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Experimental Study About the Influence of Liver Dysfunction Upon Cyclosporine Pharmacokinetics

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THE FREQUENT malabsorption and marked variability in cyclosporine (CsA) absorption and metabolism makes CsA therapy difficult in orthotopic liver transplantation. Alternations in the hepatic function would therefore be expected to change the pharmacokinetics of CsA. We have studied changes in the kinetics of CsA in two types of hepatic impairments, 70% hepatectomy and complete bile duct ligation in dogs.

In the present study, we further investigated the influences of various degrees of liver dysfunction upon CsA pharmacokinetics by using those two types of liver-impaired canine models; the degrees of dysfunction were evaluated by indocyanine green (ICG) kinetics to quantitate hepatic functional reserve.

METHODS

The pharmacokinetics of CsA were studied in 20 mongrel dogs after 70% hepatectomy or complete bile duct ligation as models of liver dysfunction. Changes in liver function were monitored by serial measurements of serum bilirubin, the maximum removal rate (ICG-R_{max}), and the plasma disappearance rate constant (ICG-K) of ICG as a hepatic functional reserve at two doses (0.5 or 5.0 mg/kg) before and after surgically induced liver impairments.¹⁻⁴

CsA was administered to dogs at either 2 mg/kg for 1.0 to 1.5 hours intravenously (IV) or 17.5 mg/kg orally (PO) on two separate occasions each week after the operation for 4 weeks. Blood samples were obtained from jugular veins just before and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours after IV administration and at 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours after PO administration. CsA

concentrations were determined by high-performance liquid chromatography (PHLC) as the parent compound CsA from whole blood.

RESULTS

Seventy percent hepatectomy created significant liver dysfunction, and these live impairment subjects recovered slowly (Fig 1). ICG-R_{max} was reduced by 57.7% ± 7.1% (mean ± SD), and ICG-K was reduced by 61.3 ± 9.7% the first week after the operation. The systemic clearance (CLs) of IV CsA was reduced by 43.9% ± 8.2%, but later the CL recovered rapidly. There was a significant prolongation of the terminal half-life of IV CsA only in the first week. However, the steady-state distribution volume of IV CsA was not significantly different after 70% hepatectomy due to too much variability. The percent bioavailability of PO CsA was reduced by 26.4% ± 14.8% (*P* < .05) the first week, and later it had recovered to within the normal range. After hepatectomy, a significant positive correlation was observed between ICG-R_{max} and the CLs of IV CsA (*r* = .62, *P* < .01). Also a significant negative correlation was observed between serial serum bilirubin levels and the percent bioavailability (*R* = -.67, *P* < .01). However, no significant correlation was observed between serial serum bilirubin levels and the CLs of IV CsA.

Bile duct ligation also induced another type of liver impairment (Fig 2). ICG-R_{max} was reduced by 39.1% ± 12.8% the second week and 45.5% ± 9.9% the third week after the operation. During the same periods, the CLs were reduced by 24.3% ± 13.0% and 36.1% ± 7.9%, respectively; the area under the curve (AUC) of PO CsA was reduced by 69.9% ± 10.7% and 60.8% ± 15.1%, respectively. The percent bioavailability was reduced by

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Influence of Liver Dysfunction on CsA Pharmacokinetics

Ohmori, G.J. Burckart, et al.

determined by high-performance liquid chromatography (HPLC) as the parent compound.

RESULTS

70% hepatectomy created liver dysfunction, and these functions recovered slowly (Fig 1). ICG-R_{max} was reduced by 57.7% ± 7.1% and ICG-K was reduced 48.2% ± 15.6% the first week after the operation. The clearance (CLs) of IV CsA was 8.2% but later the CLs recovered. There was a significant correlation between the terminal half-life of IV CsA and the distribution volume of IV CsA. The CLs of PO CsA were 14.8% (P < .05) the first week after hepatectomy, a significant correlation was observed between the CLs of IV CsA and the CLs of PO CsA. There was also a significant negative correlation between serial serum CsA levels and the percent bioavailability of CsA. However, no significant correlation was observed between serial serum CsA levels and the CLs of IV CsA. Complete bile duct ligation also induced another type of liver dysfunction (Fig 2). ICG-R_{max} was reduced by 12.8% the second week after the operation. During the same periods, the CLs of IV CsA were 13.0% and 36.1% ± 13.0% and 36.1% ± 13.0%, respectively. The area under the curve was reduced by 69.9% ± 5.1%, respectively. The bioavailability was reduced by

Fig 1. Changes in percent decreasing rates of hepatic functional reserve and kinetics parameters of CsA after 70% hepatectomy.

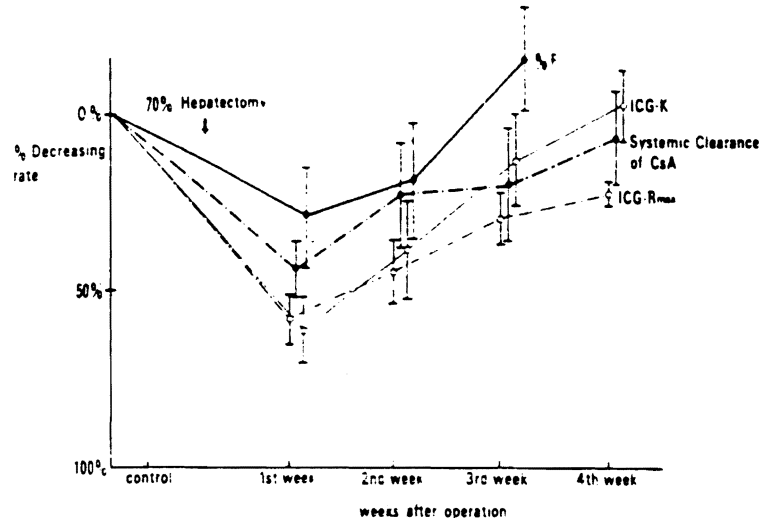


Fig 2. Changes in percent decreasing rates of hepatic functional reserve and kinetics parameters of CsA after complete bile duct ligation.

12.8% the second week and by 21.9% ± 15.6% the third week after bile duct ligation. However no significant negative correlation was observed between serial serum CsA levels and the percent bioavailability of CsA after bile duct ligation.

DISCUSSION

CsA is extensively metabolized and eliminated in the bile, but analysis of bile by HPLC revealed that less than 1% of the administered dose of CsA is secreted unchanged in the

urine. Therapeutic drug monitoring of the CsA-treated patient is necessary because it is difficult to assess interindividual variations in CsA absorption, distribution, metabolism, and elimination. Actually, in liver transplant patients, it is much more difficult to establish near-basal values and the steady-state condition because the liver is the major site of CsA metabolism. Kahan⁶ reported that patients with impaired hepatic function cleared the drug one third more slowly, thereby leading to an increased AUC from a demographic analy-

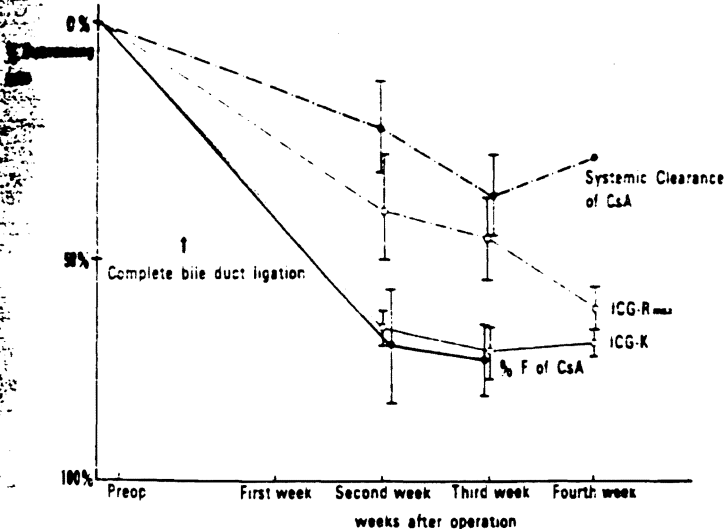


Fig 2. Changes in percent decreasing rates of hepatic functional reserve and kinetics parameters of CsA after complete bile duct ligation.

sis using radioimmunoassay (RIA). However, because the primary metabolites of CsA do not have significant immunosuppressant activity in animals and have not been tested in humans⁷ and because the deterioration of hepatic function secondary to rejection or hepatic thrombosis frequently produced a disproportionate rise in the RIA blood concentration, the use of RIA in the setting of altered hepatic function grossly underestimates the required CsA dosage to achieve the usual CsA parent compound level.⁸ In our experiments using the HPLC method of whole blood for the measurement of the parent compound, on the first week the hepatic dysfunction created by hepatectomy produced a 44% reduction of the CLs of IV CsA and a 151% prolongation of the terminal half-life (7.65 v 5.06 hours as control). This suggested that the interdose interval should be prolonged one half longer than that for the normal hepatic functional group.

The assessment of the hepatic dysfunction influence on CsA kinetics was reported by using elevated serum bilirubin levels.^{9,10} In our data, significant negative correlation was observed between serial serum bilirubin levels and percent bioavailability following hepatectomy. However no significant correlation was observed between serial bilirubin levels and the CLs of IV CsA. Furthermore, in complete bile duct ligation, no significant negative correlation was observed among the serial serum bilirubin levels, the percent bioavailability, and the CLs.

These data demonstrate that liver impairment significantly influences the pharmacokinetics of CsA, by not only creating changes in intestinal absorption but also in hepatic metabolism. Safe and effective therapy will require an improved understanding of how CsA pharmacokinetics varies with the degree and cause of hepatic dysfunction.

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