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Guiding Dose Adjustment in Pregnancy

Physiologically-based pharmacokinetic (PBPK) modeling allows the changes in drug exposure that occur during the various stages of pregnancy to be simulated, guiding dose adjustment decisions and increasing safety for this vulnerable group of patients

For ethical reasons, pregnant women are actively excluded from drug studies. As a result, there is a lack of clinical data on how the well-documented physiological and biochemical changes that occur during pregnancy will affect maternal drug exposure. Clinicians are faced with decisions to prescribe "off-label" drugs that are unlicensed for pregnant women, often scaling doses from the recommendations set for men or non-pregnant women. This can lead to under-dosing, with lack of therapeutic effect, or over-dosing, with potential toxicity that endangers both mother and developing fetus.

The challenge of dose-determination during pregnancy

Recent moves by the US FDA and European Medicines Agency are addressing this issue by requiring that post-marketing studies be conducted into the effects of drugs in pregnancy where there is a high likelihood of use in women of childbearing age. The challenge for pharmaceutical companies is not only to determine appropriate initial dosing levels—which will vary depending on the stage of pregnancy—but also account for the time-related changes in drug exposure that may occur over an extended study period. As the physiological and biological changes that occur during pregnancy are well-studied, building physiologically-based models to study pharmacokinetics (PK) is an intuitive solution.

The Simcyp Simulator gains a PBPK pregnancy model

Certara scientists developed a full PBPK pregnancy model which has been implemented in the Simcyp Simulator and tested for its ability to simulate how drug concentrations change over time. The model reflects the progression of pregnancy through changes such as body weight, blood and plasma volume, feto-placental volume, CYP450 enzymatic activity and serum albumin levels. In validation studies, good agreement was found between simulated and observed maternal exposure of caffeine, metoprolol and midazolam, three compounds which undergo hepatic metabolism by three different enzyme pathways (CYP1A2, CYP2D6 and CYP3A4).[1]

Highlights

Ethical concerns prevent clinical trials from being conducted in pregnant women leading to off-label prescribing and concerns that dose scaling may lead to over- or under-exposure and adverse effects.

Certara scientists built PBPK models to simulate changes in maternal drug exposure at various stages of pregnancy, demonstrating enormous potential for guiding dose adjustment decisions and assisting with the post-marketing studies increasingly required by regulatory agencies.

Quantifying time-dependent changes in drug exposure helps drug developers, regulators and clinicians improve the safety and efficacy of medicines prescribed during all stages of pregnancy.

The Simcyp Simulator helps determine effective dosing for pregnant women

Appropriate dosing for drugs with narrow safety windows is critical in order to avoid adverse effects that may occur with only slight alterations in clearance levels. The Simcyp model is a major advance on previous pregnancy models as it is the first to consider time-dependent factors at any stage of pregnancy. This provides drug developers and the regulatory agencies with a more versatile tool to understand compound-specific changes in drug exposure throughout pregnancy and helps compensate for a lack of clinical data in pregnant women.

PBPK modeling and simulation is increasingly featured in submissions for regulatory approval, gaining widespread acceptance for its role in optimizing study design, identifying worst-case scenarios for further investigation and informing dosage recommendations and labeling. PBPK models for pregnancy are not only relevant for the development of drugs specifically for pregnancy-related conditions but can assist with the dose adjustment decisions required to preserve the safety and efficacy of other therapies which are beneficial to expectant mothers.

References

1. Lu G, Abduljalil K, Jamei M, Johnson TN, Soltani H, Rostami-Hodjegan A. Physiologically-based pharmacokinetic (PBPK) models for assessing the kinetics of xenobiotics during pregnancy: Achievements and shortcomings. C*urr Drug Metab*. 2012; 13(6):695-720.

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