

## CASE REPORT

# Headache in an HIV-Positive Patient: Dangerous Interaction

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## SUMMARY

Ergotism is an ischaemic complication due to vasoconstriction throughout the body due to ingestion of ergotamine. A 34-year-old Hispanic man with HIV infection treated with saquinavir, ritonavir and abacavir/lamivudine presented to the emergency department complaining of left foot pain 1 week prior to admission. The affected extremity was cold with absence of pedal and tibial pulses. Arterial Doppler revealed absent arterial flow from the popliteal artery later confirmed by arteriography. Medication reconciliation revealed a recent prescription for migraine headache containing ergotamine. Drug was discontinued and the patient was started on cilostazol, enoxaparin and nitroglycerin patches on the affected limb. Complete resolution of symptoms and arteriography findings occurred 2 days after therapy began.

## BACKGROUND

Ergotism is an infrequent ischaemic complication due to vasoconstriction of vessels throughout the body after the ingestion of ergotamine.<sup>1</sup> Ergotamine, commonly used for migraines, is an ergo peptide part of the ergot family of alkaloids. It

shares structural similarities with serotonin, dopamine and norepinephrine, which favours vasoconstriction. Metabolisation occurs in the liver by cytochrome P450 3A4 (CYP3A4); therefore, inhibitors of this pathway are contraindicated.<sup>2</sup>

## CASE PRESENTATION

A 34-year-old Hispanic man positive for HIV treated with saquinavir, ritonavir and abacavir/lamivudine for the past 6 years presented with left foot pain accompanied by swelling that began 1 week prior to admission. Examination revealed a cold, purple, left foot, and absent pedal and tibial pulses. Arterial Doppler revealed absent arterial flow from the popliteal artery (figure 1) later confirmed by arteriography (figure 2). Medication reconciliation revealed initiation of a drug containing ergotamine a day prior to symptom appearance. The offending drug was discontinued and cilostazol, enoxaparin and nitroglycerin patches on the affected limb therapy was commenced. Complete resolution of symptoms and radiological findings was achieved after 2 days of therapy and discontinuation of the offending drug.

## INVESTIGATIONS

- ▶ Arterial duplex ultrasound.
- ▶ Lower extremity arteriography on presentation.
- ▶ Lower extremity arteriography post-treatment.

## DIFFERENTIAL DIAGNOSIS

- ▶ Vasculitis.
- ▶ Arterial thrombosis.
- ▶ Raynaud's phenomenon.
- ▶ Cardioembolism due to infective endocarditis.

## TREATMENT

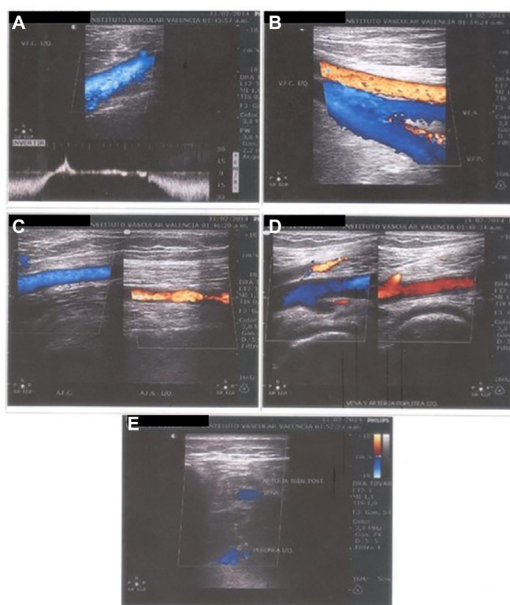
- ▶ Cilostazol.
- ▶ Low molecular weight heparin.
- ▶ Nitroglycerin patches.

## OUTCOME AND FOLLOW-UP

Complete resolution of clinical symptoms and radiological evidence of vasoconstriction 2 days after initiation of treatment and discontinuation of drug.

## DISCUSSION

Ergot is the common name of the sclerotia of *Claviceps purpurea* that produces ergot alkaloids. When ingested, it can result in intense protracted vaso-spasm due to the stimulation of  $\alpha$ -adrenergic receptors on vascular smooth muscle.<sup>3</sup> Ergotamine, an



**Figure 1** (A, B) Left common femoral vein (patent), (C) common and superficial femoral artery (patent), (D) popliteal vein and artery (patent), (E) absence of flow in the posterior tibial artery and the peroneal artery.



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**Figure 2** Multiple images of pretreatment arteriography during the injection phase: yellow arrow represents good flow until the popliteal artery; orange arrow shows diminished to absent flow below the popliteal artery; green arrow shows no flow in tibial and peroneal arteries; dotted black arrows show absence of pedal flow as well as posterior tibialis flow.

ergot alkaloid, is used to relieve headaches and other vascular-related pain because of its mechanism of action. Metabolisation occurs in the liver by the isoenzyme CYP3A4, which results in increased interactions in drugs that inhibit the before mention pathway.<sup>3</sup>

The reported incidence of sustained vasoconstriction due to ergotamine interactions with CYP3A4 inhibitors has been 0.001%–0.002%.<sup>4</sup> Cases of disseminated peripheral vasculitis and ischaemic strokes secondary to this adverse reaction have been reported.<sup>5,6</sup>

The patient's ergotism was the result of inhibition of the CYP3A4 pathway by ritonavir and saquinavir. Ritonavir is a potent CYP3A4 inhibitor co-administered with saquinavir to improve plasma concentration and therapeutic effects. This property led to acute intoxication with ergot alkaloids resulting in severe prolonged vasospasm. Toxicity with ergotamine is uncommon at a standard dose, but ritonavir has a high affinity with the aforementioned isoenzyme, which increased the risk of interaction between the two drugs.<sup>7–9</sup>

There are no guidelines regarding therapy in cases of ergotism, but removal of the offending drug is considered the mainstay of treatment. Vasodilatory therapy is also paramount in resolution of symptoms and clinical improvement. There is no evidence that one individual treatment is superior to another; therefore, therapy usually depends on the clinicians. There have been reports of nitroprusside administration, oral nifedipine, nitroglycerin and endovascular procedures for treatment, and heparin, dextrans and antiplatelet drugs for prevention of thrombosis.<sup>10</sup>

Our patient presented with left foot pain that was cold to the touch and with diminished pulses. Appropriate medical reconciliation disclosed that he was being adherent to ritonavir/saquinavir therapy and had recently started ergotamine for migraine headaches. Removal of the offending agent and vasodilatory therapy resulted in clinical improvement in 2 days, supporting the diagnosis of ergotism.

To our knowledge, there have only been six previous reported cases of interaction between ergot alkaloid with ritonavir, and

### Patient's perspective

After this experience, I have learnt thanks to my doctors to be careful of the medications I take. I was very afraid of losing my leg, but thank God I was able to overcome this and go on with my life.

### Learning points

- ▶ Medication reconciliation is an important part of the first patient encounter.
- ▶ Patients on antiretroviral therapy have a high chance of having medication interactions.
- ▶ Ergotamine is a commonly used over-the-counter medication in the USA and Central and South America; its use should be investigated in high-risk patients.

none with saquinavir. Awareness of these interactions should be raised in clinicians and the general public to prevent catastrophic complications.

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