Ergotism Related to Concurrent Administration of Ergotamine Tartrate and Ritonavir in an AIDS Patient

Ritonavir is a potent protease inhibitor recently approved by the U.S. Food and Drug Administration and the European Agency for the Evaluation of Medical Products for the treatment of human immunodeficiency virus (HIV) infection. Its mechanism of action is well-known, but its pharmacokinetics are still uncertain. Ritonavir interacts with many drugs due to its hepatic metabolism (1, 5). We report a case of ergotism in a patient in whom treatment with ritonavir was recently begun.

The patient, a 63-year-old man, had long suffered from migraines and had taken ergotamine tartrate over the last 5 years (1 to 2 mg/day). He had HIV infection (B3 stage) and was being treated with zidovudine (200 mg/8 h), zalcitabine (0.75 mg/8 h), and co-trimoxazole. In April 1996, zalcitabine was withdrawn due to tingling and burning in both the patient’s hands. The patient began treatment with zidovudine (250 mg/12 h), didanosine (200 mg/12 h), and ritonavir (600 mg/12 h). Ten days after beginning this treatment, he began having severe symptoms characterized by subacute pain, paresthesias, skin paleness alternating with areas of cyanosis, and coldness in both arms. He was admitted to Hospital Universitario Virgen del Rocío 1 week later. Physical examination revealed an absence of axillary, brachial, radial, and ulnar pulses in both arms, paresis and semiflexion of fingers of both hands, and a few petechial lesions on the dorsum of the left hand. An arteriography was performed, and it showed a unilateral doppler test was performed, and it revealed the absence of flow in both radial and ulnar arteries. Treatment with prostaglandin E1 (500 mg/12 h intravenously for 3 days) and calcic nadroparin (15,000 U/12 h subcutaneously) was begun promptly. Ritonavir and ergotamine were withdrawn. Pain, paleness, cyanosis, and coldness disappeared 3 days later. Paresis of interosseous, thenar, and hypothenar musculature and long flexors of fingers of both hands remained as sequelae.

A new episode of pain and petechial lesions on the radial portion of the dorsum of the patient’s left hand occurred 4 days later. An arteriography was performed, and it showed a uniform reduction of flow in brachial, radial, and interosseous arteries of the left upper limb, without images of thrombosis, suggesting a functional disturbance. Prostaglandin E1 was prescribed again for 3 days, and these symptoms disappeared. An electromyograph showed axonal neuropathy of both median nerves and right radial and ulnar nerves.

Poisoning with ergotamine derivatives can cause a chronic or acute arterial ischemia by arterial spasm, more frequently in lower limbs. If this situation persists, capillary endothelial lesions and thrombosis develop. Other common symptoms are headache, nausea, vomiting, diarrhea, dizziness, confusion, and somnolence (2, 6, 8). This syndrome has been described to occur in patients taking high-dose ergotamine or low-dose ergotamine in association with other drugs which inhibit its hepatic metabolism (2, 3, 7). Macrolide agents, which are inhibitors of cytochrome P-450 (CYP), are the drugs which have most often been related to this syndrome (7, 9, 10). Ritonavir has a predominantly hepatic metabolism, and evidence exists that it is also a potent CYP3A, CYP2D6, and CYP2C9/10 isozyme inhibitor (1, 4, 5). On this basis, we think that in the patient described here a raising of the plasma ergotamine concentration to toxic levels probably occurred, caused by inhibition of ergotamine metabolism by ritonavir.

This case suggests that ritonavir may be associated with the development of severe ergotism in patients treated with ergotamine derivatives. This interaction was not described in the latest technical information card for the product distributed by Abbott Laboratories (1) and has not been reported previously by other authors.

Therefore, an extensive interrogatory is necessary when treatment with ritonavir is begun, with administration of ergotamine being discontinued if appropriate.

REFERENCES