

Final Report of The Hemorrhagic Stroke Project

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

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HSP Investigators

Brown University

Edward Feldmann Janet Lee Wilterdink

University of Cincinnati

Joseph P. Broderick Thomas Brott

University of Texas at Houston

Lewis B. Morgenstern

Yale University

Lawrence M. Brass Ralph I. Horwitz Walter N. Kernan
Catherine M. Viscoli

Background

- During 1979-1993, at least 18 published case reports described hemorrhagic stroke after phenylpropanolamine (PPA) use.
- Most involved young women taking PPA for appetite suppression, often as a first-ever dose. Some, however, involved cough-cold remedies.
- In 1992, manufacturers and the FDA joined to recommend the conduct of a study specifically designed to examine the association between PPA and risk for hemorrhagic stroke.

The Hemorrhagic Stroke Project: Specific Aims

- Among women, to estimate the association between hemorrhagic stroke and PPA
 - in appetite suppressants
 - as a first-time use (either as an appetite suppressant or cough/cold remedy)
- Among men and women, to estimate the association between hemorrhagic stroke and PPA
 - for any exposure (appetite suppressant or c/c remedy)
 - by type of exposure

Case-Control Design

- Hemorrhagic stroke is a rare event among persons <50 years of age, affecting less than 25/100,000 per year.
- To examine risk for hemorrhagic stroke among young PPA users, a prospective cohort study would be unfeasible because hemorrhagic stroke is rare and a clinical trial would be unsuitable because of logistic and ethical issues.
- A case-control design is preferred in circumstances where the outcome event is rare.

Case Recruitment

- Four Research Sites
 - Connecticut/Massachusetts (23 hospitals)
 - Ohio/Kentucky (17 hospitals)
 - Texas (1 hospital)
 - Rhode Island (2 hospitals)
- Active surveillance
 - Admission/discharge logs
 - On-site surveillance personnel

Case Eligibility

Inclusion Criteria:

- Men and women ages 18-49 years
- Primary subarachnoid or intracerebral hemorrhage
 - not related to trauma

Exclusion Criteria:

- Inability to participate in an interview within 30 days of stroke event
- History of brain lesion or stroke
- In hospital for over 3 days when stroke symptoms began

Control Subject Selection

- Eligibility
 - Men and women 18-49 years of age
 - No history of stroke
- Method
 - Random digit dialing
 - Matched to case subject for age, gender, telephone exchange, and race.

Ascertainment of Exposure Data

1. Definition of Focal Time

Date/time of day before which PPA exposures are counted.

2. Specification of Focal Time

Case Subjects:

The date and time of day that marked the onset of symptoms plausibly related to hemorrhagic stroke that caused the case subject to seek medical attention.

Control Subjects:

- Set within 7 days of the control subject interview date
- Matched to case subject for day of week and time of day

Ascertainment of Exposure Data (continued)

3. Interview Methods

- Structured interview
 - Trained interviewers
 - Calendar as a memory aid
- Subjects unaware of study hypothesis
- Subjects were asked to recall:
 - Cold symptoms in the two weeks before focal time and medications used to treat them
 - Other medications used in the two weeks
- Only PPA exposures rated “definite” or “probable” by subjects were counted

Sample Size Calculation

Based on:

- Aim to determine if PPA, as a first use, increases risk of hemorrhagic stroke within 24 hours among women 18-49
- Estimate that 0.502% of controls would be exposed to PPA within 24 hours of focal time
- One tailed test of significance at 0.05 level
- 80% power to detect an odds ratio of 5.0

Result:

- 324 female case subjects and 648 control subjects, rounded to 350 & 700
- To study men, we added the same number of male case and control subjects

Statistical Analyses

- Compared case and control subjects on selected demographic, clinical, and pharmacological features
- Used logistic models to estimate both adjusted and unadjusted matched odds ratios
- Performed stratified analyses to look at PPA effects within groups defined by selected clinical features

Statistical Analyses (continued)

All logistic models included the following:

- Black race (matching was imperfect)
- History of hypertension
- Current cigarette smoking
- Other features that, when included in basic model, changed the odds ratio by 10%
 - Education was the only feature to meet this criterion

Assembly of Case Subjects

	<u>No.</u>
Eligible Case Subjects Identified	930
Not Enrolled	222
Not contacted within 30 days	182
MD or subject declined to participate	40
Enrolled	708
No control identified	3
Interviewed >30 days after stroke	2
Uncertain focal time	1
Final Case Group	702

Control Matching

	No.		No.
	Case Subjects	Matched to:	Control Subjects
	674	2 controls	1348
	28	1 control	28
TOTAL	702		1376

Quality of Control Matching (*n=1376 controls*)

Matched to case on:	No.	(%)
Gender	1376	(100)
Telephone exchange	1376	(100)
Age	1367	(99)
Race	1321	(96)

Selected Features of Case and Control Subjects

Feature	Cases (n=702)	Controls (n=1376)
Female	55%	55%
Age <40 years	42%	43%
Black race	21%	17%
Education <12th grade	20%	9 %
Current smoker	51 %	30 %
Hypertension	39%	20%
1° Family history	7%	4%
2+ ETOH drinks/day	14%	7%
Cocaine use	2%	0.1%
NSAIDS	16%	21%
Caffeine (in drugs)	7%	3%
Nicotine (in drugs)	1%	<1%

PPA and Risk for Hemorrhagic Stroke (Women)

PPA Use	Cases (n=383)	Controls (n=750)	Matched	
	% (No.)	% (No.)	Adj. OR	P
None	92.7 (355)	95.1 (713)	1.00	-
Any (3 days)	5.5 (21)	2.7 (20)	1.98	.024
Cough/cold remedy	4.2 (16)	2.5 (19)	1.54	.116
Appetite suppressant	1.6 (6)	0.1 (1)	16.58	.011
First*	1.8 (7)	0.5 (4)	3.13	.042

**All first use exposure involved cough/cold remedies*

PPA and Risk for Hemorrhagic Stroke (Men)

PPA Use	Cases (n=319)		Controls (n=626)		Matched Adj. OR	P
	%	(No.)	%	(No.)		
None	96.9	(309)	95.4	(597)	1.00	-
Any (3 days)	1.9	(6)	2.1	(13)	0.62	.203
Cough/cold remedy	1.9	(6)	2.1	(13)	0.62	.203
Appetite suppressant	0.0	(0)	0.0	(0)	-	-
First*	0.3	(1)	0.2	(1)	2.95	.241

**All first use involved cough/cold remedies*

PPA and Risk for Hemorrhagic Stroke (Men and Women)

PPA Use	Cases (n=702)		Controls (n=1386)		Matched Adj. OR	P
	%	(No.)	%	(No.)		
None	94.6	(664)	95.2	(1310)	1.00	-
Any (3 days)	3.8	(27)	2.4	(33)	1.49	.084
Cough/cold remedy	3.1	(22)	2.3	(32)	1.23	.245
Appetite suppressant	0.9	(6)	0.1	(1)	15.92	.013
First*	1.1	(8)	0.4	(5)	3.14	.029

**All first use involved cough/cold remedies*

Key Biases Considered in the Research Design & Analysis

- Confounding
- Selection
- Information
 - Temporal Precedence Bias
 - Ascertainment Bias
 - Recall Bias

Confounding Bias

Definition:

An extraneous variable, related to both PPA use and risk for hemorrhagic stroke, that wholly or partially accounts for the apparent effect of PPA on stroke risk

Safeguards in HSP:

- Matching cases and controls on age, gender, race, telephone exchange
- Adjustment for other potential confounding variables by modeling and stratification

Effect of Adjustment on the Matched Odds Ratio (Women)

PPA Use	Unadjusted	Adjusted*
	OR	OR
None	1.00	1.00
Any (3 days)	2.15	1.98
Cough/cold remedy	1.70	1.54
Appetite suppressant	12.19	16.58
First	3.50	3.13

**Adjusted for smoking, hypertension, race and education*

Stratified Analysis: Women Without HTN or Smoking

PPA Use	Cases (n=121)		Controls (n=438)		Unmatched Adj. OR*	P
	%	(No.)	%	(No.)		
None	90.1	(109)	96.8	(424)	1.00	-
Any (3 days)	7.4	(9)	1.4	(6)	5.61	<.001
Cough/cold remedy	5.8	(7)	1.1	(5)	5.04	.008
Appetite suppressant	1.6	(2)	0.2	(1)	8.16	.102
First	3.3	(4)	0.5	(2)	6.33	.038

**Exact method*

Selection Bias

Definition:

Selective referral to or loss from the study of case or control subjects based on PPA exposure

Safeguards in the HSP:

- Active surveillance for case subjects
- Enrollment of all eligible patients

Temporal Precedence Bias

A systematic error in which an exposure to PPA is counted although it occurs after the onset of the hemorrhagic stroke (and possibly in response to sentinel disease symptoms).

Sentinel Symptoms

Definition:

Transient headache hours or days before the onset of symptoms that lead a patient to seek medical attention. That headache, rather than when attention is sought, may mark the onset of hemorrhage.

Implications for the HSP:

Patient may be classified as exposed to PPA when the medication was actually taken after the first occurrence of hemorrhage.

Safeguards in HSP:

Planned analyses using alternate focal time (onset of sentinel symptoms) and excluding persons with sentinel symptoms

Odds Ratios by Sentinel Status of Case Subject

	Matched Adjusted OR	
	No Sentinel Sx (n=548)	Sentinel Sx (n=154)
Any PPA	1.33	2.19
Cough/Cold	1.12	1.71
Appetite Suppressant	12.10*	-†
First Use	3.34*	2.70

*p≤0.04

†2 cases and 0 controls exposed

Ascertainment Bias

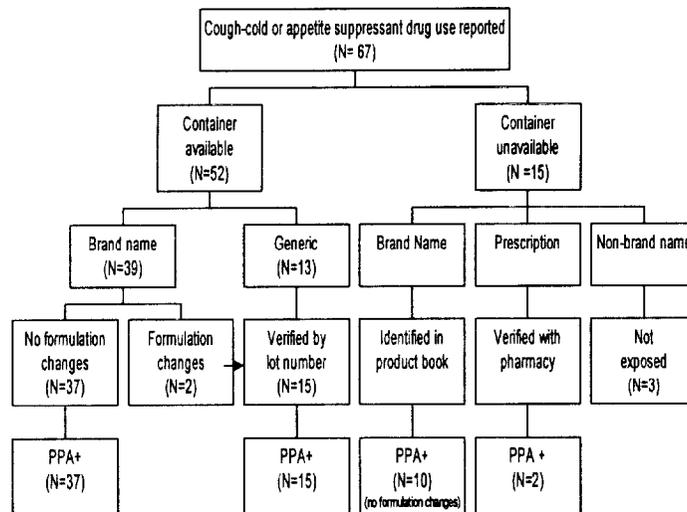
Definition:

Unequal ascertainment of exposures in case and control subjects

Safeguards in the HSP:

- Structured interview
- Blinding of subjects to study hypothesis
- Standard exposure verification procedures

VERIFICATION OF PPA EXPOSURES



Recall Bias

Definition:

The tendency of case subjects, compared with control subjects, to have more or less accurate recall of exposures

Safeguards in the HSP:

- Structured interview
 - Including specific questions on use of appetite suppressants, URI symptoms and use of medications for those symptoms
- Short interval between focal time and interview date
 - ≤ 30 days for case subjects
 - ≤ 7 days for control subjects

Potential Explanations for Different Findings for Cough/Cold Remedies and Appetite Suppressants

- Biology (susceptibility of PPA users)
- Bias or chance
- Dosage

Dosage

Exposure Type	Cases	PPA Dose in 24 hours Before Focal Time	
	N	mean	(range)
Appetite Suppressants	3	250 mg	(150-300)
Cough/Cold Remedies	18	161 mg	(20-730)

Dose Response For Any PPA Use and Risk for Hemorrhagic Stroke

Dose of PPA In 24 Hours Before Focal Time	Adjusted Matched Odds Ratio	P value
>75 mg	2.17	0.084
≤75 mg	1.16	0.397

Summary of Main Findings

Among women:

- Use of PPA in appetite suppressants within 3 days was associated with increased risk for hemorrhagic stroke.
- First use of PPA was associated with increased risk for hemorrhagic stroke.
- Since all first uses involved cough/cold remedies, increased risk was found for both formulations of PPA.

Among men:

- There were no exposures to PPA in appetite suppressants.
- There were too few exposures to PPA in cough/cold remedies and for first use to conclude that risk for hemorrhagic stroke is different from women.

Conclusions

- The results of the HSP suggest that PPA is an independent risk factor for hemorrhagic stroke.
- The data provide valid information for use in completing a contemporary assessment of the safety of PPA.