Commonly Used Drug Offers Promise for Premature Babies

http://www.firstlight.cn 2007-05-29

May 17, 2007，Scientists have found evidence that the cox-2 inhibitor celecoxib, a common pain reliever used to treat arthritis, may offer a new way to reduce the risk of the most common cause of brain damage in babies born prematurely.

The work involves shoring up blood vessels in a part of the brain that in premature infants is extremely fragile and vulnerable to dangerous bleeding, which affects an estimated 12,000 children a year, leaving many permanently affected by cerebral palsy, mental retardation, and seizures.

“Stabilizing the blood vessels right before the baby is born is a tremendous opportunity to save the baby from potentially lifelong complications,” said Maiken Nedergaard, M.D., Ph.D., a neuroscientist at the University of Rochester Medical Center who is presenting the results at a neuroscience meeting, Brain ’07, in Osaka, Japan May 20-23.

The laboratory research was done primarily in a laboratory at New York Medical College led by neonatologist Praveen Ballabh, M.D. Ballabh’s team worked with Rochester neuroscientists including Nedergaard, Steven Goldman, M.D., Ph.D., and Nanhong Lou, Ph.D. A research article describing the work appeared in the April issue of Nature Medicine, which included a cover photograph taken by the Rochester team showing the brain cells involved in the brain damage seen in some premature infants.

The research is based on extensive brain studies of infants who died prematurely as well as on findings with newborn rabbits, whose brains resemble those of premature babies in some very important ways. The medication would need to be tested rigorously in pregnant women before being considered as a treatment for their babies. But the investigators point out that celecoxib is already used widely in people, including pregnant women, making a clinical trial in people feasible.

The researchers focused on a part of the brain known in developing infants as the germinal matrix, a temporary structure that is the birthplace of all brain cells in an infant. The structure runs like a jagged coastline just below spaces in the brain called ventricles, and in premature infants it’s extremely active, churning out new brain cells that migrate and settle into other parts of the brain.

“This is a very, very important part of the brain, from which neurons and glia cells migrate out to form all the layers of the brain,” said Ballabh, an associate professor in the Department of Pediatrics, Cell Biology, and Anatomy at New York Medical College, and a neonatologist at Westchester Medical Center.

The germinal matrix is designed to be active until around week 36 of gestation. Then, with most of the infrastructure of the brain in place, the germinal matrix disintegrates and shrinks into a much smaller brain region known as the ventricular zone in adults.

The problem is that the germinal matrix is as fragile as it is crucial during its brief existence. While it’s turning out new brain cells, it demands more oxygen and more blood flow, a demand that the body meets by building a network of temporary – and very fragile, awkward, and leaky – blood vessels.

In a normally developing fetus, the blood vessels do their job and then disappear by the time the baby is born. But when a baby is born prematurely, the structure is suddenly thrust into a role for which it is not designed, handling high rates of blood flow and pressure. It’s as if a building being outfitted with strong support structures is hit by an earthquake while the scaffolding is still up and construction is underway – the whole structure is at risk of collapse.

In the case of prematurely born infants, the baby’s brain literally does not have the time to tie up its loose ends before blood vessels never intended to exist by the time an infant breathes on its own are suddenly required to carry blood. In the case of a bleed, the blood vessels break, cutting off the supply of oxygen to some brain tissue and directly damaging parts of the brain.

Babies most at risk are those born between 24 and 32 weeks gestation that weigh less than 1500 grams, or about 3 lbs., 5 ounces. About 20 percent of such infants have a bleed, known as a germinal matrix hemorrhage or an intraventricular hemorrhage. While the problem sometimes is very small and hardly noticeable, other times the bleed causes tremendous brain damage. The risk is greatest in the infant’s first 48 hours of life.

With funding from the National Institute of Neurological Disorders and Stroke and the Philip Morris Organization, the team set out to reduce the risk, focusing much of their effort on a molecule known as VEGF, which is largely responsible for answering the brain’s call for more oxygen by actively building new blood vessels. It’s the same compound that many cancerous tumors use to feed their demand for oxyge

n and to grow.

The goal was to make the germinal matrix a little hardier in cases of premature birth, by eliminating the active building of new, but very fragile, blood vessels that bleed more easily than established blood vessels. The team used celecoxib to knock down the production of cox-2, which in turn slowed production of VEGF. The team also studied an anti-cancer drug known as ZD6474, which affects another molecule, angiopoietin-2, that the body uses to build blood vessels.

The team found that in human brain tissue, the compounds greatly reduced the production of cells used to build blood vessels, and decreased levels of angiopoietin-2 and VEGF, the two molecules very active in building new blood vessels.

Results were dramatic in female rabbits that were given the drugs for two days before delivering their offspring prematurely. The team showed that celecoxib cut the risk in offspring of having a moderate or severe bleed in half, from 90 percent to 45 percent. The percentage was reduced even more when ZD6474 was used as well, from 45 to 27 percent, but Nedergaard and Ballabh point out that ZD6474 is a very potent medication not likely to be given to pregnant women in the near future.

Overall, the best way to prevent the problem, doctors say, is to do everything possible to allow a pregnant woman to carry a pregnancy for a full 40 weeks. So doctors put a great deal of effort into preventing preterm labor. But when premature labor can't be prevented, doctors do have a few tools at their disposal to try and prevent bleeds in the germinal matrix.

Steroids, commonly used to help develop the lungs of a premature infant, can help prevent bleeds too. And recent research has shown that indomethacin, which like celecoxib is a non-steroidal anti-inflammatory drug, has been shown to help prevent such bleeds and is used to treat premature infants for other problems, but it has some severe side effects, Ballabh said. And a 2002 report by researchers at Washington University and Northwestern University indicated that celecoxib – the same drug that Nedergaard and Ballabh showed helps prevent the bleeds – might also be effective in preventing preterm labor.

"This work is very exciting, but the work is ongoing, and we must investigate the use of celecoxib more thoroughly before considering it for widespread use to prevent this problem," said Ballabh. "We can fix many problems in the premature infant, but brain damage is one problem that cannot be fixed – it must be prevented. Right now there is nothing available that has been shown to be really effective at preventing this problem."

Rochester authors of the paper include Nedergaard, professor in the Department of Neurosurgery; Goldman, professor in the departments of Neurology and Neurosurgery; and Lou, research assistant professor. At New York Medical College, authors in addition to Ballabh are Hongmin Xu, Furong Hu, Alex Braun, Kira Smith, Aracelie Rivera, Zoltan Ungvari, and Anna Csiszar.

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