Ergotamine abuse and extra-hepatic portal hypertension.

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Summary: Arterial complications following ergotamine therapy have been well recognized since the beginning of this century. Venous complications, however, have only rarely been reported. A 48 year old Nigerian woman developed extra-hepatic portal hypertension coincident with a chronic overdosage of ergotamine. The literature elucidating the possible mechanisms involved is reviewed.

Introduction

It has long been recognized that toxicity due to ergotamine overdosage is directly related to its arteriospastic action (Yater & Cahill, 1936; Gould *et al.*, 1936). This most commonly results in ischaemia of the extremities (Cranley *et al.*, 1963; Sutton & Preston, 1970). Also documented are spasm of the coronary (Yater & Cahill, 1936), carotid (Greene *et al.*, 1977), cranial and renal arteries (Fedotin & Hartman, 1970; Greene *et al.*, 1977). Arteriographic studies have demonstrated spasm of the coeliac axis and superior mesenteric artery (Greene *et al.*, 1977; Stillman *et al.*, 1977) and even aorto-iliac spasm has been recorded (Glazer *et al.*, 1966; Fedotin & Hartman, 1970).

Only very rarely has a specific venous complication, as a direct result of ergotamine poisoning, been reported. Included in the literature are cases of thrombophlebitis (Greene, 1959) and deep venous thrombosis of the leg (Mintz *et al.*, 1974), following ergotamine administration.

The dearth of reported cases of venous complications following ergotamine abuse may, in part, be due to the more nebulous clinical presentation of venous occlusion, as opposed to the clear-cut clinical features of arterial insufficiency.

This report describes an association between the development of extra-hepatic portal hypertension and the chronic overdosage of ergotamine, an as yet unrecognized complication of ergotamine therapy.

Case report

A 48 year old Nigerian woman presented with an acute left-sided hemiparesis. She had suffered with severe classical migraine for 8 y, and her medication included oral ergotamine tartrate with caffeine (Cafergot, Wander Pharmaceuticals) for the acute migraine episode. She had however been taking 6 mg/day for at least the 3 months immediately previous to her admission. This constitutes a substantial chronic overdosage of ergotamine, which has a recommended maximum dose of 12 mg in any one week, and a recommended break of at least 4 days between courses for an acute migraine attack.

Her past medical history included a Caesarian section 25 y previously, and a laparotomy for secondary infertility 10 y previous to this presentation, both of which were uncomplicated. No abnormalities of the portal system were noted at either of these operations. She had otherwise, apart from her migraine, been perfectly well. Examination at presentation revealed a left-sided hemiparesis. She was normotensive and had no signs of cardiovascular disease. All investigations, including computerized tomography of the head, were normal.

It was thought unlikely that her hemiparesis represented a thromboembolic episode, and the diagnosis was made of cranial artery spasm resulting in an ischaemic episode, either due directly to a severe attack of migraine, or, more likely, due to systemic ergotamine toxicity, a well recognized complication of ergotamine abuse (Brazeau, 1970). Ergotamine was therefore withdrawn from her treatment regimen, and the hemiparesis completely resolved within one week.

One month later she re-presented with melaena and

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frank rectal bleeding, requiring resuscitation with 5 units of blood. She had been currently ingesting large quantities of aspirin to cope with a particularly severe migraine attack. Physical examination at this time revealed splenomegaly, a finding not noted previously. Otherwise examination was entirely normal.

Endoscopy revealed severe gastric erosions as expected, but an unexpected coincidental finding was the disclosure of grade 4 oesophageal varices. All blood tests, including liver function tests, were normal. Liver biopsy revealed a normal histology.

Splenoportograms and superior mesenteric angiograms did not reveal any recognizable splenic, superior mesenteric or portal veins. At laparotomy the angiographic findings were confirmed, with completely fibrosed splenic, superior mesenteric and portal veins. Splenomegaly was noted to three times normal size and there was a profusion of dilated, tortuous, variceal veins extending beyond the oesophago-gastric junction. No shunt procedure was possible, and injection sclerotherapy of her oesophageal varices was performed. She remains well at current follow-up.

Discussion

In up to 50% of patients presenting with extra-hepatic portal hypertension no cause is found (Webb & Sherlock, 1979). The present patient is of interest, because she had a well documented history of ergotamine abuse. This was thought to have been responsible for her episode of cerebral ischaemia, and the possibility exists that the ergotamine abuse could in addition have played an aetiological role in her extra-hepatic portal hypertension.

The pathogenesis of arterial disease induced by ergotamine and the clinical sequelae have been well documented. Ergotamine causes vasospasm, the production of mural thrombi and, microscopically, there is vascular smooth muscle hypertrophy and reduction of vessel lumen diameter (Yater & Cahill, 1936; Cranley *et al.*, 1963). These effects, on both arteries and veins, are mediated by partial α -adrenoceptor agonism (Boissier, 1978; Muller-Schweinitzer & Sturmer, 1974; Aellig, 1975), enhanced prostaglandin E production (Muller-Schweinitzer, 1974; Muller-Schweinitzer & Brundell, 1975) and a direct action on the vascular smooth muscle even more potent than noradrenaline (Mikkelsen *et al.*, 1981).

Although, in general, veins are poor responders to vasospastic stimulation, portal and superior mesenteric veins have been shown to be exceptional, contracting vigorously in response to a variety of catecholamines (Richardson & Withrington, 1978, 1979).

Animal studies involving perfusion of the portal vein with ergotamine (Richardson & Withrington, 1977), have shown classical dose-response contractions, with consequently markedly reduced portal blood flow. Chronic repeated dosage with ergotamine resulted in an increased number of α -adrenoceptors with corresponding increased sensitivity to ergotamine. *In vivo* human studies on forearm and hand veins (Aellig, 1976; Brooke & Robinson, 1970), although of lesser magnitude, bear out the validity of these *in vitro* studies, a dose-dependent venoconstriction resulting from the administration of ergotamine (Aellig, 1981; Tfelt-Hansen *et al.*, 1982a).

Ergotamine has a prolonged venospastic action (Aellig, 1981; Tfelt-Hansen *et al.*, 1982b), lasting for at least 8 h after a single oral dose. There is also significant accumulation (Ala-Hurula *et al.*, 1979), blood levels rising for several days after dosage interruption. Ergotamine has thus been shown to produce a reliable, long-lasting increase in venous tone and has been proposed for clinical use in the treatment of orthostatic hypotension (Mellander & Nordenfelt, 1976).

It is clear that this patient ingested a substantial overdose of a caffeine-enhanced preparation of ergotamine regularly, over a sustained period. The consequent accumulation would have resulted in a hugely elevated portal blood level within a few weeks, although extensive hepatic first-pass metabolism (Nimmerfall & Rosenthaler, 1976) would have protected her from undue systemic toxicity.

There are thus experimental grounds for believing that by virtue of its potent α -agonist action, enhanced prostaglandin-E synthesis and direct vascular smooth muscle stimulation, ergotamine may have produced a sustained constriction of the portal veins in this patient. It seems possible that the development of an increased number of adrenoceptors together with a rising portal blood level of ergotamine would not only have exacerbated this sustained spasm, but finally would have led to hypertrophy of the vascular smooth muscle, intimal damage and mural thrombus formation. The resultant extra-hepatic portal hypertension can create extensive porto-systemic anastomoses and portal vein fibrosis within a few months (Gibson *et al.*, 1965). This would have allowed ergotamine to reach toxic systemic levels, bypassing hepatic metabolism via these anastomoses, possibly accounting for this patient's initial presentation with an episode of cerebral arterial spasm.

In conclusion, we present evidence suggesting that the onset of portal hypertension in this patient was related to ergotamine abuse, a hitherto undescribed cause of extra-hepatic portal hypertension.

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