

A semi-physiologically based pharmacokinetics approach to predict hepatic and gut wall intrinsic clearances of midazolam in pediatric patients: preliminary results filling the gap between preterm neonates and infants above 1 year.

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Objectives

Clearance (CL) and oral bioavailability (F) are important drivers of oral drug exposure and dose selection. Midazolam is extensively metabolized by CYP3A, with CL being primarily driven by hepatic metabolism, while F is dependent on first pass metabolism at both the hepatic and intestinal level. Systemic and pre-systemic midazolam metabolism have already been characterized in preterm neonates [1] and children between 1 and 18 years of age [2] using semi-physiologically based pharmacokinetics (semi-PBPK) modelling. This has identified a large difference in hepatic intrinsic CL between preterm neonates ($Cl_{int} = 6.7 \text{ L/h}$) [1] and children older than 1 year (527 L/h for a 16 kg typical patient) [2] as well as differences in maturation patterns between intestinal and hepatic metabolism. We aim to fill the gap and characterize both intestinal and hepatic CYP3A-mediated metabolism of midazolam in term neonates and infants receiving therapeutic IV midazolam and an oral microdose of ^{14}C radiolabeled midazolam, using population semi-PBPK modelling.

Methods

Pharmacokinetic (PK) data of midazolam and 1-hydroxymidazolam were retrieved from a previous study in 43 term neonates and infants hospitalized in pediatric intensive care units [3]. Patients aged 2 days to 5.3 years [2.8 kg – 18 kg], simultaneously received a therapeutic IV midazolam dose and an oral micro-dose of ^{14}C radiolabeled midazolam [3]. Data from 264 post-operative children (age 1 to 18 years) and from 37 preterm neonates (gestational age 26–34 weeks) who received an oral dose of midazolam and/or midazolam via a 30-minute intravenous infusion were also available for analysis [1,2]. A previously developed model with PBPK elements

for systemic and pre-systemic CL was used [2]. This model includes physiological compartments for gut wall, portal vein and liver, and descriptive compartments to describe the distribution of midazolam and its metabolite. Age-appropriate organ blood flows and volumes were obtained from literature [4-7]. Oral absorption followed first order kinetics with an absorption rate constant fixed to $4.16 \text{ [h}^{-1}\text{]}$ [1]. Intrinsic CL and maturation profiles for these CL values in gut wall and liver were estimated based on the data, while the extraction ratios were calculated using the well-stirred model. F was calculated as the fraction escaping the first metabolic extraction in the gut wall and the liver with 100% of the drug being assumed to be absorbed in the gut wall. First, we optimized the structural model for the distribution of the parent compound using IV data. Subsequently the structural and covariate model for the presystemic and systemic intrinsic CL parameters in the PBPK-model features was performed using both IV and PO data. Body-weight dependent exponent (BDE) models [8] and functions based on a combination of weight and age-related covariates were tested to describe the maturation in intrinsic clearances.

Results

When combining the new data from 43 neonates and infants (0 – 6 years old) [3] with the data from the older children (1 - 18 years old) [2], the bodyweight-based function describing hepatic intrinsic CL in the older children [2] was found to systematically overpredict CL of infants below the age of one year. Age-related changes in hepatic intrinsic CL were better described with a body weight dependent exponent model [8]. Using this model, the exponent decreased in a sigmoidal manner with body weight from 1.314 to 0.472, with a BW50 at 5.59 kg and a Hill coefficient equal to 1.47. This lead in an average term neonate (3.3 kg) to an estimated hepatic intrinsic CL of 33 L/h, while previously in preterm neonates (0.8-1.6 kg) a value of 6.7 L/h was found. Similar maturation patterns were found for gut wall intrinsic CL.

Conclusion

The semi-PBPK approach in this project applied to data of term neonates and infants enables us to fill the age-gap and quantify the considerable developmental changes in gut and hepatic CYP3A metabolism in the first year of life. Metabolic clearances in the gut and the liver, and therefore also in first pass effect, are expected to be lower in children younger than 1 compared to children between 1 and 18 years old. Consequently, bioavailability is expected to be higher in neonates and infants than bioavailability in older children. The final model will enable the development of midazolam and potentially other CYP3A substrate dosing regimens for both oral and IV routes throughout the pediatric age-range.

References:

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