Prediction of Midazolam Concentration Profile in Obese Adolescent Population Using Physiologically Based Pharmacokinetic model

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Introduction Overweight or obese children are more likely to have chronic diseases compared with normal-weight children [1]. Approximately 1 of 6 children in the United States is obese [2]. The impact of obesity on safety, pharmacokinetics, and dosing in obese children have recently received significant attention [2,3]. In 11 out of 17 studied drugs, clinically significant pharmacokinetic alterations were observed in obese children [3]. Obesity is associated with different physiological changes, for example, in obese population there is about 36% decrease in CYP3A4, a 41% decrease in CYP3A5, a 15% increase in cardiac output and also an increase in GFR and liver volume. These changes can alter drugs kinetics, possibly leading to therapeutic failure or toxic side effects. Physiologically based pharmacokinetic (PBPK) models can integrate both the drug characteristics and the underlying physiology, along with its variability within a population, when predicting drug PK. In addition, the PBPK approach has an extrapolation capability. Once the model performance is verified for a particular drug in one population, it can be assessed in another population, since the drug-dependent parameters remain the same and only the underlying physiological characteristics change.

Objectives The objective of this study is to use PBPK approach to predict plasma concentration-time profiles in overweight and obese paediatric populations after a long term infusion of the drug used for sedation.

Materials and Methods The paediatric algorithm was coupled to the obese and morbidity obese populations in Simcyp simulator V15R1 to account for physiological changes in obese paediatric population that can affect midazolam pharmacokinetics. For all cases the user-defined height and weight relationship option was used to code specific body weight-height relationships. Total body weight was coded as a single value with zero CV and without any propagated variability from individuals height to generate a set population with exact body weight. Simulations were compared against those reported for body weight of 62 kg, 105 kg and 149 kg [4]. The trial settings were 10 trials and in each trial there were 10 individuals aged between 12 – 19 years (30% female). The dose was either 0.05mg/kg or 2mg as a single iv bolus. The full PBPK distribution model and default enzyme kinetics for CYP3A4 and CYP3A5 were used to describe disposition kinetics. The model was then used to compare the concentration time profiles in these three cases after a loading dose of 5 mg given over 5 minutes followed by a continuous infusion of 60 mg given over 60 hr.

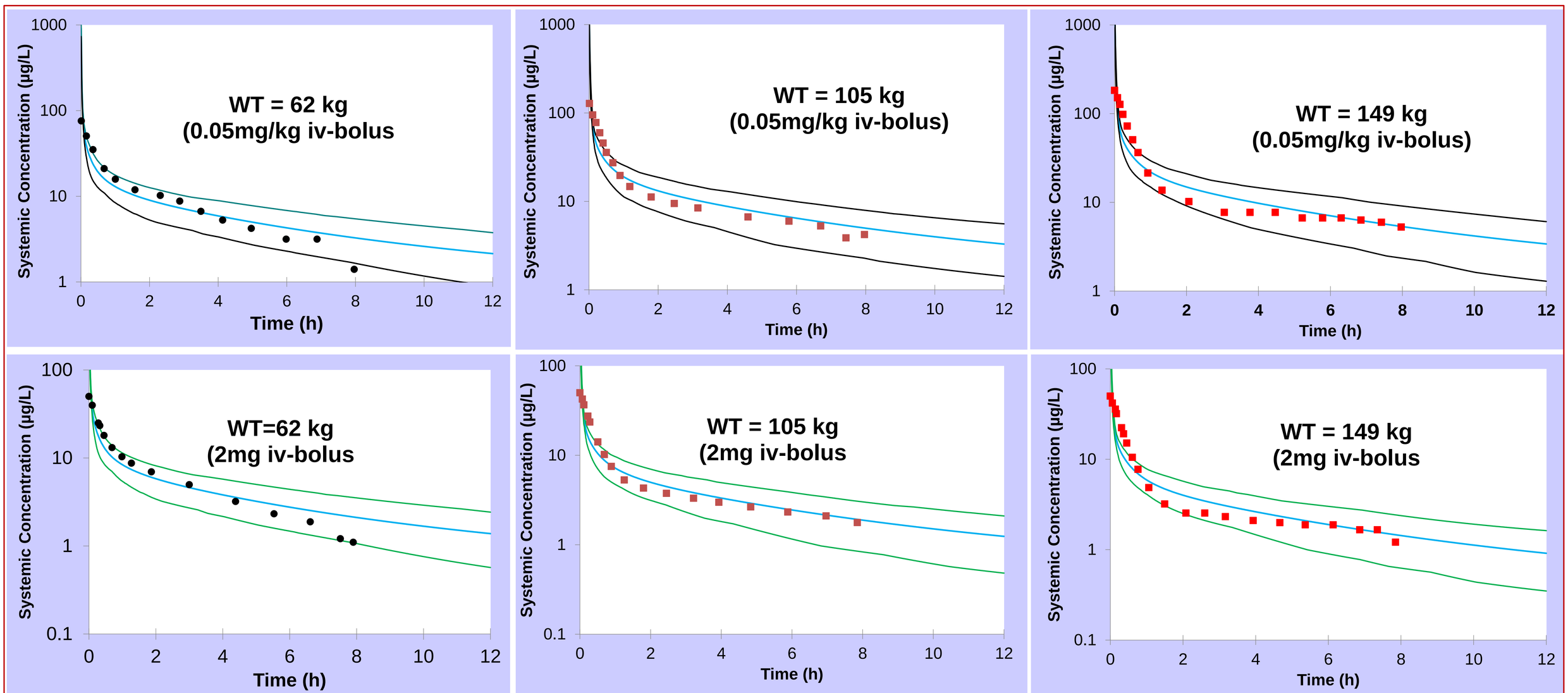

Figure 1. Predicted (lines) and reported [4](dots) plasma concentration profiles of midazolam over time in three populations with different body weights

Results and Discussion Simulated profiles were in agreement with the reported concentration time profile for midazolam in adolescent obese population (Fig. 1). The model couples together the system parameters that changes in obese populations with the algorithms from the paediatric simulator to predict clinically relevant situations for obese children. Figure 2 shows the comparison in the plasma levels of midazolam and indicates that the concentration is higher in obese populations compared with the 62 kg overweight subject. These changes reflects mainly the decrease in the CYP3A4 and CYP3A5 activity in the obese populations.

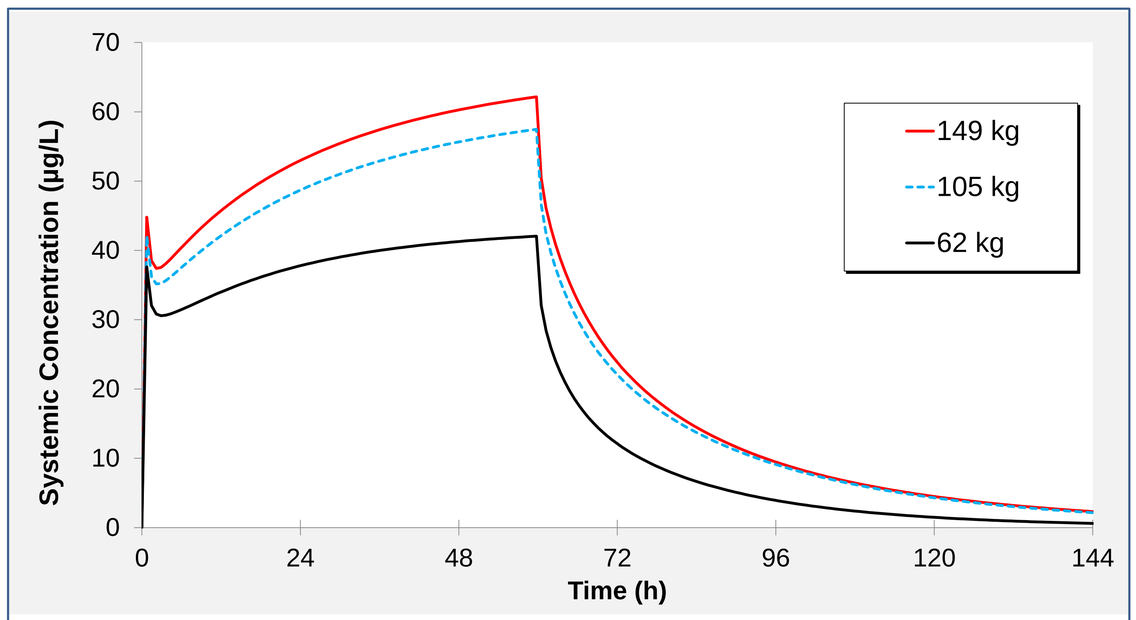

Figure 2 Mean plasma concentration profiles of midazolam in adolescents with different body weight after midazolam administration of 5 mg for 5 min followed by 60 mg infusion for 60 hr.

References

[1] Plachta-Danielzik et al. (2008) Br J Nutr. 100(1):208-18. [2] Rowe et al. (2015) Clin Ther. S0149-2918(15)01023-1. [3] Harskamp-van Ginkel et al. (2015) JAMA Pediatr. 2015 169(7):678-85. [4] van Rongen et al. (2015) Br J Clin Pharmacol. 2015 Jun 4.