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Effect of Liver Dysfunction on Cyclosporine Pharmacokinetics

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THERAPY WITH CYCLOSPORINE (CsA) constitutes a major advance leading to the success of organ transplantation.[1-3] CsA is a lipophilic drug and is poorly and variably absorbed in transplant patients.[4] It is primarily eliminated from the body by hepatic metabolism.[5] Alterations in the hepatic function would therefore be expected to change the kinetics of CsA. We determined the effect of experimentally induced hepatic dysfunction on the pharmacokinetics of CsA in dogs.

METHODS

Kinetic studies were carried out in adult mongrel dogs prior to and during week 1 after 70% hepatectomy (n = 6) or 2 weeks after bile duct ligation (BDL) (n = 6). CsA was administered as an intravenous infusion (2 mg/kg) for 1.0 to 1.5 hours or given orally (17.5 mg/kg) on separate occasions with at least a three-day washout time period between treatment. Blood samples (3 mL) were obtained from the jugular vein just prior to and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours after intravenous administration and at 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours after oral administration. Blood CsA concentrations were determined by high-performance liquid chromatography.[6] Pharmacokinetic parameters were calculated according to standard procedures.

Liver function was assessed in all the dogs by determining indocyanine green (ICG) kinetics at two doses (0.5 and 5.0 mg/kg) prior to and following surgically induced liver disease. The ICG plasma disappearance rate constant (K) and the maximal removal rate (V_{max}) were evaluated. Serum bilirubin levels were also measured in all the animals.

RESULTS

Serum bilirubin levels were significantly increased in all the animals after BDL or hepatectomy. Following hepatectomy, ICG K and V_{max} were reduced by 61.3% (±9.7%) ($P < .001$) and 57.7% (±7.1%) ($P < .001$), respectively as compared with control values. There was a significant decrease in the CsA half-life after hepatectomy. The mean (±SD) CsA clearance of 3.85 (±0.61) mL/min/kg after hepatectomy was significantly lower than the mean (±SD) clearance of 7.09 (±2.1) mL/min/kg prior to the hepatic dysfunction. However, there was no difference in the volume of distribution of CsA after hepatectomy. The absolute oral bioavailability of CsA was decreased by 26.4% ± 14.8% ($P < .05$) after hepatectomy.

BDL also induced a significant hepatic dysfunction. ICG K and V_{max} were reduced by 65.6% ± 3.6% and 39.1% ± 12.8%, respectively. The mean (±SD) clearance of CsA decreased ($P < .05$) from 7.09 ± 2.1 to 5.37 ± 0.92 mL/min/kg. There was no difference in the volume of distribution of CsA after BDL. There was a marked reduction in the mean (±SD) absolute oral bioavailability from 21.8% ± 4.4% to 5.7% ± 3.4%.

DISCUSSION

CsA is extensively metabolized in the liver by the cytochrome P-450 system.[5] Less than 1% of the drug is excreted as unchanged CsA in the bile. However, the metabolites of CsA are primarily excreted through the bile. Therefore hepatic dysfunction was expected to alter its kinetics.

Hepatic dysfunction was confirmed in all the animals after BDL or hepatectomy by elevated serum bilirubin levels and by impairment in ICG kinetics. Even though both the models produced significant alterations in CsA kinetics, the extent of impairment in kinetic parameters was different in the two

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models studied. ICG V_{max}, which is a highly sensitive index of hepatic cell function, is reduced to a greater extent after hepatectomy than after BDL. BDL resulted in a lesser impairment in the ICG V_{max} and the clearance of CsA as compared with hepatectomy. Changes in ICG V_{max} and CsA clearance appeared to parallel each other in all the animals. BDL markedly impaired the bioavailability of CsA as compared with hepatectomy. This may be due to the lack of availability of bile for the absorption of CsA in BDL animals. Though the bile flow may have been diminished to a certain extent in the hepatectomized animals, some bile was apparently available for CsA absorption. Previous studies in animals and humans indicate that bile is essential for CsA absorption.[7,8]

The present study indicates that hepatic dysfunction not only alters the elimination of CsA but also impairs its absorption. Since the impairment in CsA kinetics appears to vary with the degree and the cause of hepatic dysfunction, individualization of the CsA dosing regimen is necessary in patients with hepatic insufficiency.

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