How do children's kidneys eliminate drugs?

August 9 2021

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What dose of medicine do you give a child? That depends to a large extent on how quickly their kidneys remove the drug from the blood. For ethical reasons it is impossible to measure this directly in little patients. Ph.D. candidate Sinziana Cristea combined different types of modeling and lots of data to find out more.

"We wanted to know more about the role that kidneys play in medicine clearance for different types of drugs and at different ages," says Cristea, from the Leiden Academic Center for Drug Research. "Drug clearance by the kidneys is called renal clearance. In our research we looked at two renal processes: glomerular filtration and active tubular secretion. The better we understand these processes and their contribution to drug clearance by the kidneys, the better we will be able to predict how quickly a medicine is eliminated from the blood. Combined with age-dependent changes in renal clearance, our models can be used to determine the safest and most effective medicine dose for children of different ages."

Modeling by lack of real data

Because you obviously cannot test drugs on healthy children, the researchers had to use computer models and data from real patients to answers their questions. The first approach they used is called physiologically-based modeling. This uses drug characteristics—such as pH and molecular weight of the drug molecule—and combines them with characteristics of the patient's body—such as blood flow, organ size and abundance and activity of renal transporters. With this input, the model can predict the drug concentration, and thus drug clearance, over time. "It's an ideal method when you're lacking real measurements, because you can find a lot of the required information in the literature," explains Cristea. However, not all the required information is available yet. "We particularly lacked information about the abundance and activity of transporters in children, which is difficult to measure experimentally."

Sick children contributed to the research

Unique about Cristea's research is that she combined this approach with

another form of modeling to fill in the gaps. "This second approach required measurements from multiple sick children. After they received their medicine, doctors measured the drug concentration in their blood over time. From these measurements of children of different ages, we could determine how drug clearance changes with age. Comparing that knowledge with the predictions from the physiologically-based model, we were ultimately able to estimate the final unknown factor: the maturation of the renal transporters."

Predictions for multiple drugs

This way, Cristea and her colleagues were able to determine the maturation of two important renal transporters, the OAT1 and OAT3. Without taking kidney samples from children, they found a mathematical equation that showed this transporter matures quickly in the first year of life. Moreover, the researchers confirmed that they can also use this equation to predict renal clearance in children of drugs that are cleared by these transporters.

Cristea concludes that "other researchers and ourselves can now use these models to further quantify the maturation of other renal transporters. It's wonderful that models like this reduce the need for collecting data from real kidneys and improve both safety and effectiveness of drugs for sick children."

Provided by Leiden University

Citation: How do children's kidneys eliminate drugs? (2021, August 9) retrieved 8 July 2024 from https://medicalxpress.com/news/2021-08-children-kidneys-drugs.html

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