Performing Monte Carlo Simulation Based on Nonparametric Pharmacokinetic Parameter Distributions: Evaluation of Various Methods Applied to a Paediatric Population Study on Busulfan

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OBJECTIVES

Monte Carlo (MC) simulation techniques are increasingly used in population pharmacokinetic (PK) studies. Nonparametric (NP) population methods often result in unusual and non-Gaussian distribution shapes. Little information exists about the way to perform MC simulation compatible with such results. The main objective of this study was to evaluate the ability of various MC simulation methods to reproduce the characteristics of a NP parameter distribution observed in real patients.

METHODS

Population PK study

A population PK study was carried out using the NPAG algorithm in 42 children who received Busulfan (Bu) intravenously before bone marrow transplantation. Bu concentrations (N=166) were determined by a validated HPLC-UV method [1] as part of routine patient care. Various compartmental models were fit to data using the log-likelihood criterion. Goodness of fit and predictive performance were assessed using standard criteria.

Simulation study

7 methods were evaluated in a 1,000 subject MC simulation using Matlab software. Various options regarding parameter distributions, covariance, and other settings were tested (see **Table 1**). Methods 1 to 4 were fully parametric (FP) methods. Methods 5 to 7 were semi-parametric, two-step (TS) methods: **1**/ one point is selected in the NPAG grid according to its probability **2**/ the selected point is used as a mean vector of an assumed multivariate distribution. Percentiles of the simulated distributions were compared with those of the reference NPAG parameter distribution. A graphical examination of scatter plots of parameter pairs was also performed.

Table 1. Characteristics of the various simulation methods (note: parameter values were bounded by 0 except for method #3)

Simulation Methods		Assumed distribution for simulated parameters	Pop quantities used	Cov matrix
One-Step Fully Parametric	**M1**	N	Mean ± SD	No
	M2	N	Median ± SD	No
	M3	Log-N	Mean ± SD	No
	M4	Multivariate N	Mean & NPAG cov matrix	NPAG matrix
Two-Step Semi-Parametric	**M5**	Multivariate N around NPAG support points	NPAG grid & cov matrix	NPAG matrix
	M6	Same as #5	NPAG grid & cov matrix	NPAG matrix / Nb of grid points
	M7	Same as #5	NPAG grid & cov matrix	NPAG matrix / Nb of subjects

RESULTS

Population PK study

A linear two-compartment model fit the data very well **(Fig 1)**. NPAG provided a 27 point grid as population parameter distribution of the four parameters. For Bu volume of distribution V_D and transfer constant K_{PC}, the probability distribution was unusual **(Fig 2)**.

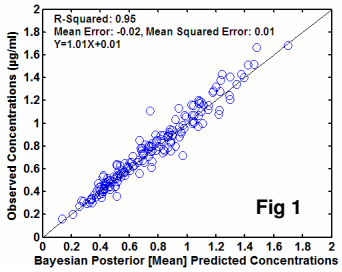

Fig 1

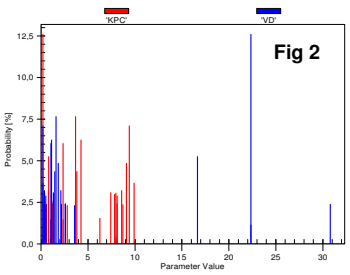

Fig 2

Table 2. Summary statistics of population parameter values

Parameter	Mean	Median	SD
K_E (h^{-1})	1.09	1.02	0.57
V_D (L)	5.66	1.52	8.69
K_{CP} (h^{-1})	1.71	1.34	1.21
K_{PC} (h^{-1})	4.38	3.68	3.50

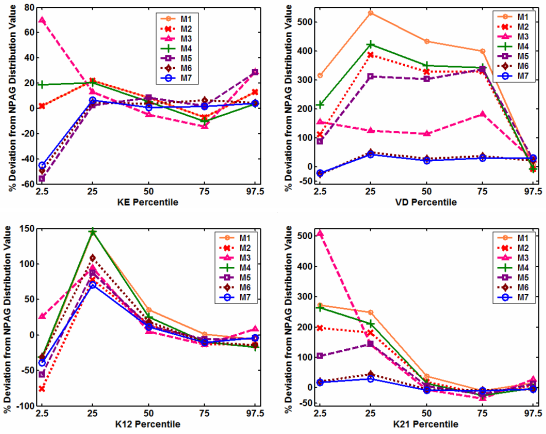

Fig 3 Percent deviations of parameter distribution percentiles from the reference distribution values

Simulation study

Overall, FP methods could not reproduce the properties of the original NP distribution. Best results were obtained with two-step methods using a small covariance matrix derived from the NPAG one (M6 and M7). Those provided the least deviations of distribution percentiles from the original population values, especially when the reference distribution shapes were unusual **(Fig 3)**. Scatter plots of parameter pairs **(Fig 4)** showed that FP methods provided many values located in areas with no corresponding NPAG support points. Two-step methods with a small covariance matrix provided values much more clustered around those points.

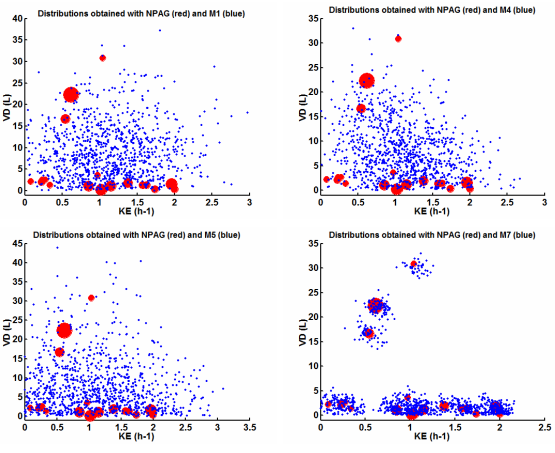

Fig 4. Scatter plots of K_E-V_D pairs provided by different simulation methods and comparison with NPAG distribution (for NPAG values, areas of the circles are proportional to the probabilities)

CONCLUSIONS

Classical parametric methods are not suited to perform MC simulation based on NP parameter distributions. This task requires specific methods. A new approach of MC simulation designed for such application has been presented.

Reference: [1] Bleyzac N, et al. J Chromatogr B Biomed Sci Appl 2000;742:427-32