Interesting Case

Acute tubulo-interstitial nephritis and renal infarction secondary to ergotamine therapy

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Introduction

Acute ergotamine intoxication is well known to cause peripheral vasoconstriction and occasionally myocardial and/or splanchnic and/or renal ischaemia. Renal failure caused by ergotamine therapy seldom is observed. This patient represents a case of chronic intoxication with ergotamine and signs of chronic peripheral and central vasoconstriction and renal insufficiency caused by tubulo-interstitial nephritis.

Case

A 48-year-old female was admitted to the hospital because of tiredness, pressing retrosternal pain, painful legs, weakness in her arms and fever up to 38.9°C. Medical history included intermittent headache, which was diagnosed as migraine and treated by ergotamine tartrate suppositories for 10 years. The daily intake of ergotamine varied between 6 and 12 mg. The patient had an acute myocardial infarction with normal coronaryography one and a half years previously, untreated mild hypertension and thyroidectomy in 1987 for which thyroid hormones were administered. She was smoking one packet of cigarettes a day. Physical examination revealed an obese hypertensive (240/130 mmHg) woman, with a regular pulse (76 b.p.m.). Her face was red and she was sweating profusely, but she had no fever on admission. Heart and lung auscultation showed nothing particular, but a bruit was audible over the left carotic artery. The abdomen was tense with normal bowel sounds and without organomegaly. There were no signs of arthritis or skin lesions. Peripheral pulses were bilaterally absent at the tibialis posterior and dorsalis pedis, and she had bimalleolar oedema. Laboratory investigation showed a serum creatinine of 5.0 mg/dl on admission (1.20 mg/dl 18 months earlier), a sedimentation rate of 115 mm/h and a leucocytosis of 15,400/mm³. Urine sediment contained 2 white blood cells/mm³ and massive red blood cells with proteinuria (100 mg/dl). Urine output was normal (3.750 l/24 h). Immunological and viral screening were negative. Renal ultrasound showed kidneys of normal size but with a defect at the right lower pole. Scintigraphy of the kidneys with DTPA showed bilaterally decreased kidney function. Doppler-derived arterial pressures showed ankle/arm indices of 0.66 on the right side and 0.70 on the left side. An arteriogram demonstrated narrow renal arteries, several arterial stenoses and even defects in the renal parenchyma (Figure 1). A renal biopsy showed normal glomeruli, but fibrosis of the medulla interstitium. The interstitium of the cortex was oedematous with an inflammatory, lymphocytic infiltrate. The electrocardiogram showed a sinus rhythm with no signs of ischaemia or of a previous infarction. Myocardial scintigraphy with Technetium showed small perfusion defects in the anteroseptal and anterolateral regions. Chest radiogram was normal. Electromyography pointed to a sensitive axonal degenerative polyneuropathy. Lesions attributed to arthrosis were seen on bone scintigraphy, in particular a coxarthrosis on the right side. Eye examination, gallium scintigraphy and a muscle biopsy to exclude sarcoidosis and vasculitis were all negative. Hypertension was treated with amlopidine (5 mg/day), bisoprolol (10 mg/day), indapamide (2.5 mg/day) and prazosine (6 mg/day). Once normal blood pressure was achieved, the headache disappeared completely. Renal function recovered partially 20 days after stopping ergotamine intake (serum creatinine 3.3 mg/dl) and completely after 6 weeks corticosteroid treatment. Serum creatinine 3.5 months after the last dose of ergotamine was 1.1 mg/dl.

Discussion

Ergotamine is a potent vasoconstrictor that can adversely affect the coronary, splanchnic and renal
circulation and the peripheral vasculature. Intravenous ergotamine induces a marked increase in systemic vascular resistance, without modifying cardiac output, and a decrease in forearm blood flow resulting in an increase in blood pressure [1]. Our patient presented with painful arms and legs and hypertension. As the work-up discovered unexplained renal insufficiency associated with an inflammatory syndrome, a kidney biopsy was performed. It revealed a tubulo-interstitial nephritis with eosinophils, suggestive of a drug or infection-induced disease. In spite of untreated mild hypertension, there was no vascular sclerosis in the renal tissue. An immune-mediated nephritis was excluded. There were no metabolic or haematological disturbances. Hereditary disease and infectious causes were also excluded. The leucocytosis and fever that were present in our patient are well-known side effects of ergotamine; they are caused by tissue ischaemia and damage [2]. The patient admitted to having taken ergotamine for several years because she suffered from chronic headache.

Several mechanisms can induce renal impairment after ergotamine intake. Retroperitoneal fibrosis with compression of the ureters [3] and reversible acute renal failure due to renal artery spasm are common complications of ergotamine intoxication [4,5]. Chronic renal failure caused by ergotamine therapy is uncommon. Medieval epidemics of ergotism were caused by the ingestion of rye contaminated by the fungus *Claviceps purpurea* or ergot [2,4,5]. Ergotism was first recognized in 1670 and called ‘St Anthony’s fire’ to describe gangrenous extremities that were blackened like charcoal and said to be consumed by the ‘Holy Fire’. The first pure ergot alkaloid namely ergotamine was obtained by Stoll in 1920. Already in 1884 the fluid extract of ergot was recommended by Thompson for relief of periodic headaches [4]. Despite the severe side effects and several contraindications such as peripheral vascular disease, hypertension, coronary artery disease, pregnancy, thyrotoxicosis, sepsis, hepatic and renal diseases and anaemia [4], ergot alkaloids are still used at present in the treatment of migraine, in postpartum haemorrhage and as pressor agents in chronic orthostatic hypotension [1,4]. Ergot has two main effects on the peripheral circulation. The first, which is a vasoconstrictor action, is due to direct stimulation of smooth muscle in the vessel walls. The second is an α-adrenergic blocking effect [4,6]. The spasm produced by ergotamine slows the bloodstream, resulting in injury to the endothelium and leakage of plasma through the vessel walls. In the capillaries, stasis occurs and may cause thrombosis and tissue necrosis [5,6]. Cigarette smoking and ergotamine intake probably have a synergistic effect, since nicotine stimulates the sympathetic tone causing vasoconstriction [4]. Acute transient ischaemic renal failure has been reported in two patients with ergotamine intoxication. Fedotin and Hartman described a patient who received ergotamine (10 mg being given over a 60-h period) where arteriospasms involved the renal arteries as well, as documented by arteriography [6]. Pursey and Rainford described a woman who had taken 10 mg of ergotamine daily for 2 weeks and 20 mg 1 day before admission, with features of renal failure caused by prolonged renal arteriospasm [7]. Both patients recovered after discontinuing the drug. In 1992, Lund reported a case of chronic intoxication with ergotamine (5–10 mg/day for years) and signs of peripheral and renal ischaemia resulting in prolonged renal dysfunction. No renal biopsy was done. She was treated with nitroglycerin infusions for 32 h and discharged from the hospital free of symptoms [8].

The patient we have described here took Cafergot® (ergotametartate 6–12 mg/day) for >10 years. In addition, she was a heavy smoker. The kidney lesions seen on biopsy were typical for an advanced tubulo-interstitial nephritis. Serum creatinine diminished but remained elevated (3.3 mg/dl) 20 days after the last dose of ergotamine, and a short treatment with corticosteroids was initiated (a total dose of 440 mg of methylprednisolone). Renal function completely recovered (serum creatinine 1.1 mg/dl) 3.5 months after the last dose of corticosteroids. It is likely that even the cardiac damage had been caused by the intake of ergotamine, since no lesions were seen at coronarography [9].

This case illustrates that ergotamine may cause a tubulo-interstitial nephritis. Although the exact mechanism of interstitial nephritis is not clear, it is highly probable that prolonged ischaemia of the renal interstitium was responsible. This is in keeping with the experimental model of renal ischaemia developed by Moran et al. [10] which was used to characterize
morphological changes and alterations in renal blood flow. The appearance of areas with tubular atrophy and interstitial fibrosis was increasing with progressive degrees of severity of ischaemia [10]. In the present case, the hypoxaemia caused by arteriospasm and the high concentration of a toxic compound together may have induced ischaemia resulting in tubulo-interstitial nephritis.

References


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