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Role of Bile and Bile Salts on Cyclosporine Absorption in Dogs

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PREVIOUS STUDIES in liver transplant patients indicate an increase in the trough cyclosporine (CsA) concentrations subsequent to the removal or clamping of the T tube.[1,2] Since less than 1% of an administered dose of CsA is excreted as the unchanged drug, enterohepatic recirculation is not responsible for such an observation.[3] It is likely that improved bile flow into the gut secondary to the clamping process increases CsA absorption and therefore the trough concentrations. Our objective was to determine the role of bile and bile salts on the absorption of CsA in dogs.

METHODS

Five male beagle dogs weighing approximately 15 kg were used in this four-phase study. During each phase of the study the dogs were fasted overnight, and food was withheld for a period of seven hours after drug administration. Water was allowed ad libitum. On day 1 of the study (phase 1) the dogs received CsA (20 mg/kg) orally. On day 8 (phase 2) the same groups of dogs received 1 g lecithin and 250 mg chenodeoxycholic acid (CCA) as a suspension in water 15 minutes prior to oral CsA (20 mg/kg). On day 9 the dogs underwent surgery (choledochoureterostomy with a right nephrectomy) to divert bile from the gut. On day 29 (phase 3) these dogs received an oral dose of CsA (20 mg/kg). On day 49 (phase 4) 1 g of lecithin and 250 mg CCA were administered 15 minutes prior to the CsA dose (20 mg/kg). During each phase blood samples were obtained at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after drug administration and analyzed for unchanged CsA by a high-performance liquid chromatographic method as described earlier.[4] Liver function tests were monitored in all the animals during the course of study. Pharmacokinetic parameters were calculated according to standard procedures.

RESULTS

The liver function tests were normal in all the dogs during the study period. Oral absorption of CsA was rapid in all the animals, with peak blood concentrations being reached with in two hours. Subsequent to the administration of lecithin and CCA, peak blood levels were observed within one hour. The mean (±SD) maximum blood concentration (C_{max}) of CSA (1,165 ± 280 ng/mL) was significantly higher in phase 2 as compared with phase 1. The mean area under the blood concentration time curve (AUC_0) in phase 2 was 46% greater than the AUC_0 during phase 1.

There was a significant decrease ($P < .05$) in the mean C_{max} (76%) and the AUC (75%) following bile diversion. The mean (±SD) AUC in phase 3 was 1,888 (±732) as compared with 7,429 (±2,032) ng · min/mL^{-1} in phase 1. The mean AUC of 3,744 (±1,405) ng · min/mL^{-1}

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during phase 4 was significantly higher than the mean AUC of 1,888 (±732) ng · min/mL^{-1} during phase 3. However, the C_{max} and time for peak blood concentrations were not significantly different between phase 3 and 4.

DISCUSSION

Lipids and lipid-soluble compounds require bile and bile salts for absorption. Since CsA is a highly lipid soluble compound one would anticipate a potential role for bile on the absorption of CsA. In liver transplant patients, we have observed significant increases in the blood CsA concentration over a dosing interval following T tube clamping.[2] Since very little unchanged CsA is excreted in the bile, enterohepatic recirculation cannot account for this observation.

In this study we have documented that bile and a bile salt are essential for CsA absorption in dogs. Biliary diversion resulted in a significant impairment in the absorption of CsA. Coadministration of bile salts improved the absorption of CsA in normal dogs and significantly increased its absorption in bile-depleted dogs. The rate of absorption of CsA as indicated by the time taken to achieve maximal blood concentration was also significantly increased by the administration of CCA to normal dogs.

The poor bioavailability of CsA observed in the liver transplant patients during the immediate postoperative period[5] and in liver disease patients[5] is presumably related to the lack of sufficient bile and bile salts for facilitation of CsA absorption. Coadministration of CsA with bile salts should be considered in patients as a possible way to increase CsA absorption.

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