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Phenylpropanolamine and stroke: The study, the FDA ruling, the implications

ABSTRACT

Following a recent case-control study that linked the use of phenylpropanolamine (PPA) in diet aids to the risk of hemorrhagic stroke, the Food and Drug Administration requested that drug companies stop marketing products that contain PPA. Dozens of over-the-counter and prescription diet aids and cough and cold remedies will need to be reformulated or discontinued. This paper reviews the study and its implications for physicians.

KEY POINTS

Investigators in the Hemorrhagic Stroke Project interviewed patients who had recently suffered a hemorrhagic stroke and compared the prevalence of PPA use in this group with that in a group of control subjects matched for age and sex.

In women, the odds ratio for recent use of PPA in diet aids was 16.58 (95% CI 1.51–182.21, $P = .02$) for stroke patients compared with control subjects. No statistically significant relationship was found, however, between the use of PPA-containing cough and cold remedies and stroke in men or women, and no men in the study took PPA-containing diet aids.

Possible mechanisms of PPA-induced hemorrhagic stroke may be through hypertension, vasoconstriction, or both.

Physicians should counsel patients to avoid PPA-containing products and to look for alternatives.

PHENYLPROPANOLAMINE (PPA), a common ingredient in dozens of cough and cold remedies and diet aids, may cause hemorrhagic strokes in a small number of users, according to a recent study.[1,2] The risk is small: the investigators estimated that one of every 107,000 to 3,268,000 women who take a PPA-containing diet pill may have a PPA-induced stroke within 3 days, and no statistically significant risk could be established with cough and cold remedies or in men. Nevertheless, with billions of doses of PPA products being sold in the United States,[3,4] PPA might cause up to 500 cases of hemorrhagic stroke per year.

Acting on these data, the Food and Drug Administration (FDA) issued a warning to consumers to immediately stop taking PPA-containing products and asked that manufacturers voluntarily withdraw these products immediately and replace PPA with a safer alternative.

This paper reviews the study on which the FDA actions were based and the implications for physicians and patients.

WHAT IS PPA?

PPA, a sympathomimetic amine, relieves nasal congestion via vasoconstriction, binding to alpha-adrenergic and beta-adrenergic receptors and stimulating release of norepinephrine. It also suppresses the appetite control center in the hypothalamus, aiding in weight loss.

In the United States, PPA was commercially available as a combination of two racemic structures (d- and l-norephedrine).

Other stereoisomers or combinations may also be called phenylpropanolamine and are available in products marketed in other countries.

PPA was available a long time. First synthesized in 1910, it was initially introduced as a parenteral medication for maintenance of blood pressure.[3] In the 1930s it began to be widely used in oral formulations as a cold remedy, and in the 1940s its popularity grew as a diet aid. Until the FDA ruling, PPA was available in dozens of over-the-counter diet aids (TABLE 1), cough, cold, and allergy products, (TABLE 2), and prescription medications (TABLE 3).

STROKE RISK SUSPECTED

Adverse effects reported with the use of PPA include hypertension, dizziness, headache, agitation, psychosis, insomnia, cardiac arrhythmias, seizures, and hemorrhagic stroke.

Over the years a number of cases were reported in which patients suffered hemorrhagic stroke after taking PPA. In a review of the literature, Lake et al[5] listed 24 such cases reported up to 1990, and several more cases were reported since then.[6–8] Other cases of hemorrhagic stroke in PPA users have been reported to the FDA, but this type of spontaneous reporting cannot determine an association or frequency of events.

The exact mechanism by which PPA might cause hemorrhagic stroke is unknown. It may be due to acute hypertension or arteritis-like vascular changes characterized by "beading" (multiple areas of focal arterial stenosis or constriction) or both.[9]

In the early 1970s, the FDA established the Nonprescription Drugs Advisory Committee to evaluate the safety and efficacy of all over-the-counter medications. The committee's recommendations are published regularly in the Federal Register. Products are classified as one of the following:

- Category I (safe and effective)
- Category II (ineffective or unsafe, and their use is prohibited)
- Category III (the data are insufficient or conflicting, but use is allowed until publication of the final monograph).

In the late 1970s, the review board recommended that PPA be listed as a category I drug for use in nasal decongestants, and in the 1980s it recommended category I listing for PPA use in appetite suppressants, with limits on the maximum daily dose. However, owing to concern about adverse effects and risk of hemorrhagic stroke, the FDA never finalized the category I status of PPA.[10–12]

In an epidemiologic study of PPA and stroke published in 1984,[13] Jick et al concluded that if there was any risk, it was small. These investigators looked at patients from a group health organization, all younger than 65 years, who were identified from prescriptions filled for PPA-containing products from 1977

TABLE 1

Over-the-counter diet aids that contained phenylpropanolamine*

PRODUCT	STRENGTH OF PPA
Acutrim 16-hour Steady Control Timed-Release Tablets	75 mg
Acutrim Late Day	75 mg
Acutrim Maximum Strength Timed-Release Tablets	75 mg
AcuTrim Diet Gum	7.5 mg
Amfed T.D. Capsules	75 mg
Appedrine	25 mg
Control	75 mg
Dexatrim Caffeine Free Extended Duration Timed-Release Tablets	75 mg
Dexatrim Caffeine Free Maximum Strength Timed-Release Capsules	75 mg
Dexatrim Caffeine Free with Vitamin C Timed-Release Caplets	75 mg
Dieutrim T.D. Capsules	75 mg
Permathene-16 Maximum Strength	75 mg
Permathene-16 Plus Vitamin C	75 mg
Phenoxine	25 mg
Phenyldrine	75 mg
Protrim Caplets	37.5 mg
Protrim S.R. Caplets	75 mg
Spray-U-Thin	6.58 mg

PPA = phenylpropanolamine
*Many manufacturers are reformulating their products

ADAPTED FROM OLIN BR, EDITOR. NONPRESCRIPTION DIET AIDS. DRUG FACTS AND COMPARISONS. ST. LOUIS: FACTS & COMPARISONS, INC. 2000, AND DOERING PL. OVERWEIGHT AND OBESITY. IN: ALLEN LV, BERARDI RR, DESIMONE EM, EDS. HANDBOOK OF NONPRESCRIPTION DRUGS 12TH ED. 2000:476.

to 1981. They calculated that the relative risk for having a hemorrhagic stroke when taking PPA was 0.58 (95% CI 0.03–2.9)— ie, there was a non-statistically significant trend toward *fewer* strokes in PPA users than in nonusers.

This study probably was not large enough to detect a difference in stroke incidence between users and nonusers of PPA in prescription products, and it did not alleviate concerns about PPA. Both the FDA and the manufacturers of PPA-containing products recommended another study be conducted to evaluate the risk of hemorrhagic stroke from taking PPA. As a result of this recommendation, the Hemorrhagic Stroke Project was formed.

THE HEMORRHAGIC STROKE PROJECT

The Hemorrhagic Stroke Project[1,2] was a case-control study, which identified a group of stroke patients and compared them with a similar group of healthy people to see if there were statistically significant differences in the prevalence of PPA use between the two groups.

Inclusion criteria

Patients with symptomatic subarachnoid or intracerebral hemorrhage were recruited at 43 hospitals in the United States between December 1994 and July 1999. Subarachnoid hemorrhage was diagnosed on the basis of clinical symptoms and specific diagnostic information, and intracerebral hemorrhage was diagnosed by symptoms and a computed tomographic scan.

Female and male patients were eligible if they:

- Were between the ages of 18 and 49 years,
- Could undergo a complete interview,
- Did not have a history of a brain lesion, and
- Did not have a previous history of stroke.

Two control subjects, matched for age and sex, were identified for each patient within 30 days of the patient's stroke.

Why this particular mix? The main objective of the study was to evaluate the risk of hemorrhagic stroke in women 18 to 49 years of age. This age range was selected on the basis of demographic data from reported cases in the literature. In the review by Lake et al,[5] all but three of the strokes were in people within this age range, and about 66% of cases were in women. Other cases reported after this review[6,7] were in women ages 17 to 36. One reported case was in an infant.[8] Although only a few reported cases were in men, the investigators wanted to evaluate potential risk in both sexes.

Methods

Stroke patients and control subjects were asked during a structured interview whether they had any cold symptoms during the 2 weeks before the stroke (or the same 2 weeks for the matched control subjects), whether they had taken any medications to treat the cold, and whether they had taken any other medications during this period. They were also specifically asked about the use of particular medications or classes of medications. To verify information about medications, they were asked to show the package, if available, and to pick out the medications they took from a book containing photographs of packages.

Similarities and differences between the groups

The stroke patients (N = 702) and the matched control subjects (N = 1,376) did not differ significantly in age, sex, history of diabetes, use of oral contraceptives, or cold or influenza-like symptoms.

The stroke patients, however, had higher rates of risk factors for stroke such as hypertension, smoking, and family history of hemorrhagic stroke. Compared with the matched controls, more of the stroke patients were black, more had used cocaine on the day of the stroke or the preceding day, more used alcohol regularly, and more had used a product that contained nicotine or caffeine in the 3 days preceding the stroke. The stroke patients also had a lower average level of education, and fewer of them had used non-steroidal anti-inflammatory drugs in the 3-day window.

Only 6 women in the stroke group had taken a PPA diet aid

More women stroke patients took PPA diet aids

Of the 383 stroke patients who were women, 6 (1.8%) had taken a diet pill that contained PPA within the 3 days preceding their stroke, com-

TABLE 2

Over-the-counter cough and cold products that contained phenylpropanolamine*

PRODUCT	STRENGTH OF PPA
Allerest Maximum Strength 12 Hour Caplets	75 mg
Alka-Seltzer Cold Medicine	20 mg
Alka-Seltzer Plus Cold Tablets	24.08 mg
Alka-Seltzer Plus Cold & Cough	20 mg
Alka-Seltzer Plus Cold & Cough Medicine Effervescent Tablets	20 mg
Alka-Seltzer Plus Night-Time Cold	20 mg
Anatuss Syrup	25 mg/5 mL
Antihist-D tablets, extended release	75 mg
A.R.M.	25 mg
BC Cold-Sinus Powder	25 mg
BC Cold-Sinus-Allergy Powder	25 mg
Bromaline Elixir	12.5 mg/5 mL
Bromanate Elixir	12.5 mg/5 mL
Bromatapp	75 mg
Children's Allerest	9.4 mg
Cheracol Plus Liquid	8.3 mg/5 mL
Chlor-Rest	18.7 mg
Chlor-Trimeton Allergy-Sinus	12.5 mg
Cold & Allergy Elixir	12.5 mg/5 mL
Cold & Allergy DM	12.5 mg/5 mL
Cold-Gest Cold Capsules	75 mg
Cold Relief	12.5 mg
Coldloc Elixir	20 mg/5 mL
Comtrex Liqui-Gels	12.5 mg
Comtrex Maximum Strength Cold & Flu Relief Non-Drowsy Liqui-Gels	12.5 mg
Comtrex Maximum Strength Cold/Flu Relief Liqui-Gels	12.5 mg
Comtrex Max Strength Multi-Symptom Cold & Flu Relief Liqui-Gels	12.5 mg
Conex Syrup	12.5 mg/5 mL
Congestant D	12.5 mg
Contac Maximum Strength 12 Hour Caplet	75 mg
Contac Severe Cold & Flu Maximum Strength Caplets	12.5 mg
Contuss Liquid	20 mg/5 mL
Coricidin D	12.5 mg
Coricidin Maximum Strength Sinus Headache	12.5 mg
Covangesic	12.5 mg
Dapacin Cold	12.5 mg
Demazin Syrup	12.5 mg/5 mL
Demazin Tablets	25 mg
Diamaphen Elixir	12.5 mg/5 mL
Diamaphen Release	75 mg
Diamaphen Tablets	25 mg
Dimetapp 4-Hour Liqui-Gels	25 mg
Dimetapp Cold & Allergy Chewable Tablets	6.25 mg
Dimetapp Cold & Flu	12.5 mg
Dimetapp Cold & Cough Maximum Strength Liqui-Gels	25 mg
Dimetapp DM Elixir	12.5 mg/5 mL
Dimetapp Elixir	12.5 mg/5 mL
Dimetapp Extentabs	75 mg
Dimetapp Tablets	25 mg
Duadacin	12.5 mg
Entac	20 mg/5 mL
Entex Liquid	20 mg/5 mL
Gelpirin-CCF	12.5 mg
Genamin Cold Syrup	6.25 mg/5 mL
Genamin Expectorant Liquid	12.5 mg/5 mL
Genatap Elixir	12.5 mg/5 mL
Gencold	75 mg
GuiaCough CF Liquid	12.5 mg/5 mL
Guaifenex Liquid	20 mg/5 mL
Guiatuss CF Liquid	12.5 mg/5 mL
Histosal	20 mg
Ipsatol Cough Formula Liquid for Children and Adults	9 mg/5 mL
Kophane Cough & Cold Formula Liquid	12.5 mg/5 mL
Maximum Strength Cold & Allergy 4-Hour Liquid Gelcaps	25 mg
Maximum Strength Comtrex Liqui-Gels	12.5 mg
Myminic Expectorant Liquid	12.5 mg/5 mL
Myminicol Liquid	12.5 mg/5 mL
Naldecon DX Adult Liquid	12.5 mg/5 mL

PRODUCT	STRENGTH OF PPA
Naldecon DX Children's Syrup	6.25 mg/5 mL
Naldecon DX Pediatric Drops	6.25 mg/1 mL
Naldecon EX Children's Syrup	6.25 mg/5 mL
Naldecon EX Pediatric Drops	6.25 mg/1 mL
Nadelate DX Adult Liquid	12.5 mg/5 mL
Night-Time Effervescent Cold Tablets	15 mg
Orthoxicol Cough Syrup	8.3 mg/5 mL
Pedicon DX Pediatric Drops	6.25 mg/1 mL
Pediacon DX Children's Syrup	6.25mg/5 mL
Pediacon EX Pediatric Drops	6.25 mg/1 mL
Pediatuss D.E. Drops	6.25 mg/1 mL
Pediatuss Liquid	12.5 mg/5 mL
Phenadex Children's Cough/Cold Drops	6.25 mg/1 mL
Phenadex Pediatric Cough and Cold Drops	6.25 mg/1 mL
Pyrroxate Caplet	25 mg
Rescon Liquid	12.5 mg/5 mL
Rhinocaps	20 mg
Robafen CF Liquid	12.5 mg/5 mL
Robatussin-CF Liquid	12.5 mg/5 mL
Saleto-CF	12.5 mg
Saleto-D	18 mg
Silactin Expectorant	6.25 mg/5 mL
Silactin Syrup	12.5 mg/5 mL
Silaminic Expectorant Liquid	12.5 mg/5 mL
Sildicon-E Pediatric Drops	6.25 mg/1 mL
Siltapp with Dextromethorphan HBr Cold & Cough Elixir	12.5 mg/5 mL
Siltussin-CF Liquid	12.5 mg/5 mL
Sil-Tex Liquid	20 mg/5 mL
Sinapils	12.5 mg
Sinulin	25 mg
Snaplets-DM Granules	6.25 mg
Snalplets-EX Granules	6.25 mg
Snaplets-Multi Granules	6.25 mg
Spec-T Sore Throat/Decongestant Lozenges	10.5 mg
Statuss Expectorant Liquid	12.5 mg/5 mL
St. Joseph Cold Tablets for Children	3.125 mg
Tavist D	75 mg
Teldrin 12-Hour Allergy Relief Capsules	75 mg
Temazin Cold Syrup	12.5 mg/5 mL
Threamine DM Syrup	12.5 mg/5 mL
Thera-Hist Syrup	12.5 mg/5 mL
Triactin	6.25 mg/5 mL
Triactin Syrup	6.25 mg/5 mL
Triaminic-12	75 mg
Triaminic Allergy	25 mg
Triaminic Chewable Tablets	6.25 mg
Triaminic Cold	12.5 mg
Triaminic DM Cough Relief Syrup	6.25 mg/5 mL
Triaminic Expectorant, Chest & Head Congestion Liquid	6.25mg/5 mL
Triaminic Expectorant Liquid	6.25 mg/5 mL
Triaminic Syrup	6.25 mg/5 mL
Triaminic Syrup Cold & Allergy	6.25 mg/5 mL
Triaminicin Cold, Allergy, Sinus Tablets	25 mg
Triaminicol Multi-Symptom Cough and Cold	12.5 mg
Triaminicol Multi-Symptom Cough and Cold Liquid	12.5 mg/5 mL
Triaminicol Multi-Symptom Relief Colds with Coughs Liquid	6.25 mg/5 mL
Tricodene Forte Liquid	12.5 mg/5 mL
Tricodene NN Liquid	12.5 mg/5 mL
Tricodene Pediatric Cough & Cold Liquid	12.5 mg/5 mL
Triminol Cough Syrup	12.5 mg/5 mL
Tri-Nefrin Extra Strength	25 mg
Triphenyl Expectorant Liquid	12.5 mg/5 mL
Triphenyl Syrup	6.25 mg/5 mL
Tussin CF Liquid	12.5 mg/5 mL
Vicks DayQuil Allergy Relief 4-Hour Tablets	25 mg
Vicks DayQuil Allergy Relief 12 Hour Tablets	75 mg
Vicks DayQuil Sinus Pressure & Congestion Relief Caplets	25 mg

PPA = phenylpropanolamine
*Many manufacturers are reformulating their products

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TABLE 3

Prescription products that contained phenylpropanolamine*

PRODUCT	STRENGTH OF PPA	PRODUCT	STRENGTH OF PPA
Alumadrine	25 mg	Guiatex	45 mg
Ami-Tex LA	75 mg	Guiatex LA	75 mg
Anatuss	25 mg	Guiatex Liquid	20 mg/5 mL
Aquatab C	75 mg	Histade	75 mg
Aquatab D	75 mg	Histalet Forte	50 mg
Atrohist Plus	50 mg	Hista-Vadrin	40 mg
Bromanate DC Cough Syrup	12.5 mg/5 mL	Histex HC Syrup	6 mg/5 mL
Bromphen DC w/ Codeine Cough Syrup	12.5 mg/5 mL	Histine DM Syrup	12.5 mg/5 mL
Bromphen/DM/PPA Syrup	12.5 mg/5 mL	Hycomine Pediatric Syrup	12.5 mg/5 mL
Bromphen T.D.	15 mg	Hycomine Syrup	25 mg/5 mL
Brompheniramine DC	12.5 mg/5 mL	Hydrocodone PA Pediatric Syrup	12.5 mg/5 mL
Codamine Pediatric Syrup	12.5 mg/5 mL	Hydrocodone PA Syrup	25 mg/5 mL
Codamine Syrup	25 mg/5 mL	Iohist Elixir	12.5 mg/5 mL
Codegest Expectorant Liquid	12.5 mg/5 mL	Iohist DM Syrup	12.5 mg/5 mL
Coldloc-LA	75 mg	Liqui-Histine-D Elixir	12.5 mg/5 mL
Conex with Codeine Syrup	12.5 mg/5 mL	Liqui-Histine DM Syrup	12.5 mg/5 mL
Cophene-X	10 mg	Myphetane DC Cough Syrup	12.5 mg/5 mL
Deconhist L.A.	50 mg	Naldecon	40 mg
Dimetane-DC Cough Syrup	12.5 mg/5 mL	Naldecon CX Adult Liquid	12.5 mg/5 mL
Drize	75 mg	Naldelate Pediatric Syrup	5 mg/5 mL
Dura-Gest	45 mg	Naldelate Syrup	20 mg/5 mL
Dura-Vent	75 mg	Nalgest	40 mg
Dura-Vent/A	75 mg	Nalgest Pediatric Drops	5 mg/1 mL
Enomine	45 mg	Nalgest Pediatric Syrup	5 mg/5 mL
Endal Expectorant Syrup	12.5 mg/5 mL	Nalgest Syrup	20 mg/5 mL
Entex	45 mg	Naldecon Pediatric Drops	5 mg/1 mL
Entex LA	75 mg	Naldecon Pediatric Syrup	5 mg/5 mL
Exgest LA	75 mg	Naldecon Syrup	20 mg/5 mL
Guaifenex PPA 75	75 mg	Nolamine	50 mg
Guaipax	75 mg	Norel Plus	25 mg

pared with 1 (0.1%) of the 750 control subjects who were women. After adjusting for the higher prevalence of risk factors for stroke (smoking, hypertension, black race, and lower education) among the stroke patients, the investigators calculated the odds ratio for having taken a PPA diet pill among women stroke patients at 16.58 (95% CI 1.51–182.21; $P = .02$).

What is an odds ratio? An odds ratio is the ratio of the odds of an event occurring in one group to the odds of the event in another group. This differs somewhat from the more commonly used relative risk, which is the ratio of the percentages of people in each group who had the event. Without adjustment, the odds ratio in this study would be: (6 women stroke patients taking PPA / 377 women stroke patients not taking PPA) / (91 women control subjects taking PPA / 749 women control subjects not taking PPA) = approximately 12. An odds ratio of 1, like a relative risk of 1, would indicate no difference between the groups.

The association was only in women, and only with diet aids. None of the men in the study had taken a PPA-containing diet pill—not one. For women who used PPA-containing cough or cold remedies, the odds ratio was only 1.54, which was not statistically significant. For men who had taken a PPA-containing cough or cold remedy the odds ratio was

PRODUCT	STRENGTH OF PPA
Ordrine AT Extended-Release	75 mg
Ornade Spansules	75 mg
Pannaz	75 mg
Partuss LA	75 mg
Phanadex Cough Syrup	25 mg/5 mL
Phenahist-TRTablets	50 mg
Phenate	40 mg
Phenchlor S.H.A.	50 mg
Phenylfenesin LA	75 mg
Poly-Histine CS Syrup	12.5 mg/5 mL
Poly-Histine-D Capsules	50 mg
Poly-Histine-D Eixir	12.5 mg/5 mL
Poly-Histine-D Ped Caps	25 mg
Poly-Histine DM Syrup	12.5 mg/5 mL
Profen II	37.5 mg
Profen II DM	37.5 mg
Profen LA	75 mg
Resaid	75 mg
Rescap-D S.R.	75 mg
Rhinolar-EX	75 mg
Rolatuss with Hydrocodone Liquid	3.3 mg/5 mL
Ru-Tuss with Hydrocodone Liquid	3.3 mg/5 mL
Rymed-TR	75 mg
SINUvent	75 mg
S-T Forte Syrup	5 mg
Stahist	50 mg
Stamoist LA	75 mg
Statuss Espectorant Liquid	12.5 mg/5 mL
Statuss Green Liquid	3.3 mg/5 mL
Tamine S.R.	15 mg
T-Koff Liquid	20 mg/5 mL
Triaminic Expectorant with Codeine Liquid	12.5 mg/5 mL
Triaminic Expectorant DH Liquid	12.5 mg/5 mL
Trihist-CS Syrup	12.5 mg/5 mL
Trihist-DM	12.5 mg/5 mL
TRINKOF-D	37.5 mg
Tri-Phen-Chlor	40 mg
Tri-Phen-Chlor Pediatric Drops	5 mg/1 mL
Tri-Phen-Chlor Pediatric Syrup	5 mg/5 mL
Tri-Phen-Chlor Syrup	20 mg/5 mL
Tri-Phen-Mine Pediatric Drops	5 mg/1 mL
Tri-Phen-Mine Pediatric Syrup	5 mg/5 mL
Tri-Phen-Mine S.R.	40 mg
Tusquelin Syrup	5 mg/5 mL
Tussanil DH	25 mg
Tuss-Allergine Modified T.D.	75 mg
Tussogest Extended Release	75 mg
Tuss-Ornade Liquid	12.5 mg/5 mL
Tuss-Ornade Spansules	75 mg
ULR-LA	75 mg
Uni-Decon	40 mg
Vanex Forte	50 mg
Vanex Forte-R	75 mg
Vetuss HC Syrup	3.3 mg/5 mL

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0.62, which was not statistically significant. TABLE 4 shows other analyses for PPA use in the two groups.

Extrapolating from these data, the investigators estimated that PPA might cause one hemorrhagic stroke in every 107,000 to 3,268,000 women within 3 days of taking a PPA-containing diet pill, which translates to about 200 to 500 hemorrhagic strokes each year in the United States.

Limitations of the study

Case-control studies in general cannot establish causation, they can only suggest an association. In particular, the Hemorrhagic Stroke Project had several limitations.

Potential bias. One limitation of the Hemorrhagic Stroke Project is the possible introduction of biases such as temporal-precedence bias, recall bias, and selection bias. The investigators attempted to minimize these biases in their study design, for example, by carefully structuring the interviews and by asking about all medication use within the preceding 2 weeks, not just 3 days.

Types of stroke included. The study included patients with stroke due to either intracerebral hemorrhage or subarachnoid hemorrhage. In a recent review, Leppälä et al[14] evaluated risk factors for different stroke

TABLE 4

The Hemorrhagic Stroke Study: Association between phenylpropanolamine use and hemorrhagic stroke

VARIABLE	STROKE PATIENTS	CONTROL SUBJECTS	ADJUSTED MATCHED ODDS RATIO* AND 95% CI	*P* VALUE
Women				
Number in analysis	383	750		
Used a PPA diet pill†	6 (1.6%)	1 (0.1%)	16.58 (1.51–182.21)	.01
Used a PPA cough or cold remedy	16 (4.2%)	19 (2.5%)	1.54 (0.76–3.14)	.23
Used any PPA product	21 (5.5%)	20 (2.7%)	1.98 (1.00–3.90)	.05
Used a PPA product for the first time‡	7 (1.8%)	4 (0.4%)	3.13 (0.86–11.46)	.08
Men				
Number in analysis	319	626		
Used a PPA-containing diet pill	0	0		
Used a PPA cough or cold remedy	6 (1.9%)	13 (2.1%)	0.62 (0.20–1.92)	.41
Used any PPA product	6 (1.9%)	13 (2.1%)	0.62 (0.20–1.92)	.41
Used a PPA product for the first time	1 (0.3%)	1 0.2%)	2.95 (0.15–59.59)	.48

*Adjusted for smoking, hypertension, race, and level of education
†Within 3 days preceding the onset of symptoms
‡Within 24 hours before the onset of symptoms, and had not used any other such products the preceding 2 weeks

ADAPTED FROM KERNAN WN. VISCOLI CM, BRASS LM, ET AL. PHENYLPROPANOLAMINE AND THE RISK OF HEMORRHAGIC STROKE. N ENGL J MED 2000; 343:1826–1832.

Many manufacturers are reformulating PPA-containing products

subtypes and demonstrated that the risk factor profiles for subarachnoid hemorrhage and intracerebral hemorrhage had little in common. These investigators suggest that studies not ignore stroke subtyping, in view of the risk of forming misleading associations. However, they did not specifically look at medication use as a risk factor in their evaluation, which was the focus of the Hemorrhagic Stroke Project.

Combination effect with caffeine. Combining medications can sometimes lead to an increase in adverse effects. A diet aid that contained the combination of PPA and caffeine was removed from the market in the 1980s because of unacceptable adverse drug reactions and abuse potential.[2,5]

In the Hemorrhagic Stroke Project, 7% of stroke patients reported ingesting caffeine, compared with 2.9% of the matched control subjects ($P < .01$). However, the amount or type of caffeine consumed was not reported. Although the odds ratio did not change after the investigators performed a basic conditional logistic model to account for reported caffeine use by study patients,[2] given the high coffee consumption in the United States, the combination effect of these two medications should not be ignored.

Combination effect with herbal products. Another potentially harmful combination not addressed in the study was herbal or natural products taken with PPA. Some of these products contain ephedrine-like substances that could possibly enhance the adverse effects of PPA when ingested concurrently. Examples of these include *Ma huang*, *Ephedra herba*, and *Ephedra sinensis*.

Does the PPA dose matter?

The Hemorrhagic Stroke Project showed a trend toward a dose-effect relationship: ie, there was a higher odds ratio in the people taking more than 75 mg per day than in those who took less than 75 mg per day. In contrast, Lake et al[5] reported that of the 24 reported cases of intracranial hemorrhage, 9 were in patients who took the recommended amount of PPA. The other 15 cases were in people who either overused or overdosed on PPA. The authors concluded from the case reports that a dose-response pattern was not evident from the data available.

Notably, most of the cases reported were not associated with use of cough and cold remedies in recommended doses. Cough and cold remedies generally contain less PPA than the diet aids; also unlike the diet aids, they are not typically formulated as sustained-release products. It is difficult, however, to make a strong conclusion from a series of case reports. A larger study powered to detect a difference in dosages of PPA and the risk of hemorrhagic stroke would be required.

IMPLICATIONS

Although the overall risk of PPA-induced hemorrhagic stroke is low (and not statistically significant for cough and cold products), the inability to predict who is at risk, along with the debilitating effects of stroke, produces serious concerns.

The FDA does not consider PPA to be safe for use in over-the-counter or prescription medications. The results of the Hemorrhagic Stroke Project prompted the FDA to:

- Recommend that manufacturers voluntarily discontinue marketing all over-the-counter and prescription medications containing PPA.
- Issue a public health advisory about the safety of PPA on October 6, 2000, indicating that over-the-counter medications containing PPA should not be recommended to patients for weight control or for symptomatic cold relief, and that prescription medications containing PPA should also be avoided.

TABLE 5

Cough and cold products with pseudoephedrine

Alka-Seltzer Plus Cold & Cough Medicine Liqui-Gels
Alka-Seltzer Plus Flu & Body Aches Liqui-Gels
Comtrex Day and Night Maximum Strength Cold and Flu Relief
Contac Non-Drowsy
Novahistine DH Liquid
PediaCare Cough-Cold Liquid
Pediacare Infants' Decongestant Plus Cough Drops
Robitussin Night-Time Cold Softgels
Robitussin PE Syrup
Robitussin Pediatric Night Relief Liquid
Robitussin Severe Congestion Liqui-Gels
Sudafed Severe Cold
TheraFlu Cold & Cough Medicine NightTime
TheraFlu Maximum Strenght Non-Drowsy Caplets
Triaminic AM Non-Drowsy Cough & Decongestant
Triaminic Sore Throat, Throat Pain & cough Liquid
Tylenol Cold Multi-Symptom
Tylenol Cold No Drowsiness
Tylenol Children's Cold Plus Cough Chewable
Vicks 44M Soothing Cough, Cold & Flu Relief
Vicks DayQuil Multi-Symptom Cold & Flu Relief LiquiCaps
Vicks DayQuil Multi-Symptom Cold & Flu Relief
Vicks NyQuil Children's Cold & Cough Relief
Vicks NyQuil Multi-Symptom Cold & Flu Relief Liquid

ADAPTED FROM OLIN BR, EDITOR. RESPIRATORY COMBINATION PRODUCTS. DRUG FACTS AND COMPARISONS. ST. LOUIS: FACTS & COMPARISONS, INC. 2000, AND TIETZE KJ. DISORDERS RELATED TO COLD AND ALLERGY. IN: ALLEN LV, BERARDI RR, DESIMONE EM, EDS. HANDBOOK OF NONPRESCRIPTION DRUGS 12TH ED. 2000:183–184.

Alternatives to PPA

Oral cough, cold, and allergy products containing pseudoephedrine (TABLE 5) or nasal decongestants such as oxymetazoline or phenylephrine are alternatives for patients seeking relief from symptoms. Caution still should be taken when recommending pseudoephedrine to patients with hypertension, hyperthyroidism, diabetes mellitus, coronary heart disease, ischemic heart disease, elevated intraocular pressure, or prostatic hypertrophy, because decongestants may exacerbate these diseases.[15] Although no studies have evaluated the occurrence of hemorrhagic stroke with the use of

pseudoephedrine, some suggest that PPA may not be the only alpha-adrenergic agonist that can cause serious adverse effects.[16] Sodium chloride nasal spray may benefit some patients without carrying the risk of serious side effects.

In view of the overwhelming number of over-the-counter products available, patients should ask their pharmacist for assistance in selecting a medication best suited for their symptoms. If your patients have questions about over-the-counter medications they have at home, suggest they bring them in the original packaging to one of their health care providers or pharmacist, since many manufacturers have or are in the process of reformulating PPA-containing products.

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