Physiologically Based Pharmacokinetic (PBPK) Model of Drug Delivery in the Female Reproductive Tract

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BACKGROUND

- Physiologically based pharmacokinetic (PBPK) modeling is a powerful tool in predicting drug exposure in specific organs or tissues by incorporating physiology and drug characteristics.[1]
- A gap exists in describing drug exposure within the female reproductive tract.
- A robust PBPK model system that includes the female reproductive tract can address questions in dosing optimization and the impact of drug formulation under oral, vaginal, intrauterine, or other routes of administration.
- Levonorgestrel (LNG) was used as a test compound for model development and validation.

METHODS

- Physiological and anatomical information were obtained from an exhaustive literature search as well as data and information collected on uterine volume and blood flow (n=12 subjects) to fill gaps in the development of a PBPK model for drug delivery to the female reproductive tract.

- Tissue-specific permeability rates were measured from freshly excised human cervicovaginal and uterine tissue samples (n=6 donors). Release rates of LNG from the intrauterine device (IUD) were taken from the Nilsson paper [3].

- The model was implemented in **R** programming language (version 4.0.4) using **mrgSolve** (version 1.0.3) (see QR code information for more details on model implementation).
- The model was validated through LNG PK data after oral, vaginal, and intrauterine administration published in the literature. [2-6]

A preliminary **mechanistic PBPK** model platform predicted **plasma, vaginal and uterine** concentrations of LNG following **oral and IUD administration**.

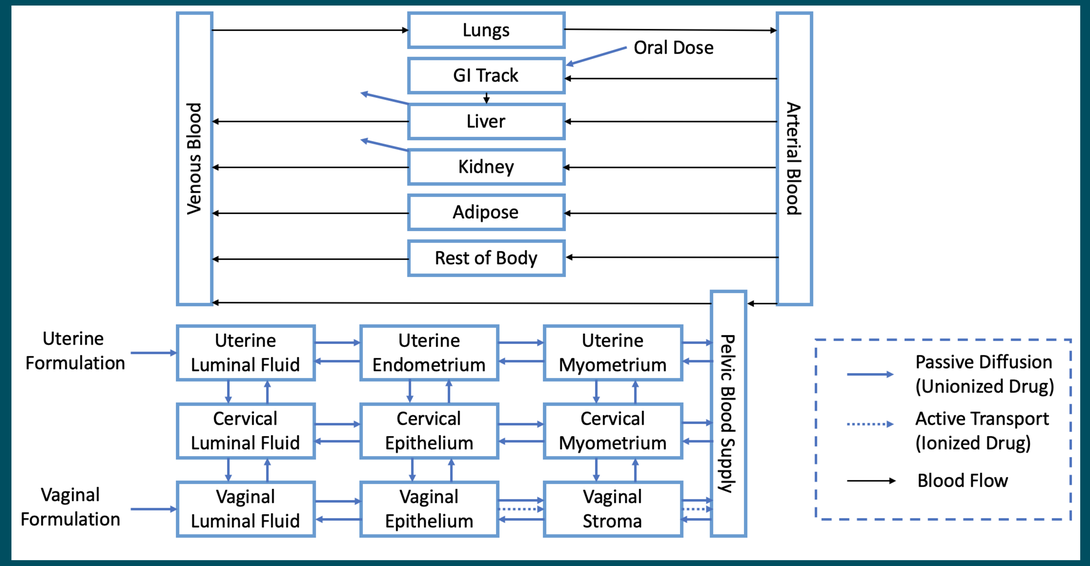

Fig 1. Female reproductive tract PBPK model structure

- **IUD Simulation [2]**

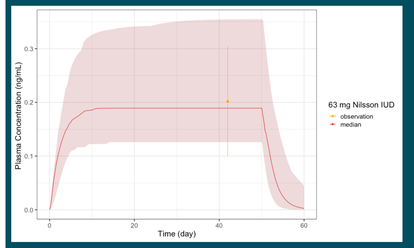

Fig 2. LNG plasma concentration after 63 mg intrauterine administration, pink shaded area is 5th to 95th percentile, line is simulated 50th percentile

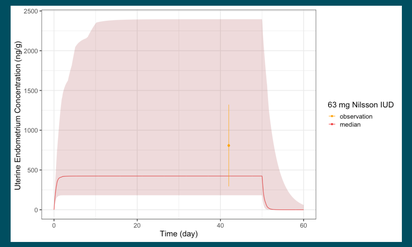

Fig 3. LNG uterine endometrium concentration after 63 mg intrauterine administration, pink shaded area is 5th to 95th percentile, line is simulated 50th percentile

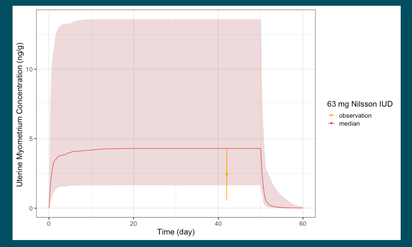

Fig 4. LNG uterine myometrium concentration after 63 mg intrauterine administration, pink shaded area is 5th to 95th percentile, line is simulated 50th percentile

RESULTS

This whole-body PBPK model reasonably predicted published plasma, uterine endometrium, and uterine myometrium LNG concentrations after oral and intrauterine administration.

- 0.75 mg Oral Single Dose Simulation [3-6]

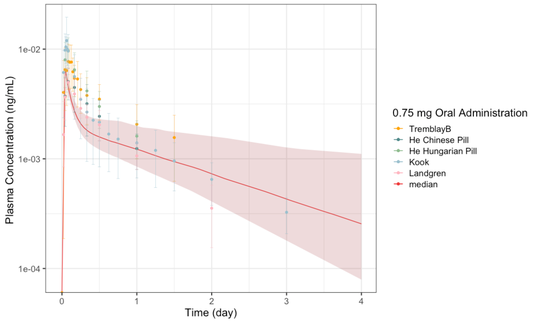

Fig 5. LNG plasma concentration after 0.75 mg oral administration. Pink line is median simulated. Shaded area shows 5th to 95th percentile prediction interval

- 2×0.75 mg Vaginal Dose Simulation [7]

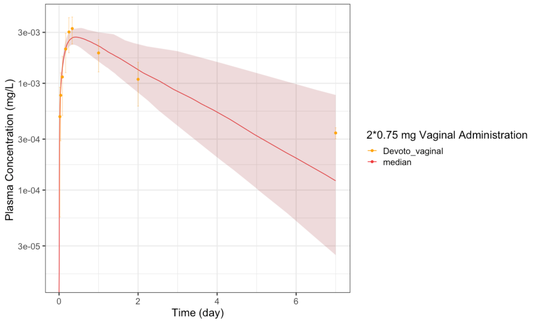

Fig 6. LNG plasma concentration after 2×0.75 mg vaginal administration. Pink line is median simulated. Shaded area shows 5th to 95th percentile prediction interval

CONCLUSIONS AND FUTURE DIRECTIONS

This PBPK model provides a platform for assessing drug exposure in the female reproductive tract. However, limitations such as the lack of data in describing the female reproductive space may impact the accuracy of prediction.

ACKNOWLEDGMENTS/DISCLAIMER

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