Application of Physiologically Based Pharmacokinetic (PBPK) Modelling to Predict the Pharmacokinetics of Alfentanil and Midazolam in Preterm Neonates

Xian Pan, Khaled Abduljalil, Trevor N. Johnson
Certara UK Limited, Simcyp Division, Sheffield, United Kingdom
Xian.Pan@certara.com

Background

Analgesics are widely used in preterm neonates for the management of pains. Alfentanil is the most used analgesic opioid in the neonatal intensive care unit, while midazolam is the preferred treatment prior to invasive procedures. Achieving adequate and tolerated therapeutic concentration of these drugs in neonates is critical. Both compounds undergo extensive metabolism by CYP3A. The rapidly changing physiological parameters (e.g., weight, height, blood flow, tissue volume and composition, blood protein contents, and metabolic enzyme ontogeny) in neonates affects the disposition of these drugs. Physiologically based pharmacokinetics (PBPK) modelling and simulation has been incorporated into the paediatric drug development process and utilised to predict suitable dose regimens. The aim of this study was to evaluate the accuracy of PBPK models in predicting alfentanil and midazolam pharmacokinetics in preterm neonates.

Methods

The Sim-Preterm population has been introduced as an extension to the Simcyp® Paediatric Simulator V17R1. The comprehensive demographic and physiological information, including weight, height, BSA, cardiac output, renal function, binding protein content, tissue volume, tissue composition, tissue blood flow, etc., were collated and integrated to build this population. The midazolam compound file was selected from the Simcyp compound library. The PBPK models of alfentanil was built and verified with clinical data in adults, and subsequently used in the preterm population. CYP3A4 ontogeny is described as a function of postmenstrual age based on the in vitro expression and activity data measured in foetal and neonate liver microsomes (*Lacroix et al., 1997; Stevens et al., 2003; Hines, 2007*). UGT1A4 ontogeny function was defined the same as term neonates at birth and incorporated into the midazolam model. The trial design was set to match the clinical studies and the postnatal age was uniformly distributed. The accuracy of paediatric exposure was evaluated by comparing the simulated concentration-time profiles and estimated pharmacokinetics parameters with clinical observations.

Results

The PBPK models of alfentanil and midazolam recovered the observed plasma concentration-time data in preterm and term neonates (Figure 1). The ratios of predicted over observed clearance and volume of distribution values for alfentanil in preterm and term neonates were within 0.5-2.0 range (two fold error) (Figure 2).

Results

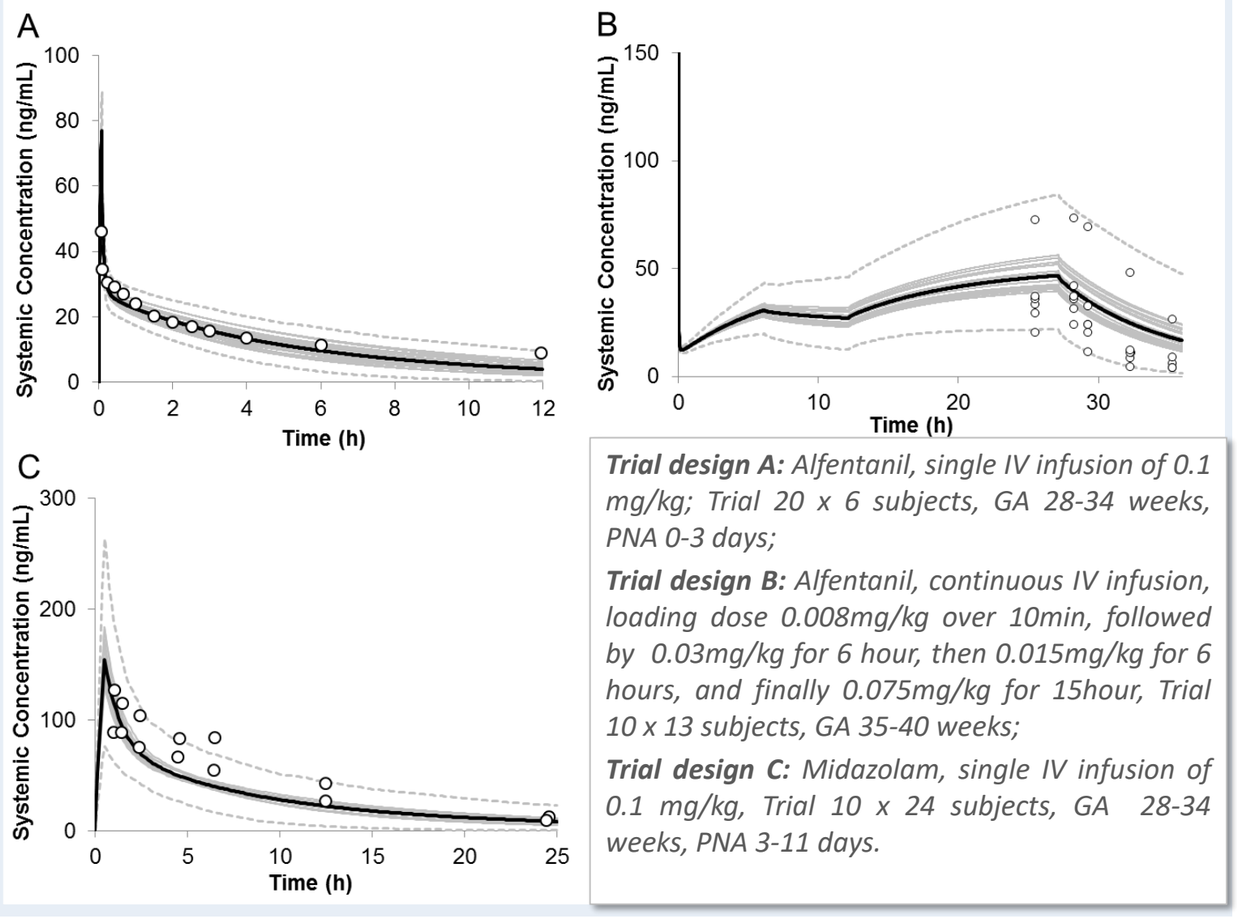

***Figure 1**. Simulated mean plasma concentration-time profiles of alfentanil and midazolam after i.v. administration (black line) versus observed (data points, (A) Davis et al., 1989; (B) Wiest et al., 1991; (C) de Wildt et al., 2001) in neonates from 28-40 gestational weeks. The grey lines represent the predictions from individual trials. Dashed lines represent the 5th-95th percentile of the total virtual population.*

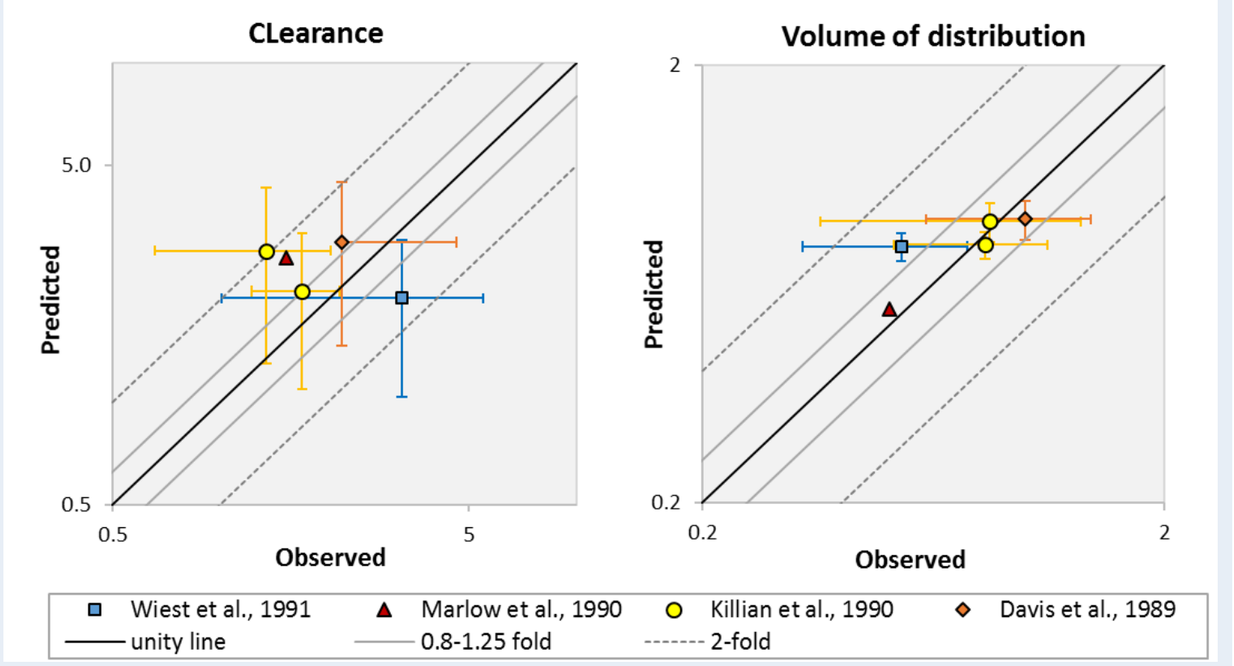

***Figure 2**. Predicted versus observed mean values (Davis et al., 1989; Killian et al., 1990; Marlow et al., 1990; Wiest et al., 1991) of alfentanil clearance and volume of distribution in neonates from 28-40 gestational weeks. The black solid line is the line of unity. The grey solid lines represents 0.8- to 1.25- fold error. The grey dashed lines represent 2-fold error.*

Conclusions

The PBPK models of alfentanil and midazolam showed a good predictive performance in preterm neonates. This study demonstrates that PBPK modelling and simulation could provide a valuable aid to decision-making with regard to dose optimization in neonates.

References

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