Treatment May Ease Sickle-Cell Pain

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WASHINGTON (AP) — Researchers have found a link between the release from malformed red blood cells of the vital protein that carries oxygen, and episodes of severe pain in people with sickle cell disease.

The discovery is leading to clinical trials to test a new treatment — whether breathing nitric oxide, an important chemical that helps regulate blood pressure by relaxing blood vessels, can help sickle cell patients with their pain, said National Institute of Health researcher Dr. Mark T. Gladwin.

The disease, in which blood cells form in an abnormal crescent shape, affects an estimated 70,000 Americans. It has no cure, though treatment can ease the periodic episodes of severe pain. The inherited condition can cause bouts of severe pain, particularly in joints and limbs, and can damage the lungs, kidneys and other vital organs.

Nitric oxide is removed from the blood plasma by hemoglobin, the compound that carries oxygen around the body, and that results in constricted blood vessels, reduced blood flow and the accompanying pain, according to a team of researchers led by Gladwin.

Traditionally, doctors have believed the pain was caused by the deformed cells, which become sticky, clumping together and blocking blood vessels. The newly reported constricting of the blood vessels could worsen those blockages.

Hemoglobin normally is contained within blood cells — it is what makes them Red — and that severely limits its ability to react with nitric oxide. The misshapen blood cells of sickle cell patients contain an unusual form of hemoglobin and release a large amount of it into the blood plasma. There, it is 1,000 times more efficient in sweeping up the nitric oxide, resulting in the constricted blood vessels, the researchers reported Sunday in the online edition of the journal Nature Medicine.

Researchers plan clinical trials involving the nitric oxide in Baltimore, Washington, Boston and possibly Oakland, Calif., in six months to 12 months, said Gladwin, of NIH's National Institute of Diabetes, Digestive and Kidney Diseases.

People in an acute pain crisis will receive treatment with either nitric oxide or an inert gas — as a placebo — to determine if there is a difference in the response.

He said other treatments may be possible, such as converting the free hemoglobin in the blood to a less active form of the chemical that would not destroy the nitric oxide.

Gladwin said in an interview that his team's finding also could have implications for people with heart bypass operations who begin to suffer problems similar to sickle cell disease if they are on a heart pump more than three hours, and may be a factor in other blood diseases.

A remaining mystery, Gladwin said, is what causes the pain crisis to occur in sickle cell patients. ``It's like migraine,'' he said. ``One of the mysteries is, what's the trigger?''

Dr. James C. Liao of the University of California, Los Angeles, said the team's work ``uncovers an important cause of sickle cell pain crisis (and) suggests that cell-free hemoglobin is indeed an NO (nitric oxide) scavenger, a question which is under open debate.''

The report also ``suggests that any therapies that reduce cell-free hemoglobin or convert it to less reactive species ... might be a useful treatment for sickle cell crisis,'' Liao said.

Dr. Jack R. Lancaster of the Center for Free Radical Biology at the University of Alabama, Birmingham, said the report ``fills in a lot of gaps ranging from the basic science aspects to clinical applications.''

On the level of basic biology, he said, the paper ``raises the very interesting possibility that this is one of the major reasons why nature has chosen to put hemoglobin inside a red cell.''

It will do its job of binding and releasing oxygen to deliver it around the body whether inside the cell or not, he said, but putting it in the cell reduces its consumption of vital nitric oxide.

Neither Liao nor Lancaster is affiliated with the NIH research team.

While sickle cell disease is most often associated with people of African descent, the Sickle Cell Disease Association of America says it can also affect people of Middle Eastern and Mediterranean descent.

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