

ABSORPTION AND INTESTINAL METABOLISM OF SDZ-RAD AND RAPAMYCIN IN RATS

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ABSTRACT:

The new immunosuppressive agent, SDZ-RAD, and its analog rapamycin were examined for intestinal absorption, metabolism, and bioavailability in Wistar rats. Intestinal first-pass metabolism studies from rat jejunum showed that at 0.5 mg of SDZ-RAD/kg rat, 50% of the parent compound was metabolized in the intestinal mucosa, and this decreased to around 30% when SDZ-RAD was increased to 5.0 mg/kg rat. Results for rapamycin at the low dose were similar to those for SDZ-RAD, but at the higher dose only 1 to 14% of the total rapamycin absorbed was metabolized by the intestine. After i.v. administration of 1 mg/kg SDZ-RAD or rapamycin, the area under the concentration curve (AUC) for rapamycin was twice that of SDZ-RAD, resulting in a systemic clearance of 6.2 ml/min and 3.0 ml/min for SDZ-RAD and rapamycin, respectively. However, the AUC for oral absorption was similar for the two

compounds: 140 and 172 ng*h/ml for SDZ-RAD and rapamycin, respectively. Because blood clearance was faster for SDZ-RAD after i.v. administration, the absolute oral bioavailability for SDZ-RAD was 16% compared with 10% for rapamycin. Overall, the data suggest that intestinal first pass is a major site of metabolism for SDZ-RAD and rapamycin and that intestinal absorption of SDZ-RAD was much faster than that of rapamycin. This allowed it to counteract the combined actions of faster systemic clearance and increased intestinal metabolism, resulting in comparable absolute exposure when given orally. Also, the coadministration of cyclosporin A with SDZ-RAD was shown to dramatically increase blood AUCs for SDZ-RAD, probably through saturating intestinal metabolism mechanisms.

Cyclosporin A (CsA)¹ is currently the main immunosuppressant used in solid organ transplantation. This compound binds to a cytoplasmic cyclophilin, and the resulting complex inhibits calcineurin and, hence, interleukin 2, which blocks transcriptional activation of T cells (Graham, 1994). This immunosuppressant initially was used in the early 1980s. Recent research has been conducted into both improving the formulation of CsA delivery and developing other compounds to improve immunosuppression either as replacements for, or to work in synergy with, CsA (Kahan et al., 1991; Lake and Canafax, 1995; Lampen et al., 1995).

Allograft rejection in organ transplantation is an area that should be reduced greatly with the advent of the new, orally active immunosuppressant, SDZ-RAD. This compound is a derivative of rapamycin, which inhibits the proliferation of T cells by a different mechanism than that of CsA, preventing their entry into the S phase of cell division (Goral and Helderman, 1997). However, animal and human studies have shown that the absorption and bioavailability of rapamycin have considerable variability (Granger et al., 1995; Ferron et al., 1997).

One of the significant contributions to intestinal uptake variability is active efflux back to the lumen by P-glycoprotein (P-gp) and other active efflux proteins present in the apical layer of enterocytes at the

villus tip of intestinal microvilli. P-gp originally was identified as an efflux pump responsible for multidrug resistance in tumor cells, but since has been found to be expressed in many tissues of normal cells including the kidney, blood-brain barrier, and enterocytes of the intestine (Cordon-Cardo et al., 1989; Augustijns et al., 1993; Hunter et al., 1993). Recent reports suggest that rapamycin is a substrate for P-gp, as are many immunosuppressive compounds including CsA and tacrolimus (Augustijns et al., 1993; Hoof et al., 1993; Hebert, 1997). Current results from our own group suggest that SDZ-RAD also is a substrate for P-gp (Crowe and Lemaire, 1998). With the confirmed presence of P-gp in the intestine and its links with metabolizing enzymes of the CYP3A class (Gan et al., 1996), emphasis is being focused on the relevance of intestinal metabolism when determining the effect of first-pass metabolism on these compounds and, hence, their bioavailability. Other *in vitro* and *in situ* studies in our laboratory indicated that SDZ-RAD has better intestinal absorption than its parent compound, rapamycin (Crowe and Lemaire, 1998). This study aims to expand on our early *in vitro* and *in situ* observations by examining the difference in absorption and disposition between SDZ-RAD and rapamycin in a rat model focusing on metabolism at the intestine. Potential synergistic action between SDZ-RAD and CsA also was explored to determine whether these two P-gp substrates could increase each other's intestinal absorption.

Materials and Methods

Materials. [³H]SDZ-RAD (44.67 MBq/μmol) and [¹⁴C]rapamycin (1.571 MBq/μmol) were prepared by Novartis' isotope laboratory and shown to be higher than 99% pure by HPLC analysis. Placebo microemulsion (as described in Schuler et al., 1997), concentrate for infusion (polyethoxylated castor oil and ethanol (65:35, w/w), nonlabeled SDZ-RAD, nonlabeled rapamycin, and CsA

¹ Abbreviations used are: CsA, cyclosporin A; P-gp, P-glycoprotein; AUC, area under the concentration curve; LC-RID, liquid chromatography-reverse isotope dilution; AUMC, area under the mean concentration curve.

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Animal Studies. The experiments were performed with male Wistar rats weighing approximately 300 g (BRL, Fuellinsdorf, Switzerland). They were anesthetized with Metofane (methoxyflurane; Mallinckrodt Veterinary Inc., Mundelein, IL) in a veterinary respirator (model HN64; Holzel). The right femoral artery was cannulated with a segment of polyethylene tubing containing heparinized saline (100 U/ml) for the collection of blood. Rats that were infused i.v. also had the right femoral vein cannulated. The tubes were passed s.c. to emerge at the base of the neck. Animals were isolated in metabolic cages and allowed to move freely. Full recovery from anesthesia usually occurred within 2 h, and the presence of the catheter(s) caused no obvious discomfort to the animals. Administration of the drugs was carried out the following day, after surgery. Animals had access to food before and after surgery, but this was removed 14 h before administration of the compounds. All animals had free access to drinking water.

Dosage and Administration. Intravenous infusion. [³H]SDZ-RAD was mixed with nonlabeled SDZ-RAD to obtain the appropriate specific radioactivity, whereas [¹⁴C]rapamycin was used without nonlabeled additions. Both compounds were dissolved in microemulsion and diluted in saline (1:2.6, v/v). The formulations were administered as a 2-h infusion (0.3 ml/h) in the cannulated femoral vein. The dose for both compounds was 1 mg/kg. Blood was collected from the cannulated femoral artery 1 h before the end of infusion, at the end of infusion (time 0), and at 0.5, 1.0, 2.0, 4.0, 8.0, 24, 32, 48, 72, and 168 h after drug infusion had ceased.

Oral administration. [³H]SDZ-RAD and [¹⁴C]rapamycin were dissolved in microemulsion and diluted to a final volume with saline. The dose ingested was 1.5 mg/kg using 5.0 ml/kg of the saline/microemulsion mixture administered by gastric intubation according to the individual body weight on the day of application. Blood was collected from the cannulated femoral artery 0.5, 1.0, 2.0, 4.0, 8.0, 12, 24, 32, and 48 h after gastric intubation of radiolabeled compounds. At various time points for both oral and i.v. administered rats, a volume of blood equivalent to that taken was replaced through the cannulated femoral artery using fresh blood from donor rats.

CsA, as Neoral containing 100 mg/ml CsA, was administered to rats either alone at 2.5 mg/kg by gastric intubation or in combination with 0.6 mg/kg [³H]SDZ-RAD for the oral coadministration study. [³H]SDZ-RAD also was used alone at 0.6 mg/kg in this study.

Mesenteric Vein Method. Adult Wistar rats (300 g) were fasted overnight before initiating the dosing study. Rats were anaesthetized for the duration of the study with i.p. injections of urethane (1.1 g/kg). The middle 10 cm of the jejunal segment was ligated in a location that allowed all blood from mesenteric branching along the ligated segment to be collected from one point just before entering the superior mesenteric vein. One milliliter of placebo microemulsion/saline mix (1:13.5), containing either 0.15 mg or 1.5 mg of a [³H]SDZ-RAD solution (189–329 μ Ci/ml), or a [¹⁴C]rapamycin solution (7.0–13.9 μ Ci/ml), was injected into the segment. The total mesenteric blood for the region was collected immediately using a 27-gauge needle and 1-ml syringe. Collection continued for as long as possible, usually 3 to 5 min, allowing no blood to enter the circulation from the ligated segment. Unlike other studies examining mesenteric vein blood that have used lengths of time of more than 30 min (Kim et al., 1993), we did not want to perfuse the animals with donor blood, limiting our study to the initial absorption phase (approximately 5 min). Blood of individual animals was examined for total radioactivity by liquid scintillation counting and for parent drug by liquid chromatography-reverse isotope dilution (LC-RID).

Parent Drug Determinations (LC-RID). Blood aliquots (200 μ l) were spiked with 200 μ l of cold compound (50 μ g/ml of either SDZ-RAD or rapamycin in acetonitrile). Water (1 ml) and 100 μ l of 5 \times concentrated Merck Titrisol, pH 9.0, buffer also were added. Two hundred fifty microliters of SDZ-RAD and rapamycin was extracted in diethylether, evaporated, and reconstituted in mobile phase consisting of acetonitrile/tertiary butyl methyl-ether and 0.1% tetramethylammonium hydrogen sulfate (370:60:500, w/w/w). Seventy-five microliters of *n*-hexane was then added. Samples were vortexed vigorously, and, after centrifugation, the hexane layer was removed. SDZ-RAD and rapamycin in the remaining phase were separated from their metabolites by HPLC. Chromatography was performed on a HPLC system (Kontron Instruments, Zurich, Switzerland). Separation was conducted on a Brownlee Spheri-10 RP2 column (4.6 \times 220 mm) at 70°C. The mobile phase was as

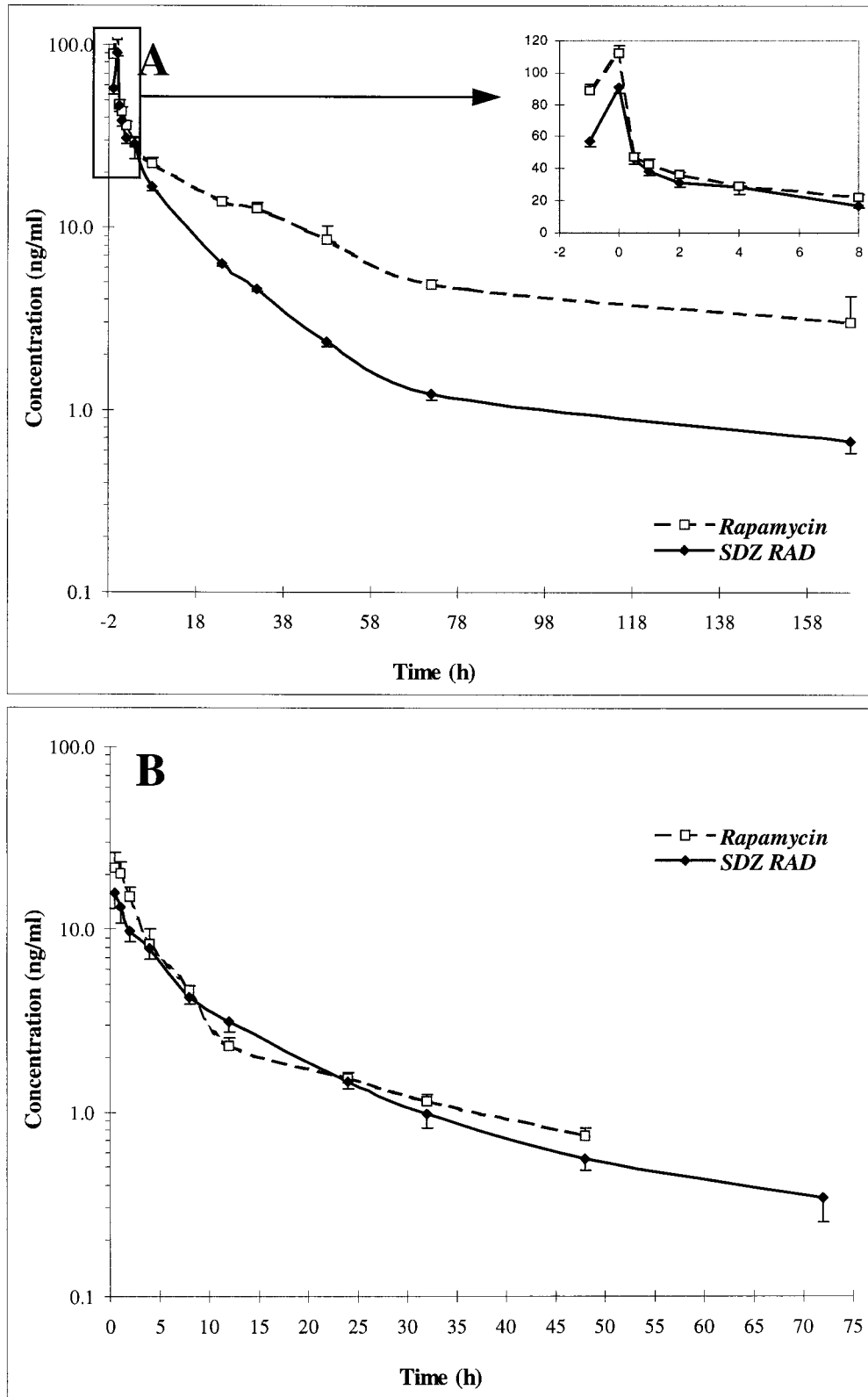
at 278 nm, and the peak corresponding to either unchanged [³H]SDZ-RAD or [¹⁴C]rapamycin was collected in a polyethylene vial by fraction collection (SuperFrac; Pharmacia LKB, Uppsala, Sweden) and subjected to radioactivity determinations. The concentration of parent compound in each sample was calculated from the ratio of the amount of radioactivity in the collected fraction to the area of the UV absorbance of the nonradiolabeled SDZ-RAD or rapamycin as used as internal standards (Everett et al., 1989).

CsA Determinations (enzyme-linked immunosorbent assay). CsA was determined using the whole-blood cyclosporin displacement immunoassay procedure. Microtest plates were coated with goat anti-mouse (Fc) in coating buffer. Twenty-five microliters of whole blood was mixed with 75 μ l of CsA displacement/lysis buffer. Biotinylated CsA and a CsA-specific monoclonal antibody were then added to the mixed blood, and the resulting samples were pipetted into the precoated wells and sealed at 4°C for 150 min. After streptavidin-peroxidase and peroxidase substrate additions, the microtiter plates were examined at 490 nm in a spectrophotometric plate reader.

Data Analysis. Blood levels of unchanged SDZ-RAD and rapamycin were evaluated by nonlinear regression analysis using the noncompartmental model of constant infusion for i.v. doses and extravascular input for oral doses using the WinNonlin Pro package for Windows NT 4.0 (Scientific Consulting Inc., Cary, NC), using a 166-MHz Pentium computer. AUC and area under the mean concentration curve (AUMC) of the blood-drug concentration time curves were obtained by the linear trapezoidal rule and extrapolated to infinite time by the additions of $C(t_m)/\lambda_z$ (AUC) and $C(t_m)/\lambda_z^2 + C(t_m)*t_m/\lambda_z$ (AUMC), where $C(t_m)$ is the last concentration above the limit of quantification at time t_m and λ_z is the slope of the terminal elimination phase. Total clearance (CL) was calculated as $\text{dose}/\text{AUC}_{i.v.}$. The volume of distribution at steady state was calculated as $V_{ss} = \text{CL}*\text{AUMC}/\text{AUC}$. Results expressed in this study are presented as the mean \pm S.E.M. Significant differences between values were examined using Student's two-tailed unpaired or paired *t* test as appropriate. Results were considered significant if $P < .05$.

Results

The mean blood concentrations of both SDZ-RAD and rapamycin after i.v. and oral administration can be seen in Fig. 1. Blood concentrations of intact SDZ-RAD from a 2-h infusion of 1 mg/kg SDZ-RAD were shown to be cleared more rapidly than that of an equivalent dose of rapamycin (Fig. 1A). When the AUCs were calculated to infinity (Table 1), it was established that rapamycin had an AUC which was double that of SDZ-RAD (1140 compared with 573 ng* μ g/ml). However, when applied via the oral route, blood concentrations of intact SDZ-RAD and rapamycin were very similar. A comparison of blood levels obtained after i.v. and oral administration indicated a low absorption of both compounds; however, the absorption that did occur proceeded very rapidly—the highest blood concentrations were observed after only 30 min (Fig. 1B). A clear biphasic response in elimination of orally presented rapamycin was observed in this study, which was much more pronounced than that of SDZ-RAD (Fig. 1B). Up to 12 h of elimination of rapamycin was quite rapid whereas elimination after 12 h was significantly lower. The first phase would correspond to rapid tissue distribution whereas the second was most likely limited by systemic metabolism (Fig. 1A). Blood samples from the oral dose rapamycin experiment was collected only for 48 h; therefore, for consistency, all results in Table 1 were calculated from the extrapolation of 0- to 48-h data. It can be seen that very little difference existed in the primary half-life of rapamycin and SDZ-RAD regardless of the route of administration. However, the terminal half-life of rapamycin was 25 h using the 0- to 48-h data compared with only 15 h for SDZ-RAD (Table 1). Again, no difference in half-life was apparent between oral and i.v. doses. The systemic bioavailability of SDZ-RAD, estimated by the ratio of dose-normalized blood AUCs, amounted to more than 16% whereas the bioavailability of rapamycin was only 10% in comparison.



Results are mean \pm SEM of 4-5 rats each

FIG. 1. Mean blood concentration in adult male rats of rapamycin and SDZ-RAD after a 2-h infusion of either 1 mg/kg rapamycin or SDZ-RAD (A; inset shows a magnification of blood concentrations over the first 8 h) and an oral gavage injection of 1.5 mg/kg rapamycin or SDZ-RAD (B).

Results are the mean \pm S.E.M. of four rats.

TABLE 1

Pharmacokinetic parameters for SDZ-RAD and rapamycin in adult rats after single oral administrations (1.5 mg/kg) and 2-h i.v. infusions (1.0 mg/kg)

Compound	Route	AUC _{0-∞} ^a	AUC _{0-∞} ^a	CL	V _{SS}	T _{1/2λ1}	T _{1/2term}	MRT	F
		ng-eq* <i>h</i> /ml ^b	ng* <i>h</i> /ml ^c	ml/min	l/kg	h	h	h	%
Rapamycin	Oral	428 ± 12	172 ± 10			2.4 ± 0.5	24.3 ± 4.6	23.8 ± 5.3	10.0
SDZ-RAD	Oral	606 ± 36	141 ± 43			2.7 ± 0.5	15.5 ± 1.5	16.4 ± 1.3	16.4
Rapamycin	i.v.	1760 ± 30	1140 ± 90	3.0 ± 0.2	27 ± 3	1.9 ± 0.1	25.2 ± 2.6	34.5 ± 4.2	
SDZ-RAD	i.v.	1350 ± 90	573 ± 32	6.2 ± 0.3	52 ± 4	3.4 ± 1.1	14.2 ± 0.4	15.9 ± 0.5	

T_{1/2λ1} is half-life of main elimination phase, and T_{1/2term} is half-life of the terminal phase based on the 0- to 48-h data only. Results are expressed as means ± S.E.M. of four to five rats.

^a AUC_{0-∞} is extrapolated to infinity from 0- to 48-h data.

^b ng-eq**h*/ml refers to the total radioactivity measured in blood.

^c ng**h*/ml refers to the parent compound.

retained in the AUCs for blood concentration indicated that when the compounds were given as a 2-h i.v. infusion almost 65% and 42.5% of the AUCs for rapamycin and SDZ-RAD, respectively, were retained as parent compound, yet when the compounds were given orally, the relative amount of parent compound decreased such that only 40% of rapamycin and 23% of SDZ-RAD were present as parent compound. These results suggested that intestinal metabolism could be important in the first-pass effect for these compounds. Therefore, we examined the metabolism of SDZ-RAD and rapamycin immediately after passage through the mesenteric vein.

The average volume of mesenteric vein blood collected was around 0.8 to 1.2 ml per rat. Collection of total blood from the mesenteric vein immediately after administration into a ligated intestinal segment ensured that none of the compound could enter the main circulation, thereby removing the possibility of metabolized compound recirculating through the mesenteric arteries. Hence, any metabolism observed in the samples had come from the intestine only. In the animals given 0.5 mg/kg of either [³H]SDZ-RAD or [¹⁴C]rapamycin, 0.05 ± 0.01% of the total amount of radioactivity available for absorption (drug and metabolites) was collected. In comparison, the proportion collected from the animals given 5 mg/kg of either compound was 0.06 ± 0.01%. Only a qualitative assessment regarding the initial jejunal absorption phase could be made from the mesenteric vein study, but the similar percentages of total collected material did suggest that there was no difference in very early absorption rates between SDZ-RAD and rapamycin and that effectively the same proportion of compound was being absorbed across the jejunal membrane into the mesenteric system regardless of the concentration applied.

The results of parent drug uptake for animals given 0.5 mg/kg [³H]SDZ-RAD (Table 2) showed that in the initial uptake phase, 60% of the transcytosed compound was metabolized; this dropped to 47% as absorption continued during the first 5 min. In contrast, the metabolism of SDZ-RAD by the gastrointestinal tract in animals given 10 times this amount (5 mg/kg) was lower; only 43% of initially absorbed SDZ-RAD was metabolized and this dropped to 29% as absorption continued. Hence, a greater percentage of parent compound was able to cross the intestinal barrier into the mesenteric blood with a combination of increasing concentration and increasing time in the luminal environment. Upward of 900 ng of unchanged SDZ-RAD/ml blood was being absorbed during the first 5 min of ligated jejunal administration (Table 2), when rats were given the higher 5-mg/kg dose. Qualitatively, this confers a reasonably good absorption profile.

The results for parent drug uptake of rapamycin were very similar to results for that of SDZ-RAD, in that the amount retained as parent compound at the low dose was significantly lower than that at the higher dose (Table 2). Also, when directly comparing the amount of intact rapamycin and SDZ-RAD together at the low 0.5-mg/kg dose,

However, at the higher dose, rapamycin metabolism through the intestine was reduced greatly. During the initial 2.5 min, more than 25% of the rapamycin transported across the intestine was metabolized by the intestine, but during the next few minutes, 99% of the absorbed compound was in its original form.

It has been shown recently that the extent of intestinal metabolism by the CYP3A subtype could be related to the affinity of P-gp toward a particular compound (Gan et al., 1996; Schuetz et al., 1996). Previous results from our laboratory have shown that in the *in vitro* intestinal Caco-2 cell model, SDZ-RAD and rapamycin were shown to be acted upon by active efflux pumps that were most likely related to P-gp (A.C. and M.L., unpublished observations). We continued this study by examining the blood levels of SDZ-RAD and CsA when both compounds were given simultaneously as an oral gavage to rats (Fig. 2 and Table 3). The AUC for blood concentrations of CsA was increased by 22% when orally coadministered with SDZ-RAD. SDZ-RAD contributed only 20% of the total drug dose in this study, which appeared to suggest a direct concentration-based response.

SDZ-RAD blood-concentration AUC was increased 5-fold when coadministered with CsA (Fig. 2; Table 3), which also was added directly to the increase in the amount of CsA over SDZ-RAD added for oral absorption. When compared, as a percentage, with the total radioactivity that was found in the blood, it was also noticed that unchanged SDZ-RAD increased from 30 to 40% of the total pool of drug and metabolites found in the blood after coadministration with CsA.

Discussion

SDZ-RAD is a structural analog of rapamycin, sharing the same mechanisms of action (Schuler et al., 1997). It was of interest to determine the oral absorption profile of the new immunosuppressant SDZ-RAD and compare it with rapamycin because a previous report by Schuler et al. (1997) reported that even though the *in vitro* activity of SDZ-RAD was less than half that of rapamycin, in their rat model, oral activity was equivalent for the two compounds.

The results of this study showed that when both compounds were given *i.v.*, rapamycin had a much longer residence time in the blood compared with SDZ-RAD. However, it was shown clearly that when both compounds were administered orally, the blood AUCs for SDZ-RAD and rapamycin were similar, consistent with the oral equipotency of these two immunosuppressants described recently (Schuler et al., 1997). Hence, the bioavailability of SDZ-RAD was 60% higher than that of rapamycin, most likely because of more rapid absorption of SDZ-RAD across the intestinal wall. This study used normal, healthy rats, but a recent study has examined the pharmacokinetics of rapamycin in human kidney transplant patients and concluded that the oral absorption was 20% (Ferron et al., 1997), about double our estimate in rats from this study. However, the variability seen in their study suggests that interpatient differences in rapamycin bioavailabil-

TABLE 2

[³H]SDZ-RAD and [¹⁴C]rapamycin recovery from adult rat mesenteric vein after in situ jejunal administration at either 0.5 or 5.0 mg/kg

Compound	Dose	Collection	Total Activity	Parent Drug	Fraction of Parent Drug
	mg/kg	min	ng-eq/ml	ng/ml	%
SDZ-RAD	0.5	0-2.5	30 ± 9	15 ± 7	40 ± 6
		2.5-5	95 ± 22	47 ± 9	53 ± 9
	5	0-2.5	520 ± 129	313 ± 88	57 ± 4
		2.5-5	1300 ± 70	913 ± 71	71 ± 8
Rapamycin	0.5	0-2.5	48 ± 16	22 ± 8	43 ± 3
		2.5-5	135 ± 43	88 ± 28	64 ± 2
	5.0	0-2.5	402 ± 123	319 ± 102	76 ± 3
		2.5-5	1420 ± 450	1450 ± 520	99 ± 7

Results are the mean ± S.E.M. of four to six samples.

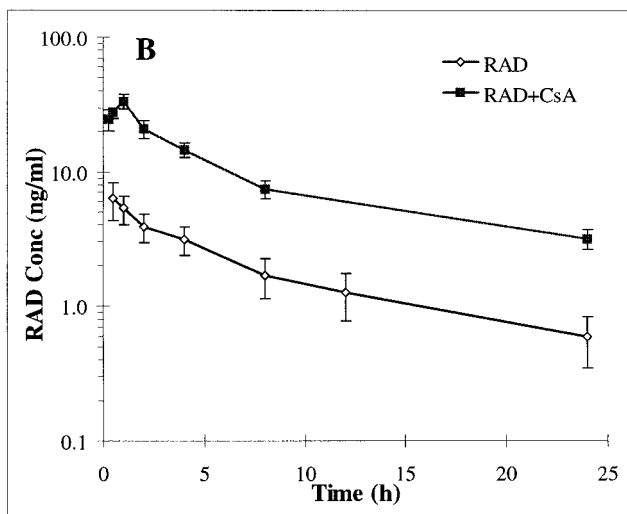
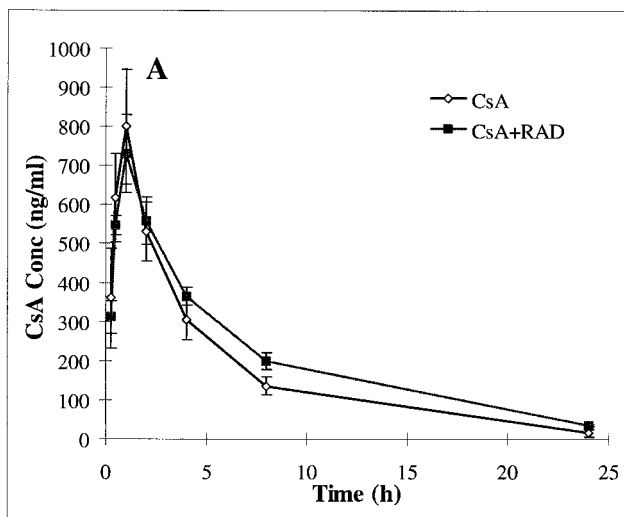


FIG. 2. Blood concentrations of CsA (A) and SDZ-RAD (B) after administration alone at 2.5 mg/kg (CsA), 0.6 mg/kg (SDZ-RAD), and coadministration at the same doses.

Results are the mean ± S.E.M. of four rats.

bioavailability of between 2 and 89% (Ptachinski et al., 1985), which is likely a result of different expression levels of MDR1, the intestinal P-gp efflux pump, in the villus tip of human enterocytes (Kolars et al.,

The first 12 h of oral absorption showed rapamycin to have a slightly faster rate of blood drug level decrease than SDZ-RAD. The opposite effect was observed after i.v. administration, which could indicate that gastrointestinal first-pass metabolism was the initial limiting factor in circulating blood levels of rapamycin, but that once most of the compound had been absorbed, then systemic clearance became the limiting factor.

Of the current immunosuppressants, P-gp's role in CsA activity and absorption has been examined by many studies (Zacher et al., 1994; Fricker et al., 1996; Tanaka et al., 1996; Terao et al., 1996). It was found that P-gp efflux at the intestinal wall accounts for almost half of the variability in bioavailability of CsA (Lown et al., 1997). After oral application in this study, the percentage of parent compound remaining in the blood was lower for both SDZ-RAD and rapamycin in comparison to i.v. dosing, suggesting that intestinal metabolism was occurring, and this was confirmed from analysis of mesenteric vein blood immediately after absorption. Therefore, we also would conclude from our animal studies that significant proportions of both rapamycin and SDZ-RAD, especially at low oral doses, are affected by intestinal first-pass metabolism and that P-gp efflux may be a factor in this effect along with CYP3A4 and other cytochrome P-450s.

The mesenteric vein study showed that SDZ-RAD was metabolized by the intestine to a greater extent than rapamycin. SDZ-RAD also was eliminated from the blood faster than rapamycin after i.v. administration because of the combined effect of increased clearance and a much higher volume of distribution. However, the AUCs after oral application were similar for both compounds, which suggests that SDZ-RAD has a very high rate of absorption to counteract its metabolism and elimination pathways. This conclusion is supported by other recent results in our laboratory that showed SDZ-RAD to have almost double the intrinsic permeability of rapamycin through our in vitro Caco-2 intestinal transport system (Crowe and Lemaire, 1998). It is interesting that SDZ-RAD differs from rapamycin solely by the addition of a 40-*O*-(2-hydroxymethyl) group. This alteration appears to be enough to completely alter membrane absorption, metabolic enzyme affinity, and pharmacokinetic profiles, as suggested here and elsewhere (Schuler et al. 1997; Crowe and Lemaire, 1998), yet with these differences, systemic exposure after oral dosing is similar for rapamycin and SDZ-RAD. Because absorption is rapid for SDZ-RAD, it may be possible to inhibit intestinal metabolism by allowing greater amounts of the compound to enter the circulation intact.

It has been shown that the addition of SDZ-RAD in conjunction with the P-gp and CYP3A inhibitor, CsA, can result in an increase in blood levels of CsA, just as CsA can equally increase blood levels of SDZ-RAD. A recent publication examined the blood concentrations of CsA and rapamycin after i.v. coadministration in rats, and rapamycin

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