

Possible Association of Ischemic Stroke With Phentermine

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Background and Purpose: Some commonly used anorexiant, including methamphetamine and phenylpropanolamine, have been associated with stroke. Because phentermine is an anorexiant with a chemical structure similar to that of amphetamines, similar side effects might be expected.

Case Descriptions: Two patients using phentermine (one was also using phendimetrazine) developed ischemic cerebrovascular disease. One suffered a cerebral infarct with angiographic evidence of vasculopathy involving multiple vascular beds. The other patient developed headache and a hemisensory disturbance of 7 days' duration.

Conclusions: Phentermine, and possibly phendimetrazine, should be considered an anorexiant and sympathomimetic drug that can be associated with ischemic cerebrovascular disease. (*Stroke* 1993;24:310–313)

KEY WORDS • cerebrovascular disorders • phentermine • phendimetrazine

Commonly used anorexiant include methamphetamine, phenylpropanolamine, fenfluramine, phentermine, and phendimetrazine (Figure 1). These drugs have similar chemical structures, share pharmacological properties, are amphetamine-like sympathomimetics, and cause hypertension and vasoconstriction.¹ Strokes secondary to the use of amphetamines² and phenylpropanolamine^{3,4} are well documented. In some of these cases the mechanism of stroke seems to be vasculitis,⁵ with an illness identical to polyarteritis nodosa by clinical, angiographic, and histological criteria. Phenylpropanolamine has been associated with intracerebral hemorrhage and histologically proven cerebral vasculitis.⁶ Monkeys given amphetamines developed histological features of vasculitis.^{7,8} Two young women who used fenfluramine developed small cerebral, retinal, and cochlear infarcts.⁹ Cases involving young women with similar clinical and pathological findings have been previously reported; however, the pathogenesis of this rare syndrome is obscure, and in previous cases the patients were not noted to be users of anorexiant. Because phentermine and phendimetrazine are compounds similar to amphetamines and phenylpropanolamine, similar side effects might be expected. To our knowledge, there are no reported cases of stroke or vasculitis implicating phentermine or phendimetrazine. We now report two such possible cases.

Case Reports

Patient 1

A 41-year-old woman was admitted to another hospital because of acute upper abdominal pain, which resolved spontaneously after several days. Two days after her admission she developed her first tonic-clonic seizure. She was noted to be hypertensive and febrile, with leukocytosis, hypokalemia, and microscopic hematuria. Abdominal computed tomography revealed a splenic infarct. Over the next 2 weeks her hypertension and hypokalemia proved difficult to control, and she had several more seizures despite treatment with phenytoin. Her fever spontaneously resolved 2 weeks after admission, and she was transferred to our hospital. She had regularly ingested phentermine- and phendimetrazine-containing diet pills for 8 months, until 2 days before the onset of her symptoms. For many years she experienced attacks of migraine with visual auras. Both her parents had hypercholesterolemia, and her father had hypertension. She had been taking oral contraceptives for 14 years. Before quitting 2 years previously, she had smoked cigarettes for 20 years. She did not consume alcohol or abuse illicit drugs.

On admission to our hospital her blood pressure was 170/100 mm Hg, she was afebrile, and general and neurological examinations were unremarkable. Goldman visual field testing revealed no deficits. Westergren sedimentation rate was 60 mm/hr; hemoglobin, 12.5 g/dl; and white cell count, 8.6/mm³. Electrolyte concentration, serum creatinine concentration, and urinalysis were normal; 24-hour creatinine clearance was 58 ml/min; and 24-hour urinary protein concentration was 0.69 g/dl. VDRL serology for syphilis was negative; antinuclear antibody testing was negative; serum complement levels were normal; immune complexes were 130 µg/ml (normal level, 0–46 µg/ml); antithrombin III level was normal; levels of proteins C and S were normal; and IgG and IgM anticardiolipin antibodies

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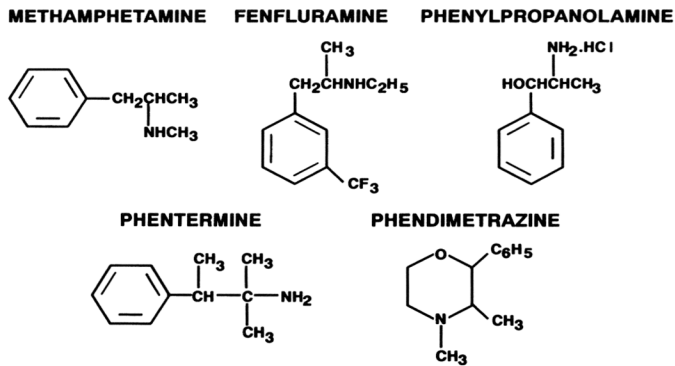


FIGURE 1. Chemical structures of methamphetamine, fenfluramine, phenylpropanolamine, phentermine, and phendimetrazine.

tests were negative. Thyroid stimulating hormone level was 12.9 $\mu\text{U/ml}$ (normal, 0.4–5.1 $\mu\text{U/ml}$); and other thyroid function tests were normal. Antimicrosomal antibody titer was high at 1:6,400. Total serum cholesterol was 354 mg/dl (normal, <200 mg/dl); triglycerides were 134 mg/dl (normal, 40–160 mg/dl); glucose concentration was normal; alkaline phosphatase level was 136 IU/l (normal, 0–120 IU/l); and other liver function tests were normal. Chest x-rays and electrocardiograms were normal. Transthoracic two-dimensional and M-mode echocardiography revealed mitral valve prolapse and left ventricular hypertrophy. Mammography

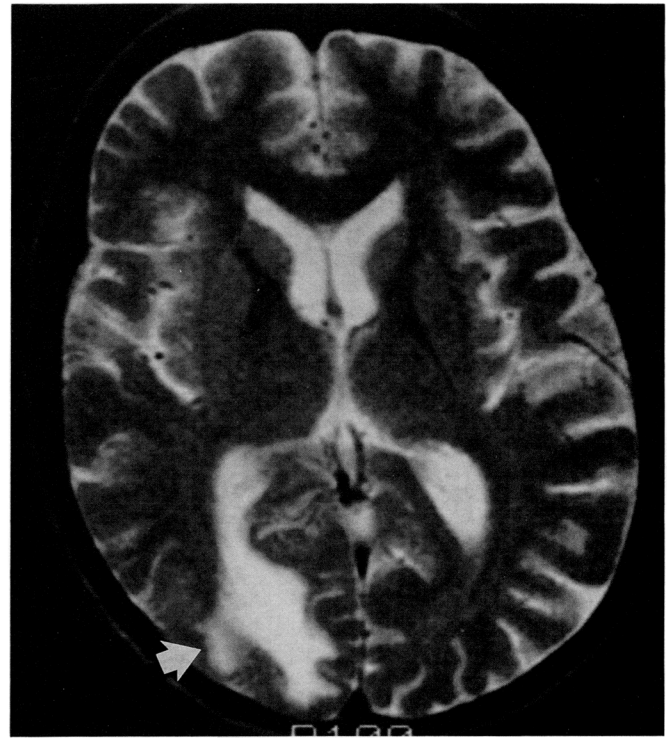


FIGURE 2. Cerebral T2-weighted magnetic resonance imaging scan (repetition time, 2,800 msec; echo time, 90 msec) showing a focal zone of abnormal high signal in the right occipital lobe white matter consistent with an ischemic infarct.



FIGURE 3. Conventional cerebral angiogram, left vertebral injection, showing two microaneurysms (arrowheads, left panel) in proximal vertebral artery and narrowing (arrows, left and right panels) in proximal basilar artery.

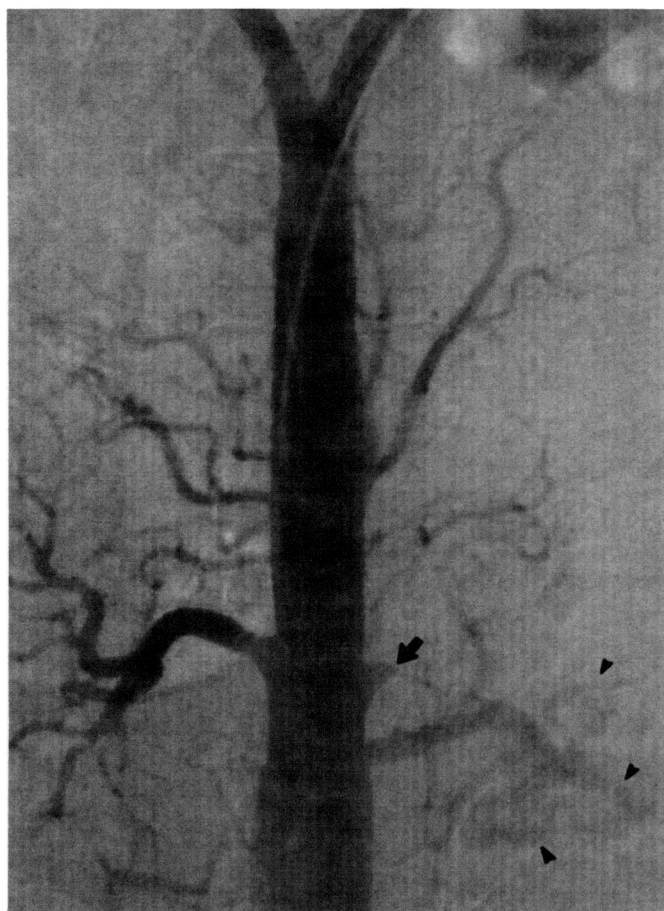


FIGURE 4. Visceral angiogram showing occlusion of the right renal artery (arrow) and right hepatic artery, with an associated tangle of vessels (arrowheads).

results were normal. Cerebral magnetic resonance imaging (MRI) revealed a right occipital infarct (Figure 2). Conventional cerebral angiography revealed two 3-mm aneurysms in the proximal left vertebral artery, 60% narrowing of the proximal basilar artery (Figure 3), and multiple marginal irregularities in both vertebral arteries. The cervical segments of both internal carotid arteries showed up to 40% narrowing, and there was a branch occlusion of the angular branch of the left middle cerebral artery. Visceral and celiac angiography revealed occlusions of the right renal artery, the splenic artery, and possibly the right hepatic artery (Figure 4).

A clinical, but not confirmed, diagnosis of vasculitis was made, and the patient was given corticosteroids (60 mg prednisone daily), phenytoin, phenobarbitone, thyroid replacement, potassium replacement, verapamil, and propranolol and placed on a low-cholesterol diet. Six weeks later she was readmitted in status epilepticus with hypokalemia; her phenytoin level was low. Over the next 3 years she remained well except for complaints of fatigue, and her sedimentation rate remained at approximately 30 mm/hr.

Patient 2

A 37-year-old woman developed subacute onset of severe left parieto-occipital headache 7 days before evaluation. At the onset of her headache she developed

left-sided face and arm numbness. When the patient was first seen, her headache had resolved; the numbness was still present but had almost disappeared. Four days previously, the numbness had spread to her left leg. For about 5 years she had mostly mild headaches intermittently, without other associated symptoms. She had recently commenced taking phentermine for weight reduction. She had not taken oral contraceptives for 8 years. She had never smoked or abused alcohol. Her twin sister, another sister, and her grandmother had a history of migraine, and her father had suffered a stroke.

Physical examination 7 days after the onset of symptoms was completely normal except for diminished pinprick sensation over the posterior left side of her head. Cerebral MRI was normal. Two-dimensional cardiac echocardiography was normal. Westergren sedimentation rate was 32 mm/hr; hemoglobin, white cell, and platelet counts were normal; IgG and IgM anticardiolipin antibodies tests were negative; and conventional four-vessel cerebral angiography was normal. She was advised to stop taking anorexiant. She was symptom free 6 weeks later.

Discussion

We propose that phentermine with or without the associated use of phendimetrazine may be associated with premature ischemic cerebrovascular disease. Both women were relatively young to have suffered stroke; their cerebrovascular disease was temporally related to the anorexiant, and they had no strokes after cessation of the agents. Our first patient's cerebral and visceral angiograms were similar to those of patients with known methamphetamine-related vasculitis. However, no pathological data were available. Several confounding variables in our first patient's clinical and angiographic findings cannot be excluded with certainty. Premature atherosclerosis may occur from cigarette smoking, hypertension, hypercholesterolemia, hypothyroidism, oral contraceptive use, and family history of vascular disease. However, her cerebral angiographic findings were highly atypical of atherosclerotic vertebrobasilar disease. Oral contraceptives can cause intimal hyperplasia in cerebral, portal, and systemic arteries and veins.^{10,11} Our patient, however, had several features that favored vasculitis or a direct immunologic/hypersensitivity reaction to the anorexiant: otherwise unexplained fever, leukocytosis, raised sedimentation rate and immune complexes, and microaneurysms, all of which are more consistent with vasculitis than with oral contraceptive-related injury. Oral contraceptives may cause diverse abnormalities on cerebral angiograms,¹² including a vasculitis-like appearance; however, we are not aware that they cause the other features suggesting vasculitis that our patient exhibited.

A very small, deep cerebral or brain stem infarct in the ascending sensory pathways is the most likely explanation for our second patient's signs and symptoms. She had never suffered a similar episode and, other than a paternal history of stroke, no known stroke risk factors were present.

A patient with intracerebral hemorrhage had used diet pills containing methamphetamine, dexamphetamine, methylphenidate, and phenmetrazine.¹³ Another patient,¹⁴ admitted with what was thought to be coma

secondary to a barbiturate overdose, was hemodialyzed to remove barbiturates; autopsy revealed an intracerebral hemorrhage and microscopic cerebral ischemic regions. She also had been taking large quantities of phendimetrazine. Neither of these cases was that of stroke due only to phendimetrazine; the latter case was reported as intracerebral hemorrhage due to hemodialysis, and phendimetrazine was not considered an etiologic factor. Inadvertent injection of phentermine into a brachial artery has been associated with vasospasm, ischemia, and severe hand pain.¹⁵

The two cases we have reported here raise the possibility that there may be an association between phentermine/phendimetrazine and stroke. These agents are structurally and pharmacologically similar to amphetamines, which are known to cause stroke and vasculitis; thus, there is biological plausibility for their association with stroke. Further study is needed to establish the exact relation between these agents and stroke.

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