POPULATION PHARMACOKINETIC OF DOXORUBICIN AND DOXORUBICINOL IN HEMATOLOGICAL PATIENTS

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OBJECTIVE

To develop a population pharmacokinetic (PK) model for doxorubicin (DX) and doxorubicinol (DXol) in hematological patients.

METHODS

29 patients diagnosed of hematological malignancy

Doxorubicin:
Infusion time = 30 min
Dosage = 50 mg/m^2

80 plasma samples (DX and DXol)

Sampling:1-5 hours after infusion

Covariates:
AGE, SEX, WEIGHT, HEIGHT, BSA, BMI, LBW, AST, ALT, serum creatinine, albumin, bilirrubin and hemoglobin

Table 1. Characteristics of the patients at start of therapy (n=29)

Parameter	Mean Value	SD	Normal Value	Median	Percentil 25-75%	Range
Men (%)*	55.2					
Women (%)*	44.8					
Age (years)	63.1	15.9		69	54 – 76	26 - 83
BSA (m^2)	1.8	0.2		1.7	1.6 – 1.8	1.4 - 2.2
BMI (kg/m^2)	26.8	4.1		25.6	24.0 – 31.1	19.9 - 37.6
LBM (kg)	48.1	8.1		47.7	40.7 – 53.2	35.7 - 65.1
Total dose (mg)	87.6	18.0	90.0	86.0	77.5 - 96.3	44.0 - 130.0
Dose/BSA(mg/m^2)	49.8	9.2	50.0	50.0	49.4 - 50.0	25.0 - 71.0
Crs (mg/dL)	0.9	0.3	0.6 - 1.2	0.8	0.7 - 1.0	0.5 - 1.6
Albumin (g/dL)	4.2	0.4	3.5 - 5.0	4.2	4.0 – 4.4	3.4 - 4.8
Bilirubin (mg/dL)	0.4	0.2	0.1 - 1.2	0.3	0.2 - 0.4	0.1 - 0.7
Hemoglobin	11.9	1.5	13 - 18	11.5	11.1 – 12.8	9.4 - 15.4
AST (U/L)	25.6	11.2	≤ 37	24.5	17.0 - 29.5	12 - 64
ALT (U/L)	21.7	12.3	≤ 41	17.0	14.8 – 25.7	7 - 64

SD, standar deviation; *16 men, 13 women; BSA, body surface area; BMI, body mass index; LBM, lean body mass, Crs, serum creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Software:

NONMEM v7.2; Four compartments model; ADVAN 3 TRANS 4; FOCEI

GAM; Akaike; Param vs Cov

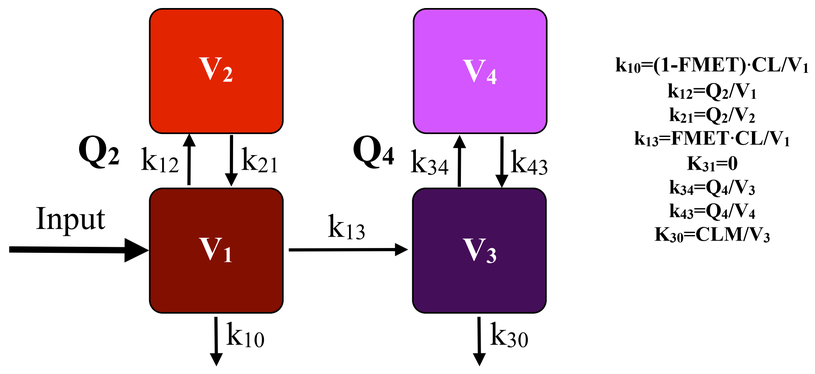
GOF; individual plots

Bootstrap (BTS)

Interface as workbench for pharmacometric modeling

RESULTS

Structural model



$k_{10}=(1\text{-FMET})\cdot CL/V_1$
$k_{12}=Q_2/V_1$
$k_{21}=Q_2/V_2$
$k_{13}=FMET\cdot CL/V_1$
$K_{31}=0$
$k_{34}=Q_4/V_3$
$k_{43}=Q_4/V_4$
$K_{30}=CLM/V_3$

Figure 1. Structural model developed for doxorubicin (compartments 1, 2) and doxorubicinol (compartments 3, 4). FMET, fraction of metabolite (doxorubicinol); CL, clearance of doxorubicin; CLM, clearance of doxorubicinol.

Table 2. PK parameters of the final model

	Units	Estimate	RSE (%)	Shrinkage (%)	Bootstrap n=1000 Median	Bootstrap n=1000 95% CI
Fixed effects parameters						
CL/LBM	L/h·kg	1.3	9	.	1.3	1.02-1.53
V1	L	23.1	.	.	23.1	.
Q2	L/h	91.3	14	.	91.4	70.87-111.64
V2	L	790.0	.	.	790	.
V3	L	38.7	.	.	38.7	.
Q4	L/h	1100.0	.	.	1100.0	.
V4	L	915.0	.	.	915.0	.
CLM	L/h	404.0	15	.	404.5	254.38-553.08
FMET		0.66	14	.	0.67	0.39-0.92
Random effects parameters*						
$\eta_{CL/LBM}$		0.06	37	34	0.06	-0.06-0.18
η_{Q2}		0.30	.	42	0.30	.
η_{CLM}		0.20	.	48	0.20	.
η_{FMET}		0.21	22	17	0.18	0.03-0.39
Residual Variability*						
ε_1		0.06	26	25	0.05	0.04-0.08
ε_2		0.17	24	16	0.16	0.09-0.24

RSE, percentage of relative standard error; CI, confidence interval; CL, clearance of DX; CLM, clearance of Dxol; FMET, fraction of DX; *Error model proportional; ε_1 & ε_2, residual variability of DX and DXol, respectively.

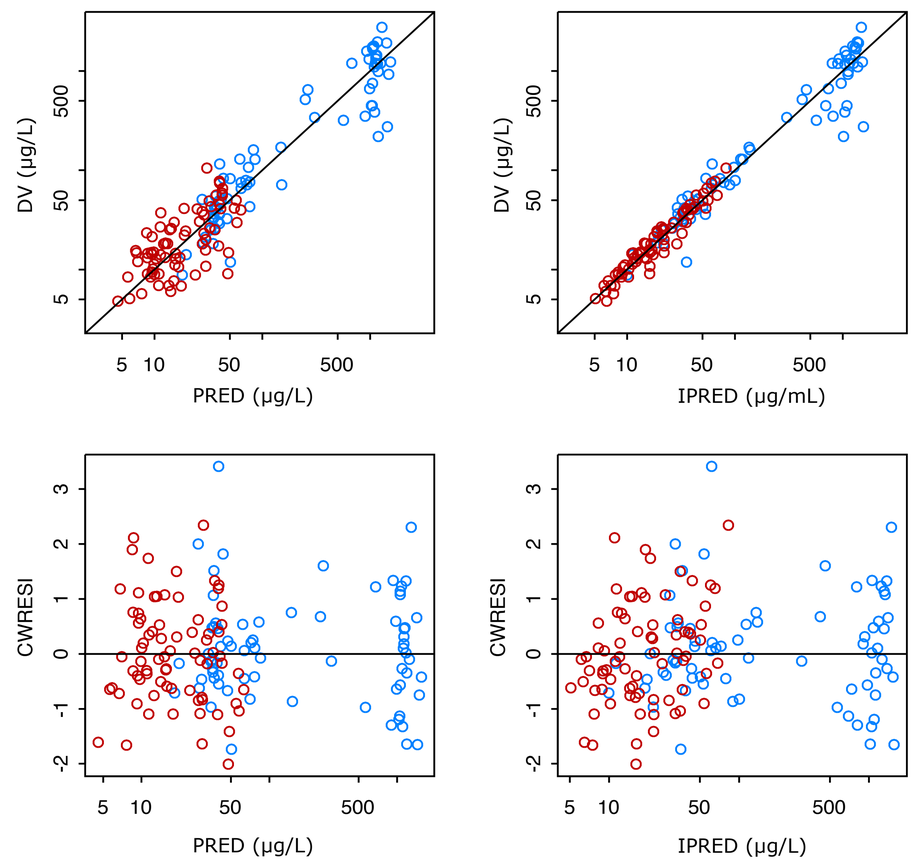


Figure 2. Goodness of fit plots of DX (○) and DXol (○)

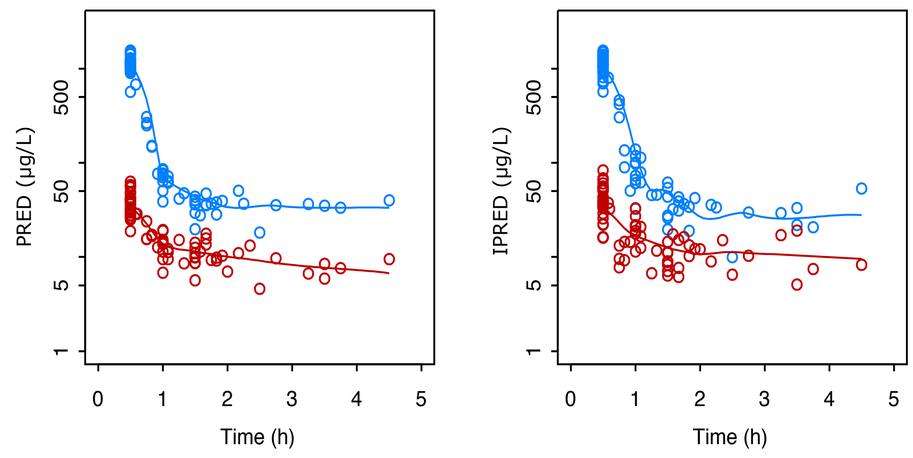


Figure 3. Population and individual concentrations predicted of DX (○) and DXol (○) over time

The maximum plasma concentrations of DX and DXol were 1138 ± 607 µg/L and 40 ± 22 µg/L, respectively (mean ± SD).

CONCLUSION

A suitable population PK model of DX and DXol in hematological patients has been developed. Although the model only included LBM on CL of DX, additional studies with a larger set of data should be performed to know if other covariates showing an apparent PK influence in the preliminary analysis might be included in a future PK model.

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