Children's Mercy KANSAS CITY

UNCOVERING FACTORS LEADING TO VARIABLE RESPONSE TO STATINS IN CHILDREN

DEVELOPING MODELS TO INCREASE MEDICATION EFFECTIVENESS

Providers who care for the developing child are seeing an increase in subclinical coronary artery disease that stems from obesity and hyperlipidemia. As with adults, when behavioral lifestyle changes fail the typical pharmacologic treatment is a statin. While statins do lower cholesterol in children, there is significant variability in the degree of reduction of low-density lipoprotein cholesterol (LDL-C).

Dr. Wagner designed a genotype-stratified pharmacokinetic study to better understand the impact of SLCO1B1 in children prescribed a statin.

The adult experience suggests that genetic variation of *SLCO1B1* significantly influences the pharmacokinetics of statins. To better understand the impact of *SLCO1B1* in the developing child who may be prescribed a statin, Jonathan B. Wagner, DO, Pediatric Cardiology and Clinical Pharmacology at Children's Mercy Kansas City, designed a genotype-stratified pharmacokinetic study. In the study, funded by the American Heart Association National Affiliate, he led a team to investigate the impact of *SLCO1B1* genotype on pravastatin and simvastatin systemic exposure in children and adolescents.

Dr. Wagner has completed fellowships in both pediatric cardiology and pediatric clinical pharmacology at Children's Mercy. His focus is precision-based cardiovascular care.

BUILDING ON PREVIOUS KNOWLEDGE

One of the first sources of variability in adults is hepatic transporter SLCO1B1. Patients with genetic variation of this transporter experience reduced drug uptake to the liver, while more of the drug remains in the plasma, which could lead to treatment failure and an increased risk of side effects. Dr. Wagner aimed to investigate whether this phenomenon occurs in children.

He designed a single-center, open-label, genotype-stratified, single-oral-dose pharmacokinetic study. Participants ages 8-20 with at least one allelic variant of *SLCO1B1* vs. wild-type controls completed a single-oral-dose pharmacokinetic study. Drug concentrations were then measured via plasma and urine samples.

STUDY FINDINGS AND NEXT STEPS

Dr. Wagner's study showed that, collectively, *SLCO1B1* genotype, body mass index and pravastatin acid interconversion contribute to large individual variability in pravastatin exposure, even with weight-adjusted dosing. This broad individual variability in the dose-exposure relationship, even within genotype groups, will continue to present a major challenge for doctors individualizing statin dosing to pediatric patients.

Now that study findings have been reported, the team is conducting secondary analysis to consider other drug transporters and metabolizing enzymes that play a role in plasma concentrations of statins. Dr. Wagner is partnering with the Genomic Medicine Center at Children's Mercy to sequence nearly 100 genes.

STUDY FINDINGS AND NEXT STEPS

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Within the next year, the team expects to have the resulting data to apply to high or low outlier patients, offering the opportunity to further individualize care.

(Wagner et al Clin Pharcol Ther 2019)

CREATING DOSE OPTIMIZATION MODELS

To help prescribers optimize dosing for each child, Dr. Wagner is developing a computer-based model to optimize statin dosing in the pediatric population. This project falls under the umbrella of the precision therapeutics program unique to Children's Mercy called Genomic- and Ontogeny-Linked Dose Individualization and cLinical Optimization for KidS (GOLDILOKs). When the model is complete, Dr. Wagner will be able to enter a set of variables about an individual patient, with a goal of predicting the plasma concentration before the patient even receives a statin dose. Next, the model will be extended to other cardiovascular drugs – and eventually be used to inform individual dosing decisions at the bedside.

This pediatric statin model development project work has been funded by a CTSA KL2 Career Development Award.

GOLDILOKs is a conceptual framework that helps researchers appropriately develop clinical trials to optimize medication dosing for children.

PRESENTATION OF FINDINGS

Dr. Wagner has shared his findings related to statins across the country. He presented his simvastatin findings at the 2016 AHA Scientific Sessions. He was a finalist for the 2016 American Heart Association Council on Cardiovascular Disease in the Young Early Career Investigator Award. In February 2019, at the 22nd Annual Update on Pediatric and Congenital Cardiovascular Disease, he presented his work on statin genomics and precision medicine.

CARDIOLOGY PHARMACOGENOMICS REPOSITORY

Dr. Wagner created a repository and patient registry – the only one of its kind in the U.S. – to study statin dosing in children and to serve as a resource for other cardiac pharmacogenomics studies. It houses biospecimens from patients in the preventive cardiology, weight management, nutrition, heart failure and endocrine clinics. The repository will support future investigation into the role of genomics in cardiovascular drug disposition.

PI GRANT SUPPORT

NATIONAL INSTITUTES OF HEALTH-NICHD
1 U54 HD090258-02, GOLDILOKs: Genomic- and Ontogeny-Linked Dose Individualization and cLinical Optimization for KidS, April 2018-present
Pilot Project: Validation of OATP Endogenous Biomarkers in Children
Pilot Project Amount: $30,000

KL2 CLINICAL AND TRANSLATIONAL MENTORED CAREER DEVELOPMENT AWARD (KL2TR002367), SEPTEMBER 2017 – PRESENT
Project: Statin Optimization in Pediatrics
Award Amount: $356,886

AMERICAN HEART ASSOCIATION NATIONAL AFFILIATE CLINICAL RESEARCH PROGRAM, JULY 2013 – JULY 2016
Project: Pharmacokinetics of pravastatin and simvastatin in pediatric dyslipidemia patients: Clinical impact of genetic variation in statin disposition
Award Amount: $150,000

CHILDREN'S MERCY HOSPITAL MARION MERRELL DOW CLINICAL SCHOLAR AWARD, JULY 2014 – PRESENT
Project: Pharmacokinetics of rosuvastatin and atorvastatin in pediatric dyslipidemia patients: Clinical impact of genetic variation in statin disposition
Award Amount: $100,000

CHILDREN'S MERCY HOSPITAL CLINICAL FELLOWSHIP RESEARCH AWARD, JULY 2013 – JUNE 2015
Project: Cardiology Pharmacogenomics Repository
Award Amount: $15,000

BEST CHILDREN'S HOSPITALS U.S. News & World Report CARDIOLOGY & HEART SURGERY 2018-19

LEARN MORE ABOUT CARDIOVASCULAR PHARMACOGENETIC RESEARCH.
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