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Scientific and Regulatory Considerations for an Ontogeny Knowledge Base for Pediatric Clinical Pharmacology

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Abstract

Understanding all aspects of developmental biology, or pediatric ontogeny, that affect drug therapy from the fetus to the adolescent child is the holy grail of pediatric scientists and clinical pharmacologists. The scientific community is now close to being able to tie together the vast amount of information collected on pediatric ontogeny over the past 60 years. An organized knowledge base and new tools would allow us to utilize this information effectively in pediatric drug development.

BACKGROUND

In May 2019, a workshop sponsored by the US Food and Drug Administration (FDA) and the University of Maryland was held on the National Institutes of Health (NIH) campus and was titled “Pediatric Ontogeny: Ready for Incorporation Into Modeling in Pediatric Drug Development?” Over the course of a day and two panel discussions, the resounding answer to this question was “Yes!” However, this event marks the start of a process and not its completion, with the major question now being “How?”

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CONFLICT OF INTEREST

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The focus on pediatric ontogeny is at the heart of most pediatric clinical pharmacology studies. Are children different and in which way? Will they need a different dose of the drug or a different level of exposure to see a drug effect? Will the drug affect the growth and development of the child? Should we expect to see different adverse effects of the drug in children? Do pathophysiological differences for some diseases in children necessitate a different therapeutic approach? These are all of the same questions asked by the pioneers in pediatric clinical pharmacology.[1] Given that the action of a drug is dependent on hundreds of interactions with tissues, receptors, enzymes, and transporters in the body, working out the puzzle of pediatric ontogeny might seem to be impossible.

In fact, the last 60 years have produced a wealth of information regarding pediatric ontogeny. This information comes from numerous studies oriented toward the study of pediatric diseases and pediatric drug therapy. Drug disposition studies in varying pediatric age groups are most common, but the applicability of this information to other drugs and diseases is unclear. Pharmacogenomic studies in pediatric patients are more limited, but also contribute to our understanding of pediatric ontogeny from birth through adolescence. Although many of these studies have dealt with the pharmacokinetics of drugs in pediatric patients, the changing susceptibility to the adverse effects of drugs is of equal concern.

Enzymes, transporters, and receptors in a complex changing patient population

The ability to make accurate dosing predictions across the spectrum of age in pediatric patients is undeniably beneficial for the best possible therapeutic outcome and yet has been elusive for many drugs. Numerous complex changes that children undergo as they transition from newborn through adolescence make drug therapy difficult to predict or model. Continual physiological maturation at a young age gives rise to rapid and often unpredictable changes in drug clearance in an individual patient. For drugs that are primarily renally eliminated, clearance rapidly changes during the first few days of life as renal function begins maturing in the neonate, as assessed by both glomerular filtration rate and active secretion activity.[2] Glomerular filtration rate continues to increase until ~ 1–2 years of age and then begins to decline to adult levels, whereas active secretion activity follows a similar trajectory until age 2 where it then follows a gradual increase into adulthood. For drugs that are hepatically metabolized, the predictions can be much more complicated. The interplay between maturing drug metabolizing enzymes, including phase I and phase II enzymes, and transporters coupled with simultaneous changes in plasma protein binding, body composition, absorption, etc. create an environment that makes accurate estimates of drug clearance a daunting task. For transporters, international collaborative efforts have improved our understanding of the role of transporters in drug pharmacokinetics, pharmacodynamics, safety, and efficacy in pediatrics.[3] Many of these drugs are known substrates for CYP enzymes as well, thus adding yet an additional layer of intricacy. The ontogeny of receptors is less clear, but may in fact be more complex.[4]

Although the direct intent of this information may not be to define pediatric disease processes, the inclusion of pharmacodynamic markers in these studies may in fact allow comparison of disease processes either within the pediatric population or to disease

processes in adults. Therefore, an indirect benefit of an ontogeny knowledge base may be an understanding as to whether efficacy extrapolation is possible for pediatric patients.[5]

The ontogeny of pediatric drug safety

Drug safety has not been studied in the same detail in children as it has been in adults. This is primarily related to the number of drugs in use in pediatric medicine, which have not gone through the FDA's drug development process. In an ambulatory care setting, as many as 30% of drugs are used off-label in some pediatric populations, and the percentage can be much higher in critically ill pediatric patients. Because of the limited safety information in some drugs used in the pediatric population, a knowledge gap exists related to the ontogenic factors that can affect drug safety.

For drugs that have gone through the FDA's development process, significant differences in the incidence of adverse drug effects can be observed between the adult and pediatric drug development studies. Drugs that are psychoactive agents are of particular concern, and sedation seems to be a consistent problem with antipsychotic agents in pediatric patients.[6] The ontogenic pattern for the development of these adverse effects related to age or developmental stage has not been studied, in contrast to adverse effects on bone growth for which considerable information is available.

The path forward: A knowledge base for pediatric ontogeny

The scientific complexity behind pediatric ontogeny is undeniable. Elucidation of many mechanisms and further understanding of drug disposition in pediatrics is not only hampered by studies with small sample sizes or lack of any clinical investigation at all but also by the conflicting or inconclusive reports that are published in literature. The necessity for the creation of an integrated knowledge base focusing on the ontogeny of drug metabolizing enzymes and impactful covariates has been identified and this need can be extended to transporters, receptors, and other key factors in drug action. With the FDA and NIH as contributing partners to an open source pediatric ontogeny knowledge base, such a knowledge base could be poised as the most up-to-date and well-researched authority on the topic.

The goals of such a knowledge base would change over time. At the present time, we need such a knowledge base to systematically identify precise, definable knowledge gaps, and thus priorities. Another key goal of a knowledge base would be to develop a clear set of usable definitions that relates to the structure of the database and that represents the most commonly used terms in the literature. Ultimately, however, a thorough understanding of developmental effects on systems will provide the necessary knowledge to integrate disease, drug use, and drug effect in pediatric patients.

Through careful weighing of all available data in the literature, aggregating the data in a systematic way, and collaborative discussion with government institutions, this knowledge base can eventually be recognized as the accepted source for pediatric ontogeny information and data to inform modeling. The models that can incorporate development physiology and pharmacology are presently referred to as physiologically-based pharmacokinetic (PBPK) models. Existing pediatric ontogeny models for incorporation into PBPK are presently

available for several software packages. The qualification of pediatric ontogeny models has been discussed[7] and would be an important step in the process of use of this information in drug development.

In the rapidly growing area of model-informed drug development, additional approaches in the future are quite possible. The current use of PBPK models in pediatric drug development is growing and is supported by the FDA guidances, such as the General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products and the Physiologically Based Pharmacokinetic Analyses – Format and Content. However, these guidances do not provide standard values for the developmental trajectory of basic ontogenic processes, such as renal function.

The inclusion of real-world data and the resulting real-world evidence will be welcome additions that expand our understanding of pediatric ontogeny. The availability of data from electronic health records provides a potential source of information to fill the scientific gaps that are identified in a pediatric ontogeny knowledge base.[8]

Given the number of ontogenic factors involved, how can a knowledge base be organized in such a way that provides up-to-date, curated information? Several examples now exist for systems that organize such complex information, including PharmGKB, Reactome, ADMETNet, and others.[9] The advantages of such a system would include (1) having all of present ontogeny information in one location; (2) providing a graphical interface that quickly allows the identification of gaps of knowledge in ontogeny related to drug, disease, or development stage; and (3) providing a consensus estimation of a pathway for inclusion in a model to be used in pediatric drug development.

As stated in the initial paragraph, properly utilizing pediatric ontogenic information to improve pediatric drug development is a process that is just beginning. The suggestion that a pediatric ontogeny knowledge base would facilitate this revolutionary change is made for the purpose of stimulating discussion in an area where pediatric patients may benefit. A system that drives both the science of pediatric ontogeny by identifying the knowledge gaps and provides our best estimates for pediatric developmental models to be used in drug development would truly be a science-based innovation for pediatric drug development.[10]

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