Physiologically-Based Pharmacokinetic (PBPK) Model for High- and Low Dose Etoposide: From Adults to Children

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Background and Objectives

Etoposide is a widely-used anticancer drug in paediatric oncology. Although it is pharmacokinetically well characterized antineoplastic agent, the interpatient variability makes it difficult to define an individualized dosing regimen.
The aim of the current project was to evaluate a generic physiology-based pharmacokinetic (PBPK) model to predict the systemic drug exposure of high- and low dose etoposide in children from a model developed with adult data.

Methods

The simulations of etoposide were performed by the software PK-SIM® (Bayer Technology Services) which contains an integrated database of known physiological parameters for adults and children.
The model was developed and evaluated using concentration-time profiles from 9 adult patients receiving intravenous etoposide in a conventional low- (normalized to 200 mg) and high (normalized to 1000 mg) dose polychemotherapy before stem cell transplantation (Busse D et al. Naunyn Schmiedebergs Arch Pharmacol. 2002; 366:218-25). To describe the main metabolism and excretion processes by the enzymes CYP3A4 and UGT1A1 and drug transporter as Pgp and MRP2, Michaelis-Menten kinetics using parameters from in-vitro experiments reported in the literature were applied.
The validated model was scaled down to two subgroups of 18 and 6 children receiving high- and low dose etoposide, respectively and finally compared to observed data in this age group (Würthwein G. et al. Anticancer Drugs. 1999; 10: 807-14 ; Würthwein G. et al. Anticancer Drugs. 2002;13:101-10). In addition, drug interactions triggered by eg. P-glycoprotein inibitors or nephrotoxic drugs such as cyclosporine A and carboplatin were elucidated.

Results: Adults

In adults mean (Fig. 1 and 2) and individual (Fig. 3a and b; Fig. 4a and b) simulated plasma concentration-time profiles of protein-bound and free etoposide for high- and low dose etoposide agreed with the observed data (Fig. 1 and 2). Mean simulated total clearance of high- and low dose etoposide were 0.74 ml/min/kg (CL_{obs}: 0.7 ml/min/kg) vs. 0.52 ml/min/kg (CL_{obs}: 0.6 ml/min/kg), respectively.

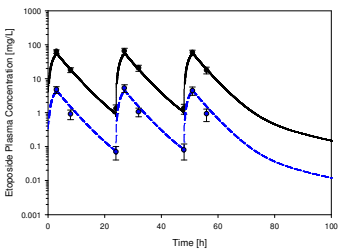

Figure 1:
Observed data vs. mean simulated concentration-time profiles of protein-bound (black line) and free (blue line) etoposide in adults for high dose etoposide

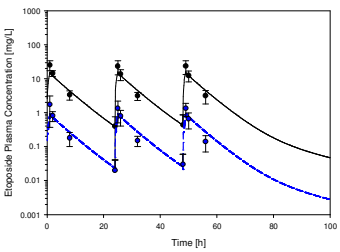

Figure 2:
Observed data vs. mean simulated concentration-time profiles of protein-bound (black line) and free (blue line) etoposide in adult for low dose etoposide

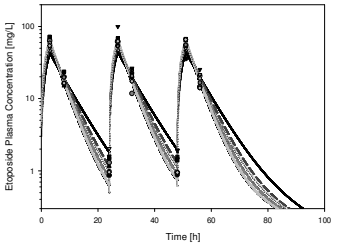

Figure 3a:
Observed data from nine individuals vs. simulated concentration-time profiles of protein-bound etoposide during high dose polychemotherapy regimen in adults

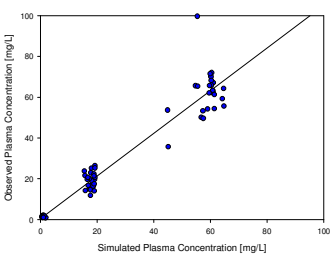

Figure 3b:
Goodness-of-fit plot for the individual simulated vs. observed plasma concentrations of high dose protein-bound etoposide in adults

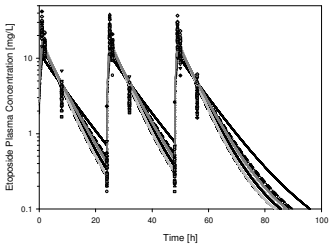

Figure 4a:
Observed data from 9 individuals (4 cycles) vs. simulated concentration-time profiles of protein-bound etoposide during low dose polychemotherapy regimen in adults

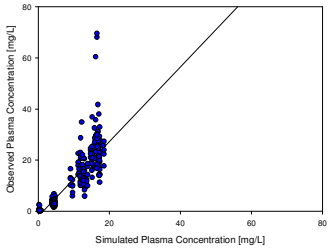

Figure 4b:
Goodness-of-fit plot for the individual simulated vs. observed plasma concentrations of low dose protein-bound etoposide in adults

Results: Children

Integrated Michaelis-Menten kinetics of metabolism and excretion pathways was adequately transformed to age-related pharmacokinetics in children using different ontogeny factors for the main enzymes CYP3A4, UGT1A1 and drug transporter Pgp and MRP2 within each age group. The predictions of the pharmacokinetics in paediatric patients of different age for high- and low dose etoposide (Fig. 5 and 6) by the PBPK model were also in good agreement with observed data.

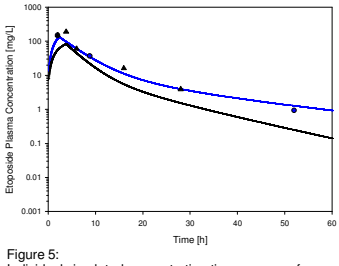

Figure 5:
Individual simulated concentration-time courses of high dose etoposide (40 mg/kg) in two representative patients; child black line: age: 6.2 years, 125 cm, 25 kg child blue line: age: 13.3 years, 157 cm, 54 kg

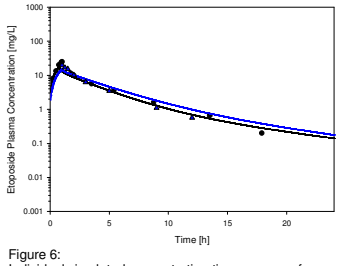

Figure 6:
Individual simulated concentration-time courses of low dose etoposide in two representative patients; child black line: age: 13 months, 78 cm, 9.3 kg; child blue line: age: 4.92 years, 109 cm, 15.7 kg

Moreover, an influence of comedication such as carboplatin or cyclosporine A on the metabolism and excretion during high dose polychemotherapy regimen was observed in children. In case of carboplatin (and melphalan) coadministration the renal clearance of etoposide in children decreased from 68% to app. 37% (Fig. 7). Cyclosporine A decreased the nonrenal clearance via CYP3A4 of etoposide by 50% The total renal clearance decreased only from 68% to 65% which was mainly affected by Cyclosporin A on the tubular secretion transport mechanisms (Fig. 8).

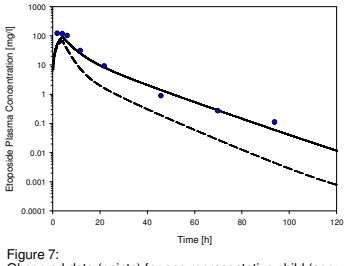

Figure 7:
Observed data (points) for one representative child (age: 4 years, 98.8 cm, 14,8 kg) vs. simulated concentration-time profile with (solid line) and without (dotted line) influence of coadministration (carboplatin-1500 mg/m^2; melphalan- 180 mg/m^2) during high dose polychemotherapy regimen (etoposide- 40 mg/kg)

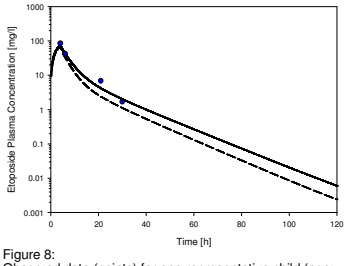

Figure 8:
Observed data (points) for one representative child (age: 0.83 years, 66 cm, 9 kg) vs. simulated concentration-time profile with (solid line) and without (dotted line) influence of comedication (cyclosporin A- 4.5-6 mg/kg iv.) during high dose polychemotherapy regimen (etoposide- 40 mg/kg)

Conclusion

The PBPK-model simulations matched the etoposide pharmacokinetics in different dosing regimens in adults. Furthermore, the scaling procedure from the adult model to children by adjusting model parameters for metabolism and excretion procedures provides adequate predictions. This approach can be useful for planning pharmacokinetic studies in children and for building hypotheses regarding the effect of comedication with drugs influencing the metabolism and excretion.