

Defining the role of macrophages in local moxifloxacin tissue concentrations using biopsy data and physiologically-based pharmacokinetic modelling



Bayer Technology Services

Andrea N. Edginton ¹⁾, Stefan Willmann ¹⁾, Gertrud Ahr ²⁾, Heino Stass ²⁾

1) Systems Biology, Bayer Technology Services GmbH, Leverkusen, Germany

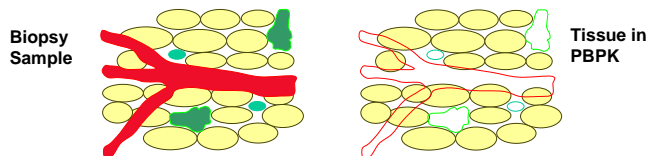
2) Clinical Pharmacokinetics, Bayer HealthCare AG, Wuppertal, Germany



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INTRODUCTION

- Physiology-based pharmacokinetic (PBPK) modeling is well established to simulate of concentration-time profiles using known physiological parameters (body and organ weights, blood flows, tissue composition etc.).
- Biopsy sampling provides hard-to-interpret PK information from target tissues of patients: they represent compound data that includes the total of the bound and free fraction in intracellular space, interstitial space, vasculature and other resident tissue components. Since unbound target concentrations drive therapeutic effect this data must be deconvoluted from biopsy results.



1. Interstitial space
2. Intracellular space
3. Vascular with blood
4. Tissue components (macrophages, neutrophils)

- Objective:** Combine PBPK modeling for the anti-infective, moxifloxacin (MXF), with in vitro and in vivo literature data on its interaction with macrophages to extract meaningful PK/PD information from biopsy data taken from abdominal resections of 40 individuals undergoing primarily colorectal surgery dosed with MXF [1].

METHODS

Experimental Biopsy Data

- Data were taken from a study [1] where patients were randomized to receive 400 mg of MXF as a one hour IV infusion prior to undergoing abdominal surgery. One plasma sample and one biopsy sample from the resection was taken at one of five time points post-administration (1, 2, 4, 7, 24 h).

Definition of PBPK Model

- Physico-chemical parameters of MXF were input into PK-Sim® (Bayer Technology Services GmbH) and simulated plasma, interstitial unbound adipose and muscle concentrations were simulated and compared to literature data [2].

Inclusion of Macrophages

- MXF accumulates in macrophages [3]. A biopsy sample was simulated, inclusive of macrophages, using the PBPK model such that:

$$C_{\text{biopsy, sim}} = f_{\text{macro}} K_{\text{macro}} C_{\text{plasma, sim}} + (1 - f_{\text{macro}}) C_{\text{tissue, sim}}$$

$$C_{\text{tissue, sim}} = f_{\text{vascular}} C_{\text{blood, sim}} + f_{\text{interstitial}} C_{\text{interstitial, sim}} + f_{\text{cellular}} C_{\text{cellular, sim}}$$

where K_{macro} is the time-dependent macrophage to plasma concentration ratio (Fig. 1), f_{macro} is the fraction volume of the biopsy occupied by macrophages (Fig. 2), f_{vascular} , $f_{\text{interstitial}}$ and f_{cellular} are the fractions of vascular (= 2.4%), interstitial (= 9.4%) and intracellular (= 88.2%) volume in the intestine, $C_{\text{blood, sim}}$, $C_{\text{interstitial, sim}}$, $C_{\text{cellular, sim}}$ and $C_{\text{plasma, sim}}$ are the simulated concentrations (not regarding tissue macrophages) in the whole blood, interstitial space, intracellular space and plasma, respectively.

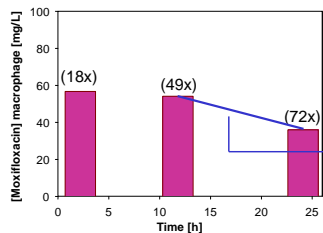


Figure 1. MXF concentrations in alveolar macrophages (AM) from bronchial lavage over time following MXF administration. Numbers over bars indicate the time-specific AM/plasma ratios. The apparent half-life of MXF in AMs was 20.8 h [3]. Linear interpolation was used to generate time relevant ratios for the simulations (to generate K_{macro}).

Estimation of f_{macro}

- Fractional macrophage content (f_{macro}) was estimated using a representative histological section taken from a resection during colorectal surgery [4] (Fig. 2)

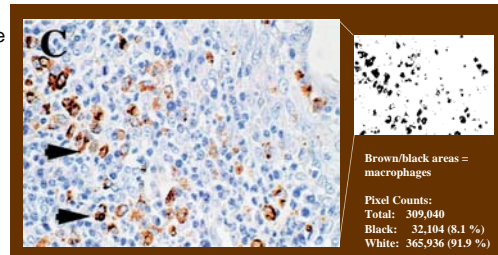


Figure 2. Histological section from Etoh et al [4]

- $f_{\text{macro}} = 8.1\%$

PBPK Simulations

- Reasons for deviations of tissue prediction to measured data were discussed and corresponding macrophage scenarios were included.

RESULTS

MXF PBPK Model Evaluation

- The model adequately simulated the plasma profile over 4 days (Fig. 3) as well as the observed plasma concentrations within the biopsy study (Fig. 4).
- The model adequately simulated the unbound interstitial concentrations from microdialysis studies for muscle and adipose (Fig. 3) [2].

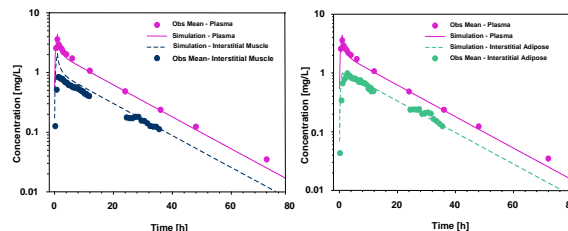


Figure 3. Observed and simulated MXF concentration time profiled in plasma, interstitial unbound muscle and adipose.

Simulated Biopsy Concentrations

- Half-life in experimental biopsy samples (21.0 h) was 2.4x greater than in plasma (8.9 h) and was equal to that in macrophages (20.8 h) (Fig. 2).
- Using the estimated value of 8.1% of macrophages in a biopsy sample, the simulated biopsy concentrations slightly overestimated observed MXF concentrations. A value of 4.8% best represented the observed data (Fig. 4).

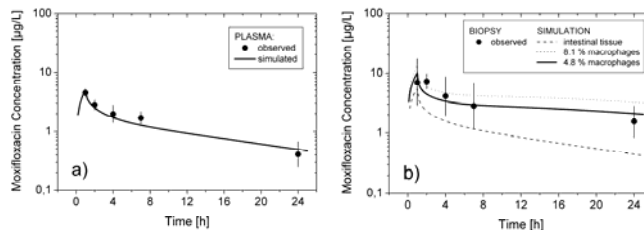


Figure 4. Observed and simulated MXF concentration time profiles in plasma (a) and biopsy (b) samples. The percentage of macrophages estimated from the literature (8.1%) slightly overestimated biopsy concentrations whereas a best fit value was 4.8%. Also presented is the simulated MXF concentration in intracellular space of intestinal tissue.

CONCLUSIONS

- PBPK is suitable for determining MXF plasma and interstitial concentrations in tissues.
- According to our results, macrophages were major contributors to tissue PK and thus need consideration when relevant PK information is required for PK/PD evaluations.
- This study demonstrated that PBPK can be used to support PK investigations in patients where extraction of the relevant PK data is complicated by the limitations of the available sampling techniques, as in the case of inhomogeneous biopsy samples.