

Model-based Approaches to Investigate Pharmacogenetic and Developmental Sources of Variation in the Pharmacokinetics of Midazolam after Oral administration in Children

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Purpose.

The purpose of this study was to model the pharmacokinetics of midazolam and its four metabolites, 1'-hydroxymidazolam, 4'-hydroxymidazolam, 1'-hydroxymidazolamglucuronide and 4'-hydroxymidazolamglucuronide in children using non-linear mixed effects and physiology-based pharmacokinetic (PBPK) modeling approaches

Methods.

Midazolam was administered as an oral suspension of 3 to 15 mg (296 subjects, aged 1-18 yr). Non-linear mixed effects modeling was performed using NONMEM. Demographic and genetic factors of body weight, age, race, sex and CYP3A4*1B, CYP3A5*3 and CYP3A5*6 genotypes were tested to identify potential parameter-covariate relationships. Using the physiology-based pharmacokinetic software, PK-Sim® (Bayer Technology Services GmbH, Leverkusen, Germany) the ontogeny of the physiological processes responsible for midazolam pharmacokinetic characteristics, including intestinal CYP3A4 and P-glycoprotein and their role in midazolam metabolism, were assessed. Plasma concentration-time curves for each child were simulated based on the age, height and weight of the child plus the physico-chemistry of midazolam and its metabolites.

Results.

Midazolam absorption after oral administration was rapid, and was best-described by a combined zero and first order absorption. A 3-compartment model best described the disposition of Midazolam and 2-compartment was used for each of its four metabolites. There was large inter-individual variability for the PK parameters. Allometrically-scaled body weight explained a significant amount of variability in Clearance and Volume of distribution for all analytes. Population values of the oral CL, V1, V2, Q2, V3 and Q3 for midazolam were 1.14 L/min (5%), 109 L (13.5%), 95.8L (22.5%), 0.7L/min (24.2%), 69.5L (17.6%), 0.3L/min (16.8%). None of the genotypes for CYP3A4/3A5 were found to significantly influence the pharmacokinetics of Midazolam, 1'-hydroxymidazolam and 4'-hydroxymidazolam. Intestinal CYP3A4 and P-glycoprotein played a role in reducing the bioavailability of midazolam across all ages.

Conclusion.

Population PK model of midazolam and its metabolites based on both approaches adequately described the observed plasma-concentration data, and the estimated parameters is consistent with other data available in pediatrics. The developed models incorporated ontogeny in intestinal CYP3A4, and may be useful in predicting the time courses, including interindividual variability, after oral administration of midazolam in children.