Cyclosporine-Methyltestosterone Interaction

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Dear Sir,

Cyclosporine toxicity may be exacerbated by concomitant administration of various drugs. Five years ago, a reversible deterioration of renal function was observed during methyltestosterone therapy in a renal graft recipient treated with high dose cyclosporine. Although circulating cyclosporine levels during that episode were not provided, this complication has been ascribed to the interaction between the two drugs [1]. We now report a similar course of events in a patient on low dose cyclosporine in whom serial measurements of cyclosporine levels as well as kidney and liver function tests enable the consideration of the potentially relevant mechanisms of this complication.

This 47-year-old man had received a cadaveric renal transplant 23 months earlier for end-stage renal failure probably due to chronic glomerulonephritis. He had been free of acute rejection episodes. Maintenance immunosuppressive therapy consisted of cyclosporine (3.7 mg/kg/day), prednisolone (7.5 mg/day) and azathioprine (50 mg/day). He was a known HbsAg carrier for almost 20 years. Serum glutamic oxaloacetic transaminase (GOT) and glutamic pyruvate transaminase (GPT) had been fluctuating slightly above the normal range since the time of transplantation. The patient complained of sexual impotence and was given methyltestosterone (15 mg/day, orally in three doses) by an urologist. At the onset of this therapy serum bilirubin was 0.8 mg/dl, serum creatinine 1.75 mg/dl and the plasma cyclosporine trough level (fluorescence polarization immunoassay, TDX Abbott) 70 ng/ml. Four weeks later, he developed anorexia and pruritus. Serum bilirubin reached 3.85 mg/dl, creatinine 2.30 mg/dl and the cyclosporine trough level 252 ng/ml (fig. 1) in the absence of significant changes in GOT, GPT, alkaline phosphatase (AP) and γ -glutamyltransferase. Methyltestosterone withdrawal together with azathioprine discontinuation and a slight reduction of cyclosporine dosage resulted in a slow decrease in the cyclosporine, creatinine and bilirubin levels to control values. During and after this episode, there was

no change in HBV status (HBsAg positive, HBeAg negative, anti-HBs negative, anti-HBc positive). Delta antibodies remained negative as well as anti-HCV antibodies (ELISA, Ortho Diagnostics). Currently, 8 months after this episode, the patient remains well; serum creatinine is 1.77 mg/dl, serum bilirubine 0.6 mg/dl and cyclosporin level 44 ng/ml with a cyclosporin dose of 3.2 mg/kg/day.

The mechanism of the interaction is not entirely clear. Although rare, cholestatic jaundice is a well-recognized side effect of methyltestosterone [7,8]. The absence of an increased AP level together with that of bilirubin, as seen in our case and in the previously reported transplanted patient [1], is characteristic of methyltestosterone-induced liver injury [8]. This hyperbilirubinemia is attributed to an interference of the drug with bile flow through bile canaliculi. As cyclosporine is eliminated mainly through biliary excretion, reduced bile flow may result in increased serum cyclosporine levels with subsequent nephrotoxicity. Alternatively, methyltestosterone

175

Plasma cyclosporine trough level
Serum creatinine

$$\frac{3}{8}\Gamma^7\frac{0}{8}$$

Fig. 1. Cyclosporine, creatinine and bilirubin levels before, during and after methyltestosterone therapy.

could compete with cyclosporine for metabolism by microsomal cytochrome P-450, the major recognized metabolic pathway for both drugs in the liver [9,10]. The resulting acute rise in cyclosporine levels could have led to both hepatotoxicity and nephrotoxicity. The peak

cyclosporine level observed in our patient is well within the range of that reported to cause hepatotoxicity [11]. However, the unchanged transaminase and AP levels, noted in our patient, are rather unusual in cyclosporine-induced liver dysfunction [11].

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