Intracerebral Hemorrhage Associated with Oral Phenylephrine Use: A Case Report and Review of the Literature

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Background: Prior reports have linked both ischemic and hemorrhagic stroke to use of sympathomimetic drugs including phenylephrine. The purpose of this study is to describe the first case, to our knowledge of intracerebral hemorrhage (ICH) after oral use of phenylephrine and to systematically review the literature on phenylephrine and acute stroke. *Methods:* A case report and review of the literature. *Results:* A 59-year-old female presented with thunderclap headache, right hemiparesis, aphasia, and left gaze deviation. Head computed tomography (CT) showed a left frontal ICH with intraventricular and subarachnoid extension. She had no significant past medical history. For the previous 30 days, the patient was taking multiple common cold remedies containing phenylephrine to treat sinusitis. CT and magnetic resonance angiography showed no causative vascular abnormality. Catheter cerebral angiography supported reversible cerebral vasoconstriction syndrome (RCVS). Phenylephrine was determined to be the most likely etiology for her hemorrhage. A review of the literature, found 7 cases describing phenylephrine use with acute stroke occurrence: female, 5 of 7 (71%); route of administration, nasal (n = 3), ophthalmic (n = 2), intravenous (n = 1), intracorporeal injection (n = 1). Stroke types were subarachnoid hemorrhage (n = 5), ICH (n = 4), and ischemic (n = 1). One case reported RCVS after phenylephrine use. *Conclusions:* It is scientifically plausible that phenylephrine may cause strokes, consistent with the pharmacologic properties and adverse event profiles of similar amphetamine-like sympathomimetics. As RCVS has been well described in association with over-the-counter sympathomimetics, a likely, although not definitive, causal relationship between phenylephrine and ICH is proposed. **Key Words:** Hemorrhagic stroke—phenylephrine—reversible cerebral vasoconstriction syndrome—sympathomimetics.

Over the past 45 years, there have been a large number of case reports, case series, autopsies, and epidemiologic studies associating stroke and cerebrovascular disease with use of both illicit and over-the-counter (OTC) sympathomimetic drugs, including phenylephrine (PHE).[1,2]

Sympathomimetic drugs, such as PHE, are commonly used as a decongestant and are main components in OTC cold medications. The mechanism by which PHE and other sympathomimetic drugs used as decongestants produce their biologic effect is through activation of

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selected alpha-adrenergic receptors found on very small blood vessels of the nasal mucosa.[3] The receptors may be activated via direct binding of the sympathomimetic agents to the binding site of the receptor, or by enhanced release of norepinephrine, producing vasoconstriction.[3,4] When PHE and other alpha-adrenergic agonists are taken systemically in doses sufficient to constrict blood vessels in the nasal mucosa, they can also have similar effects on blood vessels in other parts of the body as well. Oral decongestants have been demonstrated to affect the cardiovascular, urinary, central nervous, and endocrine systems.[5] Both ischemic and hemorrhagic strokes have been reported, occurring from early childhood into the elderly and in both males and females.[1,6,7]

Prior reports have linked both ischemic and hemorrhagic stroke to parenteral, nasal spray, and topical ocular use of PHE. To our knowledge, we report the first case of intracerebral hemorrhage (ICH) occurring after oral administration of PHE.

Case Report

A 59-year-old female presented to her primary care physician complaining of a severe headache, which started the day before and progressively worsened. During the clinic visit, she developed right-sided hemiparesis, aphasia, and left gaze deviation. She was transferred to the emergency department where a noncontrast CT scan of the brain showed a left hemispheric ICH with intraventricular and subarachnoid extension (Fig 1). Her blood pressure on admission was 149/69 mm Hg and her oxygen saturation was 100% on room air. The results of blood counts, activated partial thromboplastin time (aPTT), prothrombin (PT), and international normalized ratio (INR), and serum electrolytes, were all normal, except for a potassium of 2.8 mmol/L. The patient had no significant past medical history, specifically, no hypertension, diabetes, smoking, or documented brain vascular malformations. For the previous 30 days, the patient was taking multiple oral OTC common cold remedies to treat chronic sinus headache. For 4 days leading up to her hospitalization she only took cold medications that contained PHE as its decongestant. Most of the cold medications also contained acetaminophen, dextromethorphan, and chlorpheniramine as active ingredients. She did report that she took an oral decongestant containing pseudoephedrine within 30 days of the stroke, but with very limited use. She reported that she never took more than the maximum recommended dose and usually used small doses when treating her sinusitis with oral decongestants. The patient was not taking any prescription medications on a regular basis. She had no history of alcohol or illicit drug abuse.

Initial CT and MR angiography showed no causative vascular abnormality. Catheter cerebral angiography suggested reversible cerebral vasoconstriction syndrome (RCVS) based on the finding of multiple subtle segmental areas of narrowing in distal arteries (Fig 2). Brain biopsy at the time of surgical evacuation of the ICH showed no cerebral amyloid angiopathy, vascular malformation, or vasculitis. Laboratory tests, including measurements of erythrocyte sedimentation rate and antinuclear antibodies, were normal. Follow-up CT angiograms were performed twice during her admission and were both normal, without vasospasm or narrowing, thus supporting the diagnosis of a transient vasculopathy.

Phenylephrine was determined to be the most likely etiology for her ICH given the close temporal relationship between ingestion and onset of symptoms. She was discharged 22 days after admission to a rehabilitation center with bowel and urinary incontinence, ataxia, right-sided weakness, and expressive aphasia. Her symptoms improved and she was discharged to home after 72 days. After 27 months, her symptoms continue to improve, but still maintains residual ataxia, right-sided weakness, and expressive aphasia.

Discussion

Published literature support a causal relationship between use of sympathomimetic drugs and the occurrence of both ischemic and hemorrhagic stroke.[1] Cases, such as this one, where there is a close temporal relationship between ingestion and onset of symptoms and where other probable etiologies are excluded, are particularly suggestive.

Oral decongestants including phenylpropanolamine and pseudoephedrine have been linked to anecdotal cases of stroke,[1] but there have been no prior reports of oral PHE associated with stroke.

In the absence of other possible etiologies and given the chronic and concurrent use of cold remedies all containing PHE, we propose that PHE was the cause of ICH in our case. Over-the-counter sympathomimetics are associated with RCVS.[8-11] Our case had angiographic evidence of RCVS further supporting the etiology of her ICH from PHE-induced RCVS.

Phenylephrine (Fig 3) has similar pharmacologic characteristics and side effects to other adrenaline-like sympathomimetics[4] and prior published case reports[1,12-17] and animal studies[18,19] suggest a relationship between administration—intravenous, intranasal, and topical—and occurrence of stroke.

Systematic Literature Review

We performed a review of the literature to identify cases of stroke attributed to PHE use. We performed a PUBMED search (current as of October 15, 2013), using the terms: "Reversible Cerebral Vasoconstrictive Syndrome," "Phenylephrine," "Sympathomimetics," and "Over-The-Counter Cold Medications" matched together