Pharmacokinetic/pharmacodynamics analysis of hydrocortisone in pediatric patients with congenital adrenal hyperplasia

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Objectives: Patients with congenital adrenal hyperplasia (CAH) have no/low synthesis of cortisol. Optimisation of hydrocortisone (synthetic cortisol) therapy in this population is important, since too low or high concentrations increase the risk of adrenal crisis or Cushing’s syndrome, respectively [1]. 17-hydroxyprogesterone (17-OHP, cortisol precursor) concentrations are elevated in these patients and may serve as a disease-specific marker to evaluate therapy [1, 2]. This analysis aimed to characterise the pharmacokinetics/pharmacodynamics (PK/PD) of cortisol by using 17-OHP as a biomarker in paediatric patients with CAH.

Methods: CAH patients (n=30, age: 7-17 years) received standard hydrocortisone replacement (tablet, 5-20 mg) twice (n=17) or thrice (n=13) daily. Plasma samples were collected pre-dose and every 20 minutes up to 24 h post-dose [2]. The PK model was first developed and sequentially fixed when estimating the PD parameters using NONMEM 7.3. Use of mixture models was evaluated. Model selection was based on plausibility and goodness of fit plots. Predictive performance and parameter precision were assessed by visual predictive checks and bootstraps, respectively [3].

Results: The cortisol concentration-time profiles were accurately described by a two-compartment disposition model with sequential zero- and first-order absorption. An indirect response model with a cortisol-mediated inhibition (sigmoidal Iₘₐₓ effect model) of the 17-OHP synthesis described the data most adequately. A mixture model was used to estimate different baseline concentrations of 17-OHP for two subpopulations (5.3 and 280 nmol/L).

Conclusions: An initial PK/PD model for cortisol has been established, and additional aspects such as circadian rhythm may be included to improve model performance. When final, simulations can be performed to evaluate cortisol substitution therapy.

References: