The Risk of Major Birth Defects with the Use of Proton-Pump Inhibitors During Early Pregnancy

Many pregnant women experience gastroesophageal reflux (GER) during pregnancy. Proton-pump inhibitors (PPIs) are the most efficacious and prescribed medication for GER, yet there are limited data regarding their use and safety during pregnancy. This retrospective, cohort study was done to determine if PPI exposure during early pregnancy was associated with an increase in major birth defects.

Using health care registries, data was gathered on all live-born infants, all birth defects, and all filled PPI prescriptions in Denmark from January 1, 1996, to September 30, 2008. The European Surveillance of Congenital Anomalies (EUROCAT) was used to define major defects, and genetic syndromes and chromosomal aberrations were not included. Potential confounders such as the age of the mother at conception, hospitalization or illness during pregnancy, and the use of other medications during the first trimester were used to determine an adjusted prevalence odds ratio (OR). The primary endpoint was the incidence of birth defects in infants exposed to PPIs during the first trimester or between four weeks prior to conception and the first trimester. Secondary endpoints included the incidence of birth defects in infants exposed during the second or third trimester.

The study included 840,968 live births over 153 months. Of 5082 infants who were exposed to PPIs sometime between four weeks prior to calculated conception and the end of the first trimester, 174 (3.4%) had a birth defect compared to 21,811 infants (2.6%) with birth defects in the non-exposed group (OR 1.23; 95% CI 1.05 to 1.44). Of 3651 infants exposed to PPIs during the first trimester, 1118 (3.2%) had birth defects compared to 21,867 (2.6%) with birth defects in the non-exposed group (OR 1.10; 95% CI 0.91 to 1.34). Of 4770 infants exposed to PPIs during the second or third trimester, 149 (3.1%) had birth defects, compared to 21,836 infants (2.6%) with birth defects in the non-exposed group (OR 1.09; 95% CI 0.92 to 1.29). The study was limited because no record of adherence was available to determine how often women took their PPI therapy.

SUMMARY: Only the infants of mothers exposed to PPIs sometime between four weeks prior to conception and the first trimester experienced a statistically significant increase in major birth defects. There was not a significant difference in the number of birth defects in infants exposed to PPIs during the first, second, or third trimesters compared to infants not exposed during the same time periods.


By Eric Roberts, Pharm.D. Candidate
Health Concerns with Caffeinated Energy Drinks and Cocktails

The United States is leading the world in total money spent on energy drinks with an estimated $10 billion in 2010.\(^1\) Since the introduction of the first energy drink in 1997, over 100 different energy drinks have been marketed in the U.S., with caffeine content ranging from 50 mg to 505 mg per drink. Production and sales of alcoholic energy drinks such as Sparks\(^6\)™, Four Loko\(^7\)™, and Jäger-Bombs are increasing, along with reports of caffeine intoxication, withdrawal, and dependence.\(^1\) Pharmacists should be aware of these health concerns because of their unique position to provide health education to the public.

The FDA limited the amount of caffeine to 0.02% or 71 mg/12 fluid ounces in soft drinks.\(^1\) Energy drinks do not have a caffeine limit because the manufacturers market their products under the 1994 Dietary Supplement Health and Education Act, which states that products derived from herbs and natural sources are classified as dietary supplements rather than drugs. The main active ingredient in energy drinks is caffeine, although other substances such as taurine, riboflavin, pyridoxine, nicotinamide, other B vitamins, and various herbal derivatives are commonly included.\(^1\)

There is a potential risk of acute caffeine toxicity associated with energy drinks because of inadequate product labeling and aggressive advertising used by energy drink manufacturers. Caffeine intoxication is a clinical syndrome involving specific symptoms such as nervousness, anxiety, insomnia, tremors, tachycardia, stomach upset, psychomotor agitation, and in rare cases, death.\(^1\) In a survey of 496 college students, 61% reported consuming at least one energy drink during the previous month. Of these, 29% reported weekly episodes of transient increases in energy followed by a sustained drop in energy level, 22% reported headaches, and 19% reported heart palpitations after drinking energy drinks.\(^2\) In addition to caffeine intoxication, the consumption of energy drinks has been linked to seizures, acute mania, and stroke.\(^3\)

The most common symptom of caffeine withdrawal is a severe headache usually occurring 12 to 24 hours after the last dose of caffeine. Other caffeine withdrawal symptoms include fatigue, drowsiness, dysphoria, difficulty concentrating, depression, irritability, nausea, vomiting, and muscle aches.\(^5\) A placebo-controlled, randomized, double-blind study evaluated the effects of caffeine discontinuation in 62 patients (18-50 years old) who consumed 200-600 mg (mean 235 mg) of caffeine every day and had no history of psychiatric disorders.\(^7\) The patients were put on a caffeine-free diet for two days while they received either capsules containing caffeine in the amounts equal to their daily caffeine consumption or placebo. The primary outcome was differences in withdrawal symptoms between the two groups as indicated by a 33-item caffeine withdrawal questionnaire. After two days without caffeine, there was a significant difference in the percentage of subjects who reported moderate to severe headaches between the placebo group (52%) and the caffeine group (6%; \(p<0.05\)). The placebo group also had a significantly greater incidence of yawning, fatigue, anxiety, and dysphoric mood changes in comparison to the caffeine group (p<0.05). The authors concluded that there was a direct correlation between abruptly discontinuing caffeine intake and symptoms of caffeine withdrawal. The study was limited by its small sample size and short duration.\(^5\)

Public health officials are concerned that caffeinated alcoholic drinks can increase the risk of cardiovascular damage and that, because of the caffeine content, users might not feel the effects of alcohol intoxication, which would increase the potential of alcohol-related injuries.\(^6\) One study showed that ingestion of a caffeinated energy drink (Red Bull\(^8\)™) with vodka reduced perception of motor coordination impairment compared to vodka alone but did not significantly reduce objective measures of alcohol-induced motor coordination impairment, reaction time, or breath alcohol concentration.\(^7\)

The absence of regulatory oversight has resulted in aggressive marketing of energy drinks, targeted primarily toward young males. There are increasing reports of caffeine intoxication from energy drinks, and problems with caffeine dependence and withdrawal may also increase. The combined use of alcohol and caffeine is gaining popularity, which may increase the rate of alcohol-related injury. Pharmacists are encouraged to promote conservative caffeine intake and discourage consumption of caffeine-alcohol combinations.

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References:
Literature Highlight: Combining Aerobic Exercise with Resistance Training to Lower Hemoglobin A1c

The 2008 Federal Physical Activity Guidelines recommend aerobic exercise combined with resistance training exercise in order to reduce cardiovascular complications. The 2007 Diabetes Aerobic and Resistance Exercise (DARE) study discovered that combining aerobic exercise with resistance training decreased hemoglobin A1c more than either exercise type alone. However, the study failed to control for the time spent exercising in each group. The 9-month Health Benefits of Aerobic and Resistance Training in individuals with type 2 diabetes (HART-D) study was conducted to investigate the effects on A1c from aerobic exercise, resistance training, and a combination of both exercise types while controlling for time spent exercising.

Two hundred and sixty-two sedentary patients, 30-75 years old, with type 2 diabetes and hemoglobin A1c of 6.5% to 11.0% were randomized into three exercise groups and one control group. Patients with a BMI >48 kg/m², BP >160/100 mmHg, fasting triglyceride levels >500 mg/dL, urine protein >100 mg/dL, serum creatinine >1.5 mg/dL, or who were using an insulin pump or had a serious medical condition that prevented adherence were excluded from the study. The control group (n=41) participated in weekly stretching and relaxation exercises. The resistance training group (n=73) participated in two sets of four upper body exercises, three sets of three leg exercises, and two sets of abdominal and back exercises three days a week. The aerobic exercise group (n=72) participated in a workout equivalent to 12 kcal/kg of body weight per week while the combination exercise group (n=76) participated in a workout equivalent to 10 kcal/kg of body weight per week plus one set of each of the nine resistance training exercises. The primary outcome was the change in hemoglobin A1c, and secondary outcomes were measurements of anthropometry, fitness, strength, and changes in diabetes medications.

At nine months, the combination exercise group had a mean A1c decrease of 0.34% (95% CI 0.03% to 0.64%) more than in the control group (p=0.03). The difference between the mean change in hemoglobin A1c levels in the aerobic exercise group and the control group was 0.24% (95% CI -0.07% to 0.55%; p=0.14). The difference between the mean change in A1c levels in the resistance training group and the control group was 0.16% (95% CI -0.15% to 0.46%; p=0.32). There were no adverse reactions associated with the exercise programs. Only 18% of the combination exercise group required an increase in anti-diabetic medications compared to 22% in the aerobic exercise group, 32% in the resistance training group, and 39% in the control group. Changes in diet and caloric intake during the study were difficult to monitor. Their effects on the outcomes, therefore, were undetermined.

SUMMARY: Compared to aerobic exercise or resistance exercise alone, combination exercise was more effective in reducing hemoglobin A1c as well as decreasing need for additional diabetic medications.


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