Development of a PBPK model for Doxorubicin

Anna Pieper[1,2], Joachim Boos[2], Georg Hempel[1,2]

[1] Department of Pharmaceutical and Medical Chemistry – Clinical Pharmacy -, University of Muenster, Germany
[2] Department of Paediatric Haematology and Oncology, University Children's Hospital Muenster, Germany

WESTFÄLISCHE
WILHELMS-UNIVERSITÄT
MÜNSTER

UKM
Universitätsklinikum
Münster

Introduction

The anthracycline antibiotic Doxorubicin (DOX) is a key component in a number of regimes used in the treatment of cancers. Knowledge on the pharmacokinetics of DOX is limited.

Our aim is to develop a stable PBPK-model for DOX using the software PK-Sim® 4.2.

Doxorubicin is metabolised by several enzymes to its partly active metabolite Doxorubicinol (DOXOL) which also contributes to the cardiotoxicity. In the following figure an overview of the metabolism of DOX is shown.
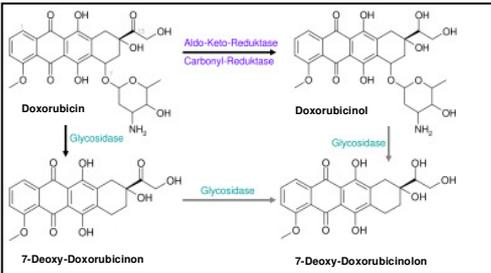
Data and Methods

The best models resulted by using the PK-Sim® standard tool. Three models were created by implementing values for different enzymes, transporters and other mechanisms influencing the pharmacokinetics of DOX. Conflicting results can be found on the rate of accumulation in blood cells. Values in the green field are precise values published. Parameters in the blue fields had to be estimated and are varying between the different models.

Organ	Parameters	V_{max} [μmol/min/kg tissue]	K_m [μmol/l]
Liver	Aldo-Keto-Reductase	275	30
	Glycosidase	12104	82.85
	Biliary Transport	10	5
	Solute like carrier	1	Model 1: 0.2 Model 2: 0.2 Model 3: 1
Kidney	Aldo-Keto-Reductase	539	52.7
	Glycosidase	484	4
	Active secretion	10	1.66
	Solute like carrier	1	1
Small intestine	Gut Transport	0.2	1.33
Heart	Glycosidase	760	6.25
Bone	Solute like carrier	1	Model 1: 0.2 Model 2: 0.4 Model 3: 5
Gonads	Solute like carrier	1	0.8

Organ	Parameters	Permeability [cm/s]
Blood	Permeability from plasma to blood cells (BPP)	Model 1: 0.5 Model 2: 1.5 Model 3: 0.15
	Permeability from blood cells to plasma (PBP)	Model 1: 0.008 Model 2: 0.015 Model 3: 0.0015

Our models were compared with previously published data from Callies et al., Wilde et al. and Eksborg et al. Some patients' data had to be excluded due to insufficiency for our analyzes. In the following table an overview of the three studies used for evaluation is shown.

Parameter	Callies et al.*	Eksborg et al.*	Wilde et al.*
Dose	45 – 75 mg/ m²	21.8 – 60 mg/ m²	25 or 35 mg/ m²
Subjects	36 patients	21 patients	30 patients
Age [years]	57 (27-73)	62 (31-85)	33.6 (17-59)
Subjects	36 patients	21 patients	30 patients
Size [cm]	172 (150-198)	No data → We used mean values deposited in PKSim®	177 (156-196)
Weight [kg]	82.7 (43.1-137)	No data → We used mean values deposited in PKSim®	74 (53.5-99)
Method of data analyses	NONMEM (Version V)	Pharmacokinetic constants were evaluated by duplicate analyses; here „feathering" technique	NONMEM (Version V 1.1)

Results

The following table shows an overview of our results. The model which fits best to published data is shown in the green fields.

Number of model/ publication used for evaluation	Clearance [l/h]	Clearance deviation [%]	AUC$_{inf}$ [μg/l*h]	AUC$_{inf}$ deviation [%]
Model 1/ Callies et al.	57.4 (44.2-68)	28.1 (±23)	1977 (1000-2700)	26.6 (±22.3)
Model 2/ Callies et al.	71.7 (54.4-126.7)	26.1 (±32.5)	1636 (800-2190)	22.3 (±18.4)
Model 3/ Callies et al.	29.6 (±4.65)	56.4 (±14.9)	3587 (±730)	147.7 (±72.1)
Model 1/ Wilde et al.	1.3 (± 0.13)	32.8 (± 13.5)	0.74 (± 0.14)	18.3 (± 7.3)
Model 2/ Wilde et al.	1.36 (± 0.19)	42.1 (± 16.4)	0.69 (± 0.14)	17.8 (± 9.3)
Model 3/ Wilde et al.	0.55 (± 0.05)	42.7 (± 5.1)	1.8 (± 0.26)	155.4 (± 36.2)
Model 1/ Eksborg et al.	1.25 (± 0.08)	44.0 (± 30.2)	36.1 (± 2.8)	47.1 (± 15.6)
Model 2/ Eksborg et al.	1.35 (± 0.07)	53.1 (± 35.7)	33.5 (± 1.98)	50 (± 15.1)
Model 3/ Eksborg et al.	0.55 (± 0.01)	39.7 (± 19)	81.55 (± 1.9)	43.1 (± 60.1)

1. Model 2 evaluated with data from Callies et al.

Clearance: 20 of 29 data sets fit to model 2 – range of 30%

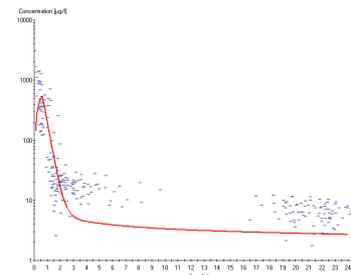AUC$_{inf}$: 23 of 29 data sets fit to model 2 – range of 30%

Alltogether 9 data sets do not fit to the range of 30 percent.
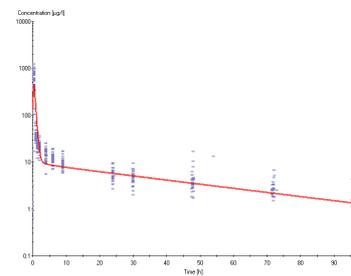
2. Model 1 evaluated with data from Wilde et al.

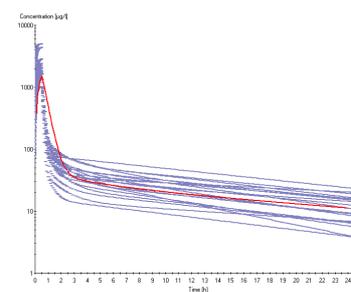Clearance: 16 of 30 data sets fit to model 1 – range of 30%

AUC$_{inf}$: 28 of 30 data sets fit to model 1 – range of 30%

3. Model 3 evaluated with data from Eksborg et al.

Clearance: 3 of 19 data sets fit to model 3 – range of 30%

AUC$_{inf}$: 1 of 19 data sets fit to model 3 – range of 30%

Discussion and Conclusion

Our first model fits with the data from Wilde et al. best, the second one with the data from Callies et al. and the third one fits best with the data from Eksborg et al. The deviations between the first and the second model are not very pronounced. Thus, we could even use model 2 for describing the cohort of Callies et al. In contrast, the data from Eksborg et al. fit much better with the third model.

Because of known variations in the pharmacokinetics of DOX we try to find a model describing all data with a maximal deviation of 30% in Cl and AUC. By considering that all studies include cohorts of patients with multimorbidity and the software PKSim® actually only describes healthy adults, our first model is able to predict the blood-plasma-concentration and some physiological parameters sufficiently. The second one might be a good alternative. Further investigations will be necessary to explain the difference of the third cohort of Eksborg et al..

It would be very helpful to compare the maximal plasma concentration at the end of the infusion but the documentation of this parameter is very error-prone as the blood plasma concentration of DOX declines very rapidly during the first hour after the end of infusion.

Further, we will investigate the predictive value of the presented models to children. Finally, one has to consider differences between healthy and severely ill patients in the software, because body composition differs in cancer patients.

*Literatur: Callies et al. – A population pharmacokinetic model for doxorubicin and doxorubicinol in the presence of a novel MDR modulator zosuquidar trihydrochloride (LY335979); Cancer Chemother Pharmacol (2003) 51: 107-118
Eksborg et al. – Pharmacokinetic Study of IV Infusions of Adriamycin; Eur J Clin Pharmacol (1985) 28: 205-212
Wilde et al. – Population Pharmacokinetics of the BEACOPP Polychemotherapy Regimen in Hodgkin's Lymphoma and its Effect on Myelotoxicity; Clin Pharmacokinetics (2007) 46 (4): 319-333