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Pharmaceutical Sciences Seminar

Wednesday, September 29, 2021
4:00-5:00 pm

Join Zoom Link

"One size fits half: precision medicine for children with obesity"

Presented by:

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Abstract: Approximately 1/3 of children in the US have overweight or obesity and are at risk of developing metabolic conditions such as insulin resistance or type 2 diabetes (T2DM). The first-line pharmacotherapy for type 2 diabetes in children is metformin, yet more than half of the children prescribed metformin are unable to achieve or maintain glycemic control and require alternative therapies. Despite such variability in response, it is currently recommended that metformin be administered at fixed doses to children. Since children are a heterogenous and dynamic population, the efficacy of metformin may be affected by variability in pharmacokinetics (dose—exposure) and pharmacodynamics (exposure—response) associated with age or stage of development, and potentially with obesity. Thus, we developed an individualized dosing approach targeting an exposure associated with maximal response that has the potential to improve the proportion of children who effectively respond to metformin monotherapy.
To estimate the target exposure and individualized doses associated with optimal response to metformin, we developed and retrospectively validated a physiologically-based pharmacokinetic (PBPK) model in a virtual population of children aged 6-18 years who develop obesity and/or T2DM.

Included in this PBPK model were novel growth curves specific to children who develop T2DM and validation of organ-size as a function of body surface area in children with obesity. We found a target exposure range (15-30 mg/L*h) and determined that younger and smaller children require smaller daily doses to achieve a similar exposure and, presumably, response, as older and larger children, who may require greater doses.

This PBPK model is currently undergoing a prospective clinical validation. Once validated, it is expected that the administration of individualized doses suggested by this model will result in a greater proportion of children who will respond favorably to metformin. Additionally, by mitigating pharmacokinetic variability through individualized dosing, variability in response to metformin due to factors such as disease or target heterogeneity can be evaluated in a more rigorously controlled environment.

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