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Review

Genomics and precision medicine to direct statin use in the young

Jonathan B. Wagner*

Ward Family Heart Center, Kansas City, MO, United States of America
Division of Clinical Pharmacology, Medical Toxicology and Therapeutic Innovation, Children's Mercy, Kansas City, MO, United States of America
Department of Pediatrics, University of Missouri-Kansas City School of Medicine, Kansas City, MO, United States of America

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ABSTRACT

The delivery of precision medicine to pediatric cardiology remains complex with a number of challenges ahead. With recent advances in whole genome sequencing, rapid acquisition of a patient's genomic data is possible. However, the challenge remains how we best implement this new data into clinical practice. Predicting drug disposition and response of the individual patient requires a thorough knowledge of the entire dose-exposure-response relationship of each individual drug and knowledge of the factors that make each individual unique. This goal of precision medicine is even more complex in the developing child where drug disposition and response pathways may still be maturing. Herein, we will illustrate the challenges and pitfalls that may occur when trying to deliver pediatric precision medicine using the statins as a prototype.

1. Introduction

Over the last decade, a strong desire exists for patients and providers to deliver optimal pharmacologic treatment to each individual patient encounter. This individualized care is interchangeably described as “personalized” or “precision” medicine. The National Research Council explicitly utilized the term “precision” in a consensus statement to avoid confusion that treatment was not developed uniquely for each individual patient [1]. The trend towards the term “precision” medicine accelerated after President Barack Obama's 2015 State of the Union address when the United States Precision Medicine Initiative was announced [2].

One could argue that encounters between healthcare providers and their patients already are “personalized” medicine. In pediatric cardiology, utilizing information unique to the individual patient (e.g. echocardiographic indices, pulmonary vascular resistance on cardiac catheterization, NT-proBNP) and working in large multi-disciplinary teams allows the results of the “personal” encounter to become “individualized.” In our subspecialty, we have been achieving these “personalized” benchmarks for decades. However, in order to improve the outcomes for a new generation of pediatric cardiovascular patients, we must embrace “precision-based” care [3].

2. Utilization of “omics” to deliver precision pharmacotherapy

Currently, a greater depth of a patient's “omic” (e.g. genomic, proteomic, and metabolomic) data can be readily generated [4–6], however, there remains a paucity of prospective data to suggest the optimal pharmacologic agent and/or dose that an individual child should receive given the results of this “omic” data. Genetic variation remains one of the largest domains of exploration to deliver precision-based pharmacotherapy. Pharmacogenomics should be leveraged as a tool to maximize drug efficacy while concomitantly providing the lowest possible risk for toxicity to our vulnerable pediatric population. With our distinct familiarity with genomic medicine, pediatric cardiology providers are uniquely primed to integrate pharmacogenomics in clinical practice. Conversely, pediatric providers must be cognizant that genetic variation is simply one component, albeit a significantly large component, that may influence cardiovascular drug disposition and response. Drug specific (e.g. protein binding, drug preparation, lipid-partition coefficient values) and patient specific physiologic characteristics (e.g. diminished cardiac output, ECMO circulation, Fontan circulation, obesity) can equally influence how “precisely” treatment is tailored to the individual pediatric patient [7].

Additionally, children are physiologically unique and are not simply small adults. Developmental patterns, alternatively known as ontogeny, of proteins and enzymes involved in drug disposition (absorption, distribution, metabolism, and excretion) have been extensively investigated and in many scenarios differential expression patterns in children compared to adults are demonstrated [8–10]. Therefore, ontogeny must be considered as an additional factor that may alter pharmacologic treatment in the individual child that pediatric

* Children's Mercy Kansas City, 2401 Gillham Road, Kansas City, MO 64108, United States of America.
E-mail address: jbwagner@cmh.edu.

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providers should recognize. Collectively, the use of data related to the genotype-phenotype relationship observed in adult pharmacologic treatment to inform pharmacogenomics-driven treatment guidelines in the developing child should occur with caution. In this manuscript, we will discuss these particular factors that influence pediatric statin exposure and response and use statins as an example on how precision-based pharmacologic care can be more readily delivered to our population.

3. Statin utilization in pediatrics

The most common cause of mortality in the United States remains cardiovascular disease with atherosclerosis as the leading etiology [11]. Atherosclerotic coronary artery disease (CAD) has its origins in childhood despite its perception as solely an adult onset disease. Post-mortem evaluation of > 45% of military service members in their 2nd and 3rd decades had evidence of CAD [12,13]. Additionally, subclinical markers of CAD (e.g. fatty streaks) were present in a much younger cohort of children and adolescents on post-mortem evaluation [14]. Several landmark studies have elucidated several risk factors (e.g. LDL cholesterol, obesity status, tobacco exposure) that lead to atherosclerosis and CAD [15,16]. Overall, these pivotal observations validate the importance of preventive cardiovascular evaluations and interventions during childhood to prevent early onset atherosclerotic disease.

Given these observational data, the National Cholesterol Education Program recommended targeted lipid screening for children with the aforementioned risk factors [17]. Compelling evidence more recently suggested that this previous targeted screening strategy remained inadequate [18]. Therefore, a large shift occurred in 2011 when the American Heart Association, American Academy of Pediatrics, and the National Heart, Lung, and Blood Institute endorsed guidelines changes recommending a universal lipid screen on all children 9–11 year and again at 17–21 years of age [19]. Collectively, this enhanced screening of many more children, adolescents, and young adults, in conjunction with the ongoing childhood obesity epidemic, leaves our community with a significant number (> 200–400,000) of children in the United States that would qualify for pharmacologic treatment of hypercholesterolemia [20,21].

4. Statin optimization in pediatrics

3-hydroxy-3-methyl-glutaryl-conenzyme A (HMG-CoA) reductase inhibitors (statins) remain the most common pharmacologic agent for pediatric hypercholesterolemia management if behavioral diet and activity modifications fail [19]. A recent comprehensive review of statin utilization in the pediatric population discovered that a majority of the existing pediatric statin trials focused on short-term safety and efficacy [22]. Thus, there remains a dearth of longitudinal trials elucidating the impact of statin initiation during childhood on long-term skeletal muscle function, neurologic development, and/or sexual maturity. For instance, exposure to statin leads to a large range of myopathic events from mild (myalgias) to severe (rhabdomyolysis). In fact, available *in vitro* and *in vivo* data suggest that the degree of myopathic events may be statin-specific, meaning that the more hydrophilic statin agents (e.g. pravastatin, rosuvastatin) are of lower risk since there exists less passive diffusion into the skeletal myocyte [23–28]. Conversely, simvastatin, a more lipophilic statin agent with more potential to diffuse into the myocyte, was associated with impaired cardiorespiratory fitness in adult patients enrolled in an aerobic training exercise program [29]. The skeletal muscle and/or cardiovascular etiology of this impaired fitness remains unknown, but it is prudent to investigate this in the developing child prescribed a statin. If this altered level of fitness were to be observed in pediatric patients prescribed a statin, impairment of regular physical activity from skeletal muscle dysfunction could be as detrimental as the benefits of treating hypercholesterolemia with a statin. A similar observation is noted for central nervous system penetration, where pravastatin, the most hydrophilic statin agent, had less concentration in the cerebral spinal fluid compared to the more lipophilic agents, simvastatin and lovastatin, where passive diffusion across the blood-brain barrier was more likely to occur [30,31].

Existing pediatric statin efficacy data suggests that on a population level, statins effectively improve LDL-cholesterol plasma concentrations [22] and clinical biomarkers of atherosclerosis (e.g. flow-mediated dilation, carotid intima-medial thickness) [32,33]. However, the aforementioned pediatric trials used a fixed-dosing strategy, meaning the effective dose (e.g. mg per kg) administered to each individual patient would be variable amongst the study population. Not surprisingly, a large range (~2–4 fold) of LDL-C reduction was noted in these trials in part due to the "one-size fits all" dosing scheme. Additionally, these studies overlooked the role of genetic variation and ontogeny on statin delivery in the growing child. The goal of the Genomic and Ontogeny Linked Dose Individualization and CLinical Optimization for Kids (GOLDILOKs ®) Precision Therapeutics Program is to deliver the "just right" dose based on the child's stage of development (ontogeny), genome, and physiologic state [34]. This process is designed to tailor pharmacotherapy to the individual patient, thereby decreasing the large range of responses observed in previous clinical trials due to variability in drug delivery (e.g. drug exposure).

5. Optimal statin exposure

One of the largest sources of variability of statin exposure amongst adults is related to the liver-specific protein organic anion transmembrane polypeptide 1B1 (OATP1B1) [35]. After oral administration and gastrointestinal absorption, OATP1B1 is the protein responsible for cellular statin transport within the liver, the primary site of cholesterol biosynthesis [35]. Genetic variation in *SLCO1B1*, the gene responsible for OATP1B1 expression and function, results in reduced hepatocellular uptake [36] and increase systemic concentration or exposure [37,38]. The consequence of increased systemic exposure is more peripheral tissue exposure leading to toxicity, the most common being myalgia. Additionally, there is less drug available within the hepatocyte to disrupt cholesterol biosynthesis, potentially leading to a variable response [39,40]. However, there exists an equal number of publications that suggest that *SLCO1B1* genetic variation does not directly lead to a variable response [41–44].

With the large range of LDL-cholesterol response noted in the previous pediatric statin trials [22], two potential explanations exist. First, there is variability in pediatric statin drug to drug target engagement due to developmental differences and/or genetic variation at the drug target (e.g. *HMGCR*). Second, the variability in LDL-cholesterol response is secondary to variable hepatocellular statin uptake leading to inadequate statin exposure within the liver leading to an attenuated response. Variable exposure at the drug target has been subject to numerous studies involving statins [45].

In adults, a genotype-phenotype relationship has been demonstrated where patients with 1 or 2 non-functional *SLCO1B1* "C" alleles (c.521TC, c.521CC) have much larger plasma concentrations than those with 2 fully functional alleles (c.521TT) [37,38,46]. Prior to our series of investigations, there only existed one study that investigated the effect of *SLCO1B1* genotype on pravastatin disposition where the genotype-phenotype relationship was discordant compared to the relationship observed in adults [37,47]. However, this pediatric genotype add-on pharmacokinetic study was complicated by a small sample size of *SLCO1B1* variants ($n = 6$). Recently, a prospective *SLCO1B1* genotype-stratified pharmacokinetic study involving a larger cohort of children ($n = 32$) dosed pravastatin and simvastatin revealed a similar relationship observed in adults, where those participants with 1 or 2 *SLCO1B1* c.521 "C" alleles had less hepatic uptake and larger systemic exposures [48,49]. Despite a statistically significant difference in the mean pravastatin and simvastatin systemic exposure amongst genotype groups, there remained significant variability in systemic exposure

within genotype groups (8- to 17-fold). Therefore, even with advances in pharmacogenomic testing, pravastatin and simvastatin exposure remains highly variable at the level of the individual patient. Overall, the variability in pediatric statin exposure and subsequent response cannot be predicted by *SLCO1B1* genotype alone.

In the era of pharmacogenomics, a challenge arises when we attempt to apply data based on the "population" to inform decisions at the level of the individual patient. For instance, there was an 11-fold range of systemic exposure in both the c.521TC and c.521TT groups after a single, labelled starting dose of pravastatin [49]. For the fully functional c.521TT group, the majority of the variability was secondary to four "high outliers." Further gene sequencing of these "high outliers" found no additional *SLCO1B1* polymorphisms contributing to the aforementioned results. Additionally, no coding region polymorphisms were found in another liver-specific pravastatin hepatic uptake transporter *SLC22A9* (OAT7). Interestingly, from a demographic perspective, pravastatin systemic exposure was moderately correlated with weight ($r^2 = 0.38$, $p = 0.015$) and BMI ($r^2 = 0.39$, $p = 0.013$) in the c.521TT group. In fact, the aforementioned "high outliers" had BMI *Z*-scores greater than +2.5. Obesity is associated with an increased risk of nonalcoholic fatty liver disease and animal models demonstrate down regulation of transporter expression, irrespective of genotype, in this disease state [50,51]. In the obese child, liver adiposity could alter hepatic transport of statins leading to increase systemic exposure and thereby, the risk of adverse events and treatment failure. This example of altered liver pathology highlights the importance of evaluating pharmacogenomics in conjunction disease state (e.g. obesity, Fontan associated liver disease, diminished hepatic clearance secondary to low cardiac output) when tailoring pharmacotherapy to the individual pediatric patient.

6. Children are different than adults

The largest challenge faced in pediatric precision therapeutics is the extrapolation of adult data, specifically pharmacogenomics data, to the developing child. In our study, we observed a pronounced difference in comparing participants amongst *SLCO1B1* genotypes that were dosed simvastatin [48]. In children, there was a 6.3-fold difference in simvastatin acid exposure between participants with c.521CC genotype (no functional alleles) compared with c.521TT participants (AUC: 2.14 ± 0.15 ng/mL vs. 0.41 ± 0.32 ng/mL, $p < 0.0001$) [48]. This was 2-fold greater than the difference in simvastatin acid exposure amongst aforementioned genotype groups in the adult cohort (3.2-fold) [38]. Collectively, these data suggest that *SLCO1B1* genotype may be more important in children prescribed simvastatin.

This discordance between children and adults was not illustrated in the same study cohort of children that were prescribed pravastatin [49], highlighting that the factors contributing to drug exposure may be statin-specific. Therefore, genotype stratified investigations must be performed for all statins agents used in the pediatric population.

7. How to make precision therapeutics a reality

We have characterized the factors leading to variable statin exposure through our series of investigations, but moving forward, we must use tools that can predict statin exposure prior to dose administration. Physiologically-based pharmacokinetic (PBPK) models can account for changes in physiology and covariates involved in drug disposition that occur in the developing child [52]. These tools can be leveraged to "predict" exposure for certain patient and drug-specific factors. Recently, this approach utilizing in vitro data confirmed the intra-genotype variability in drug exposure in children that were prospectively dosed atomoxetine, a non-stimulant drug used for attention-deficit hyperactivity disorder management [53,54]. This approach needs to be validated amongst other patient cohorts (e.g. obesity, congenital heart disease, hypercholesterolemia) to determine applicability, but certainly this approach provides promise for the future of precision therapeutics in pediatric cardiology.

Currently missing from instituting statin precision therapeutics to the developing child is the factors at the drug target that may be driving the aforementioned variability in pediatric statin response. Recently, a comprehensive review described that with improvements in characterizing the influence of development and genetic variation (e.g. *SLCO1B1* genotype) on the dose-exposure relationship that the time is now to focus our attention on the factors driving variable response, such as genetic variation of the drug target (e.g. LDL receptor) [55]. The factors influencing the dose-exposure relationship still need clarity for many drugs utilized in pediatric cardiology (e.g. CYP3A4-sildenafil, CYP2C19-clopidogrel, CYP2D6-metoprolol), however, we must simultaneously focus on how development and genetic variation of drug target (e.g. cGMP, $P2RY_{12}$, ADRB2) influences variable response. Once clarity of this process is defined at the level of the drug target, tools that incorporate the entire dose-exposure-response relationship (e.g. PBPK-PD) can be developed, ultimately leading to the development of clinical support tools that can tailor treatment to the individual patient [56].

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Declaration of competing interest

The author has no conflicts of interest relevant to the topic of this manuscript to disclose.

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