

Review Article

Ergotism and Retroviral Therapies: An Association not so Unusual

Javier Eduardo Ferrari Ayarragaray* and Mercedes Panno

Department of Cardiovascular, Sanatorio Mitre, Argentina

***Corresponding author**

Javier Eduardo Ferrari Ayarragaray, Department of Cardiovascular, Sanatorio Mitre, 1440 Larrea St., 2 B. Capital Federal. Buenos Aires, Argentina, Tel: 541148052061; Email: jferrari1962@gmail.com

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Abstract

The use and abuse of Ergot has been linked in historical form of migraine treatment. However in recent years the spectrum where there have been its consequences has been modified. The association and interaction drug of our century and the many and varied daily treatments instituted have facilitated the expansion of the spectrum where the ergot can have consequences. The mere appearance of HIV as a syndrome to be treated and the introduction of antiretroviral drugs set a benchmark for these changes. We report a case of drug interaction with Ritonavir and Ergotrate, highlighting the importance of clinical examination and therapeutic possibilities.

CASE REPORT

A 33-year-old woman was admitted to our hospital with clinical manifestations of critical limb ischemia. The patient noted a marked decrease in her walking distance and calf and foot cramping pain over the 36 hours before her evaluation. Her past medical history was remarkable for positive HIV infection treated with anti-HIV therapy since eleven years (lamivudine 300 mg/24h, Tenofovir 300 mg/24h, Atazanavir 400 mg/24h, Ritonavir 100 mg/24 h). She denied any history of type 2 diabetes mellitus, hypertension or dyslipidemia or peripheral vascular disease. She was a current smoker consuming one pack daily. 48 hours before admission she received a single dose of ergotamine tartrate (ergotamine tartrate 1 mg - caffeine 100 mg) for migraine headache. A similar situation would have been described a month ago where the symptoms and ergot consumption could not be associated by the patient. The symptoms were not significant and she did not consult.

The physical examination revealed her feet cold, cyanotic below both ankles, and very painful when moved. Both hands were cold and cyanotic. Radial, tibialis posterior, and dorsalis pedis pulses were absent bilaterally. Other peripheral pulses were diminished. Neurologic examination revealed abnormal sensory findings (paresthesia, numbness, and splitting pain in both forearms and hands). An arterial doppler test revealed the absence of flow in both tibioperoneal and radio-cubital arteries. Echography showed a uniform reduction of diameter and diffuse arterial spasms affecting the superficial femoral, popliteal, anterior and posterior tibial arteries. Thrombosis was not associated. Bidimensional echocardiography showed preserved left ventricular function. Blood ergotamine levels were not measured. We speculate that an interaction between ritonavir

and ergot was responsible for this case and antiretroviral drugs were stopped immediately we began treatment with vasodilators: Pentoxifylline (600 mg/12 h); Prostaglandin E1 (alprostadil 20 mcg /8h intravenously). Low molecular weight heparin was associated. After 48 hours the patient has only partial improvement and sildenafil 25 mg was administered every 8 hours and Bosentan 125 every 12 hours, in order to avoid further permanent damage. After 4 days peripheral pulses became palpable. Extremities recovered adequate mobility, sensitivity and temperature. The arterial doppler demonstrated that vasospasm had disappeared from all the previously involved arteries. She was discharged with a program of physical rehabilitation after an 8-day hospitalization. All drugs containing ergotamine were suspended and aspirin, cilostazol and sildenafil were prescribed for the patient until further control.

DISCUSSION & CONCLUSION

Ergot is an alkaloid. Product of a fungus (*Claviceps Purpurea*), poisoning by ergot outbreaks have been documented extensively in the Europe of the middle Ages, where thousands of people died or remained with sequelae [1]. But now the cases of ergotism are usually associated with the use or iatrogenic overdose rather than as a result of consuming contaminated food naturally.

For decades the ergot has been used to treat headache. Even though it is currently rare, the incidence of documented adverse effects is calculated at 0.001% to 0.002% of patients treated primarily by headache [2]. While today is partially offset by the use of new anti-migraine agents (triptans and other analgesics), the use of ergot derivatives still remains a major clinical problem [3]. Ergotamine is an agonist of the alpha-adrenergic receptors. Its pharmacological effects include stimulation of smooth muscle

with central and peripheral sympatholytic activity causing peripheral vascular vasoconstriction. Orally is absorbed slightly and slowly. Metabolism is via hepatic cytochrome P450. With a half life of 2 hours, 90% of the metabolites are excreted in bile. The remainders by the feces or urine are in unaltered form. The symptoms may affect different systems such as the splanchnic or renal. Coronary vasoconstriction may manifest as angina pectoris.

The so-called "Holy Fire" or "St. Anthony's Fire" was the characteristic vascular manifestation, causing burning and gangrene in the feet and hands due to arterial vasoconstrictor properties. In general the lower limbs are affected the most, although the upper extremities may be associated [4]. The symptoms are usually symmetrical [5-7] although unilateral cases have been reported [8]. Vascular compromise may differ from mild to severe and persistent, causing in some cases, permanent injury and even gangrene and amputation [5-7].

The pharmacological association of ergot derivatives in HIV positive patients began to appear in those treated with protease inhibitors. The introduction of antiretroviral drugs in 1994 in combination with other nucleoside analogues for the treatment of adult patients infected with HIV-1 with progressive or advanced immunodeficiency brought a new form of interaction related to ergotamine. These inhibitors of cytochrome P-450 (eg, ritonavir, Norvir™) can alter metabolism and significantly increase the plasma concentrations of many drugs metabolized by the same route. In this specific case, the combination of drugs can cause toxic levels and cause ergotism and severe vasospasm in certain circumstances, even in the presence of ergotamine administered in single doses or low. Ritonavir, approved by the FDA, acts as an inhibitor selective HIV protease-1 and HIV-2. This antiretroviral has hepatic metabolism and a high affinity for several cytochrome P450 forms mainly by CYP3A4. The rapid washing of the drug in the blood and prolonged symptoms presuppose that both the separation of the drug from its receptor as the presence of active metabolites prolong the persistent vasoconstrictor effect.

With the start of antiretroviral therapies used in patients with HIV infection, ergotamine-ritonavir interaction has been observed increasingly frequent, but usually reported as isolated cases. This potential drug interactions should be suspected in the presence of clinical manifestations of vasospasm and a history of ingestion of ergotamine with a drug that inhibits its metabolism or not.

The diagnosis should be by exclusion and the references in the literature suggest that ritonavir may be associated with the development of severe ergotism. In certain circumstances may be reported significant sequelae [5-9].

CONCLUSION

Numerous drug interactions between ergot and other drugs

being particularly important for substances capable of increasing the toxicity of ergotamine and therefore the likelihood and intensity of vasospasm. Even in current times where the abuse of other vasopressor drugs and stimulants is widespread, the ergot acquires a representation different from that observed in previous years. The cytochrome P450 inhibitor drugs are currently the most related to ergot and its consequences. Ritonavir is currently used as a therapeutic agent in patients with HIV. The concomitant use of ergot derivatives should be avoided when these antiretroviral therapies are started, as recommended in the information provided in the reference guide for Ritonavir. Physicians should be aware of this adverse interaction, and any administration of ergot alkaloids should be discontinued. For all the emphasis on a detailed anamnesis and clinical differential diagnosis should be recovered. A detailed anamnesis and clinical differential diagnosis should be recovered. The use of Interaction Checker Services and Treatment Selectors showing interactions between key antiretrovirals and drugs used could be useful to treat a range of common comorbidities [10]. Early recognition is essential and the choice of multiple therapeutic modalities must be considered in order to avoid, as in these cases, irreparable sequelae to modify the quality of life of patients.

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