SHORT REPORT

Twenty-eight Year Old HIV Positive Male Patient with Ergotism. Interaction of Ergot-alkaloids and Protease-inhibitors

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Ergotism is a rare clinical condition caused by ergot-alkaloid intoxication or pharmacodynamic interactions. The pathophysiology is based on arterial spasm in different segments of the arterial tree. Ergot-alkaloids are frequently prescribed as treatment for severe migraine. Ergotamine overdose is often based on interactions with other drugs using the same metabolic pathway. We report a case of a 28 year old HIV positive male patient on protease-inhibitors, who developed ergotism under the co-treatment of migraine by ergot-alkaloids.

Keywords: Ergotism; Protease-inhibitors; HIV-infection; Critical limb ischemia; Drug interaction.

Introduction

The accidental ingestion of Claviceps purpurea caused widespread epidemics of myocardial infarction or critical limb ischemia in the middle ages. The initial symptoms of such an intoxication with ergotamines are rather mild and very similar to those of a simple gastrointestinal disorder. Ergotamines exert directly vasoconstrictive and centrasympatholytic effects. The vasoconstrictive properties are mainly based on agonistic impact on 5-HT1B/1D- and 5-HT2-receptors. Furthermore, ergotamines have peripheral-noradreneric blocking capabilities. Therefore, ergotamines are frequently prescribed due to severe and lifestyle limiting migraine. Nowadays, pure nutrient-based intoxications are rare, in contrast intoxications based on pharmacodynamic interactions are frequently observed and reported in the literature.

We report a case of a 28 years old HIV-positive male patient, who is under protease inhibiting therapy. He was referred to our institution due to critical limb ischemia. He has recently been started on ergot-alkaloids according to his severe migraine. There was no obvious connection between his current medication and the objective presence of critical limb ischemia.

Case Report

We report the case of a 28 year old male patient, referred from the department of emergency medicine to our in-patient-ward. The patient reported paraesthetic pain in both legs, which had developed over the past 2 weeks. The reported level pain was increasing continuously. There was no history of claudication and no comparable episode in the patients’ history. The patient was HIV positive and an infection with hepatitis-C-virus was also known. He had a history of intravenous drug-abuse, currently prescribed methadone-substitution. The patient had been started on ergotamine therapy according to severe migraine 1 week before the onset of his leg complaints. In detail, the patients medication was doxepin 125 mg daily, carbamazepin 900 mg daily, nelfinavir 200 daily, stadivudin 80 mg daily, lamivudine 5600 mg daily, oxacepam 90 mg daily, methadone 140 mg daily.
daily and lornoxicam 8 mg daily. After admission a therapy with clopidogrel 75 mg daily was started.

Physical examination revealed pale and cool limbs. Sensory and motor functions were partly impaired. Only the groin pulse was palpable in both legs. At the time of admission there was no detectable changes in the peripheral pulse volume recordings. The systolic pressure was reduced to 40 mmHg on both Aa. tibiales anteriores. The Aa. dorsalis pedis were undetectable with hand held Doppler. The Ankle-brachial-index was 0.35 right and left, respectively. The electrocardiogram and the echocardiogram showed no signs of arrhythmia or thrombus formation. At admission, duplex-ultrasound scan revealed extraordinary thin superficial femoral and popliteal arteries. The calf-arteries were not visible with duplex ultrasound. Several laboratory analysis have been performed. The aminotransferases were slightly increased (ALT 71 U/l, AST 27 U/l). In contrast, the serum albumin level (41.6 g/l), cholinesterase level (6.1 kU/l) and the prothrombin time (100%) were within normal ranges. Creatinin kinase (198 U/l), myoglobin (356 µg/ml) and lactate-dehydrogenase (450 U/l) levels were elevated. To provide limb salvage an intra-arterial digital subtraction angiogram was performed. Similar to the ultrasound scan, the superficial femoral and the popliteal arteries were of extraordinary thin diameter and the calf-arteries were also not visible. Thrombus formations or relevant stenotic lesions have not been found during angiography. Due to the 'negative' angiogram and the pharmacotherapeutic record the suspicion of ergotamine overdose raised. According to this assumption the patient received immediately an high-dose vasodilative therapy (nitroglycerine and Alprostadil) for the following days. The signs of critical limb resolved within the first 24 h of treatment (Figs. 1–3). Duplex ultrasound the day after initialized vasoactive therapy showed a remarkable improvement. The diameter of the superficial femoral and popliteal arteries was increased compared to the initial scan. In the physical examination, all pulses of the legs were palpable. Even the pulse volume recordings returned to normal levels and the ankle-brachial index was >1.0 on both sides. Six days after the first angiography the patient underwent another angiogram to confirm this treatment success. After 8 days of in-ward treatment, the patient was dismissed in excellent clinical condition. A follow-up examination after 8 months revealed again no hemodynamic impairment documented by pulse volume recordings and measurement of the ankle-brachial-index.

Discussion

Based on recently started anti-migraine therapy containing ergotamines ergotism had been suspected and this diagnosis had been supported by ruling out other causes of critical limb ischemia. It is known from the literature, that similar therapeutic regimen can cause ergotamine overdose by interaction with protease-inhibitor therapy or other treatment. True ergotism is rare, however, of remarkably clinical importance in patients with extensive anti-viral therapy. Since the start of protease-inhibitors in medical therapy in 1994 several similar cases have been reported. The majority of patients were male and younger than 40 years of age.

It can be speculated that HIV infection itself has any impact on the development of ergotamine overdose. Additionally, an impaired liver metabolism exhibit such amplifying properties by inhibition of the
cytochrome P450 pathway. In fact our patient showed slightly elevated aminotransferases, but the serological markers of liver metabolism were within normal ranges. It is very important to do laboratory analysis frequently to rule out possible complications like acute renal failure based on crush syndrome, acidosis or shock. Additionally, it seems reasonable to monitor the patients ECG continuously, to detect possible arrhythmias in time. Pharmacotherapeutics, which are frequently used, are crystalloid infusion, mannitol and bicarbonate. Especially, last one is advocated as helpful in minimizing renal damage after rhabdomyolysis. We had to distinguish between vasospasm and atherosclerosis. The golden standard in the diagnosis of peripheral artery disease is the intra-arterial angiography. In cases of ergotamine overdose-related vasospasm, the vessel wall is smooth. In our case a simple morphological determination was difficult because of the extensive vasospasm. Therefore, the diagnosis was confirmed by the angiographic missing of any luminal narrowing and the positive effect of the vasoactive therapy.

Therapeutic options are immediately treatment stop for the presumed cause. Peripheral vasoactive substances can be safely administered, either orally or intravenously. Nitroglycerine-derivatives, calcium-channel-antagonists, alpha-blocking-agents and prostanooids are possible first-choice therapy. An additional heparin therapy seems reasonable, too. Nowadays, ergotamine overdose-related vasospasm and resulting critical limb ischemia is rare. However, due to extensive use of ergotamines in the treatment of migraine such kind of secondary vasospasm is a considerable differential diagnosis and should be kept in mind. Furthermore, migraine-therapy containing ergotamines should be administered only under certain precaution and close follow-up visits.
References


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