A Multiscale Physiologically Based Pharmacokinetic Model for Doxorubicin: Scale-up from Mouse to Human

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Objectives: Doxorubicin used either alone or in combination is the most widely applied chemotherapeutic agent. The aim of this study was to develop a state-of-art physiologically based pharmacokinetic model (PBPK) for doxorubicin to describe its multiscale (system, tissue, cellular, and subcellular) disposition in animals and then scale up to human.

Methods: A multiscale PBPK model was developed that divided tissue into four sub-compartments: vascular, interstitial, tissue cellular, and nucleus DNA bound. Drug-associated parameters in the model include cell/interstitial partition coefficient (Kp), ionization effect (Kpp), cell membrane-limited permeability (PS), and affinity to extensive DNA intercalation (KD). Equilibrium binding was assumed between doxorubicin and nuclear DNA and tissue DNA content was used to predict doxorubicin extensive tissue distributions. Various sources of data were obtained in the literature about doxorubicin PK and tissue distribution. Hepatic clearance (CLh), DNA binding affinity (KD), and Kp for each tissue were parameters optimized using ADAPT 5. The developed PBPK model based on mice data was further extrapolated to rats and humans.

Results: The concentration-time profiles of doxorubicin in plasma and 9 tissues (liver, spleen, lung, heart, etc) were well characterized by the developed multiscale PBPK model of doxorubicin. The model was optimized successfully based on mice data resulting in precise estimations of 12 parameters (CLh, KD, and Kp). The PBPK model was then scaled up to well predict PK and tissues distribution of doxorubicin in rats and human. Sensitivity analysis suggested the importance of hepatic clearance in shaping concentration-time profiles and DNA binding as the key determinant of broadly tissue distribution of doxorubicin.

Conclusions: The present study developed a multiscale PBPK model of doxorubicin. The model could be applied to predict doxorubicin PK and multiscale disposition across species.

Figure 1. Schematic of multiscale PBPK model of doxorubicin