Ischemic Stroke Associated with Cough and Cold Preparation Containing Methylephedrine and Supplement Containing Chinese Herbal Drugs

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Abstract

Methylephedrine is generally harmless and is contained in many cough and cold preparations. Likewise, Chinese herbal drugs are considered to be effective and to have few side effects. A 32-year-old woman experienced ischemic stroke attributed to concomitant administration of a cough and cold preparation containing methylephedrine and a supplement containing Chinese herbal drugs. Computed tomography and magnetic resonance imaging of the brain showed acute infarctions bilaterally in the cerebellum. Conventional angiography and magnetic resonance angiography showed transient stenosis of the left vertebral artery. These findings suggested vasospasm or dissection, presumably related to hypertension and/or angiitis or vasoconstriction of large cerebral arteries leading to local thrombosis as a result of stasis and sympathomimetic-induced platelet activation. Combining methylephedrine and Chinese herbal drugs might carry a risk of stroke.

Key words: cough and cold preparations, methylephedrine, Chinese herbal drugs, ischemic stroke


Introduction

In the past, sympathomimetics such as phenylpropanolamine and ephedrine have been common ingredients in cough and cold preparations (CCPs). Many reports have described hemorrhagic stroke following ingestion of sympathomimetics (1). A controlled trial revealed phenylpropanolamine as an independent risk factor for hemorrhagic stroke in women (2). Methylephedrine is a methylated derivative of ephedrine with a bronchodilatory β2 effect and fewer other effects than other ephedrine alkaloids (3). This substance is often contained in CCPs and no cases of cardiovascular or central nervous system adverse events have been reported with methylephedrine except for an abuse case (3).

Chinese herbal drugs (CHDs) are generally considered effective and to have few side effects. However, recent studies have highlighted potential harmful effects of some CHDs in the perioperative period (4, 5). We describe herein the case of a patient with ischemic stroke associated with a CCP containing methylephedrine and a supplement containing CHDs.

Case Report

A 32-year-old woman presented to the emergency department with nausea, dysarthria and ataxia of the left extremities. The patient woke with a feeling of numbness in the left extremities about 01:00 that day. She had noted pain in the left neck. These symptoms disappeared within 1 hour, and she went back to sleep. When she got up after 7 hour, she experienced nausea and dizziness. Dysarthria and ataxia of the left extremities appeared and left neck pain recurred in the afternoon.

She had no notable medical history, no history of neck trauma, and no major risk factors for atherosclerotic disease. Her father had a history of brainstem hemorrhage. For 6 months, she had been taking a supplement containing Chinese gutta percha (converted to crude drug: 750 mg) and panax ginseng (converted to crude drug: 250 mg) per 6 tablets (recommended daily dose). The patient had no history of smoking, alcohol or illicit drug intake.
For 3 days before presentation, the patient had taken a CCP at the recommended daily dose for a common cold. This preparation contained clemastine fumarate (1.34 mg), lysozyme chloride (as lysozyme, 90 mg), belladonna alkaloid (0.3 mg), acetylsalicylic acid (900 mg), dihydrocodeine phosphate (24 mg), noscapine (48 mg), methylephedrine hydrochloride (60 mg), caffeine (75 mg), and benfotiamine (24 mg) per 9 tablets (recommended daily dose). The patient denied taking any other medications or herbal preparations that week or in the recent past.

Initial vital signs were as follows: blood pressure, 111/68 mmHg; heart rate, 93 beats/min; respiratory rate, 12 breaths/min; and temperature, 36.9°C. Blood glucose level at triage was 137 mg/dL, and electrocardiography showed normal sinus rhythm. On physical examination, the patient appeared alert and was grossly oriented to person and place, but showed slurred speech. Ocular examination showed saccadic eye movements without nystagmus. No other dysfunctions were apparent in the territory of the cranial nerves. Muscle strength and reflexes including Babinski sign were normal and symmetrical throughout. Light touch, pain sense, temperature sensation and joint position sense were intact. Moderate ataxia of the left extremities was identified. She was right-hand dominant.

Computed tomography of the brain on admission showed acute infarctions bilaterally in the cerebellum (Fig. 1). Magnetic resonance imaging 13 days after admission demonstrated bilateral cerebellar infarctions in the territory of the superior cerebellar artery (SCA) (Fig. 2).

Findings from routine admission laboratory analyses, including a urine toxicology screen for commonly abused drugs, yielded unremarkable results. Erythrocyte sedimentation rate, hemoglobin A1c level, serum lipid profile, serum homocysteine level, coagulation studies (including thrombin time and fibrinogen), and thrombophilia panel (including antithrombin, proteins C and S, and lupus anticoagulant) were all normal.

The patient was initially treated with intravenous argatroban and edaravone, and received ventricular drainage due to obstructive hydrocephalus. She made a nearly complete clinical recovery with only mild ataxia and was discharged 31 days after admission.

Results from an extensive evaluation for ischemic stroke, including transthoracic and transesophageal echocardiography and carotid artery Doppler ultrasonography, showed no abnormalities. Conventional angiography 28 days after admission showed occlusion of the left SCA and stenosis of the left vertebral artery (VA) (Fig. 3). Magnetic resonance angiography also showed stenosis of the left VA 29 days after admission, but stenosis had disappeared by 87 days after admission (Fig. 4). These findings suggested vasospasm or dissection.

Discussion

Conventional angiography and magnetic resonance angiography in this case could be consistent with a diagnosis of ischemic stroke due to vasospasm or dissection. Strokes due to sympathomimetics are presumably related to hypertension and/or angiitis or vasoconstriction of large cerebral arteries leading to local thrombosis as a result of stasis and sympathomimetic-induced platelet activation (1, 6, 10). Previous reports of ischemic stroke associated with sympathomimetic drugs have shown normal findings for blood pressure and laboratory investigations (6). In this case, ischemic stroke occurred after taking recommended doses of methyle-
Figure 2. Magnetic resonance imaging. Axial (A) and sagittal (B) images using fluid-attenuated inversion recovery revealed infarctions in bilateral SCA territories.

Figure 3. Conventional angiography 28 days after admission, showing occlusion of the left SCA and stenosis of the left vertebral artery. A) Frontal view; B) lateral view.

Several sympathomimetics have been associated with ischemic stroke, including phenylpropanolamine (1), ephedra alkaloid (6, 7), and synephrine (8). However, methylephedrine is generally harmless when used at the recommended dose, and is contained in many over-the-counter CCPs. Indeed, no previous reports have described stroke associated with methylephedrine, with the exception of one abuse case (3). Methylephedrine thus seems unlikely as the sole cause of ischemic stroke. The patient had also been taking a supplement containing the CHDs Chinese gutta percha and panax ginseng for 6 months. Recent reports have highlighted the potential harmful effects of some herbal medicines in the perioperative period (4, 5). The most common adverse effects are impaired coagulation, cardiovascular side effects, electrolyte disturbances, and prolongation of the effects of anesthetic agents. Ginsenosides inhibit platelet aggregation in vitro and in laboratory rats, and prolong both coagulation time of thrombin and activated partial thromboplastin. Polenakovik reported a case of thalamic infarction in a healthy young adult during prolonged and excessive use of Siberian ginseng supplements (9). Polenakovik speculated that paradoxical vasoconstriction and hypercoagulability...
with long-term use might occur via the same mechanisms responsible for vasodilatation and inhibition of platelet aggregation when Siberian ginseng is used short-term. Combining methylephedrine and CHDs might cause vasoconstriction leading to local thrombosis due to stasis and sympathomimetic-induced platelet activation.

Sympathomimetics also cause ischemic stroke due to vertebral artery dissection. McDonald and Lane reported a case of right cerebellar infarction with occlusion of the right posterior cerebellar artery and bilateral VA dissections following the use of ephedrine alkaloid (7). They speculated that ephedrine alkaloid ingestion with resulting hypertension and subsequent vertebral artery dissection might have resulted in massive stroke, although blood pressure data were unavailable. In the present case, blood pressure was normal on admission, although transient hypertension might have caused left VA dissections.

The present case indicates the potential risk of ischemic stroke caused with CCPs containing methylephedrine and supplements containing CHDs. As CCPs and supplements are not generally regarded as being associated with stroke, this risk might be overlooked. Physicians should be encouraged to report suspected adverse events from these preparations and supplements. A detailed medication history, including over-the-counter CCPs and supplements, should always be obtained.

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**References**


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