2

Sherman, typ

Yale University

Ralph I. Horwitz, M.D.
Chairman
Department of Internal Medicine
Harold H. Hines, Jr. Professor of
Medicine and Epidemiology
School of Medicine

Campus address:
1072 LMP
333 Cedar Street
P.O. Box 208056
New Haven, Connecticut 06520-8056
Telephone: 203 785-4119
Fax: 203 785-6954

Chief, Beeson Medical Service
Yale-New Haven Hospital
20 York Street
New Haven, Connecticut 06510-3202

May 10, 2000

OTC #00-544

RECEIVED
MAY 11 2000
By

Charles J. Ganley, M.D.
Director, Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Document Control Room – S212
Rockville, Maryland 20850

By Federal Express

RE: Final Report of The Hemorrhagic Stroke Project
Docket No. 81N-0022

Dear Dr. Ganley:

As instructed in your letter of 4/13/00, I have sent the report of the Hemorrhagic Stroke Project to Docket No. 81N-0022. I have also sent a letter to Docket No. 76N-052N indicating that the report was submitted to Docket No. 81N-0022. A copy of our report is enclosed with this letter for your convenience.

Sincerely,

Ralph I. Horwitz

Ralph I. Horwitz

Enc: "Phenylpropanolamine & Risk of Hemorrhagic Stroke: Final Report of The Hemorrhagic Stroke Project"

Letters to Docket Management Branch dated 5/10/00

cc: Lorna C. Totman, Ph.D., Director of Scientific Affairs, Consumer Healthcare Products Association.
HSP investigators and members of the Scientific Advisory Group

81N-0022
76N-052N

RPT14
C230

PHENYLPROPANOLAMINE & RISK OF HEMORRHAGIC STROKE:
Final Report of The Hemorrhagic Stroke Project

May 10, 2000

Prepared by:

Ralph I. Horwitz, M.D.
Harold H. Hines Jr. Professor of Medicine and Epidemiology
Yale University School of Medicine

Lawrence M. Brass, M.D.
Professor of Neurology and Epidemiology and Public Health
Yale University School of Medicine

Walter N. Kernan, M.D.
Associate Professor of Medicine
Yale University School of Medicine

Catherine M. Viscoli, Ph.D.
Associate Research Scientist
Yale University School of Medicine

On Behalf of the HSP Investigators

OTC# 00-544
RECEIVED
MAY 11 2000
By dyp

EXECUTIVE SUMMARY

Case reports have linked exposure to phenylpropanolamine (PPA) to the occurrence of hemorrhagic stroke. Many of the affected patients have been young women using PPA as an appetite suppressant, often after a first dose. To further examine the association between PPA and hemorrhagic stroke, we designed a case-control study involving men and women ages 18 to 49 years who were hospitalized with a subarachnoid hemorrhage (SAH) or intracerebral hemorrhage (ICH). Eligible case subjects had no prior history of stroke and were able to participate in an interview within 30 days of their event. Case subjects were recruited from hospitals in four geographic regions of the United States. For each case subject, random digit dialing was used to identify two control subjects who were matched on age, gender, race, and telephone exchange. Cases and control subjects were interviewed to ascertain their medical history, health behaviors, and medication usage. A subject was classified as exposed to PPA if they reported use within 3 days of the stroke event for case subjects or a corresponding date for control subjects, and the exposure was verified.

The final study cohort comprised 702 case subjects and 1376 control subjects. All control subjects were matched to their case subjects on gender and telephone exchange. Age matching was successful for 1367 controls (99%) and ethnicity matching was achieved for 1321 controls (96%). For the association between hemorrhagic stroke and any use of PPA within three days, the adjusted odds ratio was 1.49 (lower limit of the one-sided 95% confidence interval (LCL)=0.93, p=0.084). For the association between hemorrhagic stroke and PPA use in cough-cold remedies within the three-day exposure window, the adjusted odds ratio was 1.23 (LCL=0.75, p=0.245). For the association between hemorrhagic stroke and PPA use in appetite suppressants within the three-day exposure window, the adjusted odds ratio was 15.92

(LCL=2.04, p=0.013). For the association between PPA in appetite suppressants and risk for hemorrhagic stroke among women, the adjusted odds ratio was 16.58 (LCL=2.22, p=0.011). For first dose PPA uses among women, the adjusted odds ratio was 3.13 (LCL= 1.05, p = 0.042). All first dose PPA use involved cough-cold remedies.

In conclusion, the results of the HSP suggest that PPA increases the risk for hemorrhagic stroke. For both individuals considering use of PPA and for policy makers, the HSP provides important data for a contemporary assessment of risks associated with the use of PPA.

INTRODUCTION

Phenylpropanolamine (PPA) is a synthetic sympathomimetic amine structurally similar to pressor amines (i.e., epinephrine, phenylephrine, and ephedrine) and central nervous system stimulants (i.e., ephedrine, amphetamine). It is a common ingredient in cough-cold remedies and appetite suppressants. Each year, billions of doses are consumed in the United States, making PPA one of the most commonly used non-prescription medications(1).

Since 1979, over 30 published case reports have described the occurrence of intracranial hemorrhage after PPA ingestion(1-3). Early reports involved diet pills including both PPA and caffeine(4-7), a combination that was removed from the market in 1983 because of abuse potential(8). Later reports involved use of PPA alone(9, 10), often as a reported first-ever dose (7, 11-14). Like the earlier ones, however, the later reports primarily involved PPA in diet pills. Affected patients were most commonly young persons, particularly women, ages 17 to 45 years. At least five reports, however, involved PPA in cough cold preparations(15-19).

Other than case reports, there has been only one epidemiologic study of PPA and stroke, published in 1984(20). Investigators at a large health maintenance organization examined the occurrence of cerebral hemorrhage among patients ages less than 65 years who filled a prescription for PPA during 1977-1981. The relative risk for hemorrhage for PPA users compared to non-users was 0.59 (95% confidence interval 0.03-2.9). Since the relative risk was less than one and the upper bound of the confidence interval was about three, the authors concluded that any hemorrhage risk related to PPA, if present at all, is very small.

Responding to on-going concern about PPA and risk for hemorrhagic stroke, in 1992 the United States Food and Drug Administration joined with manufacturers of products containing phenylpropanolamine to recommend the conduct of an epidemiological study of the association.

Because several case reports involved young women using PPA as an appetite suppressant, often after a first dose, the FDA and manufacturers identified women as having high priority in research planning. In response, the investigators of this research designed and implemented the Hemorrhagic Stroke Project (HSP), with three co-equal specific aims: Among men and women ages 18-49 years, to estimate the association between PPA and hemorrhagic stroke; Among the same target group, to estimate the association between PPA and hemorrhagic stroke by type of PPA exposure (cough-cold remedy or appetite suppression); And among women ages 18-49 years, to estimate: a) the association between first use of PPA and hemorrhagic stroke and b) the association between PPA in appetite suppressants and hemorrhagic stroke.

METHODS

Recruitment and Classification of Patients with Hemorrhagic Stroke

Between December 1994 and July 1999, we identified potential case subjects from two hospital networks located in Connecticut/Southern Massachusetts and Southern Ohio/Northern Kentucky and two tertiary care hospitals in Providence, Rhode Island and Houston, Texas through active surveillance of all admissions (See Appendix A for list of hospitals). Surveillance involved review of admission rosters and direct monitoring of admissions by one or more designated individuals, such as a discharge planner or stroke nurse. As a check on the completeness of case ascertainment, discharge rosters were reviewed from each participating hospital.

Case subject eligibility criteria included admission to a participating hospital, age between 18 and 49 years (inclusive) and symptomatic primary subarachnoid hemorrhage (SAH) or primary intracerebral hemorrhage (ICH). Subdural hematomas and hemorrhages related to ischemic infarctions, trauma, thrombolytic therapy, or cerebral vein thrombosis were not considered primary events and were not eligible for this study. A SAH was diagnosed based on clinical symptoms and specific diagnostic information. Required symptoms included sudden, severe headache, stiff neck or change in level of consciousness. Required diagnostic information included the presence of a high intensity signal in the subarachnoid space on computed tomography, or xanthochromasia on lumbar puncture not explained by other etiologies (e.g. liver disease, increased CSF protein, hypervitaminosis A). An ICH was diagnosed by symptoms (sudden headache, focal neurological symptoms, or change in consciousness) accompanied by a

computed tomographic (CT) scan showing a hyperintense signal within brain parenchyma. Magnetic resonance imaging was accepted for the diagnosis of SAH or ICH only if other studies were not diagnostic. Subjects were ineligible for enrollment if they died within 30 days, were not able to communicate within 30 days, had a previously diagnosed brain lesion predisposing to hemorrhage risk (e.g. arteriovenous malformation, vascular aneurysm, or tumor), or a prior stroke. We also excluded patients who first experienced stroke symptoms after being in the hospital for 72 hours (e.g., for an unrelated matter).

Permission to contact each potential case subject was sought from the treating physician. If permission were received, a researcher met with the patient and reviewed pertinent data to confirm eligibility.

Once subject interviews were completed and medical records were acquired, a second and final check on eligibility was completed at the central office in New Haven by a researcher who was kept unaware of medication exposures. This procedure was designed to ensure uniform standards for documentation and eligibility across all research sites. The researcher reviewed medical records and all study forms except the interview booklet. (For subjects enrolled in the Ohio/Kentucky site, medical records were reviewed on site. Study forms, however, were also checked in New Haven). Missing radiology or laboratory data was obtained. Patients with uncertain eligibility were reviewed with the local investigator and the New Haven investigators before being disqualified.

Recruitment of Controls

We attempted to identify two matched controls for each case subject. Matching criteria included: 1) gender; 2) ethnic group (black versus non-black); and 3) age (within 3 years for case

subjects less than 30 years and within 5 years for cases 30 years or over). In addition, all control subject interviews had to be completed within 30 days of the case's stroke event to minimize seasonal differences in the likelihood of exposure to cough-cold remedies. A computer-generated list of random telephone numbers (matching the first three digits of the case subject telephone number) was used to identify potential control subjects. Eligibility criteria for control subjects were the same as for case subjects except for those criteria related to the stroke event.

Subject Interviews

Eligible patients were invited to participate and give verbal informed consent. During the consent procedure, all subjects (cases and controls) were told that the study was designed to examine causes of hemorrhagic stroke in young persons without specific mention of PPA or other potential risk factors. Case subjects who did not speak English (n = 35) were interviewed using a translator who, with five exceptions, was not a relative or acquaintance. Most case-subject interviews were conducted in the hospital, but some were completed at home and three were completed by telephone. Most control-subject interviews were conducted in person in the control subject's home, a doctor's office, or other convenient location (44 were conducted by telephone). Control subjects were offered twenty dollars to defray their expenses.

Specification of Focal Time

The first step of the interview process was to determine the focal time for each case subject. This time refers to the calendar day (i.e. index day) and time of day that marked the onset of symptoms plausibly related to hemorrhage and that caused the case subject to seek medical attention. The correct assignment of a focal time was critical because exposures to PPA

were defined in relation to this temporal anchor (i.e., only exposures that occurred prior to the focal time are relevant to the analysis). To establish the focal time, we obtained from each case subject a detailed account of his or her symptoms from onset to diagnosis. Additional information was obtained from acquaintances or witnesses to the case subject's illness.

Some patients with SAH or ICH may have a transient headache hours or days before the event that actually causes them to seek medical attention(21). These preceding symptoms have been termed "warning leaks" or "sentinel headaches"(22). The cause of these sentinel headaches is not known, although clinicians infer that some of them may be due to minor bleeding(23). As expected, we encountered patients with sentinel headache and recognized the possibility that the first onset of bleeding may have coincided with that symptom. Since we defined the focal time by the onset of the symptoms that actually brought them to medical attention, we needed an additional research strategy to account for the possibility of an earlier onset of bleeding. Accordingly, we defined an alternate focal time as the time of onset of the sentinel headache. A separate interview was conducted for this alternate focal time (for the case and matched controls). How data on the alternate focal time were analyzed is described below in the statistical analysis section.

The focal time for control subjects was established according to two rules: first, it occurred on one of the 7 days prior to the control interview; and second, it was matched to the case subject's focal time according to day of week and time of day. For example, if the case subject's focal time occurred on a Monday at 2:00pm and their control subject was interviewed on a Thursday, then the focal time for the control subject interview would be 2:00pm on the Monday preceding the control interview. We maintained a short interval between control subjects' focal times and interview dates to improve control subjects' recall of pre-focal time

exposures; the short interval was necessary to balance case subjects' greater stimulation for recall of exposures occurring before their stroke. The focal time matching was intended to minimize differences between case subjects and control subjects for differences in medication use and other exposures (e.g. alcohol, cigarettes) that may occur by the day of week (e.g., weekday vs. weekend) and time of day.

Ascertainment of Exposure Data and Other Subject Information

Case and control subjects were interviewed by a trained interviewer using a structured questionnaire developed for this study. To assist subjects in recalling details of their medication use, they were asked to refer to a calendar for the period encompassing the index date (before the focal time) and the preceding 14 days. The calendar was marked with notable personal events, such as trips, birthdays and doctor's visits that occurred during this period. As a memory aid, subjects were asked to recall if specific symptoms of a cold or flu (i.e., cough, runny nose, nasal congestion, or sore throat) were present in this two-week period. If present, the subject was asked if they had used any medication to treat the symptoms. The subject was then asked to recall the names of any other medications (purchased over the counter or prescribed by a doctor) taken during this time period. After all volunteered medications were recorded, subjects were asked if they had taken any of several specific classes of medications in the two-week period before the focal time (i.e., aspirin, acetaminophen, non-steroidal anti-inflammatory medications, anticoagulants, asthma medications, and medications for depression). Subjects were specifically asked about their lifetime use and last use of diet pills. For each medication reported taken during the two-week period, details were obtained regarding certainty of use (definite, probable, or uncertain) and amount taken on the index day prior to focal time and on each of the preceding

three calendar days. For each medication, the timing and amount of the last dose taken before the focal time was noted. Only uses that were reported as probable or definite were counted in the analysis.

Verification of each reported medication was done after the interview. Participants were asked to pick out reported brand-name medications from a book containing photographs (Product Identification Book). They were then asked to produce the actual container of each medication reported. The exact name of the medication and the manufacturer's lot numbers were recorded. If a container was not available, use of a brand name medication was considered verified if the subject had identified it in the Product Identification Book. Among 28 reported PPA uses in a three day window for case subjects, 27 (96%) were verified. Among 35 reported PPA uses for control subjects, 33 (94%) were verified.

To determine the active ingredients in each verified medication, we relied on published sources(24, 25). For national brands and prescription drugs that had possible formulation changes during the study period and for generic or store brand medications, we verified active ingredients directly with the manufacturer.

Definition of Exposure

The exposure window refers to the interval before the focal time when subject's exposure status to PPA is assessed. For all analyses except first-dose use, the exposure window was defined as the index day before focal time and the preceding three calendar days. For first-dose use, a subject was considered exposed if the PPA use occurred on the index day before the focal time or on the preceding calendar day, with no other PPA uses during the preceding two weeks. Subjects were only considered exposed to PPA within the appropriate window if their reported

exposure was verified by the procedures described above. To maintain a consistent reference group for all analyses, non-exposure was defined by no use of PPA within two weeks of the index date.

Sample Size

The sample size was based on the need to determine if PPA, taken as a first use, increases the risk of hemorrhagic stroke within 24 hours among women ages 18-49. Based on available market data, we estimated that 0.502% of controls would report an exposure to PPA within 24 hours of the index date. For a one-tailed test of significance at the 0.05 level and 80% power to detect an odds ratio of 5.0 for first use exposure in women, 324 female case subjects and 648 control subjects were required. Because our research interest extended to men and to exposures other than PPA, we doubled our sample size to include 350 men and 350 women for a total of 700 case subjects and 1400 controls.

Statistical Analysis

In the first phase of the analysis, we compared case and control subjects on a variety of clinical and demographic features, including those used in matching. Statistical comparisons were made using chi-square tests and the Fisher's exact test, where appropriate, for categorical variables and the Student *t*-test for continuous variables (SAS Institute Inc, Cary, North Carolina). In the second phase of the analysis, conditional logistic models for matched sets (with a variable number of controls per case) were used to estimate odds ratios, lower limits of the one-sided 95% confidence intervals and p-values for the risk factors under investigation. We report one-tailed statistical results because the focus of this research was restricted to the effect of PPA

in increasing the risk of stroke. Each logistic model was estimated with two mutually exclusive, binary exposure terms: the first term captured the subject's primary exposure status as defined by the specific aim (e.g., PPA use in 3-day window; yes/no); the second term captured users of PPA who were not exposed according to the primary definition (e.g., no PPA use in the three day window, but some PPA exposure within two weeks of the focal time). This modeling technique was employed in order to retain all matched subject-sets in the estimation of the primary exposure of interest while maintaining a consistent reference group of no-PPA use in two weeks for all analyses. Unadjusted estimates were calculated using exact methods (LogXact Program, version 2.1, Cytel Software Corporation, Cambridge, MA).

In multivariate conditional logistic models (using asymptotic methods), we adjusted for race (black compared with non-black) because not all cases and controls were successfully matched on this factor, and for history of hypertension (yes/no) and current cigarette smoking (current compared with never or ex-) because these are the major risk factors for SAH or ICH(26, 27). We also examined other subject features to determine if any of them, when added to this basic adjusted model, altered the matched odds ratio by at least 10%. Clinical features examined included body mass index, diabetes, polycystic kidney disease, congestive heart failure, sickle cell anemia, and clotting disorders. Other subject features included education (less than high school/high school or more), family history of hemorrhagic stroke in a first degree relative, consumption of more than two alcoholic beverages per day, cocaine use within one day of the index day, current oral contraceptive use, and several other pharmacological exposures. The final model included race, current cigarette use, hypertension, and any features that changed the adjusted matched odds ratio by at least 10%.

The study design incorporated two interim examinations of the data. As specified in the protocol, each interim analysis examined the association between stroke and any PPA use in the three-day window for the entire cohort and first PPA use in women. To preserve the specified alpha level for statistical inference (type I error rate), the O'Brien-Fleming multiple testing procedures were used for testing the significance of effect estimates(28). For three looks at the data (two interim and one final look) and a final alpha level of 0.05 for a one-tailed test of each objective, the O'Brien-Fleming chi-square statistics corresponded to one-tailed p-values of 0.008 (first look), 0.023 (second look), and 0.044 (final look).

As described above, we encountered patients with sentinel symptoms for whom we defined an alternate focal time. If the actual disease onset is defined by the alternate focal time rather than the primary focal time, an analysis based on the latter could lead to a biased estimate of the odds ratio by two mechanisms. First, case subject exposure to PPA between the alternate (earlier) and primary (later) focal time may actually be in response to the disease (and not a potential cause of the disease). If such exposures occur within the appropriate time window, however, they would be counted in the analysis using the primary focal time and would lead to an overestimate of the odds ratio. This bias is sometimes referred to as temporal precedence bias(29, 30). Second, case subject exposure to PPA before the alternate focal time may actually be causally associated with the disease. If these earlier exposures were outside the appropriate time window for the primary focal time analysis, however, they would not be counted and the error would lead to an underestimate of the odds ratio. To examine the potential effect of these two sources of bias, we performed two ancillary analyses, one excluding all subject sets where the case subject had a possible sentinel symptom and one using the alternate focal time.

Oversight

An external Scientific Advisory Group (SAG) operated autonomously from the investigators and study sponsors and provided general oversight for the conduct of the HSP. The SAG reviewed the research protocol and suggested revisions, reviewed research progress, developed criteria for early termination, and evaluated interim and final analyses. Nevertheless, the investigators accept all responsibility for the conduct of the study, the analysis of the data, and the interpretation of the results. A list of advisory group membership is included at the end of this report.

RESULTS

Study Participants

Between December 1994 and July 1999, 1,714 potentially eligible patients with hemorrhagic stroke were identified (Table 1). Among these, 784 subjects were ineligible for enrollment (389 died, 194 were unable to communicate within 30 days of the event, 120 had a history of stroke, 48 had a known brain tumor or arteriovenous malformation, and 33 were in the hospital over 72 hours before their event). Among the 930 eligible subjects, 222 were not enrolled (182 were not contacted within 30 days, 37 declined to give informed consent, and for 3 their physician did not give permission for contact). The total number of eligible case subjects enrolled was 708. There were no significant differences ($p<0.05$) in age or ethnicity between the 708 enrolled patients and the 222 eligible patients who were not enrolled. Subjects in the enrolled case group, however, were more likely to be female (55% compared with 45%, $p = 0.02$) and to have a SAH (60% compared with 47%, $p < 0.01$). Six patients were not included in the final analysis because no eligible controls were identified (three patients), the interview date was over 30 days from the stroke event (two patients), or the focal time could not be determined (one patient). Thus, the final case group comprised 702 subjects, including 425 subjects (60%) with a SAH and 277 (40%) with an ICH. Hemorrhage was associated with an aneurysm in 307 patients (44%), an arteriovenous malformation in 50 patients (7%), and a tumor in one patient (0.1%). (See Appendix B for additional details on case enrollment)

Two control subjects were located for 674 case subjects (96%) and one control subject for 28 case subjects (4%). All control subjects were matched to their case subjects on gender and telephone exchange. Age matching was successful for 1367 controls (99%) and ethnicity

matching was achieved for 1321 controls (96%). On average, for each case subject, we called 151 telephone numbers (range 3-1119) and identified 2.8 eligible persons for each enrolled control (range 1-12).

The mean interval between the case index date and the interview date was 13 days (range 0 to 30) for case subjects and 19 days for their matched control subjects (range 0 to 35). All control subjects except six were interviewed within 30 days of the case subject's index date. We allowed enrollment of six controls within an interval of 31-35 days since the purpose of interviewing controls within 30 days of the case subject's index date was simply to ensure seasonal similarity when collecting data on pharmaceutical exposures.

Table 2 shows selected characteristics of case and control subjects. Compared to control subjects, case subjects were significantly ($p<0.05$) more likely to be black (21% compared with 17%). Case subjects were also more likely to report lower educational achievement (20% did not graduate from high school compared with 9% of control subjects), current cigarette smoking (51% compared with 30%), a history of hypertension (39% compared with 20%), family history of hemorrhagic stroke (9% compared with 5%), heavy alcohol use (14% compared with 7%), and recent cocaine use (2% compared with <1%). For all other clinical variables examined, case and control subjects were not dissimilar.

Table 3 shows non-PPA pharmacological exposures of case and control subjects. Case subjects were significantly ($p<0.05$) less likely to report use of NSAIDS and significantly more likely to report use of caffeine and nicotine in the three days before their focal time.

To identify variables for inclusion in subsequent multivariable models, we sequentially tested each clinical feature (Table 2) and pharmacological exposure (Table 3) in the basic conditional logistic model that included race, hypertension, and current cigarette smoking.

Under any PPA exposure definition, only education changed the adjusted odds ratio for the association between PPA and hemorrhagic stroke by more than 10% and was included in all subsequent models.

Association Between PPA and Hemorrhagic Stroke

Our first co-equal specified aim was to determine whether PPA users, compared to non-users have an increased risk of hemorrhagic stroke. In Table 4, frequencies are shown for exposures to PPA in an unmatched format for the case and control subjects, with unadjusted and adjusted matched odds ratios provided. (See Appendix C for exposures presented in matched format.) The odds ratios were calculated from conditional logistic models for matched sets; the adjusted models included the same four variables: race, history of hypertension, current cigarette smoking, and education. For any use of PPA within three days (either for cough-cold remedy or appetite suppression), the unadjusted odds ratio was 1.67 (p=0.040) and the adjusted odds ratio was 1.49 (lower limit of the one-sided 95% confidence interval (LCL)=0.93, p=0.084).

Our second co-equal specific aim was to estimate the association between use of PPA and hemorrhagic stroke according to type of PPA exposure. The results are shown in Table 4. (See Appendix C for exposures presented in matched format.) For the association between PPA use in cough-cold remedies within the three-day exposure window, the unadjusted odds ratio was 1.38 (p=0.163). The adjusted odds ratio was 1.23 (LCL=0.75, p=0.245). For the association between PPA use in appetite suppressants within the three-day exposure window, the unadjusted odds ratio was 11.98 (p=0.007) and the adjusted odds ratio was 15.92 (LCL=2.04, p=0.013).

To examine the relation between recency of PPA exposure and risk for hemorrhagic stroke, we calculated odds ratios according to the timing of most recent PPA use (Table 5). For

this analysis, the pre-specified definition for current use was use of any PPA-containing product on the index day before focal time or the preceding calendar day. Prior use was defined as use two or three calendar days before the focal time. As shown in the table, the odds ratio was slightly higher for current use (adjusted OR (AOR)=1.61, LCL=0.93, p=0.078) than for prior use (AOR=1.16, LCL=0.47, p=0.393). Within current use, we then calculated odds ratios according to first use or not-first use. First use was defined as current use with no other use within the prior two weeks. Not-first use included other uses within the two-week interval. The odds ratio was higher for first use (AOR=3.14, LCL=1.16, p=0.029) than for not-first use (AOR=1.20, LCL=0.61, p=0.329). All first uses of PPA (n=13) reported in these data were in cough-cold remedies.

Our final co-equal specific aim was to estimate the association between PPA and risk for hemorrhagic stroke among women for two exposure definitions: appetite suppressant use within three days and first dose use (See Appendix D). For the association between PPA in appetite suppressants and risk for hemorrhagic stroke among women, the unadjusted odds ratio was 12.19 (p=0.006) and the adjusted odds ratio was 16.58 (LCL=2.22, p=0.011). Among HSP subjects, all appetite suppressant use within the three-day exposure window occurred among women. For first dose PPA uses, eleven of the 13 exposures were among women (seven cases compared with four controls). The unadjusted odds ratio was 3.50 (p=0.039) and the adjusted odds ratio was 3.13 (LCL= 1.05, p = 0.042). Appendix C shows exposure data for cases and controls in a matched format.

Additional Analyses

Based on the findings that risk for hemorrhagic stroke seemed to be concentrated among current users, we examined the association between current PPA dose and risk for hemorrhagic stroke. Among 21 exposed control subjects, the median current dose of PPA (i.e., total amount taken on the index day or preceding day) was 75mg. Analysis according to dose shows that the odds ratio was higher for current doses above the median (>75mg) (AOR=2.31, LCL=1.10, p=0.031) than for lower doses (AOR=1.01, LCL=0.43, p=0.490). Among first dose users, four of eight cases and two of five controls were exposed to >75mg of PPA.

To examine the potential effect of ambiguity in the correct focal time, we recalculated the odds ratios after excluding all 154 case subjects who were classified as having a definite (n=76) or uncertain (n=78) sentinel symptom. The magnitude of the adjusted odds ratios did not change substantially (see Appendix E). We also recalculated the odds ratios using the alternate focal time data for the 53 patients who, with their matched control subjects, had a completed interview for this focal time. Again, the adjusted odds ratios did not change substantially (see Appendix F).

Description of Case and Control Subjects

Table 6 describes the 27 case subjects who reported an exposure to PPA on their index day before focal time or during the preceding three days. Among the 27 exposed case subjects, 21 (78%) were women and 6 (22%) were men. Known risk factors for SAH or ICH (i.e., smoking, hypertension) were present for 18 subjects (66%). About half of all exposures to PPA occurred within 6 hours of the focal time, with a range of 6 minutes to 3.5 days and about half of all exposures (n = 17) involved slow release preparations. The amount of PPA consumed at the

last dose ranged from 7 mg to 150 mg (mean 82 mg). Eight of 27 last dose exposures (30%) exceeded normal adult doses of 50 mg for immediate release preparations and 75 mg for sustained release preparations(31).

Table 7 describes the 33 control subjects who reported an exposure to PPA on their index day before focal time or during the preceding three days. Among the 33 exposed case subjects, 20 (61%) were women and 13 (39%) were men. Known risk factors for SAH or ICH (i.e., smoking, hypertension) were present for 18 control subjects (54%). One third of all exposures to PPA occurred within 6 hours of the focal time, with a range of 40 minutes to 3.2 days and about half of all exposures (n = 17) involved slow release preparations. The amount of PPA consumed at the last dose ranged from 12 mg to 150 mg (mean 61 mg). Five of 32 last known dose exposures (16%) exceeded normal adult doses. In summary, compared to PPA-exposed case subjects, exposed control subjects were less likely to be female (61% compared with 78%), to have stroke risk factors (54% compared with 66%), to consume PPA within 6 hours of the focal time (33% compared with 52%), and to take excessive doses of PPA (16% compared with 30%). Further details of PPA-exposed and non-exposed subjects are presented in Appendix G.

DISCUSSION

In the Hemorrhagic Stroke Project of subjects between ages 18 and 49 years, PPA use was associated with an increased risk for hemorrhagic stroke. The increased risk was evident for PPA used as an appetite suppressant and for first use exposure. Because first uses of PPA in the HSP always involved cough-cold remedies, the association of PPA with risk for hemorrhagic stroke is present for both customary indications for PPA (as a cough-cold remedy and an appetite suppressant). The association of PPA with risk for hemorrhagic stroke was evident in the overall group of case and control subjects and among women. Because so few men were exposed to PPA in the HSP (n=19), we were unable to determine if their risk for hemorrhagic stroke (with use of PPA) is different from that of women.

Prior to the HSP, information concerning the association between PPA and risk for hemorrhagic stroke in humans came from clinical trials(8), case reports(2), and one epidemiological study(20). Clinical trials on the effectiveness of PPA are not informative on the risk of brain hemorrhage because they did not enroll enough patients to observe occurrences of this rare event. The one epidemiologic study found no association between PPA and hemorrhagic stroke, but design limitations reduce its contribution to the assessment of PPA safety. The only direct evidence for an association between PPA and risk for hemorrhagic stroke in humans has come from case reports. Although these reports effectively called attention to the possible association between PPA and hemorrhagic stroke, the absence of control subjects means that these studies cannot provide evidence that meets the usual criteria for valid scientific inference. The HSP, therefore, provides the most comprehensive and valid evidence to date on the association between PPA and risk for hemorrhagic stroke.

Other than a valid association between PPA and stroke, possible alternative explanations for our findings include residual confounding, bias in the design of the study, and chance findings in the analysis. Residual confounding refers to incomplete adjustment for factors related to both exposure and outcome. Although some residual confounding may be present within the HSP, our data provide little support for the presumption that it is significantly distorting the observed association between PPA and hemorrhagic stroke. In particular, adjustment for known potential confounders did not produce odds ratios that were markedly different from the unadjusted figures (Tables 4 and 5).

Biases that most commonly affect the design of case-control studies include temporal precedence bias, recall bias, and selection bias. Temporal precedence bias refers to a systematic error in which an exposure is counted although it occurs after the onset of the disease under study, often in response to disease symptoms(30). We checked for temporal precedence bias with specific analytic strategies for patients with sentinel symptoms and found no evidence that it has an important influence on the measured odds ratios.

Recall bias refers to the tendency of case subjects, compared with control subjects, to have more or less complete recall of exposures or to report exposures that may never have happened(32). Although it is possible that our case subjects over-reported PPA exposure in an attempt to explain their illness, in our data case subjects were no more likely than control subjects to report exposures to aspirin or non-PPA oral sympathomimetics. These negative findings suggest that recall bias was not an important source of distortion in the HSP, especially considering the well-publicized risk of hemorrhage with aspirin. It seems likely, furthermore, that case-subjects in the HSP may have had impaired recall of exposures due to brain injury. This impairment would have biased the study toward a finding of no association between PPA

and hemorrhagic stroke. Our data provide some evidence for a bias in this direction because case-subjects in the HSP more frequently reported "uncertain" exposures to PPA than control subjects. When these "uncertain" exposures are counted, the odds ratios increase by over 10% for all exposure definitions except for first dose use. For first dose use the odds ratio falls from 3.14 ($p = 0.029$) to 2.88 ($p = 0.044$). In addition, to address differential recall stimulus we set the index day for control subjects within one week of their interview (compared with up to 30 days for case subjects). The close proximity of the index date and interview date for control subjects was intended to overcome the imbalance in stimulus for recall between controls (who experienced no major life event on the index date) and cases (who did). Although recall bias is commonly discussed in relation to case-control research, it rarely has a meaningful impact on research findings(33, 34).

Selection bias refers to the preferential referral to a case-control study of case or control subjects with (or without) the exposure under study(35). Selection bias in the HSP might result from publicity about PPA and stroke, leading physicians to preferentially seek a diagnosis of hemorrhage in a PPA user or to preferentially refer a patient to the study if there were a history of PPA use(36). We adopted several strategies to reduce the possibility of selection bias, including active case surveillance and enrollment of subjects who met our eligibility criteria, regardless of the diagnostic impression of their physicians. To check for possible selection bias, we compared eligible, enrolled case-subjects with eligible, non-enrolled patients and found no differences in age or ethnicity. Non-enrolled patients, however, were more likely to be female and to have an ICH rather than a SAH. We did not assess the eligible, non-enrolled patients for their ability to communicate within 30 days; if we had, it is likely that many would have been reclassified as non-eligible. Because ICH is more likely than SAH to impair communication,

this reclassification would be expected to narrow the difference between eligible, enrolled and eligible, non-enrolled patients in stroke type. Another potential source of selection bias in the HSP is non-participation by eligible control subjects who did not answer their telephone or who refused participation. We do not know if such persons were more or less likely to use PPA than the controls who agreed to participate.

Chance seems an unlikely explanation for our findings. Odds ratios for appetite suppressant use and first use (all involving cough-cold products) reached the conventional threshold for statistical significance ($p<0.05$). Although the odds ratio for the association between any PPA use in three days did not reach this threshold, chance remains an unlikely explanation for the observed value of 1.49 ($p=0.084$).

Several features of the HSP support a valid association between PPA use and risk for hemorrhagic stroke. First, in addition to the finding of elevated odds ratios that reached statistical significance, the magnitude of the odds ratios for PPA use as an appetite suppressant (15.92) and as a first use (3.14) were large in magnitude even after adjustment for important clinical features. Second, these data show an association with brain hemorrhage across the two major formulations of PPA (i.e., cough-cold remedy and appetite suppression).

There are potential limitations to our research. First, because we excluded dead and non-communicative patients we cannot know if PPA is more or less associated with brain hemorrhage in these patients compared with those studied. Epidemiologists have long recognized a form of research bias termed prevalence-incidence bias that may occur if survivors of a potentially fatal illness have a different clinical profile from those who die(37). This bias may either increase or reduce the odds ratio associated with an exposure under investigation. In the HSP, for example, if PPA confers a survival advantage in hemorrhagic stroke, the odds ratio

among survivors will be spuriously increased. If PPA increases mortality, on the other hand, the odds ratio among survivors will be spuriously reduced. Although we cannot be fully certain that prevalence-incidence bias has not affected the HSP, we are unaware of a plausible mechanism by which PPA might increase or decrease the likelihood of survival after a stroke.

A second possible limitation of our study is the number of case and control subjects who were exposed to PPA (n=60). This number of exposed subjects limits the opportunity for subgroup analysis. It is worth noting, however, that the exposure rate observed in women for the first dose use analysis (0.533%) achieved the rate anticipated in the research design (0.502%). As a final limitation, the HSP interviewers were not blinded to the case-control status of subjects and some were aware of the study purpose. Blinding would have provided extra protection against unequal ascertainment of PPA exposure in case subjects compared with control subjects. Instead of blinding, we relied on a highly structured and scripted interview instrument. Overall, none of the limitations are sufficiently important to invalidate our findings.

In conclusion, the results of the HSP suggest that PPA increases the risk for hemorrhagic stroke. For both individuals considering use of PPA and for policy makers, the HSP provides important data for a contemporary assessment of risks associated with the use of PPA.

HSP INVESTIGATORS

Ralph I. Horwitz, M.D.
Harold H. Hines Jr. Professor of Medicine and Epidemiology
Yale University School of Medicine
New Haven, Connecticut

Lawrence M. Brass, M.D.
Professor of Neurology and Epidemiology and Public Health
Yale University School of Medicine
New Haven, Connecticut

Joseph P. Broderick, M.D.
Professor of Neurology
University of Cincinnati College of Medicine
Cincinnati, Ohio

Thomas Brott, M.D.
Professor of Neurology
Mayo Medical School
Rochester, Minnesota

Edward Feldmann, M.D.
Professor of Neurosciences
Brown University School of Medicine
Providence, Rhode Island

Walter N. Kernan, M.D.
Associate Professor of Medicine
Yale University School of Medicine
New Haven, Connecticut

Lewis Morgenstern, M.D.
Assistant Professor of Neurology and Epidemiology
The University of Texas Medical School and School of Public Health
Houston, Texas

Catherine M. Viscoli, Ph.D.
Associate Research Scientist
Yale University School of Medicine
New Haven, Connecticut

Janet Lee Wilterdink, M.D.
Associate Professor of Neurosciences
Brown University School of Medicine

SCIENTIFIC ADVISORY GROUP MEMBERS

Louis C. Lasagna, M.D. (Chair)
Dean, Sackler School of Graduate Biomedical Sciences
Professor of Pharmacology and Experimental Therapeutics
Tufts University

J. P. Mohr, M.D.
Sciarra Professor of Neurology
College of Physicians and Surgeons
Columbia University

Samy Suissa, Ph.D.
Professor of Medicine and Epidemiology and Biostatistics
McGill University

REFERENCES

1. **Morgan JP.** *Phenylpropanolamine. A critical analysis of reported adverse reactions and overdosage* Fort Lee, New Jersey: Jack K. Burgess, Inc.; 1986.
2. **Lake CR, Gallant S, Masson E, Miller P.** Adverse drug effects attributed to phenylpropanolamine: A review of 142 case reports. *American Journal of Medicine.* 1990;89:195-208.
3. **King J.** Hypertension and cerebral haemorrhage after Trimolets ingestion. *Medical Journal of Australia.* 1979;2:258.
4. **Kikta DG, Devereaux MW, Chandar K.** Intracranial hemorrhages due to phenylpropanolamine. *Stroke.* 1985;16:510-512.
5. **Fallis RJ, Fisher M.** Cerebral vasculitis and hemorrhage associated with phenylpropanolamine. *Neurology.* 1985;35:405-407.
6. **Johnson DA, Etter HS, Reeves DM.** Stroke and Phenylpropanolamine use. *Lancet.* 1983:970.
7. **McDowell JR, LeBlanc HJ.** Phenylpropanolamine and cerebral hemorrhage. *The Western Journal of Medicine.* 1985;142:688-691.
8. **Lasagna L.** *Phenylpropanolamine: A review* New York, NY: Wiley & Sons, Inc.; 1988.
9. **Maher LM.** Postpartum intracranial hemorrhage and phenylpropanolamine use. *Neurology.* 1987;37:1686.
10. **Forman HP, Levin S, Stewart B, Patel M, Feinstein S.** Cerebral vasculitis and hemorrhage in an adolescent taking diet pills containing phenylpropanolamine: case report and review of literature. *Pediatrics.* 1989;83:737-741.
11. **Stoessl AJ, Young GB, Feasby TE.** Intracerebral haemorrhage and angiographic beading following ingestion of catecholaminergics. *Stroke.* 1985;16:734-736.
12. **Kase CS, Foster TE, Reed JE, Spatz EL, Girgis GN.** Intracerebral hemorrhage and phenylpropanolamine use. *Neurology.* 1987;37:399-404.
13. **Traynelis VC, Brick JF.** Phenylpropanolamine and vasospasm. *Neurology.* 1986;36:593.
14. **Chung Y-T, Hung D-Z, Hsu, C-P, Yang, D-Y, Wu, T-C.** Intracerebral hemorrhage in a young woman with arteriovenous malformation after taking diet control pills containing phenylpropanolamine· A case report. *Chinese Medical Journal.* 1998;61:432-435.
15. **Humberstone PM.** Hypertension and cold remedies. *British Medical Journal.* 1969;i:846.
16. **Sloan MA, Kittner MA, Rigamonti D, Price TR.** Occurrence of stroke associated with use/abuse of drugs. *Neurology.* 1991;41:1358-1364.
17. **Bernstein E, Diskant BM.** Phenylpropanolamine: a potentially hazardous drug. *Annals of Emergency Medicine.* 1982;11:311-315.
18. **Tonks CM, LLoyd AT.** Hazards wtih monoamine-oxidase inhibitors. *British Medical Journal.* 1965;i:589.
19. **Rumbaugh CL, Fang HCH, Higgins RE, Bergeron RT, Segall HD, Teal JS.** Cerebral microvascular injury in experimental drug abuse. *Investigative Radiology.* 1976;11:282-294.
20. **Jick H, Aselton P, Hunter JR.** Phenylpropanolamine and cerebral haemorrhage. *Lancet.* 1984:1017.
21. **Linn FHH, Wijdicks EFM, van der Graaf Y, Weerdesteyn-van Vliet FAC, Bartelds AIM, van Gijn J.** Prospective study of sentinel headache in aneurysmal subarachnoid hemorrhage. *Lancet.* 1994;344:590-593.
22. **Mayer PL, Awad IA, Todor R, et al.** Misdiagnosis of symptomatic cerebral aneurysm. Prevalence and correlation with outcome at four institutions. *Stroke.* 1996;27(9):1558-63.
23. **Edlow JA, Caplan LR.** Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. *The New England Journal of Medicine.* 2000;342:29-36.
24. **Medical Economics Company.** *Physicians' Desk Reference.* 53 ed Montvale: Medical Economics Company, Inc.; 1999.
25. **Knodel LC, Young LL, Kendall SCe.** *Nonprescription Products: Formulations and Features ('98-'99)* American Pharmaceutical Association; 1997.
26. **Longstreth WT, Koepsell TD, Yerby MS, van Belle G.** Risk factors for subarachnoid hemorrhage. *Stroke.* 1985;16:377-385.
27. **Teunissen LL, Rinkel GJ, Algra A, van Gijn J.** Risk factors for subarachnoid hemorrhage: a systematic review. *Stroke.* 1996;27(3):544-9.

28. **O'Brien PC, Fleming TR.** A multiple testing procedure for clinical trials. *Biometrics*. 1979;35:549-556.
29. **Forsyth BW, Horwitz RI, Acampora D, et al.** New epidemiologic evidence confirming that bias does not explain the aspirin/Reye's Syndrome association. *Journal of the American Medical Association*. 1989;261:2517-2524.
30. **Horwitz RI, Feinstein AR, Harvey MR.** Temporal Precedence and other problems of the exposure-disease relationship. *Archives of Internal Medicine*. 1984;144:1257-1259.
31. **Trudeau TW, Wright W, Staff DRE.** Phenylpropanolamine. In: Gelman CR, Rumack BH, Sayre NK, eds. *Drugdex System*. Englewood, Colorado (Edition expires 12/1999): Micromedex Inc.
32. **Schlesselman JJ.** *Case-Control Studies. Design, Conduct, Analysis* New York: Oxford University Press; 1982.
33. **Austin H, Hill HA, Flanders D, Greenberg RS.** Limitations in the applications of case-control methodology. *Epidemiologic Reviews*. 1994;16:65-76.
34 **Aitken J, Bain C, Ward M, Siskind V, MacLennan R.** How accurate is self-reported family history of colorectal cancer? *American Journal of Epidemiology*. 1995;141:863-871.
35. **Breslow NE, Day NE.** *Statistical Methods in Cancer Research. Volume I -The Analysis of Case-Control Studies* Lyon: International Agency for Research on Cancer; 1980.
36. **Jick H, Vessey MP.** Case-control studies in the evaluation of drug-induced illness. *American Journal of Epidemiology*. 1978;107:1-7.
37. **Sackett DL.** Bias in analytic research. *Journal of Chronic Diseases*. 1979;32:51-63.

Table 1.
Assembly of Cohort

	No.
Hemorrhagic Strokes Identified (Dec. 1994 – Aug. 1999)	1,714
Ineligible Subjects	784
Died within 30 days of stroke	389
Not able to communicate within 30 days of stroke	194
Prior history of stroke	120
Prior history of brain tumor or AVM	48
In hospital > 72 hours before stroke	33
Eligible Subjects[1]	930
Not enrolled	222
Not contacted within 30 days	182
Refused participation	37
No MD approval to contact	3
Enrolled	708

[1]For non-enrolled subjects, stroke events were confirmed to be eligible but ability to communicate within 30 days of event was not assessed.

Table 2.
Sociodemographic and Clinical Features
of Case and Control Subjects

		Cases[1] (n=702)		Controls (n=1376)		
		No.	%	No.	%	
Sociodemographic Features						
Female		383	55%	750	55%	
Black race		146	21%	232	17%	*
Age:	< 40	296	42%	592	43%	
	40-49	406	58%	784	57%	
Education[2]:	<HS graduate	143	20%	121	9%	*
	High school graduate	280	40%	395	29%	
	College+	277	40%	860	62%	
Clinical Features						
Cigarette smoking:	Current	358	51%	419	30%	*
	Ex	150	21%	367	27%	
	Never	194	28%	590	43%	
Hypertension (hx)[2]		272	39%	281	20%	*
Diabetes (hx)[2]		44	6%	72	5%	
Primary family history[2]		51	9%	56	5%	*
Alcohol use (>2drinks/day)		95	14%	96	7%	*
Cocaine use[3]		12	2%	2	<1%	*
Oral contraceptive use[4] (% women)		36	9%	74	10%	
Body mass index (wt/ht^2)[2]:	<24	233	33%	391	29%	
	24-30	295	42%	659	48%	
	>30	169	24%	322	23%	
URI symptoms (in two weeks)		114	17%	269	20%	

*P-value (two-sided)<.05.
[1]Among the 709 enrolled subjects, 6 were excluded from the analysis (3 subjects had no controls identified; 2 subjects completed interviews more than 30 days after their stroke event; and the index date for 1 subject could not be determined).
[2]Missing or uncertain responses: Education (2 cases), hypertension (1 control), diabetes (5 cases and 2 controls), primary family history (137 cases and 246 controls), body mass index (5 cases and 4 controls), URI symptoms (39 cases and 54 controls).
[3]Current use (defined as use on ID or preceding day).
[4]Use in 3-day window.

Table 3.
Other Pharmacologic Exposures
of Case and Control Subjects[1]

	Cases (n=702)		Controls (n=1376)		
ASA	79	11.3%	133	9.7%	
NSAIDS	114	16.2%	292	21.2%	*
Dextromethorphan hydrobromide	25	3.6%	44	3.2%	
Sympathomimetic (non-PPA)					
Oral preparations[2]	58	8.3%	115	8.4%	
Inhaled preparations	11	1.6%	32	2.3%	
Nasal preparations	8	1.1%	15	1.1%	
Stimulants/anorexiants (non-PPA)	4	0.6%	12	0.9%	
Oral anticoagulants	2	0.3%	6	0.4%	
Caffeine	49	7.0%	40	2.9%	*
Nicotine	9	1.3%	1	0.1%	*

*P-value (two-sided)<0.05.
[1]Use in 3-day window before focal time.
[2]Pseudoephedrine hydrochloride, phenylephrine, ephedrine and epinephrine contained in medications.

Table 4.
Phenylpropanolamine (PPA) Exposure
and Risk of Hemorrhagic Stroke

	Cases (n=702)		Controls (n=1376)		Unadjusted Matched	Adjusted Estimates[1]		
	No.	%	No.	%	OR	Matched OR	LCL[2]	p-value
No use[3]	664	94.6%	1310	95.2%	--	--	--	--
Any PPA[4]	27	3.8%	33	2.4%	1.67	1.49	0.93	.084
Cough/cold remedy	22	3.1%	32	2.3%	1.38	1.23	0.75	.245
Appetite suppressant	6	0.9%	1	0.1%	11.98	15.92	2.04	.013

[1]Adjusted for smoking, hypertension, race and education.
[2]Lower limit of one-sided 95% confidence interval.
[3]No PPA use in 2-week period before focal time; 11 cases and 33 controls used PPA between 2 weeks and 3 days before focal time.
[4]One female case used PPA in both a cough/cold remedy and an appetite suppressant in 3-day window.

Table 5.
Recency of PPA Exposure
and Risk of Hemorrhagic Stroke

	Cases		Controls		Unadjusted Matched	Adjusted Estimates[1] Matched		
	No.	%	No.	%	OR	OR	LCL[2]	p-value
No use[3]	664	94.6%	1310	95.2%	--	--	--	--
Current use[4]	21	3.0%	21	1.5%	1.98	1.61	0.93	.078
First use[5]	8	1.1%	5	0.4%	3.20	3.14	1.16	.029
Not-first use	13	1.9%	16	1.2%	1.62	1.20	0.61	.329
Prior use[6]	6	0.9%	12	0.9%	1.01	1.16	0.47	.393

[1]Matched odds ratio adjusted for smoking, hypertension, race and education.
[2]Lower limit of one-sided 95% confidence interval.
[3]No PPA use in 2-week period before focal time; 11 cases and 33 controls used PPA between 2 weeks and 3 days before focal time.
[4]Current use is defined as use of any PPA-containing product on index date (ID) before focal time or preceding calendar day. All uses are within 24 hours of Focal Time (FT).
[5]Current use and no other uses in 2-week period before ID.
[6]Use of any PPA-containing product 2 or 3 calendar days prior to ID.

Table 6.
PPA Exposed Case Subjects

					PPA Exposure			
	Stroke Type	Age	HTN Hx.	Current Smoker	Form (S=slow; I=immed release)	Dose in 3 days (mg)	Last Dose (mg)	Time of Last Dose (hrs before FT)
Female Cases								
1.	SAH	22	-	-	S[1]	75	75	84.0
2.	SAH	26	-	Y	S[1]	600	150	13.8
3.	SAH	30	-	-	S[2]	75	75	1.0
4.	SAH	31	-	Y	I	890	123	1.2
5.	SAH	31	Y	Y	S[2]	75	75	8.0
6.	SAH	34	-	Y	S[2]	300	150	2.0
7.	SAH	38	-	Y	I	48	48	43.0
8.	SAH	38	-	Y	S[1]	300	75	3.8
9.	SAH	38	Y	Y	S[1]	150	75	50.0
10.	SAH	42	-	-	S[2]	150	150	1.0
11.	SAH	42	-	-	S[2]	75	75	2.0
12.	SAH	44	-	Y	I	75	25	13.2
13.	SAH	44	Y	-	I	480	48	4.5
14.	SAH	46	Y	-	I&S[3]	640	150	9.0
15.	SAH	49	-	-	I	60	20	17.5
16.	IPH	25	-	Y	I&S	225	75	0.5
17.	IPH	32	-	-	S[1]	225	75	36.0
18.	IPH	36	-	-	S	600	75	0.1
19.	IPH	45	-	-	I[2]	75	75	3.5
20.	IPH	45	-	-	I	13	7	36.0
21.	IPH	48	-	Y	S[2]	150	150	6.0
Male Cases								
22.	SAH	20	-	Y	I[2]	150	150	1.0
23.	SAH	31	Y	Y	I	120	40	15.0
24.	SAH	47	Y	-	S	75	75	54.6
25.	IPH	33	Y	Y	S	450	50	5.5
26.	IPH	42	Y	-	I	160	40	1.5
27.	IPH	47	Y	Y	S	225	75	18.0

[1]Appetite suppressant use.
[2]First dose use.
[3]Subject used both appetite suppressant and cough/cold remedy.

Table 7.
PPA Exposed Control Subjects

				PPA Exposure			
	Age	HTN Hx.	Current Smoker	Form (S=slow; I=immed release)	Dose in 3 days (mg)	Last Dose (mg)	Time of Last Dose (hrs before FT)
Female Controls							
1.	39	-	Y	S	150	75	2.5
2.	25	-	-	I[1]	150	75	9.0
3.	33	-	-	I	75	37	2.0
4.	43	-	Y	S	300	75	13.5
5.	43	-	Y	I	50	50	57.0
6.	40	Y	Y	I	175	25	0.6
7.	44	-	-	S[2]	150	75	54.8
8.	42	Y	-	I	225	75	24.5
9.	44	-	Y	S	525	75	4.0
10.	34	Y	-	I	225	25	24.0
11.	43	Y	-	S	75	75	3.0
12.	40	-	-	S	150	75	75.0
13.	27	-	Y	S	225	75	20.0
14.	42	Y	-	S	600	75	3.0
15.	33	Y	-	S	450	150	14.5
16.	40	-	Y	I	80	40	9.5
17.	38	-	-	I[1]	37	37	40.0
18.	36	-	Y	S	75	75	14.3
19.	41	-	-	S[1]	75	75	5.8
20.	30	-	Y	I[1]	825	75	2.5
Male Controls							
21.	47	-	-	I	96	48	42.5
22.	48	Y	Y	S	150	75	55.0
23.	37	-	Y	I	50	12	38.5
24	47	-	-	S	225	75	23.8
25	34	-	-	I[1]	120	40	4.0
26	48	Y	Y	I	25	25	77.5
27	30	-	-	I	300	75	28.0
28	32	-	-	S	75	75	70.2
29	36	-	-	S	525	75	6.2
30	33	-	-	S	75	75	38.1
31	28	-	Y	I	25	25	1.0
32	38	-	-	I	175	25	3.5
33	43	-	-	S	135	45	48.0

[1]First dose use.
[2]Appetite suppressant use.

APPENDIX A

HSP Participating Hospitals

Connecticut and Massachusetts	Cincinnati, Ohio/Northern Kentucky
Backus	Bethesda North
Baystate	Bethesda Oak
Bridgeport	Deaconess
Danbury	Good Samaritan
Gaylord	Our Lady of Mercy/Anderson
Greenwich	Our Lady of Mercy/Clermont
Griffin	Our Lady of Mercy/Fairfield
Hartford	Providence
Hospital for Special Care	St. Elizabeth/North
Lawrence Memorial	St. Elizabeth/South
Manchester	St. Francis/St. George
Middlesex	St. Luke/East
Mount Sinai	St. Luke/West
New Britain	The Christ
Norwalk	The Jewish
Rehabilitation Hospital of Conn.	U. Cincinnati, Medical Center
St. Francis	Veterans Adm.
St. Joseph	**Providence, Rhode Island**
St. Mary	Miriam
St. Raphael	Rhode Island
St. Vincent	**Houston, Texas**
Stamford	Hermann
Waterbury	
Yale-New Haven	

APPENDIX B

Case Subjects Excluded after Enrollment:
Overall and by Site

	Total	CT	OH	TX	RI
Case subjects enrolled	746	268	233	136	109
Less: Case subjects excluded after review	38	16	6	7	9
Ineligible events	32	13	4	6	9
No evidence for hemorrhage	19	7	2	3	7
Hemorrhage due to trauma	6	3	0	1	2
Venous thrombosis	4	2	1	1	0
Subdural hemorrhage	2	1	0	1	0
TPA induced bleed	1	0	1	0	0
Ineligible subjects	6	3	2	1	0
History of AVM or tumor	4	1	2	1	0
Event > 72 hrs. after admission	1	1	0	0	0
History of SAH	1	1	0	0	0
Equals: Eligible case subjects enrolled	708	252	227	129	100
Less: Other exclusions	6	3	1	1	1
Equals: Final case group	702	249	226	128	99

Legend: Appendix B displays the number of case subjects enrolled overall and by site (CT=Connecticut, OH=Cincinnati, Ohio, TX=Houston, Texas, RI=Providence, Rhode Island). Reasons for exclusions of enrolled case subject following validation review are listed. Six eligible and enrolled case subjects were excluded from the final case group for the following reasons: no matched controls identified (3 subjects), interview date for case subject was over 30 days from index date (2 subjects), and index date for stroke event was uncertain (1 subject).

APPENDIX C

PPA Exposures: Matched Format

		All Subjects			Women			Men		
		No. Controls Exposed			No. Controls Exposed			No. Controls Exposed		
Any PPA		0	1	2	0	1	2	0	1	2
Case:	Exposed	25	2	0	20	1	0	5	1	0
	Not exposed	646	27	2	344	17	1	302	10	1
Cough/cold remedy										
Case:	Exposed	21	1	0	16	0	0	5	1	0
	Not exposed	651	27	2	349	17	1	302	10	1
Appetite suppressant										
Case:	Exposed	6	0	0	6	0	0	0	0	0
	Not exposed	695	1	0	376	1	0	319	0	0

Legend: Appendix C displays the number of case/control sets overall and by gender according to the exposure status of the case subject and number of matched controls exposed to any PPA in the 3-day window and to PPA in cough/cold remedy and appetite suppressants. (Note: Except for 28 cases with one matched control, each case subject was matched to two control subjects. All 16 female and 12 male case-control pairs were concordant as not-exposed to any PPA and are included in the lower left entries in each table.)

APPENDIX D

Analyses Stratified by Gender: Phenylpropanolamine (PPA) Exposure and Risk of Hemorrhagic Stroke

WOMEN

	Cases (n=383)		Controls (n=750)		Unadjusted Matched	Adjusted Estimates[1]		
	No.	%	No.	%	OR	Matched OR	LCL[2]	p-value
No use[3]	355	92.7%	713	95.1%	--	--	--	--
Any PPA[4]	21	5.5%	20	2.7%	2.15 (p=.014)	1.98	1.12	.024
Cough/cold remedy	16	4.2%	19	2.5%	1.70 (p=.089)	1.54	0.85	.116
Appetite suppressant	6	1.6%	1	0.1%	12.19 (p=.006)	16.58	2.22	.011

MEN

	Cases (n=319)		Controls (n=626)		Unadjusted Matched	Adjusted Estimates[1]		
	No.	%	No.	%	OR	Matched OR	LCL[2]	p-value
No use[3]	309	96.9%	597	95.4%	--	--	--	--
Any PPA	6	1.9%	13	2.1%	0.90 (p=.529)	0.62	--	.203
Cough/cold remedy	6	1.9%	13	2.1%	0.90 (p=.529)	0.62	--	.203
Appetite suppressant	0	0.0%	0	0.0%	--	--	--	--

[1]Adjusted for smoking, hypertension, race and education.
[2]Lower limit of one-sided 95% confidence interval.
[3]No PPA use in 2-week period before focal time.
[4]One female case used PPA in both a cough/cold remedy and an appetite suppressant in 3-day window.

APPENDIX D, continued

Analyses Stratified by Gender: Recency of PPA Exposure and Risk of Hemorrhagic Stroke

WOMEN

	Cases (n=383)		Controls (n=750)		Unadjusted Matched OR	Adjusted Estimates[1] Matched OR	LCL[2]	p-value
	No.	%	No.	%				
No use[3]	355	92.7%	713	95.1%	--	--	--	--
Current use[4]	16	4.2%	16	2.1%	1.97 (p=.041)	1.67	0.91	.084
First use[5]	7	1.8%	4	0.5%	3.50 (p=.039)	3.13	1.05	.042
Not-first use	9	2.3%	12	1.6%	1.50 (p=.241)	1.24	0.59	.317
Prior use[6]	5	1.3%	4	0.5%	2.61 (p=.132)	3.82	1.05	.043

MEN

	Cases (n=319)		Controls (n=626)		Unadjusted Matched OR	Adjusted Estimates[1] Matched OR	LCL[2]	p-value
	No.	%	No.	%				
No use[3]	309	96.9%	597	95.4%	--	--	--	--
Current use[4]	5	1.6%	5	0.8%	2.03 (p=.237)	1.26	0.34	.385
First use[5]	1	0.3%	1	0.2%	2.00 (p=.556)	2.95	0.24	.241
Not-first use	4	1.2%	4	0.6%	2.06 (p=.285)	0.95	--	.479
Prior use[6]	1	0.3%	8	1.3%	0.25 (p=.140)	0.25	--	.098

[1]Matched odds ratio adjusted for smoking, hypertension, race and education.
[2]Lower limit of one-sided 95% confidence interval.
[3]No PPA use in 2-week period before focal time.
[4]Use of any PPA-containing product on index date (ID) before focal time or preceding calendar day.
[5]Current use and no other uses in 2-week period before ID.
[6]Use of any PPA-containing product 2 or 3 calendar days prior to ID.

APPENDIX E

Analyses Stratified by Sentinel Symptoms: Phenylpropanolamine (PPA) Exposure and Risk of Hemorrhagic Stroke

NO SENTINEL SYMPTOMS

	Cases (n=548)		Controls (n=1075)		Unadjusted Matched	Adjusted Estimates[1] Matched		
	No.	%	No.	%	OR	OR	LCL[2]	p-value
No use[3]	519	94.7%	1022	95.1%	--	--	--	--
Any PPA[4]	20	3.6%	26	2.4%	1.55 (p=.104)	1.33	0.77	.194
Cough/cold remedy	17	3.1%	25	2.3%	1.35 (p=.221)	1.12	0.64	.371
Appetite suppressant	4	0.7%	1	0.1%	7.96 (p=.046)	12.10	1.39	.029

SENTINEL SYMPTOMS PRESENT OR UNCERTAIN

	Cases (n=154)		Controls (n=301)		Unadjusted Matched	Adjusted Estimates[1] Matched		
	No.	%	No.	%	OR	OR	LCL[2]	p-value
No use[3]	145	94.2%	288	95.7%	--	--	--	--
Any PPA	7	4.6%	7	2.3%	2.13 (p=.141)	2.19	0.80	.099
Cough/cold remedy	5	3.2%	7	2.3%	1.48 (p=.365)	1.71	0.58	.206
Appetite suppressant	2	1.3%	0	0.0%	4.83 (p=.111)	--	--	--

[1]Matched odds ratio adjusted for smoking, hypertension, race and education.
[2]Lower limit of one-sided 95% confidence interval.
[3]No PPA use in 2-week period before focal time.
[4]One case used PPA in both a cough/cold remedy and an appetite suppressant in 3-day window.

APPENDIX E, continued

Analyses Stratified by Sentinel Symptoms: Recency of PPA Exposure and Risk of Hemorrhagic Stroke

NO SENTINEL SYMPTOMS

	Cases (n=548)		Controls (n=1075)		Unadjusted	Adjusted Estimates[1]		
	No.	%	No.	%	Matched OR	Matched OR	LCL[2]	p-value
No use[3]	519	94.7%	1022	95.1%				
Current use[4]	17	3.1%	18	1.7%	1.85 (p=.054)	1.42	0.78	.169
First use[5]	6	1.1%	4	0.4%	3.00 (p=.077)	3.34	1.08	.040
Not-first use	11	2.1%	14	1.3%	1.55 (p=.196)	1.02	0.50	.479
Prior use[6]	3	0.6%	8	0.7%	0.76 (p=.481)	0.98	--	.489

SENTINEL SYMPTOMS PRESENT OR UNCERTAIN

	Cases (n=154)		Controls (n=301)		Unadjusted	Adjusted Estimates[1]		
	No.	%	No.	%	Matched OR	Matched OR	LCL[2]	p-value
No use[3]	145	94.2%	288	95.7%	--	--	--	--
Current use[4]	4	2.6%	3	1.0%	2.67 (p=.173)	2.95	0.76	.096
First use[5]	2	1.3%	1	0.3%	4.00 (p=.259)	2.70	0.34	.215
Not-first use	2	1.3%	2	0.7%	2.06 (p=.395)	3.17	0.53	.145
Prior use[6]	3	2.0%	4	1.3%	1.53 (p=.418)	1.51	0.36	.318

[1]Matched odds ratio adjusted for smoking, hypertension, race and education.
[2]Lower limit of one-sided 95% confidence interval.
[3]No PPA use in 2-week period before focal time.
[4]Use of any PPA-containing product on index date (ID) before focal time or preceding calendar day.
[5]Current use and no other uses in 2-week period before ID.
[6]Use of any PPA-containing product 2 or 3 calendar days prior to ID.

APPENDIX F

Analyses using Alternate Index Date: Phenylpropanolamine (PPA) Exposure and Risk of Hemorrhagic Stroke

	Cases (n=702)		Controls (n=1376)		Unadjusted Matched	Adjusted Estimates[1]		
	No.	%	No.	%	OR	Matched OR	LCL[2]	p-value
No use[3]	663	94.4%	1310	95.2%	--	--	--	--
Any PPA[4]	28	4.0%	33	2.4%	1.74 (p=.028)	1.57	0.98	.059
Cough/cold remedy	23	3.3%	32	2.3%	1.45 (p=.122)	1.31	0.80	.186
Appetite suppressant	6	0.8%	1	0.1%	12.01 (p=.007)	16.02	2.06	.013

Analyses using Alternate Index Date: Recency of PPA Exposure and Risk of Hemorrhagic Stroke

	Cases (n=702)		Controls (n=1376)		Unadjusted Matched	Adjusted Estimates[1]		
	No.	%	No.	%	OR	Matched OR	LCL[2]	p-value
No use[3]	663	94.4%	1310	95.2%	--	--	--	--
Current use[5]	22	3.1%	20	1.4%	2.18 (p=.010)	1.78	1.03	.042
First use[6]	9	1.3%	4	0.3%	4.50 (p=.009)	4.49	1.58	.009
Not-first use	13	1.8%	16	1.2%	1.62 (p=.141)	1.20	0.61	.326
Prior use[7]	6	0.8%	13	0.9%	0.94 (p=.558)	1.08	0.45	.444

[1]Adjusted for smoking, hypertension, race and education.
[2]Lower limit of one-sided 95% confidence interval.
[3]No PPA use in 2-week period before focal time.
[4]One female case used PPA in both a cough/cold remedy and an appetite suppressant in 3-day window.
[5]Use of any PPA-containing product on index date (ID) before focal time or preceding calendar day.
[6]Current use and no other uses in 2-week period before ID.
[7]Use of any PPA-containing product 2 or 3 calendar days prior to ID.

APPENDIX G

Gender and Age Distribution
of PPA-Exposed and Non-Exposed in the HSP

	Case Subjects				Control Subjects			
	Exposed		Not Exposed		Exposed		Not Exposed	
	No.	%	No.	%	No.	%	No.	%
Any PPA								
Women	21	78%	362	54%	20	61%	730	54%
Men	6	22%	313	46%	13	39%	613	46%
Age < 40	15	56%	281	42%	17	52%	575	43%
Age ≥ 40	12	44%	394	58%	16	48%	768	57%
Cough/cold remedy								
Women	16	73%	367	54%	19	59%	731	54%
Men	6	27%	313	46%	13	41%	613	46%
Age < 40	10	45%	286	42%	17	53%	575	43%
Age ≥ 40	12	55%	394	58%	15	47%	769	57%
Appetite suppressant								
Women	6	100%	377	54%	1	100%	749	54%
Men	0	0%	319	46%	0	0%	626	46%
Age < 40	5	83%	291	42%	0	0%	592	43%
Age ≥ 40	1	17%	405	58%	1	100%	783	57%

Legend: Appendix G displays the number and percentage of case and control subjects who were exposed and not-exposed to PPA (definite/probable uses) in the 3-day window by gender and age group. Data are displayed for any PPA-containing product and for PPA in cough/cold remedy and appetite suppressants.