new article

Extraction Ratio of Cyclosporine in a Liver Transplant Patient with Organ Rejection

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To the Editor:

Cyclosporine, a cyclic polypeptide with potent immunosuppressive properties,[1] has been successfully used to prevent the rejection of transplanted organs such as kidneys, livers, hearts, and bone marrow.[2-5] It is highly lipophilic and is eliminated primarily by metabolism in the liver.[6] Recent studies in transplant patients indicate cyclosporine to be a low-to-intermediate clearance drug. We had a unique opportunity to directly determine the hepatic extraction ratio of this drug in a pediatric liver transplant recipient.

The patient was a 4-year-old male who underwent liver transplantation for α_1-antitrypsin deficiency. Subsequent to his first transplantation, he progressed well until 1 month following surgery when he developed hepatic artery thrombosis. He received a second liver 53 d after the first transplant. On the day prior to the second transplant, the liver function tests were as follows: alkaline phosphatase, 63 IU/L; serum glutamic oxaloacetic transaminase (SGOT), 654 IU/L; serum glutamic pyruvic transamine (SGPT), 273 IU/L; bilirubin (total), 1.0 mg/dL; bilirubin (direct), 0.2 mg/dL. This indicated that the patient did not have a normally functioning liver. The patient did not receive any drugs known to induce or inhibit the drug-metabolizing enzyme systems of the liver at any time prior to the second transplant. At the time of the study, the patient received cyclosporine and a low dose of prednisolone as immunosuppressants, captopril for the treatment of hypertension, and systemic antibiotics. Prior to the operation, 30 mg im of secobarbital was administered. Just prior to the removal of the first transplanted liver, simultaneous blood samples were obtained from the hepatic and portal veins. Blood samples were kept frozen until analyzed for whole blood cyclosporine concentration by HPLC.

The blood was extracted using the procedure of Sawchuck and Cartier.[7] Samples were analyzed using a 5-μm C_{18} column (Supelco, Bellefonte, PA) heated to 70°C and UV detection (model 441; Waters Associates, Milford, MA) at 214 nm. Standards were prepared in blank blood, and the internal standard was cyclosporine D (Sandoz Pharmaceuticals, Basel, Switzerland). The mobile phase was 68% acetonitrile, delivered at 1.8 mL/min. Under these conditions, the retention time for cyclosporine was 9.8 min and that for cyclosporine D was 12.8 min. The CV of the analytical method was 3.95% at 600 ng/mL (n = 10). The concentration of cyclosporine in the portal vein (PV) was 596 ng/mL, whereas the hepatic vein (HV) concentration was 500 ng/mL. The hepatic extraction ratio was:

$$\text{Hepatic Extraction Ratio} = \frac{PV - HV}{PV} = 0.161$$

In this patient, the first transplanted liver was 740 g in weight. The hepatic blood flow in humans is 100 mL/100 g of liver weight.[8] Therefore, based on an estimated blood flow of 740 mL, one would predict a cyclosporine clearance of 119 mL/min or 7.6 mL/min/kg in this patient. This predicted clearance value compares well with the mean (± SD) blood clearance of 8.4 (± 3.6) mL/min/kg estimated in 10 pediatric liver transplant patients subsequent to an intravenous infusion of cyclosporine.[9] These intravenous studies were conducted within 10 d after transplant. It is likely that the metabolizing ability of the liver would improve with time and that one might observe a higher cyclosporine clearance in a clinically stable patient.

From the above observation, it appears that cyclosporine is a drug with a low-to-medium extraction ratio. In the present study, the extraction ratio was determined at a concentration of 500–600 ng/mL of cyclosporine. The extraction ratio of certain drugs are concentration dependent. Presently, there is no evidence to suggest that cyclosporine undergoes nonlinear elimination kinetics in humans when administered in therapeutic doses. It should also be realized that the extraction ratio of cyclosporine was calculated in a liver with hepatic artery thrombosis. It is not known to what extent the metabolizing capacity of the liver will be altered by hepatic artery thrombosis. In addition, the effect of chronic immunosuppressive therapy with cyclosporine and a low dose of prednisolone on cyclosporine metabolism is not known at the present time. In any case, the fact that cyclosporine is primarily metabolized in the liver and that it is a drug with low-to-intermediate extraction indicates that its clearance can be altered significantly by changes in the intrinsic clearance and blood protein binding and to a smaller extent by changes in the liver blood flow. Recent studies have reported increased metabolism of cyclosporine in patients treated with phenytoin, phenobarbital, or rifampin, which are known to induce drug-metabolizing enzymes.[10-12] Ketoconazole, which is known to inhibit drug-metabolizing enzymes, has also been reported to increase cyclosporine blood levels in kidney transplant patients.[13] In conclusion, the present observation agrees with the recent studies indicating cyclosporine to be a drug with low-to-intermediate clearance.

References and Notes

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