COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Pharmaceutical Sciences Seminar

Wednesday, November 10, 2021
4:00pm
2548 NUB or Zoom

"Physiologically Based Pharmacokinetic (PBPK) Modeling Based Pharmacogenetics, Sex Differences and Drug-Drug Interaction Study of Methylphenidate"

Presented by:

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Abstract: The pharmacokinetics (PK) of methylphenidate (MPH) differ significantly among individuals. Carboxylesterase 1 (CES1) is the primary enzyme metabolizing MPH, and previous studies have demonstrated that CES1 genetic variants, drug-drug interactions, and sex could affect CES1 enzymatic function; moreover, each of these factors could alter MPH PK. The present study develops physiologically based pharmacokinetic (PBPK) models to predict the effect of the interplay among CES1 genetic variants, drug-drug interactions, and sex on MPH PK. The effect of several selected CES1 genetic variants on MPH metabolism was studied utilizing 102 individual human liver S9 (HLS9) fraction samples. PBPK models were developed using the HLS9 incubation data and previously published results regarding the CES1-mediated drug-alcohol interaction between MPH and ethanol and the differences in hepatic CES1 expression between males and females. The models were then utilized to simulate MPH PK profiles under various physiological conditions (i.e., genotypes, drug-alcohol interactions, and sex). The HLS9 incubation study showed that subjects heterozygous for G143E (rs71647871) metabolized MPH at a rate approximately 50% of that in non-carriers. The developed PBPK models successfully predicted significant impacts on MPH PK from the G143E genetic variant, ethanol-MPH DDI, and sex. Importantly, specific patient populations who are at a higher risk of MPH overexposure were identified, such as male subjects who both carry the G143E variant and consume alcohol. PBPK modeling provides a means for better understanding the mechanisms underlying interindividual variability in MPH PK and PD, and could be utilized to develop a more effective MPH pharmacotherapy regimen.

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