Postpartum Phenylpropanolamine-Induced Intracerebral Hemorrhage

Robert N. Walker, M.D., and John Carlson, M.D.

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Abbreviations: CT, computed tomography; PPA, phenylpropanolamine

Robert N. Walker, M.D. (Email: rnwalker@geisinger.edu), is in the Department of Radiology, Geisinger Medical Center, Danville, PA, United States of America.

John Carlson, M.D., is in the Department of Neurology, Geisinger Medical Center, Danville, PA, United States of America.

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Abstract

Phenylpropanolamine-induced vasculitis and related intracerebral hemorrhage has moved from the spotlight it occupied following its withdrawal from the market at the end of 2000 after the Food and Drug Administration ruled that it was not safe and effective, but the risk from medicines purchased prior to that time and still in the possession of the public can still pose a health hazard. We present the case of a patient who developed intracerebral hemorrhage following phenylpropanolamine ingestion post-partum 4 years following the recall, as well as her difficult recovery process. This case emphasizes the point that physicians should consider phenylpropanolamine when evaluating young females with few risk factors for stroke.

Introduction

Phenylpropanolamine (PPA) is a sympathomimetic amine that gained popularity as an over-the-counter cold remedy and diet aid. Related to amphetamines, pseudoephedrine, and ephedra, PPA, norpseudoephedrine, and other sympathomimetics have a long history of intracranial hemorrhage [1]. The mechanism behind this outcome has variously been described as necrotizing angiitis, vascular spasm, and hypertensive crisis [1,2]. PPA is not unique in causing adverse events; ephedra, phenylephrine, and pseudoephedrine have all been associated with hypertension, stroke, seizure, and death [3]. Although PPA was withdrawn from the United States market in December 2000 with much fanfare, after the Food and Drug Administration (FDA) ruled that it was neither safe nor effective (the European analog norpseudoephedrine was withdrawn in March 2000), many in the general public may be unaware that this recalled drug may remain in their medicine cabinet as expired medication, making the continued risk of intracerebral hemorrhage from PPA rare but still present. We present

here one case of PPA-induced hemorrhagic stroke that occurred several years after all such drugs were last sold to consumers in the United States.

Case Report

A 36-year-old woman with past medical history of migraine headaches and recent uncomplicated pregnancy and childbirth presented to our emergency department, one week post-partum, with complaint of excruciating headache. The remainder of her past medical history was benign, without evidence of hypertension prior to or during pregnancy. She did not have pre-eclampsia. Her recent pregnancy and delivery were uncomplicated. The current headache was described as different from her prior migraine headaches. She subsequently developed left arm paralysis and left leg weakness.

Her initial exam in the emergency department revealed left arm plegia, 3/5 muscle strength in the left leg, a right gaze preference, and left facial droop. Her presenting blood pressure was 136/88. A non-contrast head CT revealed acute right basal ganglia and right frontal hemorrhage with adjacent subarachnoid and intraventricular hemorrhage (Fig. 1). An urgent cerebral angiogram was negative for AVM or aneurysm, but showed luminal irregularities in vertebral arteries and middle cerebral arteries bilaterally, highly suggestive of vasculitis (Figs. 2-5). Venous run-off was completely normal (Fig. 6).

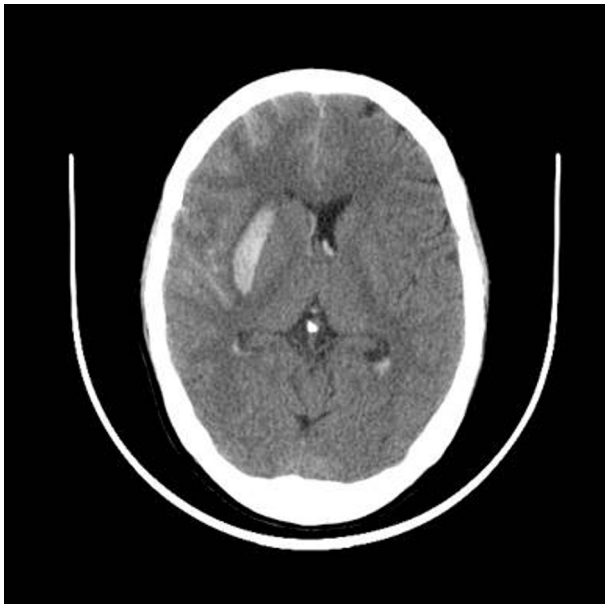

Figure 1. 36-year-old postpartum woman with phenylpropanolamine-induced intracerebral hemorrhage. Noncontrast CT scan shows acute intracerebral hemorrhage with adjacent subarachnoid and intraventricular hemorrhage.

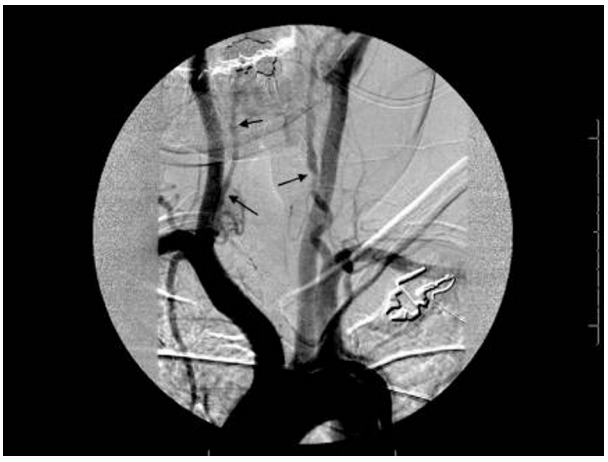

Figure 2. 36-year-old postpartum woman with phenylpropanolamine-induced intracerebral hemorrhage. Arteriogram, arch injection, LAO 30 degree projection, shows luminal irregularities of the vertebral arteries.

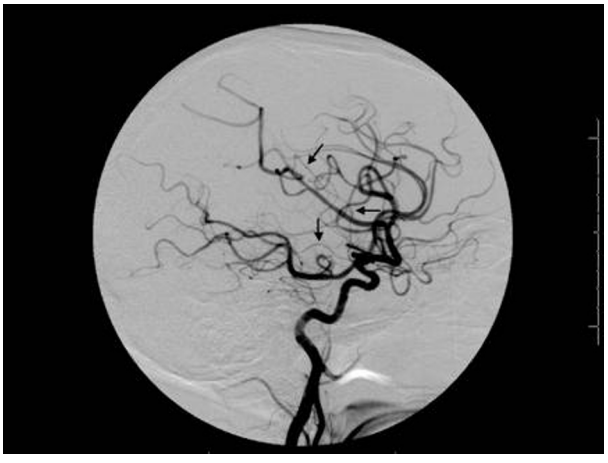

Figure 3. 36-year-old postpartum woman with phenylpropanolamine-induced intracerebral hemorrhage. Arteriogram, right internal carotid injection, LAO 90 degree projection, shows luminal irregularities in the right MCA branches

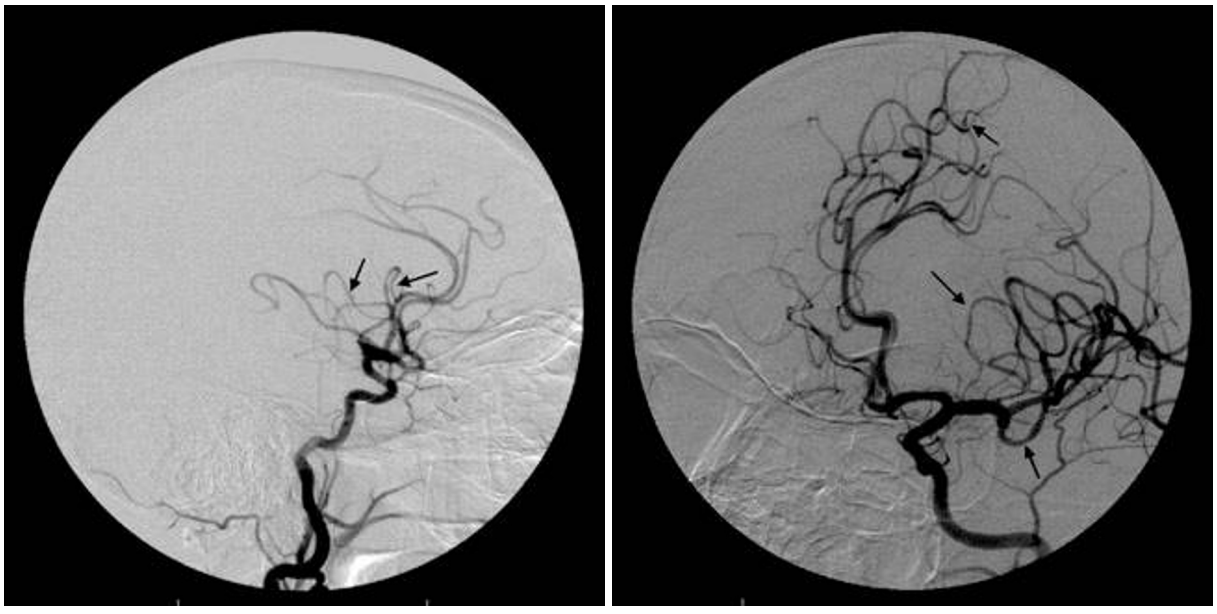

Figure 4A. 36-year-old postpartum woman with phenylpropanolamine-induced intracerebral hemorrhage. Arteriogram, left common carotid injection. **(A)** LAO 90 degree projection shows intracranial luminal irregularities. **(B)** LAO 24 degree projection shows luminal irregularities of the left anterior circulation.

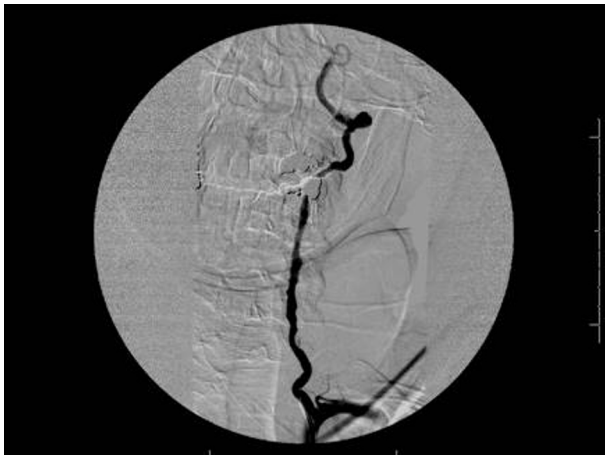

Figure 5. 36-year-old postpartum woman with phenylpropanolamine-induced intracerebral hemorrhage. Arteriogram, left vertebral injection, LAO 12 degree projection, shows multiple proximal luminal irregularities.

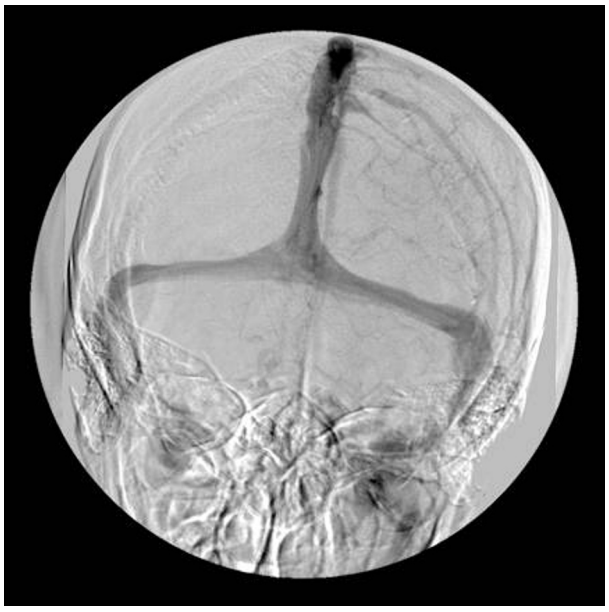

Figure 6. 36-year-old postpartum woman with phenylpropanolamine-induced intracerebral hemorrhage. Venous run-off from cerebral angiogram does not demonstrate filling defects.

The patient was admitted to the intensive care unit and treated with intravenous corticosteroids. Work-up included rheumatologic evaluation and drug screen. The drug screen was positive for PPA and pseudoephedrine; no other substances were identified. No other cause of vasculitis was found. The patient's husband confirmed that she had taken over-the-counter cold remedies following delivery, and that these included expired medications from pre-2000. The patient progressed well, and was discharged on a long steroid taper with mild left hemiparesis.

The patient was re-admitted two days later, and during that admission she was found to have dural sinus thrombosis. She was cautiously anticoagulated; her left arm hemiparesis rapidly improved, and she was discharged to rehabilitation with mild left hemiparesis. Following her course of rehabilitation, she did not have a noticeable residual deficit.

Discussion

PPA has a long history in the United States. First synthesized in 1910, it was used to support blood pressure. In the 1930's it gained popularity as a cold remedy and later as a diet aid [4]. During the FDA's review of OTC products in the 1970's, PPA was reviewed. In 1976 an expert panel recommended that PPA be recognized as effective and safe, although the FDA did not finalize this recommendation due to concerns regarding occasional reports of hemorrhagic stroke associated with PPA. In 1982, the recommendation of generally safe and effective was again made, this time in relation to its use as a diet aid, but was again not finalized [5]. Between 1979 and 1994 there were 30 reported cases of intracranial hemorrhage in the United States [6], although the actual number may be much higher due to under-reporting [7]. More recent investigations of phenylpropanolamine as a risk factor for intracerebral hemorrhage have confirmed earlier findings [8].

Spurred by these reports, in 1992 the FDA and PPA manufacturers collaborated to study the association between PPA and hemorrhagic stroke [3]. The Kernan study found that women age 18-49 who had taken PPA as a cold remedy had an increased odds ratio of 3.13 for intracranial hemorrhage. The findings of the study prompted the FDA to issue a public health warning regarding PPA and to ban both OTC and prescription products containing PPA [2]. Within hours pharmaceutical companies

had removed medications containing PPA from public availability [9]. The results of this report and subsequent FDA actions were widely reported in the popular press [10]. Although this has made PPA-induced intracranial hemorrhage more rare, cases continue to be reported [11]. These continued reports indicate that the efforts of the FDA and health-care industry have failed to eliminate the threat posed by PPA.

The mechanism of PPA-induced vasculitis is not clear, however PPA and similar sympathomimetics (such as methamphetamine and ephedrine) have been known to cause a characteristic beading pattern seen on angiography [12]. It is important, however, to evaluate for other causes of cerebral vasculitis; these are most commonly autoimmune in nature.

In young females with few risk factors, PPA must remain in the differential diagnosis for intracerebral hemorrhage; the remaining differential for post-partum hemorrhagic stroke with an angiographic appearance of vasculitis is short. Beyond autoimmune diseases, a rare process that can have an identical radiographic appearance is postpartum cerebral angiopathy. Postpartum cerebral angiopathy is a rare entity described as ischemic or hemorrhagic stroke within the early postpartum period. Clinical presentation can include headache, seizure, or focal neurologic deficit [13]. Cerebral angiography in postpartum cerebral angiopathy is also described as focal narrowing and ectasia of the intracranial vessels (as with PPA-induced vasculopathy) [14]. Postpartum cerebral angiopathy should be considered if other causes of vasculitis are excluded.

References

1. Cantu C, Arauz A, Murillo-Bonilla LM, López M, Barinagarrementeria F. Stroke associated with sympathomimetics contained in over-the-counter cough and cold drugs. Stroke. 2003;34:1667-1673. [PubMed]

2. Montalban J, Ibanez L, Rodriguez C, Lopez M, Sumalla J, Codina A. Cerebral infarction after excessive use of nasal decongestants. J Neurol Neurosurg Psychiatry. 1989;52:541-543. [PubMed]

3. Brust, JC. Editorial comment: over-the-counter cold remedies and stroke. Stroke. 2003;34:1673. [PubMed]

4. Mersfelder TL. Phenylpropanolamine and stroke: the study, the FDA ruling, the implications. Cleve Clin J Med. 2001;68:208-209, 213-219, 223. [PubMed]

5. Food and Drug Administration Science Background Safety of Phenylpropanolamine. Available at: http://www.fda.gov/cder/drug/infopage/ppa/science.htm. Last accessed 4 October, 2008.

6. Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. N Engl J Med. 2000;343:1826-1832. [PubMed]

7. La Grenade L, Graham DJ, Nourjah P. Underreporting of hemorrhagic stroke associated with phenylpropanolamine. JAMA. 2001;286:3081. [PubMed]

8. SoRelle R. Cardiovascular News. FDA warns of stroke risk associated with phenylpropanolamine; cold remedies and drugs removed from store shelves. Circulation. 2000;102:9041e-9043e. [PubMed]

9. Yoon BW, Bae HJ, Hong KS, et al. Phenylpropanolamine contained in cold remedies and risk of hemorrhagic stroke. Neurology. 2007;68:146-149. [PubMed]

10. Noonan D. An ingredient under fire: drugmakers are jittery after an FDA panel ruling. Newsweek. 2000;136:59. [PubMed]

11. Delorio NM. Cerebral infarcts in a pediatric patient secondary to phenylpropanolamine, a recalled medication. J Emerg Med. 2004;26:305-307. [PubMed]

12. Forman HP, Levin S, Stewart B, et al. Cerebral Vasculitis and Hemorrhage in an Adolescent Taking Diet Pills Containing Phenylpropanolamine: Case Report and Review of Literature. Pediatrics. 1989;83(5):737-741. [PubMed]

13. Konstantinopoulos PA, Mousa S, Khairallah R, et al. Postpartum cerebral angiopathy: An important diagnostic consideration in the postpartum period. Am J Obstet Gynecol. 2004;191(1):375-377. [PubMed]

1 4. Stella CL, Jodicke CD, How HY, et al. Postpartum headache: is your work-up complete? Am J Obstet Gynecol. 2007;196(4):318.e1-318.e7. [PubMed]
