Editorial

Perspectives on Pediatric Drug Development

It has been approximately 50 years since Dr. Harry Shirkey at the Children's Hospital in Alabama originally described pediatric populations as "therapeutic orphans" due to their clinical neglect during drug development.[1,2] While some significant advances have been made, pediatric patients are still largely considered therapeutic orphans when it comes to drug discovery and development. Several contributing factors to their status include the smaller market, the common occurrence of dysphagia, safety risks, the acute nature of many pediatric diseases, the limited number of clinical centers willing to perform pediatric trials, and the fact that few medicines have been developed specifically for children.[1,2] This is particularly true in children under the age of 5, where worldwide morbidity and mortality rates are considerably higher than in other populations. For example, the World Health Organization estimated that more than 7.6 million deaths in children under the age of 5 occurred worldwide in 2010, with greater than 99% of these deaths occurring in low to middle income countries. To our knowledge, drug safety trials have not been performed in healthy children, in stark contrast to clinical testing in adults. Further exacerbating the issue is the fact that approximately 70% of all medicines currently on the market have not been tested in children. Clearly, the therapeutic intervention of pediatric disorders remains a critical area for continued research in both industrialized and developing countries.

While the regulatory agencies have issued new policies to encourage the development of pediatric medicines, current pediatric clinical practice still often relies on the off-label use of adult medications, which may lead to adverse drug reactions. The development of safe and effective medicines for children requires that the differences in drug absorption, distribution, metabolism and elimination (ADME) in adult and pediatric populations be thoroughly understood. Presently, these differences are poorly understood, if at all. For example, the effects of age on drug metabolizing enzymes, on gastrointestinal (GI) physiology and absorptive transporters, and on drug distribution within the body have received little attention comparative to what has been performed in adults. These factors dictate drug absorption and disposition in a patient by patient manner, ultimately determining whether the therapeutic effect will be achieved and adverse reactions avoided. A better understanding of the ontogenic factors that influence the pharmacokinetics (PK), and even pharmacodynamics (PD), of drugs and dosage forms are required for the design of pediatric clinical trials that will enable true translation of pediatric medicines to the marke.[3-7] The ability to develop flexible pediatric dosage forms that provide high compliance and exposure levels required to elicit a safe and efficacious response in the age-based populations is required. [3,4,6,7]

Enhancing the understanding of drug PK and PD ontogenic response is critical for both traditional and new drug discovery programs in the pharmaceutical industry. Regulatory agencies can continue to issue new policies and amendments to provide incentives for companies to develop pediatric medicines. However, the risk of liability from adverse drug events have limited the development of pediatric formulations because doctors are hesitant to prescribe doses suggested that have not been fully confirmed by research and long term

use in children or traditional adult dosages that have been utilized in children which are conventional means that are tried and true. Consequently, when clinically tested pediatric formulations are not available, physicians will often administer extemporaneous preparations of adult dosage forms only when the risk of the disease far exceeds the potential for an adverse drug event.[8] For example, current clinical practice for many serious diseases largely employs the use of off-label adult dosages in pediatric patients, e.g. isoniazid.[9]

However, deciding on the appropriate risks can be arbitrary due to a number of factors including parental pressures, diagnostic assessment variation in determining the disease severity, and empathy towards the patient. The repeated practice of using extemporaneous formulations of adult formulations routinely could also inadvertently lead to a wider utility of using higher risk medicines for the intervention of considerably less severe disorders in children. In each of these cases, the increased potential dose to the pediatric patient may also have serious therapeutic consequences including: 1) drug plasma levels above the minimum toxic concentration for the patient; 2) a neglect of potential food effects, which may significantly alter drug absorption and consequently therapeutic efficacy; 3) altered dosing to the child if all of the extemporaneous formulation is not administered.

Consequently, research to address the current lack of age-appropriate formulations has drawn considerable industrial, regulatory, and clinician interest.[3,4] It is now incumbent upon us to begin focusing on research that will enable us to reach the goal of treating pediatric age-based populations in a safe and efficacious manner. In order to accomplish this mission we must begin to focus on research projects including the development of compatible pediatric formulations that will enable compliance, validate new preclinical methods for the assessment of pediatric drugs, elucidate the ontogeny of drug metabolizing enzymes and transporters along the GI tract and in the developing liver and kidneys, and establish safer means for performing clinical trials. Most importantly, we need to bring the development of pediatric medicines to the forefront of our field so that prior to the 100th anniversary of Dr. Shirkey's infamous statement, we will be able to retire the "Therapeutic Orphan" classification.

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Referencias

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