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

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

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.

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 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.

Inclusion of Macrophages

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

\[
C_{\text{biopsy,stim}} = f_{\text{macro}} C_{\text{macrophage,stim}} + (1-f_{\text{macro}}) C_{\text{tissue,stim}}
\]

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

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).

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).

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 homogenous biopsy samples.


![Simulation results showing MXF concentration time profiles in plasma and biopsy samples.](image1)

![Biopsy sample histological section showing macrophage content.](image2)