IV Diazoxide Effective In Hypertensive Crisis

BY MITCHEL L. ZOLER
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LISBON — Intravenous diazoxide was as safe and effective as intravenous hydralazine for treating hypertensive crisis during pregnancy in a study with 124 patients.

Diazoxide has the advantage of working very quickly, and it may be a good option for physicians who are uncomfortable with hydralazine, Dr. Annemarie Hennessy said at the 15th World Congress of the International Society for the Study of Hypertension in Medicine. Intravenous β-blockers, another option for physicians in the United States, are not approved for use in Australia.

Women with severe hypertension at Royal Prince Alfred Hospital in Sydney were randomized so that 63 were assigned to treatment with diazoxide and 61 were scheduled to receive hydralazine. Treatment was actually administered to 59 women in the diazoxide group and 51 women in the hydralazine group, said Dr. Hennessy, a nephrologist at the University of Sydney and managing director of the preeclampsia research laboratory at the hospital.

The dosage used for diazoxide was a 15-mg bolus administered every 3 minutes to a maximum of 300 mg. In the hydralazine group, patients received 5 mg every 20 minutes to a maximum of 15 mg. The study's primary end point was need for cesarean section because of fetal deterioration as determined by cardiotocography.

The cesarean section rate was 70% in the hydralazine group and 76% in the diazoxide group, not a statistically significant difference.

The average time to reach target blood pressure was 34 minutes in the hydralazine group and 19 minutes in the diazoxide group, a statistically significant difference that is probably not very significant clinically, Dr. Hennessy said.

Episodes of persistent, severe hypertension occurred in 38% of women receving hydralazine and 16% of those receiving diazoxide, a statistically significant difference. There was one episode of severe hypotension in the hydralazine group and none in the diazoxide group. The incidence of other adverse events was 11% in both groups.

Dr. Hennessy attributed the absence of diazoxide-related hypotensive episodes in this study to the use of 15-mg boluses, which produced a controlled reduction in blood pressure. ■

High Vitamin E in Pregnancy Lowers Asthma Risk in Kids

Children whose mothers consumed the highest levels of vitamin E during pregnancy had less asthma and wheezing than did their peers whose mothers consumed less vitamin E while pregnant, according to findings from a cohort study.

Dr. Graham Devereux and colleagues from the University of Aberdeen (Scotland) found that 5-year-old children of women with the highest intake of vitamin E during pregnancy had the lowest incidence of wheezing, physician visits because of wheezing, and both suspected and physician-diagnosed asthma (Am. J. Respir. Crit. Care Med. 2006;174:499-507).

A group of 2,000 expectant mothers was initially recruited in 1997 and 1999 from prenatal clinics, at a median of 12 weeks' gestation. A total of 1,856 women completed a questionnaire, underwent a skin-prick test to assess atopic status, and provided a blood sample. At 32 weeks' gestation, 1,704 women answered a food-frequency questionnaire (FFQ) to assess dietary intake during the preceding 3 months. Upon delivery, maternal and infant (cord blood) plasma was sampled in 1,134 mothers and 877 infants and analyzed for antioxidant content via liquid chromatography.

Six weeks after their singleton children turned 5 years old, a questionnaire was mailed to each child's family to assess history of wheezing and asthma; 1,253 were completed and received. A total of 1,120 parents who responded to this questionnaire filled out an additional FFQ based on the child's diet, and parents of 797 children accepted an invitation to take the child to the hospital for spirometry, skin-prick testing, and fraction of exhaled nitric oxide measurement.

Ultimately, "children born to mothers with the lowest quintile of vitamin E intake [were] 3.47 times more likely to be of the persistent wheezing phenotype than [were] children born to mothers with the highest quintile of vitamin E intake," the investigators wrote.

They had reported an association between maternal vitamin E intake during pregnancy and asthma at age 2 years in the same cohort.

—John R. Bell

DRUGS, PREGNANCY, AND LACTATION

Do NSAIDs Cause Birth Defects?

BY GERALD G. BRIGGS, B PHARM.

Both prescription and over-the-counter nonsteroidal anti-inflammatory drugs are frequently used in pregnancy, including during the first trimester. When used around the time of conception, there is evidence that NSAIDs impair fertility by interfering with blastocyst implantation, resulting in spontaneous abortions.

Exposure to these agents in the latter part of the second trimester and throughout the third is known to cause functional toxicity in the fetus and newborn consisting of renal impairment, oligohydramnios, premature closure of the ductus arteriosus, and primary pulmonary hypertension of the newborn. Increased risks for other toxicities—such as intraventricular hemorrhage, necrotizing enterocolitis, patent ductus arteriosus requiring ligation, platelet dysfunction, and gastrointestinal bleeding—have been reported in association with prenatal exposure to NSAIDs, but a causative role has not yet been proved.

When used in the first 3 months of gestation, there have been conflicting reports associating the use of NSAIDs with structural anomalies. However, a Canadian study published in September has strengthened the argument that NSAIDs can cause birth defects, particularly cardiac septal defects. In the following discussion, the evidence for and against this association is examined:

► A large observational cohort study conducted in Denmark compared the outcomes of 1,106 pregnancies exposed to NSAIDs in the first trimester with 17,529 controls and found no significant association between NSAID use during pregnancy and congenital defects (BMJ 2001;322:266-70). A weakness of this study was that it included only women who had received an NSAID prescribed at doses equivalent to 400 mg or 600 mg of ibuprofen. The study did not identify women who might have taken NSAIDs that were available as OTC products at doses equivalent to 200 mg of ibuprofen.

► A Food and Drug Administration analysis of Michigan Medicaid data on a large number of women exposed in the first trimester to three NSAIDs between 1985 and 1992 found no evidence of an increased risk of cardiac or orofacial defects for any of the drugs. There were 19 birth defects among the 258 women (7.4%) exposed to diflunisal, 143 birth defects among the 3,178 women (4.5%) exposed to ibuprofen, and 70 birth defects among the 1,448 women (4.8%) exposed to naproxen. These rates were higher than the expected number of birth defects (10, 129, and 62, respectively), but these types of studies only raise hypotheses and cannot show causation (Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation. 5th ed. Baltimore: Williams & Wilkins, 1998: ix).

► A 2001 prospective observational cohort study that examined the relationship between first-trimester exposure to NSAIDs in 2,557 women and congenital defects found no association with birth defects in general. However, significant associations with cardiac defects and orofacial clefts were noted: There were 36 cardiac defects, representing an odds ratio of 1.86, and 8 orofacial defects, an odds ratio of 2.81. Both were statistically significant increases over the expected rates (Reprod. Toxicol. 2001;15:371-5).

► A 2003 study using data from Swedish health registers of 1,142 infants with orofacial clefts (isolated or nonisolated) found a greater risk associated with naproxen exposure. Compared to the expected number (2.9), 8 of the infants had been exposed to naproxen, a relative risk of 2.72 (Cleft Palate Craniofac. J. 2003;40:624-8).

Another study identified 5,015 infants in the same registry with cardiovascular defects, and compared them with 577,730 controls, finding no significant association when all NSAIDs were grouped together or with individual agents, with the exception of naproxen. Among babies born to 1,679 women exposed to naproxen, 24 had cardiovascular defects, a statistically significant odds ratio of 1.7 (Reprod. Toxicol. 2003;17:255-61).

► The latest study, a case-control study conducted in Quebec, found a significant association between congenital anomalies, specifically cardiac septal defects, and the use of NSAIDs in the first trimester. Case infants were those with any congenital anomaly diagnosed in the first year of life, who were matched with up to 10 controls (infants without a congenital anomaly) for maternal age, urban or rural residence, gestational age, and diabetes status. The data were adjusted for common comorbidities.

There were 93 infants (8.8%) with congenital anomalies born to 1,056 mothers who had filled prescriptions for NSAIDs in the first trimester. Among controls, there were 2,478 infants (7%) with anomalies born to 35,331 mothers who had not filled such a prescription. Among women who had filled a prescription for an NSAID during the first trimester, the adjusted odds ratio for any congenital anomaly was 2.21, and the adjusted odds ratio for cardiac septal closure was 3.34. Both odds ratios were statistically significant. There were no significant associations for oral clefts or defects involving other major organ systems.

The five NSAIDs most commonly used by these women were naproxen (35%), ibuprofen (26%), rofecoxib (15%), diclofenac (9%), and celecoxib (9%). The only statistically significant association was between ibuprofen prescriptions in the first trimester and congenital defects (Birth Defects Res. B. Dev. Reprod. Toxicol. 2006;77:268-79).

The data from these studies provide increasingly convincing evidence that NSAIDs are human teratogens, especially for cardiac septal defects and, possibly, for orofacial clefts. More research is needed, but women who are or may become pregnant should be counseled regarding this possible risk. Importantly, they should be made aware that NSAIDs are available without a prescription and that although the OTC strength is lower than the prescription product's, a safe dose has not been determined.

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