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. 2000; 366:218-25). To describe the main metabolism and excretion processes by the enzymes CYP3A4 and UGT1A1 and drug transporter as Pgp and MRP2, Michaels-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 inhibitors or nephrotoxic drugs such as cyclosporin 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\text{free} 0.7 ml/min/kg) vs. 0.52 ml/min/kg (Cl\text{free} 0.6 ml/min/kg), respectively.

Results: Children

Integrated Michaels-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.

Conclusion

The PBPK-model simulations matched the etoposide pharmacokinetics in different dosing regimes 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 comodication with drugs influencing the metabolism and excretion.