

Common practice of prescribing H2 blockers

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Researchers in an NIH network have found that premature infants given a common class of non-prescription drugs used to treat acid reflux are slightly more likely to develop a potentially fatal bowel disorder than are infants who are not treated with the drugs.

The drugs, known as H2 blockers, inhibit the production of stomach acid and may put premature infants at risk of necrotizing enterocolitis, a serious inflammation of the intestines. The study appears in the February 2006 *Pediatrics* and was conducted by researchers in the NIH's National Institute of Child Health and Human Development Neonatal Research Network.

The researchers pointed out that it is not possible to tell from the study whether or not the drugs caused the condition, but nonetheless advised caution with their use for premature infants.

"This study strongly suggests that the common practice of prescribing H2 blockers to prevent or treat acid reflux in premature infants be discontinued, until more evidence on the safety of this practice becomes available," said A. Elias Zerhouni, M.D., Director of the National Institutes of Health.

Necrotizing enterocolitis affects from 5 to 10 percent of infants born extremely prematurely, explained the study's first author, Ronnie Guillet, M.D., Ph.D., of the University of Rochester in Rochester, New York, a member institution of the NICHD Neonatal Research Network.

With necrotizing enterocolitis, tissue lining the wall of the intestines dies. The surviving tissue becomes swollen and inflamed, and the digestive tract is unable to digest or transport food. In some cases, damage to the intestines may require that portions of the intestines be removed. In other cases, the damage is so severe that the infant dies. The cause of the disorder is unknown.

Common H2 blockers are cimetidine (Tagamet), famotidine (Pepcid), ranitidine (Zantac), and nizatidine (Axid).

To conduct the study, Dr. Guillet and her coworkers analyzed the records of more than 11,000 very low birth weight infants who had been treated in the NICHD Neonatal Research Network. Of these, 787 premature infants had developed necrotizing enterocolitis. The infants ranged in weight from 401 grams to 1500 grams (about 14 ounces to just over 3 lbs). The researchers found that infants who received H2 blockers were 1.71 times more likely to develop necrotizing enterocolitis than were infants who had not received them.

In their article, Dr. Guillet and her coauthors wrote that it is not possible to determine from the analysis whether or not H2 blockers cause necrotizing enterocolitis. Another possible explanation, they wrote, is that infants likely to develop necrotizing enterocolitis might also have symptoms that require treatment with H2 blockers. The records that the researchers analyzed did not contain information on why physicians prescribed the drugs.

No other studies have been conducted on large numbers of premature infants receiving H2 blockers, said the program scientist of the NICHD Neonatal Research Network, Rosemary Higgins, M.D., of NICHD's Pregnancy and Perinatology Branch. However, the practice is widespread in neonatal intensive care units around the country.

Physicians prescribe H2 blockers to premature infants for several reasons, Dr. Higgins said. If premature infants are experiencing a lot of acid reflux, physicians might prescribe the drugs to prevent damage to the esophagus.

Dr. Higgins added that some physicians may prescribe H2 blockers to a premature infant who is not experiencing reflux out of concern that excessive stomach acid may lead to stomach ulcers. Some physicians believe that reflux may

predispose an infant to apnea--the cessation of breathing during sleep. Dr. Higgins said that this belief is controversial and no research has been conducted to determine its validity. In other cases, physicians may prescribe H2 blockers to prevent excess stomach acidity among infants who, because they are unable to feed unassisted, must be fed through a tube inserted through the esophagus.

In the paper, Dr. Guillet and her coworkers hypothesized that, by decreasing acidity in the digestive tract, H2 blockers might result in excessive levels of a type of bacteria known as gram negative bacteria. These high bacterial levels, in turn, might lead to necrotizing enterocolitis. The gram negative bacteria, normally harmless, are presumably kept in check by stomach acid, and might increase to unhealthy levels in the absence of sufficient stomach acid.

In support of their hypothesis, the researchers cited a study which found that experimental animals with reduced stomach acid levels had higher levels of gram negative bacteria and a high likelihood of developing necrotizing enterocolitis. The researchers also cited a study which found that premature infants fed human milk with a slightly higher acidity level than normal had lower levels of gram negative bacteria and were less likely to develop necrotizing enterocolitis than were infants fed milk with a normal acidity level.

The researchers did not study any other drugs used to reduce stomach acidity and do not know whether premature infants given these drugs have an increased likelihood of necrotizing enterocolitis.

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