Population pharmacokinetics of cyclophosphamide and its 4-OH metabolite in patients with glomerulonephritis

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Objectives

The purpose of this study was to develop a population pharmacokinetic (PK) model for cyclophosphamide (CY) and its 4-hydroxy cyclophosphamide (4-OH CY) metabolite in patients with glomerulonephritis secondary to lupus and small vessel vasculitis and to identify patient characteristics that may influence the drug's absorption and disposition.

Methods: The study consisted of patients with glomerulonephritis (n=23) who participated in pharmacokinetic evaluations of CY and 4-OH CY. All patients had received monthly i.v. cyclophosphamide prior to study participation. The i.v. cyclophosphamide dosages were dependent on body surface area; mean dose 0.8±0.2 g/m^2. Blood samples for CY and 4-OH CY determination were collected at the beginning of the infusion and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18 and 24 h after commencement and were assayed by LC/MS/MS method. Kidney function, serum albumin and polymorphisms in drug metabolism and transport genes were evaluated. Plasma concentration-time data of CY and 4-OH CY (metabolite) were analyzed in two stages with a population approach using NONMEM®. 4-OH CY was analyzed conditional to the results of CY. VPC plots were generated with Phoenix®.

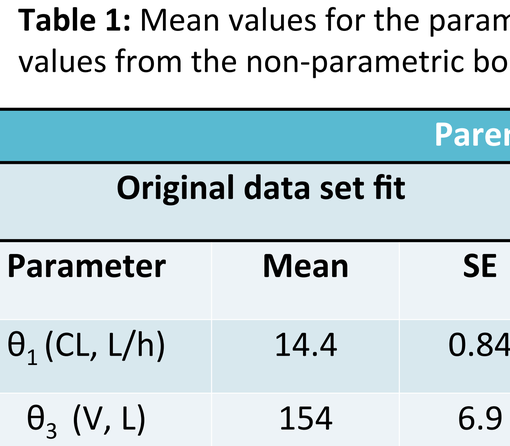
Results: **The parent drug (CY)** model was found to be one compartment with linear elimination.

$$CL_p = \theta_1 (WT/95)^{\theta_2} * exp(\eta_1) \quad \text{Eq. (1)}$$

$$V_p = \theta_3 * (WT/95)^{\theta_4} * exp(\eta_2) \quad \text{Eq. (2)}$$

Table 1: Mean values for the parameters of the parent drug and mean values from the non-parametric bootstrap.

Parent drug				
Original data set fit			Non-parametric bootstrap	
Parameter	Mean	SE	Estimate	SE
θ_1 (CL, L/h)	14.4	0.84	14.38	0.86
θ_3 (V, L)	154	6.9	153.2	6.7
θ_2	0.471	0.2	0.465	0.19
θ_4	0.373	0.12	0.382	0.14
IIV_{CL} %	20.4	1.59	18.7	4.3
IIV_V %	21.2	1.90	20.1	4.6
Additive error	1.33	0.18	1.32	0.17



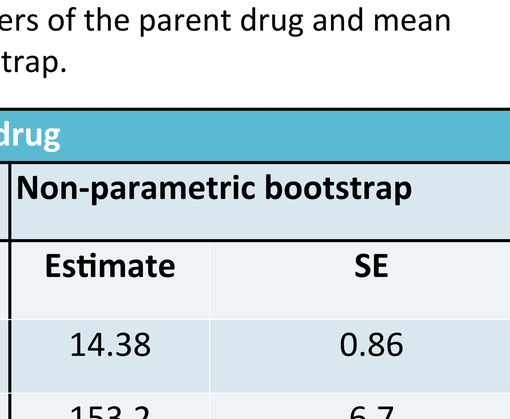


Fig.1: (i) Predicted vs Observed concentration and (ii) Individual predicted vs Observed concentration of cyclophosphamide.

Parent plus metabolite (4-OH CY): was modeled as one compartment with linear elimination. The production rate was proportional to the elimination of the parent drug.

$$K_{met} = \theta_3 * exp(\eta_3) \quad \text{Eq. (3)}$$

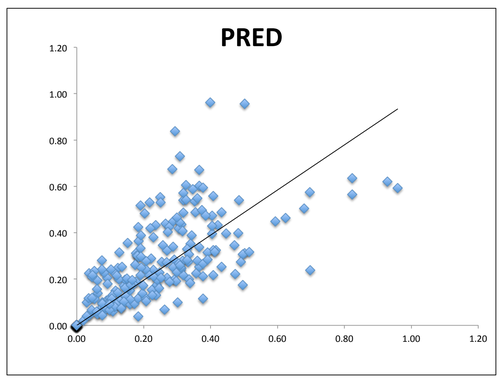
$$DADT(1) = -CL/V * A(1) \quad \text{Eq. (4)}$$

$$DADT(2) = \theta_4 * CL/V * A(1) - K_{met} * A(2) \quad \text{Eq. (5)}$$

Table 2: Mean values for the parameters of the parent-metabolite model and mean values from the non-parametiric bootstrap.

Parent-Metabolite model				
Parameter	Original data set fit		Non-parametric bootstrap	
	Mean	%SE	Estimate	%SE
θ_3 (K_{met},h^{-1})	8	3.7	8.65	3.7
θ_5 (V_m, L)	17.3	7.9	17.5	7.2
θ_4 (F_m)	0.441	0.04	0.413	0.06
Ω_3 (IIV_{Kmet} %)	33	3.9	33	6.4
Prop error (%)	48.8	6.4	47.7	6.3

Elimination rate constant of the 4-OH CY was K_{met}=8 h^{-1}. The production rate constant of 4-OH CY was $F_m * CL_P/V_P$=0.041 h^{-1} and was found to be lower than the K_{met}, therefore half-life of 4-OH CY is determined by its production rate rather than its elimination (flip-flop pharmacokinetics).



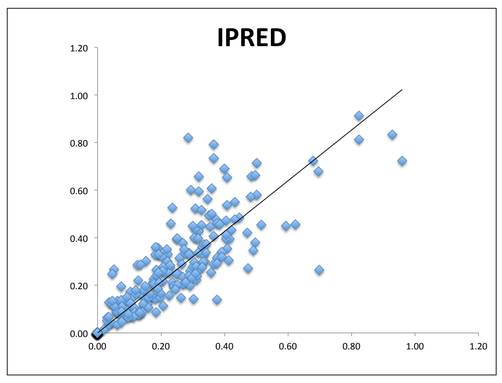


Fig. 2: (i) Predicted vs Observed concentration and (ii) Individual predicted vs Observed concentration for the final parent-metabolite model.

Visual Predictive Check

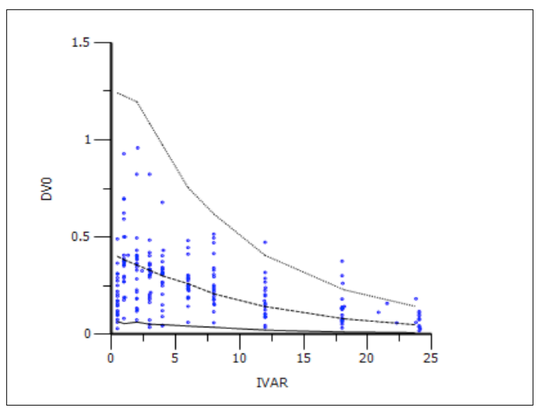


Fig. 3: Visual Predictive Check (parent-metabolite model). The dots are the observed quantiles (5, 50 and 95%) and the solid lines the predicted quantiles (5, 50 and 95%).

Conclusions: The population PK data described here suggest that only 44% of CY gets metabolized to the 4-OH CY metabolite in patients with glomerulonephritis, while this percentage is around 75% for patients receiving CY as an anti-cancer therapeutics.