Vitamins C, E Fail to Prevent Preeclampsia

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DALLAS — Supplementation with vitamins C and E did not prevent preeclampsia, reduce its severity, or lower adverse neonatal outcomes in a World Health Organization randomized trial of 1,365 high-risk women.

The observed negative results are consistent with those of most previous antioxidant trials, although none of the previously reported adverse effects, such as earlier and more severe preeclampsia or reduced birth weight, were observed in the current trial, Dr. Mario Merialdi said at the annual meeting of the Society for Maternal-Fetal Medicine.

Secondary outcomes of low birth weight, small size for gestational age, and preterm delivery trended lower with supplementation, but were not statistically different.

"We found no evidence of harm to either mother or fetus attributable to supplementation with vitamin C and E," he said.

Still, lead investigator Dr. Jose Villar, a senior fellow in perinatal medicine at the University of Oxford (England), advised caution. "It is always of concern to give ineffective drugs to pregnant women, even if one study does not demonstrate harm," he said in an interview.

The recent VIP (Vitamins in Preeclampsia) trial showed that concomitant vitamin C and E supplementation did not reduce preeclampsia among 2,395 women at risk, but did increase the rate of babies born with a low birth weight (Lancet 2006;367:1145-54).

The WHO trial parallels the VIP trial, but specifically targeted high-risk women with nutritional deficiencies who lived in India, Vietnam, South Africa, and Peru. Because previous failed antioxidant trials were conducted in women with adequate nutritional status, the investigators theorized that supplementing potentially vitamin-deficient women might produce beneficial results, explained Dr. Merialdi, a reproductive health specialist with WHO in Geneva.

In all, 687 women were randomized to daily vitamin C (1 g) and vitamin E (400 IU), and 678 women were randomized to placebo before gestational week 20. Their mean age was 27 years. Risk factors were similar between the intervention and control groups, including history of previous preeclampsia (217 vs. 205), chronic hypertension (163 vs. 170), and multiple pregnancies (81 vs. 100). Compliance was similar in both groups at about 87%.

Supplementation did not reduce the risk of preeclampsia (relative risk 1.0), eclampsia (RR 1.5), or severe gestational hypertension (RR 0.8). Adjustment for maternal age did not modify these results, he said. The incidence of preeclampsia was not significantly different between the intervention and placebo groups (24.5% vs. 23.3%).

The secondary outcomes of low birth weight (defined as less than 2,500 g, and found in 33% of the intervention group vs. 36% in controls), small size for gestational age (defined as less than 10th percentile, in 23% vs. 26%), and preterm delivery (defined as delivery before 37 weeks, in 21% vs. 24%) tended to be lower with supplementation, but were not statistically different (RR 0.9 for all three).

Perinatal death also tended to be lower with supplementation, but did not reach statistically significant levels (RR 0.8), and the trial was underpowered to test this outcome.

A stratified analysis of those women with a history of preeclampsia demonstrated similar rates of preeclampsia in the supplement and control groups (26% vs. 28%), said Dr. Merialdi, who reported no financial conflicts of interest. ■

DRUGS, PREGNANCY, AND LACTATION

Droperidol's Black Box

In December 2001, the Food and Drug Administration placed a black box warning on droperidol (Inapsine) because of concerns over QT prolongation and torsades de pointes.

This action took the medical and pharmacy communities by surprise and created tremendous controversy. Although the labeling information always had contained warnings of serious and even life-threatening arrhythmias, droperidol had a 30-year history of safe and effective use in a wide range of patients.

Since its release in 1970, droperidol had been one of the preferred antiemetics for the prevention and treatment of postoperative nausea and vomiting (PONV) and also had been used to treat hyperemesis gravidarum (HG). But the FDA's action resulted in a marked decrease in its use for both these indications.

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In the early 1990s, manufacturing problems curtailed the availability of the other preferred antiemetic for these indications, parenteral prochlorperazine.

With no other viable alternatives, there was a large increase in the use of ondansetron (Zofran), which was expensive at the time, but is now available as a generic.

What remains unresolved is the use of droperidol in clinical situations, where it is the preferred agent for PONV, including after cesarean section, and for HG.

Several small studies that compared droperidol and ondansetron for PONV found no differences between the two in terms of efficacy and toxicity.

However, a large study with more than 2,000 subjects concluded that droperidol (1.25 mg IV) was superior to ondansetron (4 mg IV) for both vomiting and nausea (Anesth. Analg. 1998;86:731-8).

A review of 76 trials of 5,351 patients receiving 24 different droperidol regimens found no serious adverse events (Can. J. Anaesth. 2000;47:537-51). Other studies from California and Montreal reported that droperidol infusions were highly effective in the treatment of HG (Am. J. Obstet. Gynecol. 1996; 174:1801-6; J. Soc. Obstet. Gynaecol. Can 2001;23:133-9). None of the above studies found any evidence that droperidol was related to torsades de pointes.

A 2005 study of droperidol (0.625-1.25 mg) for antiemetic prophylaxis during general anesthesia in outpatient surgery observed no significant increase in the corrected QT (QTc) interval, compared with saline (Anesthesiology 2005;102:1101-5).

A French study the same year observed QTc prolongation after IV bolus doses of droperidol (0.75 mg) and ondansetron (4 mg) for PONV shortly after surgery. Before antiemetic administration, however, 21% of the patients had a prolonged QTc interval that was significantly correlated with lower body temperature and a longer duration of anesthesia. The mean maximal prolongation for droperidol and ondansetron was 17 milliseconds and 20 milliseconds, respectively, with the interval significantly lower after 90 minutes for both drugs.

A 2007 study from the Mayo Clinic reported no documented cases of torsades de pointes among the 16,791 patients exposed to droperidol over the 3-year period preceding the black box warning. The authors concluded that the FDA warning for low-dose droperidol was excessive and unnecessary (Anesthesiology 2007;107:531-6).

A 2004 editorial voiced the same opinion (N. Engl. J. Med. 2004;350:2511-2). In a small study we conducted, 49 women with hyperemesis gravidarum received droperidol 1 mg/hr for 37 hours. The pretreatment QTc interval was 404 milliseconds, compared with 412 milliseconds at 37 hours, a clinically insignificant increase.

A 2007 report analyzed data received under the Freedom of Information Act used by the FDA to support their black box warning. After exclusion of duplicate reports, there were 65 cases of cardiac toxicity possibly caused by droperidol.

Some of these reports appeared to have occurred more than 30 years in the past, not merely over the past 4 years as suggested by the FDA. Only two of the cases involved doses commonly used in the United States, one of which was a patient with preexisting cardiovascular disease. In addition, the FDA used European data that involved doses 50-100 times higher than those used in the United States. The authors concluded that it did not appear that drugs such as ondansetron were safer than droperidol with regard to QT interval prolongation (Am. J. Health-Syst. Pharm. 2007;64:1174-86).

For 23 years, my colleagues and I have successfully used droperidol infusions for HG. Before receiving droperidol, patients must have normal concentrations of potassium and magnesium; they are excluded if they have a history of QT prolongation (slow heart rate), congestive heart failure, cardiac arrhythmias, or are taking other drugs known to increase the QT interval.

Because there is a genetic component for QT prolongation, women also are excluded if there is a history of an immediate blood relative (mother, father, or sibling) with QT prolongation or sudden cardiac death secondary to cardiac arrhythmia. Not a single patient has had to be excluded because of personal or family histories, or because of the use of other medications. Nor have we observed any serious adverse effects in the six to seven patients with hyperemesis gravidarum we treat each month.

Considering the strong evidence of safety and efficacy, it is time for the FDA to remove the antiemetic doses of droperidol from the black box warning.

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