For decades a number of sympathomimetic drugs have been marketed as over-the-counter diet pills, decongestants, or both. During the 1980s and 1990s one of these, phenylpropanolamine (PPA), accounted for an estimated 5 billion doses annually in the United States. In humans PPA produces arousal; unlike amphetamine it does not produce euphoria. It is a recognized street drug, however, sometimes misrepresented as amphetamine (“look-alike pills”), and by mail order it has been available as a “legal stimulant.”1

Complications of PPA include acute hypertension, psychosis, seizures, and stroke, especially hemorrhagic. More than 30 case reports describe intracerebral or subarachnoid hemorrhage following either recommended or excessive dosage. Proposed mechanisms include surges of hypertension, cerebral vasospasm (sometimes evident at angiography), and vasculitis (in one case evident at leptomeningeal biopsy).2 In 2000 Kernan and coworkers reported results of a multicenter case-control study addressing the association of PPA use and intracerebral or subarachnoid hemorrhage.3 Patients (n = 702) and controls (n = 1375) were 18 to 49 years of age. This study confirmed PPA as an independent risk factor for hemorrhagic stroke. The odds ratio was 16.58 (P = 0.02) for women using appetite suppressants containing PPA and 3.13 (P = 0.08) for women using cough or cold remedies containing PPA. For men there was no increased risk of hemorrhagic stroke in association with cough or cold remedies; no men reported use of appetite suppressants. The greater risk of appetite suppressants was attributed to higher dose, but strokes followed recommended as well as excessive doses, and with cough and cold remedies they were associated with first use. It was concluded on the basis of this study that PPA causes between 200 and 400 strokes annually in the United States.4 Later that year the FDA ordered products containing PPA to be withdrawn from the market.5

Ephedrine and pseudoephedrine, present in over-the-counter decongestants and bronchodilators, also have low abuse potential, yet dependence does occur.6 Complications include hypertensive crisis and psychosis. Ischemic and hemorrhagic strokes have occurred in ephedrine users, and intracranial hemorrhage has followed pseudoephedrine use.7,8 Ischemic and hemorrhagic strokes are also described in recreational users of “dietary supplements” containing ephedra alkaloids (“ma huang”).9 Case reports describe cerebral infarction and retinal artery branch occlusion in chronic intranasal abusers of sprays and drops containing phenoxyamine or oxymetazoline.10,11

Evidence that ephedrine, pseudoephedrine, or topical intranasal agents are stroke risk factors is thus anecdotal. Moreover, in contrast to its ban on PPA-containing diet remedies, the FDA’s ban on cough or cold remedies containing PPA was based on a trend that fell short of conventional statistical significance. More convincing data on the association of stroke and cough and cold remedies would thus be welcome. In this issue of Stroke, Cantu and coworkers describe 22 patients with stroke temporally associated with use of these products.12 Patients were culled from a consecutive stroke registry of 2500. Ten were men aged 17 to 57 years; 12 were women aged 17 to 78 years. Twelve were younger than 40 years old. Twenty-one strokes were hemorrhagic (17 intracerebral, 4 subarachnoid). Sixteen patients used PPA, 4 pseudoephedrine, and, by nasal route, 1 phenylephrine and 1 oxymetazoline. With PPA and pseudoephedrine, strokes followed both recommended and excessive doses and either single or daily use. Acute hypertension was present in 8 of the 22 patients. Cerebral angiography was normal in 8 and showed vasospasm or beading in 10.

These patients do suggest an association between sympathomimetic cold remedies and stroke. In fact, the number of drug-associated strokes was very likely underestimated by excluding patients with aneurysmal subarachnoid hemorrhage or vascular malformation. (Among patients with cocaine-associated intracranial hemorrhage, sacular aneurysms or vascular malformations were found in nearly half who were studied angiographically.13) The report by Cantu et al is anecdotal, however, for controls are conspicuously lacking.

On the basis of what was at stake, the FDA justifiably banned cough and cold remedies containing PPA despite a probability value of only 0.08. Unfortunately, the ban makes it impossible, at least in the United States, to conduct a study that would definitively confirm the FDA’s wisdom. It is not too late, however, to conduct a study assessing the risk of cold remedies containing other sympathomimetic agents. The report presented by Cantu et al suggests that such an endeavor might be fruitful.

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References


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