Intracranial Hemorrhages Due to Phenylpropanolamine

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SUMMARY We describe 2 patients with intracranial hemorrhage after ingestion of diet pills containing phenylpropanolamine (PPA) in combination with caffeine. The first patient had bilateral simultaneous intracerebral hemorrhages, and the second had a subarachnoid hemorrhage. PPA is widely used most often without prescription and causes intracranial hemorrhage more often than has been realized. The mechanism may be induction of a transient hypertensive crisis.

Caffeine is a sympathomimetic agent that is widely used in 3 types of preparations: decongestants (nonprescription or prescription), diet pills (nonprescription), and "look-alike" stimulants (distributed by mail-order and sold on the street as amphetamines). Adverse reactions include psychic changes, seizures, and hypertensive crises.1 The widespread use of caffeine needs no emphasis, and certain preparations from each of the above 3 categories of agents containing PPA contain caffeine as well. We now report 2 cases of intracranial hemorrhage that bring a number of important points to light.

Case Reports

Patient 1

This 56-year-old right-handed Japanese-American woman presented with acute onset of severe headache and vomiting, followed within one hour by right superior extremity weakness. The symptoms began at noon, and one hour prior to onset, the patient had taken 2 Thera-Trim diet pills, each pill containing PPA, 75 mg, and caffeine, 140 mg. These were the first 2 diet pills she had taken, verified by a pill count. Her past medical history was negative except for very rare mild headaches. She had no history of hypertension and used no other medications.

On physical examination, she was afebrile, with a blood pressure of 140/100 and a pulse of 80. She was in moderate distress due to throbbing bioccipital and bifrontal headache, and was slightly lethargic. She had no neck stiffness and no bruits over the neck, head, or orbits. She had moderate diffuse weakness of the right face and limbs. Visual fields, fundi, sensory examination, and the rest of the neurological examination were normal.

(CT) of the head (fig. 1) revealed bilateral independent left frontoparietal and right occipitoparietal intracerebral hemorrhages. They were small and of nearly identical size and attenuation characteristics. Each hemorrhage had a secondary component of subarachnoid hemorrhage, the left into the interhemispheric fissure, and the right into the sulci over the right hemisphere and into the sylvian fissure.

Laboratory tests, including complete blood count, prothrombin time, platelets, bleeding time, sedimentation rate, and antinuclear factor were normal.

After several days, the lethargy, headache, and hemiparesis began to improve. She was discharged with mild hemiparesis at two weeks, and went on to return to normal over a three-month period with an unremarkable course over the subsequent year. Blood pressure remained slightly elevated for only the first 24 hours of hospitalization, and subsequently remained normal. Repeat CT one week after onset showed little change on the unenhanced scan, and a contrast-enhanced scan showed no surrounding enhancement.

Patient 2

A 45-year-old black woman presented with severe headache. Five days prior to admission, she took a hot bath, then a single Dexatrim diet pill, containing PPA, 50 mg, and caffeine, 200 mg. She washed down the diet pill with a cola, then immediately went to bed. One hour later, she was awakened by a severe bifrontal headache, nausea, and vomiting. The nausea disappeared after one day, but the headache persisted unchanged and finally prompted her to seek medical care.

She had no significant past medical history, including no hypertension, trauma, or previous headaches. She had used the diet pills occasionally in past years, but not in recent months. She used no medications, but habitually drank 32–64 oz of cola per day.

On physical examination, blood pressure was 120/80 and other vital signs were also normal. She was in moderate discomfort, but was alert and her neck was supple. The rest of her general and neurological examination was normal.

CT of the head, unenhanced and contrast-enhanced, was normal. Lumbar puncture revealed opening pressure of 235 mm water, and the fluid was mildly xanthochromic and contained red cells 1440 per mm³ and white cells 30 per mm³, 98% lymphocytes, with protein 70 mg/dl, glucose 61 mg/dl, and negative smears and cultures.
HEMORRHAGES INDUCED BY PPA/Kikia et al

Figure 1. Patient 1, representative slice of initial unenhanced CT.

Bilateral carotid and vertebral angiography revealed no aneurysm or vascular malformation. Laboratory tests, including complete blood count, prothrombin time, partial thromboplastin time, platelets, and sedimentation rate were normal.

Her headache partially resolved over 10 days of hospitalization.

Discussion

An etiologic relationship of the diet pills to the intracranial hemorrhages is strongly suggested in our patients by a striking temporal relationship, the multiple simultaneous nature of clear hemorrhage in the first patient, and the exclusion of other causes. In 2 cases of PPA-induced intracerebral hemorrhage previously reported, one featured “several small hemorrhages in the region of the left internal capsule” after the patient took diet pills containing 170 mg total of PPA, and in the second, a large parieto-occipital hemorrhage resulted from “look-alike” capsules containing a total of 100 mg PPA combined with caffeine as well as ephedrine. The latter report also included a case of fatal subarachnoid hemorrhage after similar ingestion combined with alcohol. Subarachnoid and intracerebral hemorrhage have been documented in rats after intraperitoneal injection of either PPA or PPA plus caffeine and were possibly caused by acute blood pressure elevation.

The close structural and functional similarity of PPA to other sympathomimetic agents, including the primarily alpha-adrenergic vasopressor agents like metaraminol, the primarily beta-adrenergic agents like ephedrine, and the primarily central-acting stimulants like amphetamine, has been reviewed elsewhere. Hypertensive responses induced by PPA have been reported in humans, and a study of the acute blood pressure effects of PPA in normal medical students revealed striking findings. Diastolic elevation above 100 mm Hg occurred in 12 of 37 subjects ingesting an 85 mg PPA capsule, with as high as 142 mm Hg diastolic pressure in one individual despite rapid intervention with intravenous antihypertensive agents. Fifty milligrams of PPA produced acute hypertensive change in only a few of the subjects. That study may suggest the mechanism for PPA-induced intracranial hemorrhages. A case of transient severe blood pressure elevation combined with intracerebral hemorrhage, after ingestion of an “amphetamine-like” substance, was recently reported.

From a different perspective, lobar intracerebral hemorrhages and multiple simultaneous intracerebral hemorrhages are coming more to the attention of practitioners. This is due to the advent of CT with its excellent sensitivity to hemorrhage, and perhaps to the decreasing incidence of the more common primary (chronic hypertensive) intracerebral hemorrhage. In a recent series of 26 cases of lobar intracerebral hemorrhage, the majority were idiopathic. In a report of 45 cases of lobar intracerebral hemorrhage (within a large series of intracranial hemorrhages), only 12 of the lobar intracerebral hemorrhages were considered idiopathic; yet, within these 12 fell all 5 cases of multiple simultaneous intracerebral hemorrhages from the large series. In 2 recent reports of multiple simultaneous intracerebral hemorrhages, comprising a total of 14 cases, 12 were considered idiopathic. In none of the above 4 detailed reports was the possibility of drug ingestion, other than anticoagulants, mentioned.

In addition to PPA, other sympathomimetic agents have been incriminated in intracerebral hemorrhages, prominently amphetamines, but also ephedrine, and pseudoephedrine. But none of these drugs is used nearly as widely as PPA. In some instances, the patients reported purchase of street amphetamine which could have actually been look-alike PPA. A review of the generic drug indices of a recent “Physicians’ Desk Reference (PDR)” and “PDR for Non-Prescription Drugs” revealed 115 and 80 compounds respectively which contained PPA, and this includes primarily decongestants. Almost none of the diet pills and “look-alike” stimulants are included. This makes PPA the most frequently listed of all generic drugs, ahead of vitamin B complex, acetaminophen, aspirin, and chlorpheniramine, in that order. The Food and Drug Administration is currently taking a hard look at PPA, and the availability of at least the diet pills and stimulants containing PPA must be of great concern. It should be noted that despite the widespread use of decongestants, no intracranial hemorrhage secondary to a PPA-containing decongestant has yet been reported. Also, the PPA that induced intracranial hemorrhage exceeded the usual decongestant maximum dose of 75 mg and/or was combined with another sympathomimetic or with caffeine. We urge practitioners to question patients with lobar or multiple intracerebral hemorrhage, or subarachnoid hemorrhage, about drug ingestion. Drug screening, using optimal techniques, may also provide surprising information.

References

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Multiple Transient Ischemic Attacks, Lupus Anticoagulant and Verrucous Endocarditis

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SUMMARY A young adult with lupus anticoagulant and systemic lupus erythematosus had onset of multiple transient ischemic attacks four years after a major left hemispheric infarct. The symptoms were stereotyped, recurred several times daily over three years and ceased when aspirin was added to steroid therapy.

It is speculated that her symptoms were due to recurrent embolism from the heart in the presence of a thrombotic state.

LUPUS ANTICOAGULANTS are immunoglobulins of either the IgG or IgM class which interfere with phospholipid-dependent coagulation tests, without inhibiting the in-vivo activity of specific coagulation factors.1,2 Though in laboratory tests the lupus anticoagulant prolongs the partial thromboplastin time, the seeming paradox is that it's presence in the patient's circulation appears to be associated not with bleeding but with a tendency to thrombosis.3,5 It is frequently associated with both false positive serologic tests for syphilis and mild thrombocytopenia (possibly due to antibody activity against phospholipid antigen in the platelet membrane).

It is most frequently found in patients with S.L.E., but occasionally in others. Most associated thrombotic episodes have affected the venous side of the circulation and deep venous thrombosis, pulmonary embolism, cerebral venous thrombosis and axillary vein thrombosis have all been described.4,6 There have been several recent reports of cerebral ischemia in patients with lupus anticoagulant, both with and without S.L.E.5,9 Most reported patients had cerebral infarction, but a few had several transient ischemic attacks. Reported effective treatments include corticosteroids, antiplatelet agents and anticoagulants. Preliminary evidence suggests that lupus anticoagulants inhibit prostacyclin production by arterial walls, possible by interfering with the release of arachidonic acid from the cell membranes.10

Case Report

The patient was a 26 year old right-handed female who was referred in November, 1983 because of multiple transient ischemic attacks.

In 1976 she was admitted to another hospital following sudden onset of a right hemiplegia and aphasia. She had recently resumed oral contraceptives, which had been stopped 6 months earlier following an episode of phlebitis. Examination on admission revealed the following: Blood pressure 130/80. Pulse 80 per minute and regular. Respiratory rate 12 per minute and regular. No cardiac murmur was detected. Examination of her central nervous system showed a right he-
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