Integrating Cellular Disposition of Doxorubicin into A Multiscale Physiologically Based Pharmacokinetic Model in Mice and Scale-up to Humans

T-01

Hua He[1, 2], Yun Wu[3], Can Liu[1], Yanguang Cao[1*]

[1] DPET, School of Pharmacy, University of North Carolina at Chapel Hill, NC， USA; [2] China Pharmaceutical University, Nanjing, China; [3] Department of Biomedical Engineering, University at Buffalo, State University of New York, Buffalo, NY, USA

Objective

The objectives of this study was to develop a state-of-art multiscale multispecies physiologically based pharmacokinetic model (PBPK) for doxorubicin and further apply this model to quantitatively predict its anti-tumor efficacy and cardiotoxicity.

Method

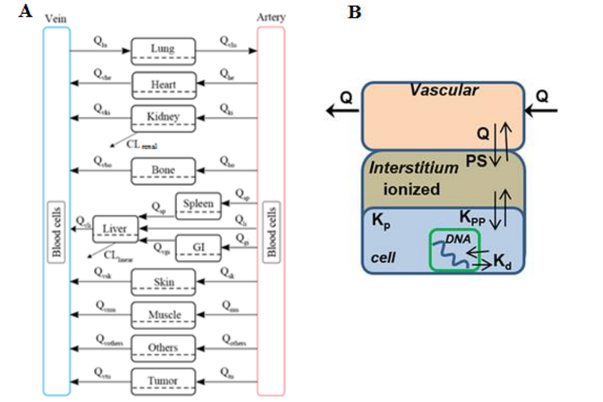

Fig.1 Schematic of multiscale PBPK model of doxorubicin.

Totally 11 organs were constituted in the model and 4 sub-compartments (vascular, interstitial, cellular, nucleus) were considered for each organ. Perfusion-(*Q*) and permeability-limited (*PS*) models were used to describe the distribution of doxorubicin from blood to interstitial fluid and from interstitial to cellular. Quasi-equilibrium was assumed for DNA-doxorubicin binding. Biliary (92%) and renal (8%) secretion accounted for clearance. Equilibrium dissociation constant of DNA binding (K_d), cell/interstitial fluid partition coefficient of doxorubicin (K_p) were all optimized based cellular uptake data, and animal data of PK and bio-distribution of doxorubicin in multiple species. Clearance was allometrically scaled. Rat and human data was used to assess model predictive performance.

Model fitting

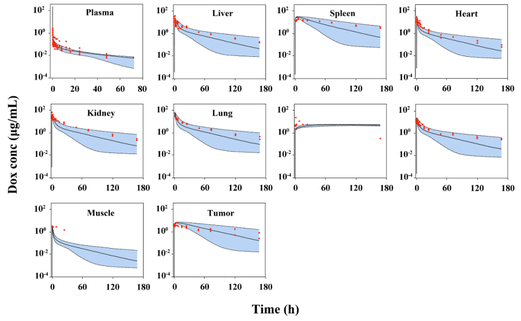

Fig.2 Observed (•) and predicted doxorubicin (Dox) concentration in plasma and various tissues in mice. —— : predicted median, ····· : 5th and 95th percentiles, ▭ : predicted 90% CI area.

Scale up to rat and human

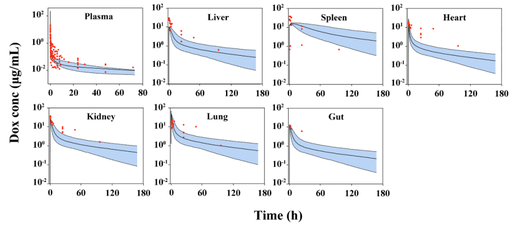

Fig.3 Observed (•) and predicted doxorubicin (Dox) concentration in plasma and various tissues in rats. —— : predicted median, ····· : 5th and 95th percentiles, ▭ : predicted 90% CI area.

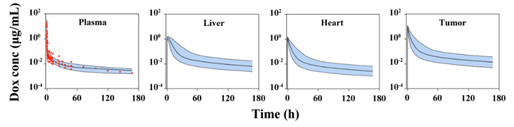

Fig.4 Observed (•) and predicted doxorubicin (Dox) concentration in plasma and various tissues in humans. —— : predicted median,····· : 5th and 95th percentiles, ▭ : predicted 90% CI area.

Model Application

Rationale: It has been well documented that 6 hours infusion in clinical shows significant less cardiotoxicty than bolus dosing [1]

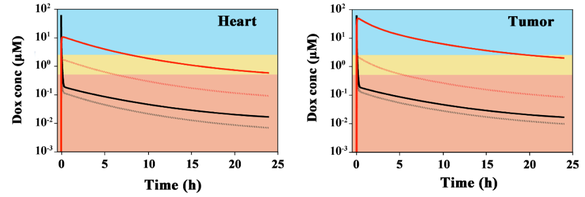

Fig.5 Predicted doxorubicin (Dox) disposition in heart and tumor. Plasma (—), interstitial (·····), intracellular free (·····) and DNA bound (—) doxorubicin concentration-time profiles were simulated after bolus. DNA bound (▭), topoisomerase II inhibition (▭) and oxidative stress (▭) were the main three types of cytotoxic mechanism of doxorubicin with distinguished concentration ranges.

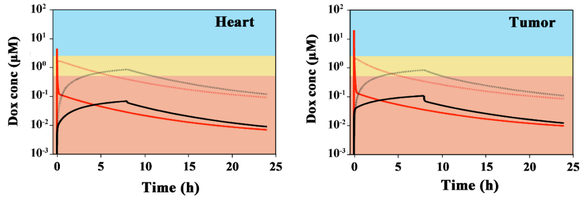

Fig.6 Doxorubicin (Dox) dosing schedule comparison. Interstitial fluid (—) and (·····) intracellular free Dox concentration-time profile by bolus; interstitial fluid (—) and intracellular free (·····) Dox concentration-time profile by 8h infusion. DNA bound (▭), topoisomerase II inhibition (▭) and oxidative stress (▭).

Table 1. Metrics used to distinguish dosing schedule-dependent cardiotoxicity

Mechanism [2]	Dosing	Interstitial fluid			Intracellular		
		C_{max}, C_{av} (μM)	AUC (μM·h)	Duration (h)	C_{max}, C_{av} (μM)	AUC (μM·h)	Duration (h)
DNA bound (< 0.5 μM)	Bolus	0.029	0.707	23.97	0.22	3.94	17.65
	Infusion	0.03	0.722	24.0	0.25	4.23	16.6
Topoisomerase II inhibition (0.5~2.5 μM)	Bolus	1.06	0.0238	0.0225	0.90	5.71	6.35
	Infusion	/	/	/	0.67	4.99	7.44
Oxidative stress (> 2.5 μM)	Bolus	4.45	0.0239	0.007	/	/	/
	Infusion	/	/	/	/	/	/

Table 2. Metrics used to distinguish dosing schedule-dependent antitumor effect

Mechanism [2]	Dosing	Interstitial fluid			Intracellular		
		C_{max}, C_{av} (μM)	AUC (μM·h)	Duration (h)	C_{max}, C_{av} (μM)	AUC (μM·h)	Duration (h)
DNA bound (< 0.5 μM)	Bolus	0.035	0.845	23.88	0.207	3.79	18.3
	Infusion	0.045	1.08	24	0.246	4.03	16.4
Topoisomerase II inhibition (0.5~2.5 μM)	Bolus	1.05	0.103	0.098	0.946	5.39	5.70
	Infusion	/	/	/	0.627	4.76	7.59
Oxidative stress (> 2.5 μM)	Bolus	19.89	0.1799	0.023	/	/	/
	Infusion	/	/	/	/	/	/

Results: In consistent with previous studies, the model predicted that DNA bound was likely the primary cytotoxic mechanism in tumor suppression. This is different with cardiotoxicity, which was suggested to be driven by free doxorubicin inside myocardial cells [3]. Our simulation suggested that DNA bound Dox is much higher in tumor than heart, primarily due to high concentrations of DNA at solid tumors. In contrast, oxidative stress, which is usually caused by high concentrations of free Dox or its metabolism, is believed as the major cytotoxic mechanism in heart [3]. Topoisomerase II inhibition may exist in both targeted organs [4]. Slow infusion prolonged Dox-DNA bound over the cytotoxic level, but reduced the exposure of free Dox that are associated with topoisomerase II inhibition and oxidative stress. Results in Fig. 5 and Table 1 and 2 well explain the reduced cardiotoxicity in 6 hours infusion in comparison with bolus.

Conclusion

The present study developed a multiscale PBPK model of doxorubicin which predicted the detailed disposition of doxorubicin in human tissues. The model could help to explore the cytotoxicity mechanism and thus improve the chemotherapy approach of doxorubicin.

1. van Dalen EC, et al. Cochrane Database Syst Rev. 2016; 3:CD005008.
2. Gewirtz DA. Biochem Pharmacol. 1999; 57(7):727-41.
3. Minotti G, et al. Pharmacol Rev. 2004; 56(2):185-229.
4. Vejpongsa P, et al. Clin Pharmacol Ther. 2014; 95(1):45-52.

We appreciate discussion with Dr. William J Jusko at SUNY Buffalo, and Dr. Xinyuan Zhang, Peng Zou, et al., at FDA.

FDA U01 FD005206.