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EFFECT OF BILE ON CYCLOSPORINE ABSORPTION IN DOGS

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Abstract

Oral absorption of cyclosporine was studied in dogs with and without bile diversion. Blood and bile cyclosporine concentrations were determined by a high pressure liquid chromatographic method. The absorption of cyclosporine was signficantly impaired ($p < 0.05$) in dogs with bile diversion. Bile and bile salts appear to be essential for the absorption of cyclosporine.

Introduction

The use of cyclosporine as an immunosuppressant has resulted in improved graft and patient survival following liver, kidney, heart and bone marrow transplantation (1-4). However, the various factors that influence the pharmacokinetics and pharmacodynamics of cyclosporine have not been completely characterized. The kinetics of cyclosporine are highly variable between patients and within a patient over a time period (5). In particular liver transplant patients present a unique challenge in the optimization of immunosuppressive therapy with cyclosporine (6).

Recently, Andrews et al (7) reported significant increases in the trough blood cyclosporine concentrations in liver transplant patients following clamping of the T-tube inserted into the bile duct. A marked reduction in the daily dose of cyclosporine was required in order to maintain the desired trough blood concentrations in these patients. Since very little unchanged cyclosporine is excreted in the bile in liver transplant patients (9), enterohepatic recirculation cannot explain the influence of bile diversion on cyclosporine blood concentrations. Increased absorption of cyclosporine in presence of bile is most likely responsible for such an observation. We report the results of a study to quantitate the effect of external biliary drainage on cyclosporine absorption in dogs.

Materials and Methods

Four male mongrel dogs weighing between 17.3 to 24 kg were used in this study. The animals were fasted overnight but were allowed free access to water at all times. Food was withheld from the animals for at least 4 hours following drug administration. The dogs received 20 mg/kg of cyclosporine (Sandimmune, Sandoz Inc., NJ) orally on two separate occasions. During phase 1 (control) the drug

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was administered to the dogs with an intact biliary system. Phase 2 (biliary diversion) studies were carried out in the same group of dogs following the insertion of a cannula into the bile duct to exteriorize bile drainage. The dogs were allowed to recover for at least 4 days following surgery prior to the second phase of the study. Blood samples were obtained in heparinized tubes at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours following drug administration during each phase and analyzed for unchanged cyclosporine.

Cyclosporine concentrations in whole blood and bile were analyzed by a high pressure liquid chromatographic assay (9). Terminal disposition rate constant (λ_z), area under the blood concentration versus time curve from time 0 to 24 hours $(AUC)_0^{\lambda}$ and time 0 to ∞ $(AUC)_0^{\infty}$ were calculated according to standard techniques. A paired T-test was used to determine the significance of any differences in the AUC's between the two phases.

Results and Discussion

Our study design was such that each dog served as its own control. The blood concentration versus time profile of cyclosporine in dog #4 pre and post bile diversion is shown in figure 1. The blood level of cyclosporine during the biliary diversion phase were considerably lower when compared to the levels obtained with intact biliary system.

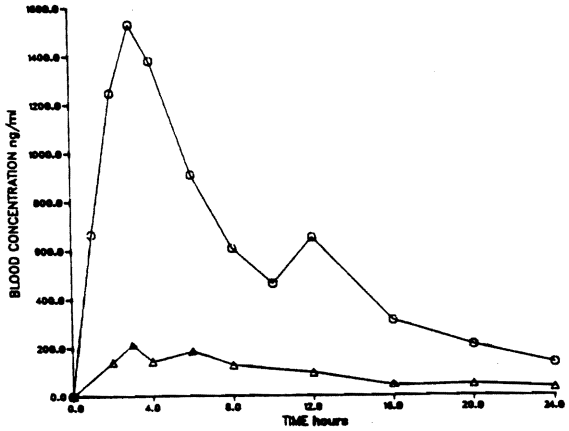

Figure 1. Blood cyclosporine concentrations as a function of time following oral administration of 20 mg/kg of cyclosporine in dog #4 with intact bile duct and (O) with biliary diversion (Δ).

The mean (± S.D) peak blood concentration of 1235 (±325) ng/ml observed during the control phase was significantly ($p < 0.05$) higher compared to the peak concentrations of 273 (±88) ng/ml following biliary diversion. Though the mean time to peak blood concentrations tended to be longer in the dogs with biliary diversion (4.5 hours) when compared to the control dogs (3.0 hours) the differences were not statistically significant. The mean (± SD) disposition rate

constant of 0.111 (± 0.027) hours^{-1} during the control phase was not significant ($p < 0.05$) from the disposition rate constant of 0.100 (± 0.041) during the biliary diversion phase. The harmonic mean half life was 6.2 hours in phase 1 and 6.9 hours in phase 2. The mean (± S.D) $(AUC)_o^{\lambda}$ was 11293 ± 2611 ng.hr/ml during the control phase and 2943 ± 734 ng.hr/ml during the biliary diversion phase. The mean (± S.D) AUC_o^{∞} was 12679 ± 2386 ng·hr ml^{-1} during control phase and was 3351 (± 755) ng·hr ml^{-1} during the bile diversion phase (Table 1).

Table 1.
Effect of Biliary Diversion on Cyclosporine Bioavailability in Dogs

Dog #	Dose	$(AUC)_o^{\lambda}$ Control	$(AUC)_o^{\lambda}$ Bile Diverted	$(AUC)_o^{\infty}$ Control	$(AUC)_o^{\infty}$ Bile Diverted	% Relative Bioavailability[a]	
	(mg)	(ng·hr·ml^{-1})				b	c
1	480	8456	3751	10732	3972	44	37
2	450	9717	2141	12499	2464	22	24
3	350	13199	3339	14631	3985	25	27
4	480	13800	2540	14853	2981	18	20
Mean	440 ±	11293 ±	2943 ±	12679 ±	3351 ±	27 ±	27 ±
S.D.	64	2611	734	2386	755	10	6

[a] [AUC (Bile diverted)/AUC (Control)] x 100

[b] Based on $(AUC)_o^{\lambda}$ values

[c] Based on $(AUC)_o^{\infty}$ values

This difference in the AUC between control and the bile diversion phase was significant ($p < 0.05$) and independent of whether AUC_o^{∞}'s were compared or the $(AUC)_o^{\lambda}$'s were compared. Less than 1% of the administered dose of cyclosporine is excreted as unchanged cyclosporine in the bile in dogs following a dose of 20 mg/kg. The similar half lives observed during the two phases and the presence of less than 1% of the dose as cyclosporine in the bile indicate that the differences in AUC observed are due to differences in the extent of absorption of cyclosporine. The relative bioavailability of cyclosporine in the dogs with biliary diversion was 27% when compared to the control period with intact biliary system. Presence of bile results in approximately threefold increase in the bioavailability of cyclosporine.

Our study indicates that bile is essential for the absorption of cyclosporine. Bile has been shown to be necessary for the absorption of lipids and lipid soluble compounds such as vitamins A, D, E, and

K, (10) certain macromolecules such as insulin (11), heparin (12), and riboflavin (13), and sulfa drugs (14). Further studies to determine the effect of coadministration of bile salts on cyclosporine absorption are currently underway. If exogenous bile salts can improve cyclosporine absorption, oral cyclosporine therapy can be facilitated in liver transplant patients or in patients who malabsorb cyclosporine and the cost of cyclosporine therapy can be greatly reduced.

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