Drug dosage for children could be improved with new method under development

28 June 2021, by Marcene Robinson

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When prescribing medicine to children, doctors often rely on guidelines that simply scale down the dosage that adults receive. This imprecise and common practice fails to capture the nuances of childhood, which include rapid growth spurts.

To improve upon this method, a University at Buffalo-led team of researchers developed a single, open source mathematical equation that compares the physiological relationships between age with organ weight and organ blood flow rate, both critical factors for drug absorption and clearance that change as organs quickly mature during childhood.

The equation, published in *The AAPS Journal*, will allow researchers and clinicians to better simulate the impact of drug dosage on children by age, weight and sex, as well as develop updated pediatric pharmacokinetic (the way a drug moves through the body) models.

"Children are not little adults. This widely-used statement captures the complexity of changes in human physiology during development, which needs to be accounted for while determining drug doses for pediatric patients," says lead investigator Dhaval Shah, Ph.D., associate professor of pharmaceutical sciences in the UB School of Pharmacy and Pharmaceutical Sciences.

"Adult-to-pediatric dose scaling through body weight, surface area, or size is popular; however, all these scaling strategies often fail to achieve optimal concentrations of drugs across the entire pediatric age range," he says. "Also, the safety and effectiveness of many drugs on the market are understudied in children due to restrictions on their inclusion in clinical trials. Consequently, off-label drug usage [unapproved use of an approved drug] is the unfortunate norm in pediatrics."

Additional investigators include Hsuan Ping Chang, first author and doctoral candidate, Se Jin Kim, doctoral candidate, and Di Wu, Ph.D., research fellow, all in the UB School of Pharmacy and Pharmaceutical Sciences; and Kushal Shah, Ph.D., scientist at Vertex Pharmaceuticals.

Attempts to develop pediatric pharmacokinetic models have been made in the past, but the models either reference outdated information; are not freely available to the public; or require the use of a different equation for each variable, making its application cumbersome, according to Shah.

The researchers examined the most recent data available from the Centers for Disease Control and Prevention, World Health Organization and more than 50 research studies that measured organ weight and organ blood flow rate throughout childhood.

Using the data, they developed a single equation that could be modified to calculate the relationship between organ weight and age for male or female infants from birth to two years old, and male or female youths between 2-20 years old. The equation could also be adjusted to estimate the

relationship between organ blood flow rate and age for male or female children from birth to 20 years old.

Children younger than two years old were separated in the equation due to the first two years of life being a period of rapid development, where body fat and brain size increase quickly, and kidney weight falls by 25%. The formula was also divided by sex to account for higher organ weights in males and higher body fat in females. The analysis found that organ blood flow rates did not change rapidly during childhood.

More information: Hsuan Ping Chang et al, Age-Related Changes in Pediatric Physiology: Quantitative Analysis of Organ Weights and Blood Flows, *The AAPS Journal* (2021). DOI: 10.1208/s12248-021-00581-1

Provided by University at Buffalo