Introduction

Ergotamines have direct central sympatholytic and vasoconstrictive properties, which are mainly based on agonistic effects on 5-HT1B/1D- and 5-HT2-receptors. These drugs also have peripheral noradrenergic blocking capabilities. Therefore, ergotamines are frequently prescribed for severe migraine. Nowadays, pure nutrient based intoxications are rare, although frequently, intoxications originating from pharmacodynamic interactions are observed and reported in the literature (1, 2). Ergotamines are hepatically metabolised by a subgroup of the cytochrome P-450 iso-enzyme CYP3A4. Protease inhibitors such as ritonavir and indinavir, used for their antiviral purposes in patients infected with human immunodeficiency virus (HIV), are also metabolised through the cytochrome P-450 pathway and these drugs are potent inhibitors of the CYP3A4 iso-enzyme (1). The co-administration of protease inhibitors with ergotamines decreases hepatic metabolisation of ergotamines and causes complex clinical manifestations such as peripheral vasospasm, thrombosis, neurologic side effects (headache, psychosis) and alimentary symptoms (nausea, cramping, diarrhoea) that are collectively referred to as ergotism (1).

Herein we report a case of 31-year-old female patient with HIV infection presenting with symptoms of severe lower extremity ischaemia due to the administration of lopinavir/ritonavir and ergotamine tartarate concurrently.

Case report

A 31-year-old female patient with HIV infection was admitted to the hospital with complaints of severe pain and coldness on her lower extremity. Four months previously, she had been investigated for submandibular lymphadenopathy and was diagnosed as having lymphoma. During clinical follow up, HIV positivity necessitating antiretroviral therapy (zidovudin 2 × 300 mg, po., lamivudin 2 × 150 mg, po., and lopinavir/ritonavir 2 × 1, po.) was detected. The patient was hospitalised because of worsening pain in her lower extremity. She did not have a history of cigarette smoking, hyperlipidaemia, hypertension, diabetes or any other atherosclerosis inducing disease. She had been treated with ergot preparations following the diagnosis of migraine and the last time she had used the drug ergotamine tartrate (0.75 mg) was about one month previously. On physical examination, both lower extremities, especially the left one, were cold and the peripheral pulses of the popliteal artery and dorsalis pedis were hardly palpable. There were no other pathologic findings during physical examination. On admission, laboratory results were as follows; white blood cell count 9,800/mm³ (neutrophil, 7,600/mm³; lymphocyte, 1,500/mm³; monocyte, 600/mm³); haemoglobin, 14.2 g/dl; haematocrit 42.3%; (MCV, 109.7 fl; MCH, 36.8 pg; MCHC, 33.5 gr/dl); platelets, 373,000/mm³; erythrocyte sedimentation rate, 14 mm/h; C-reactive protein, 1.1 mg/L. CD4 T lymphocyte count was 179/mm³ and HIV viral load level, 2,000 copy/ml. The doppler ultrasonography of the left lower extremity did not reveal any thrombus formation or intraluminal pathology. In digital subtraction angiography, a remarkable decrease of calibration in all arterial structures in the lower extremities was observed, probably due to diffuse vasospasm. The arteries of the left foot could not be visualised. For the pre-diagnosis of vasculitis, such as Wegener granulomatosis and Raynaud’s phenomenon, specific serologic tests were performed and resulted in; anticardiolipin antibody negative, anticyclic cardiolipin IgM < 6.3 MPLU/ml (0-10); anticyclic cardiolipin IgG, 8.6 GPLU/ml (0-11); cytoplasmic antineutrophil cytoplasmic antibody (C-ANCA), negative; perinuclear neutrophil cytoplasmic antibody (P-ANCA), negative; myeloperoxidase (MPO), 27.1 RU/ml (0-9); proteinase 3 (PR3), negative. A punch biopsy was performed from the skin to exclude possible vasculitis or Kaposi’s sarcoma, but only necrotic changes were seen with no evidence of vasculitis or Kaposi’s sarcoma. Nifedipine (30mg, qd), acetylsalicylic acid (300 mg, qd), and enoxiparine sodium (0.4 ml bid) treatments were empirically started for the patient. The ischaemic signs and symptoms of the patient were gradually regressed and eventually resolved completely. These clinical manifestations were considered to be ergotism caused by concurrent use of ritonavir and ergot alkaloids.
Discussion

Ergotism is a well-known issue which may have various clinical manifestations (3). Symptoms of toxicity include peripheral vasospasm, thrombosis, neurologic side effects (headache, psychosis) and alimentary symptoms (nausea, cramping, diarrhoea). Arteriograms may reveal generalised vasospasm, formation of collateral vessels and, in some cases, thrombosis (4). Although most ergot toxicity is due to an overdose of the drug, ergotism has been also reported with extremely small and regular recommended doses (1). In our case, ergotism developed with only one tablet (0.75 mg) of ergotamine tartrate that had been taken one month previously.

Patients using drugs for HIV infection should be cautiously interrogated because these patients, especially those under the ritonavir-based ART, are at risk of serious adverse drug interactions. Ergotamine toxicity due to interaction with protease-inhibitor therapy (1, 2, 5-7) or with other treatments (8) is reported in the literature. Plasma levels of protease inhibitors are enhanced by co-administration of the agents inhibit p450 metabolism. Ergot alkaloids are metabolised by the p450 isoform CYP3A4 that is strongly inhibited by ritonavir (9). Many similar cases of ergotism associated with concurrent use of protease-inhibitors have been reported. In these cases, the patients were male and younger than 40 years of age (1, 2, 5-7).

As the survival of patients with HIV increases, the risk of serious drug-drug interactions increases (9). Physicians practicing in all situations must have a heightened appreciation of potentially fatal complications when prescribing ergot alkaloids for patients receiving protease inhibitors.

References


A. A. Cagatay
Dicle Cad.
45 ADA
Mimoza 1-1B
Atasehir-Kadikoy
34710 Istanbul, Turkey
Tel. : +90 216 455 24 88
Fax : +90 216 455 24 88