Development of an Integrated Population Pharmacokinetic Model Characterizing the Tissue Distribution of Azithromycin and Erythromycin in Healthy Subjects

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Objectives: Emerging evidence suggests that the use of azithromycin triggers macrolide resistance. This effect seems to be less pronounced for other macrolides, such as erythromycin or clarithromycin. The objective of our study was to determine if a causal relationship exists between the physicochemical properties of macrolides, their corresponding pharmacokinetics, and subsequent resistance development.

Methods: Azithromycin (500mg QD) or erythromycin (500mg QID) were administered orally to 6 healthy male volunteers for three days. Free concentrations in the interstitial space fluid (ISF) of muscle and subcutaneous adipose tissue as well as total concentrations in plasma and polymorphonuclear leukocytes (PMLs) were determined on days 1, 3, 5, and 10. All concentrations were modeled simultaneously for both drugs in NONMEM 7.2 using a mechanism-based tissue distribution model that integrates information on the drugs' physicochemical properties, protein binding, unspecific tissue binding and pH differences between tissues to characterize macrolide distribution in tissues in general and in PMLs in particular.

Results: The developed and qualified mechanism-based model enabled describing of drug concentrations across sampling sites. The overall pharmacokinetics of azithromycin is driven by the release of drug from acidic cell/tissue compartments, and the model estimated a more than 30-fold higher distribution factor for the unionized azithromycin concentrations in the cytosol of PMLs (C_{PML(cytosol,unionized AZM)}) compared to that for erythromycin. Model-predicted C_{PML(cytosol,unionized)} for both drugs were comparable to measured ISF concentrations in muscle and subcutis on day 10, whereas total PML concentrations were more than 1000-fold higher for azithromycin. In contrast to erythromycin, subinhibitory azithromycin concentrations were observed in plasma and interstitial space of both soft tissues through day 10.

Conclusions: The development of a drug class-specific model for macrolides allowed for the characterization of their tissue distribution kinetics on a mechanistic basis with differences in ionization being the main driver. Compared to azithromycin, erythromycin resides much shorter in the body at subinhibitory concentrations, which may explain differences in the emergence of resistance between both drugs.