Title: Whole-Body Physiologically-based Pharmacokinetic (WB-PBPK) Population Modelling to Simulate the Influence of Weight and Age on the Pharmacokinetics (PK) of a combined Oral Contraceptive Containing Drospirenone (DRSP) and Ethinylestradiol (EE)

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Obesity has reached epidemic proportions. WHO's latest projections indicate that in 2005 approximately 1.6 billion adults were overweight.[1] The body fat fraction is an important determinant of the PK and can become the dominant factor for highly lipophilic compounds such as steroids.
This study aimed to use a WB-PBPK model to investigate the influence of age and weight on the PK to be expected after administration of a fixed dose combination of EE and DRSP in a combined oral contraceptive (COC).

WB-PBPK models were built for DRSP and EE using the software PK-Sim®.[2,3] The simulated plasma concentration-time profiles were validated using observed data from 48 women.[4-6] In a second step, the PK-Pop module of PK-Sim® was used to build virtual populations of normal weight, overweight, obese and highly obese females aged 14-45 yrs using the body mass index (BMI) to discriminate between weight groups. Steady state (SS) PK parameters (AUC, C_{max}, C_{trough}, $t_{1/2}$) and concentration time profiles of DRSP and EE were compared between the different virtual populations.

The WB-PBPK model matched the experimentally measured concentration-time profiles and derived PK parameters in the validation population[4-6] comprising women with slight underweight to slight overweight very well.
Age-related differences of PK parameters were not observed for DRSP and EE in women >14 yrs. Plasma AUC and C_{trough} were simulated to be similar for both compounds at SS across the different BMI groups. In silico tissue distribution suggest a substantial distribution of both hormones in fat resulting in a decrease in the EE C_{max} to C_{trough} ratio and a decrease of C_{max} and C_{trough} of DRSP in the obese compared to the normal weight population. Nevertheless, a prospective post-marketing surveillance study found DRSP/EE containing COCs to be equally effective in obese and non-obese populations.[7]

The WB-PBPK population modelling approach provided an excellent description of the experimental data. Our analysis complements the classic population PK approach since we could mechanistically study the influence of co-factors like age or BMI. The possibility to predict tissue concentrations enables model-based PK/PD predictions for populations of interest not covered by available clinical data.

References:
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