Hyperbilirubinemia in a Renal Transplant Patient due to Cyclosporin A Therapy

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Dear Sir,

Cyclosporin A is one of the major agents used in transplant surgery. Hepatotoxicity due to cyclosporin A has been reported with elevated serum bilirubin and bile salt levels. Herein, we report a renal transplant patient receiving cyclosporin A with elevated serum levels of alkaline phosphatase (ALP), trans-aminase (ALT) and bilirubin.

A 50-year-old man with a history of renal transplantation 6 and 2 years ago, was admitted to hospital because of fever, jaundice and fatigue. On admission time his blood analysis was as follows: hematocrit 49%, white blood cell 7 × 10^9/1, serum ALT 20 U/1 (5-35 U/1), total bilirubin 6.0 mg/dl, conjugated bilirubin 5.45 mg/dl, ALP 263 U/1 (50-305). He was treated with cyclosporin A (3.5 mg/kg/day), azothiopurine (1.4 mg/kg/day), prednisolone (4 mg/day) and amlodipine (5 mg/day). Following Doppler ultrasonography and a biopsy of the transplanted kidney, chronic rejection was diagnosed. He showed symptoms of prostatism and urinary tract infection was established.

Cyclosporin A was withdrawn. On follow-up examinations, his bilirubin levels immediately decreased, but ALP and ALT increased (ALP 306 U/1, serum aspartate transaminase 79 U/1; 5-40 U/1; ALT 65 U/1). His hepatic viral markers, including anti-HCV, were negative. On the 16th day of admission, all hepatic function tests were within normal levels. He objected to further investigation and was discharged on cyclosporin A 100 mg/day.

Three months later, he was again admitted because of jaundice. Blood findings were: total bilirubin 3.4 mg/dl, conjugated bilirubin 2.0 mg/dl, ALP 400 U/1, ALT 72 U/1. Eleven days after stopping cyclosporin A therapy, all blood analyses were normal.

Cyclosporin A is known to be eliminated mainly via the biliary pathway after bio-transformation. However, the uptake of the drug by liver cells is still unclear. The uptake of cyclosporin A by hepatocytes is neither saturable, nor is it driven by metabolic energy. Cholestasis caused by cyclosporin A treatment is therefore not the result of mutual competition for a carrier protein, however it seems to interact with the bile acid transport system by noncompe-titive inhibition of bile salt uptake [1].

A study of intraperitoneal administration of cyclosporin A (10 mg/kg/day) in the rat for 3 weeks did not cause liver dysfunction or hepatic histological lesions, but a significant reduction in bile flow and bile acid secretion was observed [2].
Cyclosporin A is said to inhibit the uptake of cholate into isolated hepatocytes in a noncompetitive manner [3]. It has also been shown to block the formation of cheno-deoxycholic acid in bile acid synthesis [4].

Endothelin, a peptide causing vasoconstriction of the portal vasculature, increases glycogenolysis and alters hepatic oxygen consumption. It is a potent cholestatic agent secreted by the liver. Does it potentiate the cholestatic action of cyclosporin A [5]?

There are many drugs that interact with cyclosporin A. Calcium channel blockers are said to increase the blood levels of cyclosporin A. Our patient was treated with amlodipine, a calcium channel blocker, but we never found blood cyclosporin A levels above normal range. On the contrary, they were almost always near the lower limit.

Our case is interesting, as it shows the effect of cyclosporin A on ALP and ALT besides bilirubin levels. With low doses of cyclosporin A (100 and 50 mg/day) our patient’s laboratory findings were normal, except for mild hyperbilirubinemia. After stopping cyclosporin A, serum bilirubin levels returned to normal. Is this a dose-dependent effect of cyclosporin A?

Is the altered hepatic physiology caused by the administration of cyclosporin A? Further studies are needed to answer these questions.

References