



Pharmacokinetic Modelling Of Methotrexate From Routine Clinical Data In Patients With Acute Lymphoblastic Leukemia

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OBJECTIVES

Develop a population pharmacokinetic model for methotrexate (MTX) in patients with acute lymphoblastic leukaemia (ALL), receiving a high-dose MTX followed by folinic acid rescue.

METHODS

PATIENTS AND PROTOCOL

- Population pharmacokinetics of MTX was investigated in 273 patients aged between 2-23 years (mean= 13 years), who received high-dose MTX therapy (5 g/m²).
- All patients were treated for ALL.
- They were enrolled at the time of diagnosis according to the European Organization for Research and Treatment of Cancer (EORTC) protocol 58951 [1] approved by an institutional review committee for clinical trials.
- For each patient, the blood samples were collected in dry tubes protected from light at 24, 48, 72, 96 h after the end of infusion and rapidly centrifuged at 2500 g and stored at -20°C until simultaneous analysis.
- The population data set comprised 2582 concentration measurements.
- MTX concentrations were measured with ABBOTT FL_x fluorescence polarization immunoassay (FPIA).

PHARMACOKINETIC ANALYSIS

- Population pharmacokinetic modelling was applied using **NONMEM VI software** (NONMEM Project Group, University of California, San Francisco, USA) to estimate pharmacokinetic parameters, intersubject and residual variability (random effects), and explain this variability in terms of patient specific information such as age or body weight (fixed effects).
- Graphical diagnostics and comparison of competing models using the objective function values (OFV) in the likelihood ratio test and Akaike information criterion (AIC) guided the model development.
- A three-compartment open model with elimination from the central compartment described the pharmacokinetics of methotrexate.
- The population means parameters; between-subject variance and residual variance were estimated using the first order conditional estimate (FOCE) interaction method (residual intraindividual variability was modeled as log-normally distributed, by log transforming the concentrations and the using an exponential model to describe residual variability of MTX concentration using the PREDPP subroutine ADVAN 11 of NONMEM VI (level 1.1). Convergence criterion was three significant digits and MAXEVAL=9000. Microsoft windows Vista™ was used to compile and execute NONMEM.
- The most important covariates affecting the disposition of methotrexate were age (AGE, year), body weight (BW, Kg), and creatinine clearance (CLR, l/h-1).
- The final model was evaluated by the bootstrap method.

Normalized Prediction Distribution Error (npde) for the Evaluation of Nonlinear Mixed-Models :

npde was used for model evaluation in population pharmacokinetic using **R** software . It's based on the whole predictive distribution.

RESULTS

- The final model with exponential disposition of MTX was :

$$(CL, l/h) = (6.11 + WT \cdot 6.7310^{-2}) + (1.0810^{-4} \cdot CLR) \cdot \exp^{(1.9510^{-1})},$$

$$(V, l) = 10.8 + (AGE \cdot 9.310^{-2}) \cdot \exp^{(9.110^{-1})},$$

$$Q(l/h^{-1}) = 2.0410^{-3} \cdot WT.$$

Figure 1 : Scatter plots of population model predicted concentration versus observed concentrations

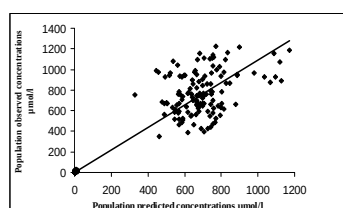


Figure 2 : Representation of the selected model with three compartments.

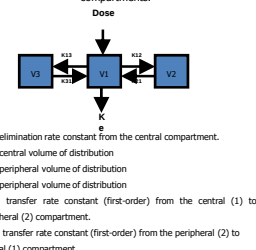
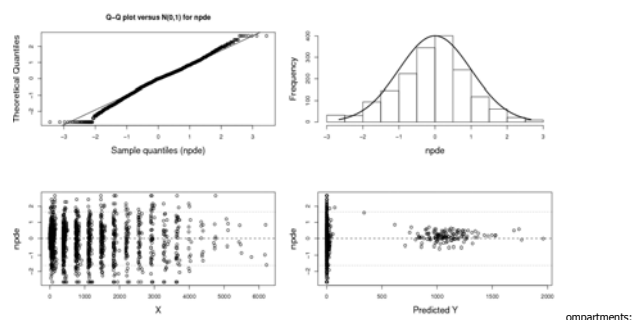


Tableau 2 : the expected pharmacokinetic parameter estimates

Parameter	Estimates	Inter-individual variability CV %	Relative Standard error RSE %	IC 95 %
CL (l/h)	8.72	44	13	[0.14-0.24]
V1 (l)	17.49	95	3.7	[0.85-0.98]
V2 (l)	6.048	56	7.5	[0.27-0.36]
V3 (l)	0.015	53	7.19	[0.23-0.31]
Residual variability	σ	75		

Figure 3 : graphically representation of npde distribution for the Evaluation of Nonlinear Mixed-Models



	npde distribution and statistical analysis
Mean	- 0.092
Variance	1.12 (SE= 0.086)
Skewness	-0.1794
kurtosis	-0.1003
Wilcoxon signed rank test	0,00475 **
Fisher variance test	0,000308 ***
Shapiro-wilks test of normality	6,0610⁻¹⁹ ***
Global adjusted p-value	1,8210 ⁻¹⁷ ***

Significant codes: ***p<0.01 and **p<0.05

DISCUSSION

In this analysis, mean values for clearance and central volume of distribution, were close to previous values reported in other population pharmacokinetic studies by Piard et al., CL, 8.8 l/h⁻¹; V1, 17,3 and Rousseau et al., CL, 7.4 l/h⁻¹; V1, 18,2 l [3, 4].

Population pharmacokinetics of methotrexate in children with ALL was determined using an extended least squares approach to nonlinear mixed effects modeling. Estimates of mean pharmacokinetic parameters correspond well with values previously reported in the literature. However, the population approach has provided estimates of intersubject variability and a method by which to explain some of this variability in terms of subject specific covariates.

CONCLUSION

The MTX population pharmacokinetics in patient with ALL is well described by this investigation. Substantial interpatient variability is explained by incorporating patient specific data into regression equations predicting pharmacokinetic parameters

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