How to determine medication dosages for premature babies

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Premature babies almost always require treatment with medication. Doctors usually determine the dosages based on data from children who were not born prematurely, while preterm infants often develop

differently. Medication researcher Aline Engbers investigated three commonly used drugs, focusing on what to consider in preventing over- or under-dosing in these tiniest patients. Engbers will defend her thesis on 19 December.

In the Netherlands, approximately 11,500 babies are born prematurely each year, after less than 37 weeks of pregnancy. About 1,800 of them are extremely premature, born before 32 weeks. Most of them require medication. "Many babies born extremely prematurely, for example, receive caffeine to prevent temporary cessation of breathing," says Engbers.

Dosage based purely on weight

There is currently insufficient knowledge about the correct dosage for these tiniest patients. As a result, doctors currently determine the dosage of many medications based on data from children born on time. They often do this solely based on body weight, says Engbers.

"The dosage for a full-term baby weighing 4 kilograms would be halved for a premature baby weighing 2 kilograms." This can lead to over- or under-dosing because body weight alone does not provide a complete picture of the child's development.

The three most commonly used drugs

For her doctoral research, Engbers, in collaboration with Erasmus MC Sophia Children's Hospital, studied the dosage of three commonly used drugs in premature babies: caffeine, ibuprofen, and fluconazole. Newborns receive ibuprofen not as a pain reliever but to stimulate the closure of the connection between their aorta (large body artery) and pulmonary artery.

This closure typically occurs a few days after birth, but in prematurely born children, it often does not. The antifungal drug fluconazole is given to premature infants preventively or as a treatment because they are susceptible to fungal infections.

Scarce data from blood samples

To determine the exposure of the tiniest patients to these medications, Engbers examined the concentration of the drugs in the blood after receiving a specific dosage. This is a challenging measurement due to the limited amount of blood that you can draw from premature infants. Engbers: "Through an opportunistic study design, it was sometimes possible to take a little extra blood when the patients had to be pricked for their treatment anyway."

Using advanced mathematical models, Engbers combined this scant data from different patients to describe the drug concentration in the blood during the treatment. She took into account the age and weight of the babies, as well as the duration of the pregnancy.

The concentration of caffeine, the most administered medication, was found to strongly depend on the number of days the baby is old. So, to maintain consistent exposure, the dosage needs to be increased as the child gets older. In her thesis, Engbers also provides dosage recommendations for ibuprofen and fluconazole based on more factors than just weight.

Thanks to the unique direct collaboration with doctors from Erasmus MC Sophia Children's Hospital, Engbers' findings directly contribute to the optimal treatment of the tiniest patients. "My co-supervisor, who is a doctor, was eager to apply my results," she says. "And the Kinderformularium—a knowledge base on medication use in children—has implemented some of the findings into their

recommendations."

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