

CLINICAL UPDATE

Phenylpropanolamine and hemorrhagic stroke in women

Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med* 2000;343(25):1826-32.

Background: Phenylpropanolamine (PPA), a synthetic sympathomimetic agent, is a common ingredient in appetite suppressants and over-the-counter cough and cold remedies. Since 1969, the use of PPA-containing products has been associated with the occurrence of hemorrhagic stroke in more than 30 published case reports and in 22 spontaneous reports to the US Food and Drug Administration (FDA).¹ Subjects typically were young to middle-aged women who had taken PPA-containing appetite suppressants, in many instances for the first time. Because of the concerns raised by these reports, investigators at 5 American universities collaborated with the FDA and the manufacturers of PPA in a case-control study called the Hemorrhagic Stroke Project. It was designed to examine the association between PPA and hemorrhagic stroke.

Question: Is PPA associated with hemorrhagic stroke in men and women between the ages of 18 and 49 years?

Design: Between December 1994 and July 1999, subjects between the ages of 18 and 49 with subarachnoid or intracerebral hemorrhage were identified and recruited at 43 participating hospitals in the United States. The diagnosis was based on compatible symptoms and findings on cranial CT scan or lumbar puncture, or both. Subjects were excluded if they exhibited a brain lesion such as an aneurysm, tumour or arteriovenous malformation that increased the risk of hemorrhage, or if they had a history of stroke or were unable to communicate and complete an interview within 30 days of the index event. Two control subjects were identified

for each stroke patient through random-digit dialing. They were matched for telephone exchange, age, race and sex.

Trained research personnel administered a structured questionnaire in face-to-face interviews with the patients and the control subjects. Information obtained through the interviews included demographic, clinical, behavioural and pharmaceutical variables. Subjects were asked to recall cold symptoms, medications used to treat them and any other medications taken during the 2 weeks before the onset of symptoms. They were also asked specifically about their use of ASA, anticoagulants and diet pills. Subjects' medication recall was verified by using books containing photographs of packages of brand-name medications.

Exposure data from the case and control subjects were compared using χ^2 or Fisher's exact test, adjusted for race, smoking status and history of hypertension. Association between PPA use and hemorrhagic stroke was expressed as an adjusted odds ratio (OR) with a 95% confidence interval (CI).

Results: Of the 702 patients participating in the study, 425 (61%) had subarachnoid hemorrhage and 277 (39%) intracerebral hemorrhage. Compared with the 1376 control subjects, patients were significantly more likely to be black, hypertensive, less well educated and cigarette smokers ($p < 0.05$).

After adjustment for these differences in the logistic regression model, the OR among women was 16.58 (95% CI 1.51-182.21, $p = 0.02$) for the association between the use of appetite suppressants containing PPA and the risk of hemorrhagic stroke and 3.13 (95% CI 0.86-11.46, $p = 0.08$) for the association with the first use of a product containing PPA. All first uses involved cough or cold remedies. Among men, there was no reported use of appetite suppressants

and no increased association of hemorrhagic stroke with PPA-containing cough or cold remedies.

Commentary: Case-control studies frequently generate controversy because they are subject to both recall bias (when case subjects and control subjects demonstrate differential recall of exposure) and selection bias (when presence of exposure influences whether a person is identified as a case subject for entry into the study). This study attempted to minimize recall bias by blinding subjects to the study hypothesis and limiting the period of recall to the 30 days preceding the onset of symptoms of the index event. Selection bias was addressed by maintaining active surveillance of patients and using objective criteria to determine eligibility. In this study, the width of the 95% CI around the OR makes it difficult to be certain of the true magnitude of the association. Misclassification of even a small number of subjects' exposure to PPA-containing medications could have altered the study's results significantly.

Practice implications: On the basis of this study, the FDA, on Nov. 6, 2000, issued a health advisory and announced that it is taking steps to remove PPA from all drug products and has requested that all drug companies stop marketing PPA-containing products. Health Canada issued a health advisory later the same day. Patients should be advised about the risks of PPA and the need to dispose of any products containing it. — Donald Farquhar

The Clinical Update section is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont. The updates are written by members of the division.

Reference

1. Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med* 2000;343(25):1826-32.