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Addisonian Crises Induced by Rifampicin

To the Editor: One aspect of the treatment of tuberculosis is the possibility of interactions occurring between the antituberculosis medication and other drugs prescribed to the patient. We present the case of a patient with Addison's disease in whom the treatment of miliary tuberculosis led to the appearance of addisonian crises.

The patient was a 37-year-old woman who had suffered from adrenal insufficiency for more than 30 years and was being treated with 50 mg/d of oral hydrocortisone. She presented with dyspnea, cough, and a diminished level of consciousness that had started a few days earlier, at which time she suspended her usual corticosteroid therapy. The patient was finally admitted to our hospital where her serum sodium level was found to be 129 mmol/L and was treated empirically with glucocorticoids, to which the clinical response was good. An x-ray and computed tomography scan of the chest showed a miliary lung infiltrate. The diagnosis of miliary tuberculosis was confirmed after *Mycobacterium tuberculosis* was isolated in the urine culture, although other tests, including bronchoscopy and bone marrow aspirate, were negative. Antituberculosis treatment was initiated empirically with isoniazid, rifampicin, and pyrazinamide. During the course of her treatment, the patient suffered several addisonian crises despite receiving treatment with intravenous glucocorticoids at a dosage of 100 mg/6 h, thus requiring additional increases in corticosteroids. In light of these crises and of the appearance of elevated transaminase levels (alanine aminotransferase, 345 U/L; aspartate aminotransferase, 151 U/L), antituberculosis treatment was withdrawn and the patient's addisonian crises ceased. After 7 days, treatment was reinstated with cycloserine, ethambutol, and ofloxacin and after 25 days, when liver function had returned to normal, isoniazid was reinstated and was well tolerated, after which the patient was discharged.

The role of rifampicin in the induction of addisonian crises is clearly shown in this case by the relationship between the timing of the crises and the timing of the treatment, and by the fact that the patient's adrenal insufficiency was previously kept under control with her usual dosage of oral glucocorticoids.

The patient was suffering from miliary tuberculosis that developed subsequent to the diagnosis of Addison's disease, thus differentiating it from forms of adrenal insufficiency caused by tuberculous involvement of the adrenal glands. One of the aspects of antituberculosis treatment, particularly with rifampicin, is the possibility of interactions with other drugs being taken by the patient. Interaction with glucocorticoids and the induction of addisonian crises is, however, exceptional and has not been described in Spain. Several studies have shown that clearance of various glucocorticoids from the blood was increased in subjects taking rifampicin, compared to the control subjects.[1-3]

There is only one published study showing addisonian crises caused by taking rifampicin. In this study, administering rifampicin to 3 patients with Addison's disease and tuberculosis caused the appearance of addisonian crises that (as with our patient) were brought under control by increasing the dosage of glucocorticoids.[4] The mechanism of interaction between glucocorticoids and rifampicin is based on the ability of rifampicin to induce the cytochrome CYP3A4, which metabolizes glucocorticoids in the liver.[5] This phenomenon explains the drop in plasma concentrations of glucocorticoids despite the high doses prescribed and the resulting appearance of addisonian crises. This case appears to be clearly relevant to the management of tuberculosis in patients with Addison's disease. It is advisable to treat these patients with therapy that does not include rifampicin, in order to avoid the described effects.

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