Effect of Pyrazinamide on Ciclosporin Levels

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Dear Sir,

Ciclosporin is an effective immunosuppressive agent metabolized by isoenzymes of the hepatic cytochrome P-450 enzyme super-family. Coadministration of drugs that interact with this system may affect ciclosporin metabolism [1-3]. We report a case that would suggest that pyrazinamide interacts with ciclosporin.

A 28-year-old man with chronic renal failure secondary to interstitial nephritis underwent cadaveric renal transplantation. Immunosuppression was achieved with prednisone, azathioprine and low doses of ciclosporin during the first 2 months, and then the maintenance treatment was prednisone (10 mg daily) and ciclosporin (approximately 5 mg/kg body weight daily). The outcome was satisfactory, achieving a normal renal function. The patient was well until the 13th month, when he began to experience persistent high fever unresponsive to broad antibiotic treatment. He had no history of tuberculosis or positive skin tests for tuberculosis. The patient became increasingly ill. Twenty days later a miliary pattern and unilateral pleural effusion was demonstrated on chest radiography, results of which had been normal before. Sputum and gastric aspirate were negative for acid-fast bacilli. A pleural biopsy revealed several caseating epithelioid granulomas. Miliary tuberculosis was diagnosed. Pleural fluid cultures were positive for *Mycobacterium tuberculosis*. The patient was treated with isoniazid (300 mg daily), rifampicin (600 mg daily) and ethambutol (1,200 mg daily). The ciclosporin dosage was increased progressively up to 8.3 mg/kg daily after the starting tuberculostatic therapy. The patient did not improve, persisting fever, sweats, weight loss and high serum C-reactive protein.

Pyrazinamide was begun, at a dose of 15 mg/kg daily. At that moment, the dose and mean whole-blood levels of ciclosporin determined by monoclonal specific antibody were 8.3 mg/kg daily and 90 ng/ml, respectively. Two days after the start of pyrazinamide the blood ciclosporin concentration fell to 53 ng/ml, without any reduction in ciclosporin dosage. No other medication was added. The ciclosporin dosage was increased to 9.3 mg/kg daily and the level of ciclosporin measured again 3 days after was 94 ng/ml, similar to levels prior to the start of pyrazinamide therapy. This drug was increased progressively up to 30 mg/kg daily, and the dose of ciclosporin was increased simultaneously up to 11.5 mg/kg daily. In this state the mean levels of ciclosporin were 175 ng/ml. During pyrazinamide therapy the patient improved. In the last few weeks of treatment with pyrazinamide mild hepatotoxicity was observed. The patient completed 14 weeks of treatment with pyrazinamide. At that moment, the patient was receiving 10 mg ciclosporin/kg daily and the mean whole-blood level was 322 ng/ml. Pyrazinamide was stopped and the ciclosporin dosage was reduced to

8.2 mg/kg daily. Four days later, the through ciclosporin blood concentration was 159 ng/ml and the serum creatinine was 106 $\mu\text{mol/l}$ (1.2 mg/dl).

Although this case may be anecdotal, we think that it suggests the fact that pyrazinamide associated in stages with other tuberculostatic drugs interacts with the ciclosporin, producing an additional descent in the ciclosporin levels, supplementary to that seen in the treatment with isoniazid and rifampicin. Pyrazinamide therapy may be used to treat tuberculosis in patients receiving ciclosporin, but must be closely monitored in order to avoid insufficient immunosuppression.

References

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