Population Pharmacokinetics of Morphine in Patients with Non-Alcoholic Steatohepatitis (NASH) and Healthy Adults

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Objectives: Altered expression and function of hepatic transporters in NASH patients may affect the pharmacokinetics (PK), efficacy, and toxicity of drugs [1]. A population PK model was developed to assess differences in morphine and morphine-3-glucuronide (M3G) disposition in NASH patients and healthy volunteers.

Methods: A total of 267 serum and 42 urine samples from 21 volunteers (14-healthy; 7-NASH) were analyzed using NONMEM 7.3. Two- and three-compartment linear mammillary models were evaluated for morphine and one- and two-compartments for M3G [2]. Morphine clearance (CLₔ) and volume of distribution were allometrically scaled using total body weight. Morphine serum concentrations below the limit of quantification were fitted using the M3 method. NASH status, Fibroscan® score, AUC and fasting Cₘₚ₉ of total serum bile acids were tested as covariates to explain inter-individual variability in CLₔ, M3G clearance (CL₃₉₉) and volume of distribution (V₃₉₉) using stepwise covariate modeling with PsN (Perl-speaks–NONMEM). Goodness-of-fit plots, parameter plausibility and residual squared errors, and numerical and visual predictive checks (VPC) were used as criteria to evaluate model performance.

Results: A three-compartment model best described morphine disposition with a liver transit compartment accounting for the delay in M3G appearance in serum. M3G was best described by mono-exponential kinetics. Use of NASH status on CL₃₉₉ and V₃₉₉ resulted in a 10- and 8-point drop in the objective function value, respectively. The model predicted a 28% and 22% decrease in CL₃₉₉ and V₃₉₉, respectively, for NASH patients compared to healthy volunteers. VPC plots indicate adequate fit for morphine and M3G (Figure 1).

Conclusions: NASH status was the most significant predictor of differences in M3G exposure, which reflects altered transporter expression and function in this disease state. The final covariate model predicts higher AUC and Cₘ₉ of M3G, for NASH patients compared to healthy volunteers.

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References:
Figure 1
A) VPC of morphine in serum with a horizontal reference line representing LLOQ of 8.24 nM for the assay
B) VPC of M3G in serum
Blue and pink shades represent the model predicted confidence interval around the 95th, 5th, and 50th percentile of the simulated data, respectively. Light blue dots with connected blue lines represent the 95th, 50th, and 5th percentiles of the observed data.