

Letters

Intracranial haemorrhage in association with pseudoephedrine overdose

Sir: Intracranial haemorrhage has been reported with use or abuse of amphetamine, dexamphetamine, and methamphetamine in 17 patients.^{1,2} In four of these patients, all of whom had evidence of subarachnoid haemorrhage, carotid angiography revealed a beaded appearance of the proximal and distal cerebral arterial branches, with areas of segmental narrowing and dilatation. Such beading has also been described in association with drug abuse alone.³ We report similar observations in association with an overdose of pseudoephedrine, a weak sympathomimetic amine.^{4,5}

A 17-year-old girl, who had made an attempt at self-poisoning 12 months previously, but was not a drug abuser, was admitted four hours after ingesting 20 tablets containing pseudoephedrine hydrochloride 60 mg. She was slightly disorientated with a blood pressure of 120/70 mmHg, and a pulse of 84/min, with sinus rhythm. Over the next 24 hours she developed headache, drowsiness, and a right hemiparesis with sensory deficit; blood pressure remained normal. Examination of the CSF on the fourth day of admission showed blood-stained xanthochromic fluid under raised pressure. Full haematological and biochemical profiles, auto-immune screen, serological tests for syphilis, chest and skull radiographs, and electrocardiogram were normal. CT scan showed a haematoma in the left frontal area, and a small lucency in the head of the right caudate nucleus. Bilateral carotid angiograms on the seventh day of the illness confirmed the presence of an avascular space-occupying lesion in the left frontal region and, in addition, revealed widespread segmental narrowing of the major and smaller branches of the intracranial carotid arteries (fig). She was managed conservatively and rapidly recovered. Six months later she was normal, and repeat CT scan showed resolution of the haematoma with a small residual cavity.

Of the 17 previously reported patients with amphetamine-associated intracranial haemorrhage, six had had an intracerebral

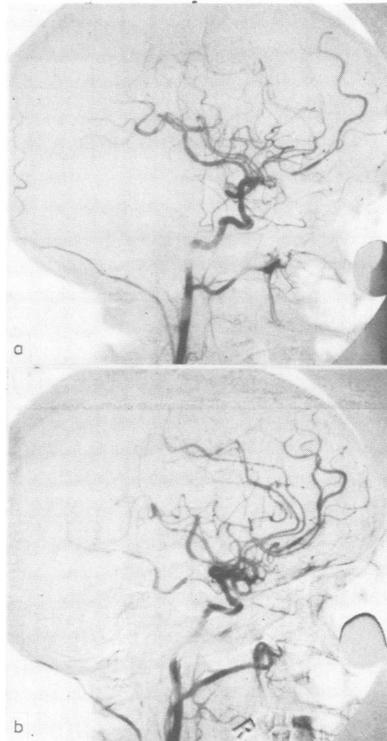


Fig (a) Left lateral carotid angiogram (subtraction view), showing segmental narrowing of middle and anterior cerebral arterial branches. (b) Right lateral carotid angiogram (subtraction view), showing widespread segmental narrowing, "beading", of posterior, middle and anterior cerebral arterial branches, contra-lateral to the haematoma.

clot; five subarachnoid haemorrhage; and six had both;^{1,2,6-14} Four had used or abused amphetamine-like drugs for the first time,^{2,6-8} even at normal dosage.² There were six deaths, four within hours of the ictus; nine patients were left with residual disability (eight hemiparesis, one epilepsy); and two recovered fully, as did our patient. The location of the haematomas was lobar in 10 (seven frontal, one parietal, two temporal), and basal-ganglionic in two. This contrasts with the recent finding that 71% of all haematomas, and 95% of hypertensive ones, are situated in the basal ganglia-thalamus region,¹⁵ suggesting that hyper-

tension may not be the only explanation for haemorrhage in amphetamine abusers. Indeed, hypertension was noted in only six of the 17 patients, and was not recorded at any stage in our patient, whose hemiparesis developed about 24 hours after ingestion of pseudoephedrine.

A possible explanation for the haemorrhage and arterial beading noted in our patient could be that pseudoephedrine, taken at a high dosage, induced a necrotising arteritis; an initial intense vasoconstriction (by direct action on smooth muscle, or indirect action on the noradrenergic nerves, or both), or toxic damage to the vessel wall, could have led to segmental fibrinoid necrosis giving rise to both the haemorrhage and the angiographic appearance of segmental narrowing and dilatation. Experimental¹⁶ and clinico-pathological^{8,10,17-21} evidence supports this view.

It is interesting to note that angiographic beading in drug addicts has been shown to resolve after about 14 days,^{9,16,17,21,22} which strongly suggests that it occurs as an acute reversible phenomenon, at least in the cerebral arterial system. This is further supported by the experimental observation that methamphetamine produces arterial beading within 10 minutes of the first intravenous injection.¹⁶ Arteriographic beading is not pathognomonic of drug abuse: it can occur in cerebral inflammatory disease,²³ collagen diseases,²⁴ trauma, and rarely with intracerebral haematomas and subarachnoid haemorrhage.²⁵

Pseudoephedrine has only rarely produced neurological complications,²⁶ because it is a very weak sympathomimetic amine, which has not achieved status as a drug of abuse or addiction. The present case, however, serves to illustrate its potential dangers.

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- Indomethacin and propranolol combined treatment for Shy-Drager syndrome¹**
- Sir: Indomethacin has been recently proposed for symptomatic relief of postural hypotension in Shy-Drager syndrome as well as in idiopathic orthostatic hypotension.^{2,3} We report the results of combined treatment with indomethacin and a β -adrenergic blocking agent (propranolol) in a patient who showed clinical signs of multiple system atrophy, autonomic failure, including orthostatic fall of the blood pressure and severe systo-diastolic hypertension when reclining. A 45-year-old woman was referred to our department because of a two year history of progressive gait disorder, speech and hand-writing difficulty, urinary and rectal incontinence, syncopal episodes lasting a few seconds, without loss of consciousness, all related to rising. No neurological illness was detected in the family. She had severe systo-diastolic hypertension for five years, untreated previously. On admission to the ward, her blood pressure reading was 210/135 mm Hg when lying, but unrecordable when standing. Neurological examination showed features of Parkinsonism (hypokinesia, amimic face, cogwheel rigidity of limbs), pyramidal signs (left sided sustained clonus, bilateral extensor plantar and Hoffmann responses) and cerebellar symptoms (gross dysmetria on finger to nose and heel to shin, poor alternating movements, dysarthric speech and tremor, both at rest and with movement). Gait could not be examined as the patient was unable to stand without fainting. Bilateral iris atrophy, positive Schirmer test and an atonic bladder were found. Verbal and performance IQ test indicated intellectual deterioration.
- During her two months of hospital stay, blood pressure and pulse-rate were recorded three times a day. No drugs were given for the first three weeks and the patient took a free diet. The following laboratory findings including CBC, VDRL, urine analysis, CSF, liver and thyroid function tests, serum and urine electrolytes, plasma-volume, 24/hour urinary excretion of catecholamines and vanil-mandelic acid, and folic acid, urinary excretion of B₁₂, were normal. Plasma renin activity, plasma and urine aldosterone levels were within the normal range. ECG was unremarkable. A systemic, cardiac and renal diseases were excluded. Radiographs of skull and chest were normal. CT scan showed cerebral atrophy, but no focal softening. On EEG, there were diffuse slow waves. Autonomic failure was documented by the orthostatic fall of the blood pressure from 220/135 mm Hg to 40 systolic, recorded twice after 3 to 4 minutes in upright position, and by the ECG monitoring of heart rate variation in response to standing⁴ and during deep breathing.⁵ The R-R interval ratio at 30 and at 15 beats was exactly 1:00 and the expiration:inspiration ratio was found to be less than 9%. The two latter findings were strongly suggestive of autonomic dysfunction,^{4,5} which was confirmed by the lack of systolic overshoot in Valsalva's manoeuvre.⁶ Sweating response to whole body heating was absent on limbs and trunk. In addition, plasma renin activity, and plasma and urine aldosterone levels, failed to rise on tilting⁷ as well as after a low-sodium diuretic stimulation,⁸ suggesting the inability of autonomic nervous system to stimulate renin release by the kidney.^{7,8}
- Indomethacin and propranolol were started at the same time. Indomethacin (25 mg three times daily) was given on account of its reported effect on postural hypotension,^{2,3} possibly due to inhibition of prostaglandin synthesis.³ According to Kochar and Itskovitz,³ an absolute or relative excess of vasodilator prostaglandin activity, particularly PGI₂ has to be considered in Shy-Drager syndrome. The β -adrenergic blocking agent (propranolol, 40 mg daily, raised to 60 mg thereafter) was administered to lower the systo-diastolic hypertension, when reclining. After five days on full treatment, the patient could sit without change in blood pressure or orthostatic symptoms. One month later, she could walk with assistance because of slightly broad-based and ataxic gait. Her blood pressure ranged from 160/95 to 140/80 mm Hg, after treatment was started. Only one episode of orthostatic fall occurred 48 hours following reduction of indomethacin to 50 mg daily. Treatment with