of compounds like MXF, devoicing piperazinyl ring at position 7, are not affected by acidic conditions. 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 have shown that 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, adequacy of tissue perfusion, co-administration of drugs, competition of the same metabolic pathways, etc. Moreover, it is known that genetic variability of the metabolic pathways represents a major modifying factor. It is evident that co-existence of more than one modifying factors on a given patient makes determination of the individual contribution, practically impossible. Nevertheless, MXF revealed similar pharmacokinetic characteristics (e.g. $C_{\text{max}}$, $C_{\text{trough}}$, $\text{AUC}_{24}$ and $\text{AUC}_{24\text{PF}}/\text{AUC}_{24\text{PL}}$) 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 the $T_{\text{maxPF}}$ in the group of patients with empyema/parapneumonic effusion and the slightly lower $C_{\text{maxPF}}$. Correspondingly, the same group of patients tends to achieve higher 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 raise a barrier to prompt penetration into the pleural space. Notwithstanding, MXF was able to achieve in pleural fluid AUC’s equal or higher to 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 inflammatory process. However, patients with empyema/PPE showed a remarkable variation in AUC$_{24PF}$, 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. Firstly, both groups had similar plasma pharmakokinetic profiles despite the age difference. Secondly, patients from both groups with similar age maintained the same PF pharmacokinetic characteristics as the original groups. Therefore it is reasonable to assume that delay in $T_{\text{maxPF}}$ in the case of empyema/parapneumonic effusion does not result from age-dependent differences in MXF tissue distribution.
The results of the present study support the wide empirical use of MXF in the treatment of parapneumonic effusion and empyema providing evidence, for the first time in actual clinical conditions that MXF sufficiently penetrates into the pleural space and exhibits a favorable pharmacokinetic profile regardless of pleural fluid origin. The delay in achievement of maximum pleural fluid MXF concentration observed in patients with PPE/empyema may trigger further studies on the penetration of different antibiotics into the pleural space.

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Funding: None.

Competing interests: None declared.

Ethical approval: The study protocol was approved by the Institutional Review Board of the hospital and written informed consent was obtained from all study participants.

REFERENCES


Table 1. Demographic data and clinical characteristics.

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<th>Patients with empyema/Parapneumonic effusion (n=12)</th>
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<tr>
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<td>Weight (Kg)</td>
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<td>Length of hospital stay (days)</td>
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M, Male; F, Female
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<tr>
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<td>Mean±SD</td>
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<td>7.3±0.1</td>
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<td>LDH (IU/L)</td>
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<td>546.2±418.8</td>
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<td>Proteins (g/dL)</td>
<td>4.3±0.9</td>
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<td>Glucose (mg/dL)</td>
<td>70.7±68.4</td>
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<td>WBC count (cells/mm³)</td>
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<td>Differential</td>
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**Table 2.** Pleural fluid characteristics.
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<tr>
<td></td>
<td>Mean ±SD (Range)</td>
<td>Mean ±SD (Range)</td>
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<tr>
<td>Cmax&lt;sub&gt;PL&lt;/sub&gt; (mg/L)</td>
<td>4.64±0.68 (3.57-5.56)</td>
<td>4.28±0.69 (3.12-5.97)</td>
<td>0.288</td>
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<tr>
<td>Ctrough&lt;sub&gt;PL&lt;/sub&gt; (mg/L)</td>
<td>0.37±0.13 (0.20-0.63)</td>
<td>0.39±0.07 (0.25-0.52)</td>
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<td>Tmax&lt;sub&gt;PL&lt;/sub&gt; (h)</td>
<td>1.00±0</td>
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<tr>
<td>AUC&lt;sub&gt;24&lt;/sub&gt;&lt;sub&gt;PL&lt;/sub&gt; (mg/L* h)</td>
<td>28.39±5.47 (22.11-38.08)</td>
<td>28.06±4.37 (20.32-35.38)</td>
<td>0.627</td>
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<td>T1/2 (h)</td>
<td>13.98±10.49 (3.84-36.20)</td>
<td>10.71±2.48 (7.96-15.28)</td>
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<td>CL (L/h)</td>
<td>12.17±3.96 (6.82-19.10)</td>
<td>12.14±2.27 (9.87-16.78)</td>
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<td>Vd (L)</td>
<td>165.12±62.77 (82.66-310.95)</td>
<td>155.22±24.99 (106.77-187.68)</td>
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Table 3. Pharmacokinetic parameters of moxifloxacin in plasma.

C<sub>m</sub>ax, peak concentration; C<sub>trough</sub>, concentration at the end of 24h; Tmax, time when the Cmax is achieved; AUC<sub>24</sub>, area under the concentration-time curve from time zero to 24-hours; T<sub>1/2</sub>, elimination half-life; CL, total body clearance; Vd, volume of distribution.
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<th>Malignant effusion (Mean ±SD)</th>
<th>P</th>
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<tbody>
<tr>
<td>Cmax&lt;sub&gt;PF&lt;/sub&gt; (mg/L)</td>
<td>2.23±1.31</td>
<td>2.96±1.45</td>
<td>0.288</td>
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<tr>
<td>C&lt;sub&gt;t&lt;/sub&gt;rough&lt;sub&gt;PF&lt;/sub&gt; (mg/L)</td>
<td>0.99±0.84</td>
<td>0.73±0.46</td>
<td>0.365</td>
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<tr>
<td>AUC&lt;sub&gt;24PF&lt;/sub&gt; (mg/L·h)</td>
<td>31.83±23.52</td>
<td>32.81±12.66</td>
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<tr>
<td>AUC&lt;sub&gt;PF&lt;/sub&gt;/AUC&lt;sub&gt;PL&lt;/sub&gt;</td>
<td>1.11±0.74</td>
<td>1.17±0.39</td>
<td>0.810</td>
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<tr>
<td>Tmax&lt;sub&gt;PF&lt;/sub&gt; (h)</td>
<td>7.50±2.39</td>
<td>3.58±1.38</td>
<td>&lt;0.001*</td>
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Table 4. Main pharmacokinetic parameters of moxifloxacin in pleural fluid.
Figures 1A and 1B. Mean ±SD moxifloxacin concentration-time curves in plasma and pleural fluid in patients with empyema/parapneumonic effusion (1A) and malignant effusion (1B).
Fig. 1A: Moxifloxacin concentration in plasma and pleural fluid of patients with empyema/PPE
Fig. 1B: Moxifloxacin concentration in plasma and pleural fluid of patients with malignant effusion