Ensuring Therapeutic Equivalence for Drugs to be Used in Pregnant Patients: A Literature Review and Modeling Exercise to Extrapolate BE Results from Non-pregnant Individuals to Pregnant Individuals

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Overview

This study aims to ensure the therapeutic equivalence of drugs during pregnancy. It investigates the potential impact of pregnancy-associated physiological and pharmacokinetic changes on the bioequivalence (BE) outcomes of generic drugs in pregnant individuals compared to non-pregnant individuals. Mechanisms behind these physiological and pharmacokinetic changes and the utility of different modeling approaches, such as population pharmacokinetic modeling (popPK) & physiologically-based pharmacokinetic modeling (PBPK), for extrapolating BE results from non-pregnant to pregnant individuals are being investigated in this study. Our preliminary findings highlight the need for further research to explore the mechanisms underlying these pharmacokinetic changes and their impact on generic drug development for specific drug classes used by pregnant individuals.

Introduction

Pregnancy induces profound changes in maternal physiology which may affect the pharmacokinetics of drugs.[1] This study aims to investigate the potential impact of physiological and pharmacokinetic changes during pregnancy on the bioequivalence (BE) outcomes of generic drugs in pregnant individuals compared to non-pregnant individuals. Use of high-quality generic medication during pregnancy is crucial to ensure the health of mother and the fetus. Typically, BE studies are conducted in healthy subjects and results are extrapolated to support therapeutic equivalence in various patient populations following the labeling. The overarching goal of this work is to explore the potential of modeling and simulation approach for extrapolating BE results from non-pregnant individuals to pregnant individuals in order to understand potential risk factors that may impact therapeutic equivalence of generic drugs in pregnant individuals.

Method

A comprehensive literature review was conducted to identify relevant data related to physiological changes and PK alteration during pregnancy, considering different routes of drug administration and various elimination pathways that may impact drug clearance under pregnancy. A list of potential drug candidates with altered PK during pregnancy was prepared. The PK profiles of these drugs are being compared between non-pregnant and pregnant individuals. We are also developing popPK & PBPK models for some of the selected drugs to extrapolate BE results from non-pregnant individuals to pregnant individuals for our modeling and simulation exercise.

Results and Discussion

Our current literature search reveals that PK profiles of some drugs administered through oral and pulmonary routes of administration are impacted by the physiological changes during pregnancy. **Table-1** shows pregnancy associated physiological changes related to oral and pulmonary routes of drug administration.

Table-1: Physiological Changes During Pregnancy Associated with Drug Absorption.

Parameter	Change During Pregnancy
Oral Route	
Intestinal motility	Decreased
Gastric pH	Increased
Metabolizing enzymes	Increased
Pulmonary Route	
Respiratory tract swelling	Increased
Tidal volume	Increased
Alveoli Volume	Decreased

Additionally, higher variability in PK parameters for these drugs were observed in pregnant individuals.

Results and Discussion

As a candidate oral drug, we started with rilpivirine (an anit-HIV drug) and looked into the PK of rilpivirine during pregnancy and compared it with non-pregnant individuals. **Figure-1** shows the comparative plasma profiles of rilpivirine obtained from published literature.[2] **Table-2** represents the PK parameters in these populations.

Figure-1: Rilpivirine Plasma Concentration after Oral Administration of 25 mg Once Daily Rilpivirine Tablet.[2]

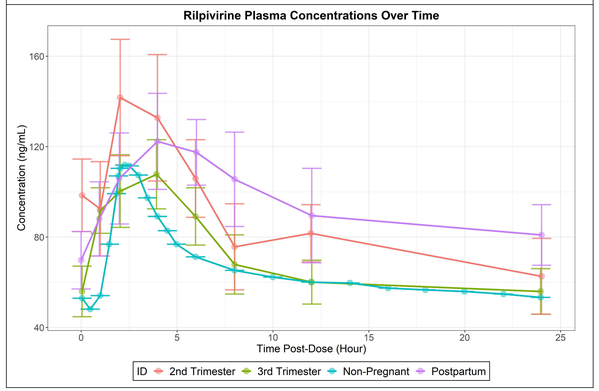

Table-2: Comparison of Mean PK Parameters.[2,3]

Parameter	2nd Trimester N=18	3rd Trimester N=30	Post-partum N=28	Non-Pregnant N=679
AUC_{24} (ng*hr/mL)	1969	1669	2387	2397
C_{max} ng/mL	145	134	134	74
T_{max}	4	2	4	4

For rilpivirine, reduced AUC and increased C_{max} were observed in pregnant individuals. Additionally, a lag in absorption was also observed in around 50% subjects during 2nd trimester and around 43% subjects during 3rd trimester. Higher inter-subject variability for PK parameters were also observed in this study.

Currently, we are in the process of understanding the mechanisms behind these changes and exploring different modeling approaches (popPK & PBPK) for extrapolating BE results from non-pregnant to pregnant individuals.

Conclusion

Understanding the physiological changes during pregnancy and their potential interactions with generic formulations coupled with modeling and simulation approaches could help us to understand potential risk factors that may impact the therapeutic equivalence of generic drugs in pregnant individuals. Moreover, our preliminary findings highlight the need for further research to explore the mechanisms underlying these pharmacokinetic changes and their impact on generic drug development for specific drug classes used by pregnant individuals.

Disclaimer

The views expressed in this poster that of authors and should not be construed to represent FDA's views or policy.

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