Interaction Between FK 506 and Cyclosporine in Dogs

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FK 506 is a macrolide isolated from the cultures of the fungus *Streptomyces tsukubaensis*.[1] It is nearly 200 times more potent than cyclosporine (CyA) in inhibiting lymphocyte proliferation in mixed lymphocyte cultures.[2] FK 506 has been shown to prevent or reverse the rejection of heart, liver, kidney, pancreas, lung, intestine, and skin grafts in mice, rats, dogs, monkeys, and baboons.[3,4] FK 506 is currently undergoing clinical trials at the University of Pittsburgh. Preliminary results indicate that FK 506 provides better immunosuppression in liver transplant recipients than CyA.[5]

Previous in vitro and in vivo studies have shown synergism of immunosuppressive activity between FK 506 and CyA.[2,6] Coadministration of FK 506 with CyA has also been shown to result in increased nephrotoxicity in animals and humans.[7,8] The mechanism of such an interaction is currently not understood. Such interaction may be mediated through an influence of FK 506 on the absorption, distribution, or elimination of CyA. The objective of the present study was to characterize the mechanism responsible for the observed interaction between CyA and FK 506 in an animal model.

METHODS

Six male mongrel dogs weighing 12.8 to 15 kg (mean 13.8 kg) were used in this study. Animals were fasted overnight before each study day and food was allowed 4 hours after drug administration. On day 1, the animals received a single IV dose of 40 mg CyA as a short 1-minute infusion. Blood samples were collected in heparinized vacutainers at 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, and 32 hours after dosing. On day 5, the animals received an oral dose of 150 mg CyA in the form of the commercial oral solution, and samples were collected at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, and 32 hours after dosing. On days 7 through 28, the dogs received a single oral dose of 2 mg/kg per day of FK 506 (solid dispersion in a hard gelatin capsule). The IV CyA study was repeated on days 8 and 22, and the oral study was repeated on day 28. Blood CyA was measured by HPLC.[9]

Pharmacokinetic parameters of CyA were estimated from the data using standard model-independent analysis.[10] One-way ANOVA was used to test for statistical significance of the differences in various parameters in different treatment groups after the IV studies and a two-tailed, paired t test was used to compare the oral data. The differences were considered significant if $P \leq .05$.

RESULTS

The plasma concentration-time profiles following IV and oral CyA in one of the dogs, before and after FK 506 administration, are illustrated in Figs 1 and 2. The various pharmacokinetic parameters of CyA in dogs before and after acute or chronic administration of FK 506 are summarized in Table 1.

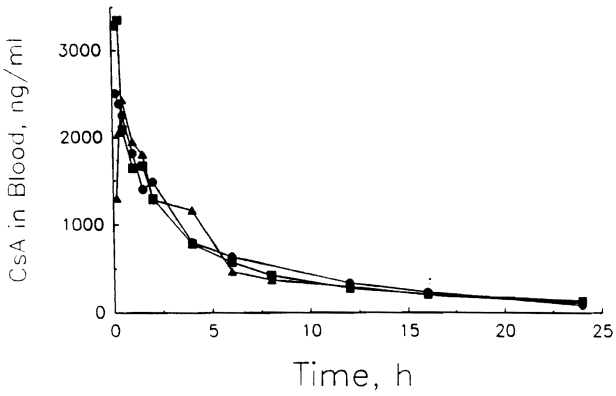

Fig 1. Blood CyA concentration versus time profile in one dog (IV dose of 40 mg as a bolus) before (●), after acute (▲), and after chronic (■) treatment with FK 506.

In all the animals, there were no significant differences among the three IV profiles, whereas the oral profiles differed considerably. The total body clearance, TBC, was

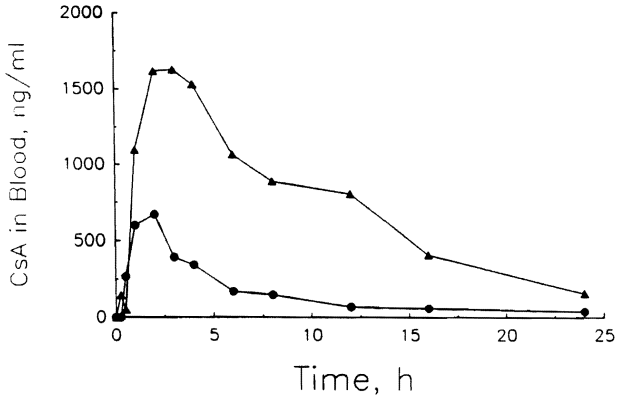

Fig 2. Blood CyA concentration versus time profile in one dog (PO dose of 150 mg) before (●) and after chronic (▲) treatment with FK 506.

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Table 1. Influence of FK 506 on CyA Kinetics in Dogs*

Parameters	Control	Acute	Chronic	Significance†
(h^{-1})	0.102 ± 0.047	0.141 ± 0.116	0.087 ± 0.031	NS
$t_{1/2}$ (h)	8.89 ± 5.75	7.07 ± 3.64	9.08 ± 4.27	NS
MRT (h)	9.40 ± 3.24	7.37 ± 3.65	9.73 ± 3.74	NS
TBC (mL/min/kg)	4.61 ± 1.31	5.13 ± 1.54	4.48 ± 1.47	NS
V_{ss} (L/kg)	2.32 ± 0.63	2.01 ± 0.61	2.39 ± 0.20	NS
V_{area} (L/kg)	2.95 ± 1.34	2.77 ± 0.91	3.16 ± 0.44	NS
V_1 (L/kg)	0.75 ± 0.40	0.69 ± 0.26	0.69 ± 0.30	NS
C_{max} (ng/mL)	746 ± 109		1488 ± 293	.01
Fraction absorbed	0.111 ± 0.023		0.401 ± 0.058	.005

*Mean ± SD.
†IV data compared using one-way ANOVA; oral data using a two-tailed paired *t* test.

4.6 ± 1.31, 5.13 ± 1.54, and 4.48 ± 1.47 mL/min per kilogram on days 1, 8, and 22, respectively. The terminal disposition half-life after IV administration was 8.89 ± 5.75, 7.07 ± 3.64, and 9.08 ± 4.27 hours. The steady-state volume of distribution was 2.32 ± 0.63, 2.01 ± 0.61, and 2.39 ± 0.61 and 2.39 ± 0.20 L/kg. None of the parameters calculated from IV data differed significantly among treatments. On the other hand, the fraction of the oral dose of CyA that was absorbed increased significantly from 11.1 ± 2.3% before FK 506 treatment to 40.1 ± 5.8% after chronic dosing with FK 506. The observed maximum blood CyA concentration also increased significantly from 746 ± 109 to 1488 ± 293 ng/mL (Table 1).

DISCUSSION

Combination of multiple immunosuppressive drugs are often used to maximize the immunosuppressive efficacy and to minimize the potential side effects. Preliminary results indicated increased nephrotoxicity and increased disposition half-life of CyA (based on whole blood TDX) in patients treated with FK 506. FK 506 has been shown to impair hepatic drug metabolism in rats.[11,12] In vitro studies also indicate FK 506 to be an inhibitor of CyA metabolism.[13] The present study was designed to investigate the effect of FK 506 pretreatment on the kinetics of CyA. Reasonable size, permitting frequent blood sampling, as well as similarity of GI physiology to man, prompted the choice of dogs as the animal model for the present study.

In the present study, pretreatment with FK 506 did not produce any significant change in the clearance or volume of distribution of CyA. This indicates that, at the doses used, FK 506 did not alter hepatic drug metabolism in the dogs. The dose of FK 506 selected for this study has been shown to be immunosuppressive in previous studies. A single oral dose of 1 mg/kg of FK 506 in mongrel dogs results in a mean (SD) peak plasma concentration of 2.9 ± 1.2 ng/mL in a mean time of 1.4 hours.[14] The dose of 2 mg/kg used in this study is expected to provide a peak concentration of approximately 6 ng/mL. At this concentration, FK 506 appears to have no effect on the hepatic drug metabolizing enzyme activity.

On the other hand, pretreatment of dogs with 2 mg/kg of FK 506 orally for 21 days produced a dramatic fourfold increase in the mean oral bioavailability of CyA. There is evidence to suggest that CyA undergoes intestinal first-pass elimination.[15] Inhibition of intestinal first-pass elimination of CyA by FK 506 appears to explain, at least in part, the enhancement of CyA bioavailability in dogs. Erythromycin, another macrolide, appears to enhance CyA blood concentrations by a similar mechanism.[16] Erythromycin is an inhibitor of cytochrome P-450IIIc, the enzyme responsible for CyA metabolism.[17] FK 506, perhaps, inhibits this enzyme in the intestinal tract, since it is present at this site at a fairly high concentration. A physical interaction between CyA and FK 506 is not likely, since CyA was administered 1 hour after the FK 506 dose. It is possible that FK 506 may alter intestinal permeability of CyA, even though there is no experimental evidence to support this hypothesis. FK 506 does not interfere with the HPLC analysis of CyA.

It may be inferred from the results of the present study that FK 506 pretreatment results in an enhancement of CyA absorption; therefore, caution should be exercised when patients receiving FK 506 are switched to CyA. Furthermore, if combined therapy of CyA and FK 506 is recommended, the dose of CyA should be reduced more than proportionately to compensate for the enhanced absorption, and guard against the development of toxicity.

CONCLUSIONS

Pretreatment with FK 506 for up to 21 days did not appear to alter the distribution or elimination characteristics of CyA in dogs. On the other hand, a significant increase in the fraction of CyA absorbed was observed after FK 506 pretreatment for 21 days, possibly due to inhibition of intestinal first-pass metabolism.

REFERENCES

1. Kino T, Hatanaka H, Hashimoto M, et al: J Antibiot 40:1249, 1987

2. Zeevi A, Duquesnoy R, Eiras G, et al: Transplant Proc 19:40, 1987

3. Starzl TE, Makowka L, Todo S: A Potential Breakthrough in Immunosuppression. Philadelphia, Grune & Stratton, 1987

4. Ochiai T, Nakajima K, Kagata M et al: Transplant Proc 19:1284, 1987

5. Todo S, Fung JJ, Demetrius A et al: Transplant Proc (in press)

6. Todo S, Makowka L, Starzl TE: Surg Res Commun 1:330, 1987

7. Nalesnik M, Lai HS, Murase N, et al: Transplant Proc 22:87, 1990

8. McCauley J, Takaya S, Fung JJ, et al: Transplant Proc 23:1444, 1991

9. Ptachcinski RJ, Venkataramanan R, Rosenthal JT, et al: Clin Pharm Ther 38:296, 1985

10. Gibaldi M, Perrier D: Pharmacokinetics (2nd ed). New York, Marcel Dekker, 1985

11. Habucky K, Venkataramanan R, Kubitsky J, et al: Pharm Res 6:189S, 1989

12. Venkataramanan R, Warty VS, Zemaitis M, et al: Transplant Proc 20:30, 1987

13. Omar G, Shah A, Thompson AW, et al: Transplant Proc 23:934, 1991

14. Furukawa H, Imventarza O, Venkataramanan R, et al: Transplantation (in press)

15. Schwinghammer T, Przepiorka D, Venkataramanan R, et al: Brit J Clin Pharmacol 32:323, 1991

16. Gupta SK, Bakran A, Johnson RWG, et al: Brit J Clin Pharmacol 27:475, 1989

17. Bertault PP, Bonfils C, Fabre G, et al: Drug Metab Dispos 15:391, 1987