Letter to the Editor

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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-glutamyl transferase. 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-HBe 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 onset of laboratory abnormalities after the introduction of methyltestosterone, as well as their reversibility after discontinuation of the drug strongly suggest a cause-to-effect relationship. Other causes of acute hepatic damage are unlikely. A bout of hepatitis B can be ruled out by the absence of rise of transaminase levels. Acute hepatitis C also appears unlikely because of the stability of transaminase levels, the lack of recent blood transfusion and the negativity of repeated anti-HCV antibody testings [2]. Azathioprine hepatotoxicity can also be reasonably excluded because of the previous long-term use of the drug at the same dose without side effects and the lack of a concomitant increase in the AP level [3]. Azathioprine therapy was, however, not resumed after this episode to avoid further potential additive hepatotoxicity. An interaction between methyltestosterone and cyclosporine best explains the combined liver and kidney dysfunction observed in our patient. Furthermore, other sex hormone molecules have also been implicated in a similar potentiation of cyclosporine toxicity [4–6]. As in our case jaundice was, however, only reported after methyltestosterone therapy [1].

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

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<th>ng/ml</th>
<th>Plasma cyclosporine trough level</th>
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<td>Serum creatinine</td>
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Whatever the mechanism(s), our case further stresses the fact that methyltestosterone added to cyclosporine may result in severe hepatic and renal dysfunction, even at low doses of cyclosporine. The importance of this risk is not known. The chronic hepatic dysfunction of our patient might have acted as a predisposing factor. Genetically determined susceptibility is also known to play a role, both in the occurrence of methyltestosterone-induced cholestasis [8] and in the individual characteristics of cyclosporine kinetics [12]. Transplant clinicians should be aware of this interaction, the occurrence of which may be leading to severe cyclosporine toxicity.

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

Methyltestosterone
Cyclosporine 100 mg
Azathioprine mg
Prednisolone mg
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].

References


