**Determining the Optimal Dosing of Methyldopa in Pregnancy-Induced Hypertension Using PBPK- PD Modeling**

Xinyang Liu¹, Defang Ouyang¹,\*

1State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences (ICMS), University of Macau, Macau, China

**Background:** Pregnancy-induced hypertension is a significant risk factor for adverse maternal and fetal outcomes, with methyldopa being a commonly prescribed antihypertensive for its safety profile[1,2]. However, the physiological changes during pregnancy may alter methyldopa's pharmacokinetics and pharmacodynamics, complicating the establishment of optimal dosing regimens.

**Objective:** This study aims to develop and validate a pregnancy-specific PBPK- PD model for methyldopa to optimize dosing strategies and support individualized treatment plans for managing pregnancy-induced hypertension effectively.

**Methods:** The PBPK- PD model for methyldopa was developed using PK-Sim, MoBi, and MATLAB software, incorporating pregnancy-specific physiological parameters from the literature (figure 1). The development process involved: first, constructing and validating a PBPK model for non-pregnant individuals based on intravenous and oral administration, including renal clearance, serum clearance, and enzyme clearance; second, extending the model to a pregnant PBPK model and validating it for oral administration; third, constructing a PK/PD model using the maximum effect model; and then, integrating the PBPK and PK/PD models to form a unified PBPK- PD model. This model was then used to simulate mean arterial pressure (MAP) responses across different stages of pregnancy. Finally, the optimal dosing regimen was calculated.

**Results:** The model verification results show a good fit, indicating that the parameters are appropriate. The pregnancy model indicated no significant change in PST activity during pregnancy. The PBPK- PD simulations across different stages of pregnancy show fluctuations in both PK and PD; however, these variations are not particularly significant. Ultimately, the results indicate that 500 mg is the optimal dosing regimen for patients with MAP ≤ 130 mmHg. For MAP > 130 mmHg, additional antihypertensive medications are recommended. Due to its delayed onset, methyldopa should be combined with other antihypertensives during the first 48 hours.

**Conclusion:** The PBPK- PD model developed in this study provides a valuable tool for optimizing methyldopa therapy, supporting personalized treatment strategies, and improving blood pressure management and maternal and fetal health outcomes in pregnancy-induced hypertension.



**References:**

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(2) Khedagi AM, Bello NA. Hypertensive Disorders of Pregnancy. *Cardiology Clinics*. 39(1), 77–90 (2021).