Folic acid reduces risk of neural tube defects linked to HIV drug dolutegravir

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The corresponding author of this work pictured here: Dr. Robert Cabrera. Credit: Baylor College of Medicine

Dolutegravir is a preferred medication for treating HIV infection, but it recently has been linked to a 6- to 9-fold increase in the risk for neural tube defects among babies born to mothers receiving the drug during early gestation. Researchers at Baylor College of Medicine suspected that folic acid (vitamin B9), which is known to prevent the vast majority of neural tube defect cases, could be a part of the puzzle of dolutegravir's negative side effects.

The body transforms dietary folic acid into folate, which mediates normal neural tube development. The researchers discovered that the drug interferes with the binding of folate to its receptor, thus promoting neural tube defects. Importantly, folic acid supplementation can mitigate the risk of the medication in an animal model, suggesting that having folic acid-fortified foods available to the population at risk would significantly reduce the chance of dolutegravir triggering this type of neurodevelopmental problems. The study appears in the journal *AIDS*.

"Neural tube defects occur when the development of the neural tube, the embryonic central nervous system that gives rise to the brain and spinal cord, is disrupted during early stages of embryonic development. In humans, this refers to gestational days 17 to 30," said first and corresponding author Dr. Robert Cabrera, associate professor in the Center for Precision Environmental Health and the Department of Molecular and Cellular Biology at Baylor College of Medicine.

Thanks to a number of clinical research studies conducted during the past 50 years, researchers know that dietary folic acid has a protective effect against the vast majority of neural tube defects. This finding led to the implementation of mandatory folic acid fortification of grains and cereal products in 87 countries, including the U.S. since 1999, and consequently to the prevention of the vast majority of neural tube defect cases in these countries.

The body requires folic acid to conduct a number of cellular processes, including the synthesis of the building blocks of DNA, which is essential for proliferating cells. Lacking enough folic acid inhibits DNA synthesis and cell proliferation and can have serious consequences, especially in the growing embryo, which is engaged in active cell proliferation. Folic acid deficiency in the embryo, together with genetic and environmental factors, can result in failed closure of the neural tube and lead to defects.

"My colleagues and I have experience studying folate and its interaction with its receptor, which mediates folate effects, so we decided to investigate whether the association between dolutegravir and higher risk of neural tube defects

involved folate receptor interactions with folate," Cabrera said.

Previous evidence has indicated that interfering with the folate receptor can lead to neural tube defects. Studies in laboratory animals have shown that this disruption can result in developmental defects in the offspring. In addition, Cabrera and his colleagues had previously found that the levels of antibodies to folate receptor are higher in serum of mothers with babies with neural tube defects.

Using a variety of laboratory techniques, the researchers discovered in this study that at therapeutic concentrations the drug does disrupt the binding of folate to its receptor. This disruption involves at least four players: folate, folate receptor, dolutegravir and calcium ions. It is known that calcium increases folate binding to its receptor and that doluteglavir has affinity for positively charged ions such as calcium. The researchers propose that dolutegravir alters folate receptor binding by interacting with calcium, and the resultant complex is less soluble and less available to carry its biological functions.

Furthermore, working with the zebrafish animal model, Cabrera and his colleagues also discovered that exposing embryos to dolutegravir starting one to three hours after fertilization completely disrupted embryo development; but, importantly, this toxicity was mitigated by simultaneously providing folate to the embryos. Interestingly, exposing embryos to the drug five to eight hours after fertilization did not alter their development, indicating that early development is the critical period in which embryos are most susceptible to doluteglavir toxicity.

In populations that have folic acid-fortified foods available, women of childbearing age have a reduced risk of having babies with neural tube defects. For instance, the Centers for Disease Control and Prevention report that in the U.S. less than 1 percent of the population is deficient in folic acid. But in other countries such as Botswana that do not have this type of fortified foods, up to 40 percent of the people can be deficient in folate, Cabrera explained.

"In Botswana, up to one-third of the women are HIV-positive and this medication is being used mainly by women of childbearing age. Considering that these same women probably also are deficient in folate and other vitamins and minerals and may have anemia caused by iron deficiency, the combined effect with the medication increases the chance of neural tube defects on their babies," Cabrera said. "It's like the perfect storm, but the good news is that there is an easy solution that several countries have already implemented—provide foods fortified with folic acid."

More information: Robert M. Cabrera et al, The antagonism of folate receptor by dolutegravir, *AIDS* (2019). DOI: 10.1097/QAD.0000000000002289

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