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Technical Note

The Effect of End-to-Side Portacaval Shunt on Cyclosporine Pharmacokinetics in Rats

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INTRODUCTION

Variability in the clearance of cyclosporine (CS) prohibits standard dosing regimens both in patients after organ transplantation and in patients suffering from autoimmune diseases. Even continuous blood-level monitoring and dosage adjustments do not guarantee the achievement of therapeutic blood concentrations.

In adult patients the clearance of CS is, on average, 0.3 liter/min calculated from a specific measurement in whole blood (1). Since CS is eliminated predominantly by hepatic metabolism (2) and because hepatic blood flow in adults averages 1.4 liters/min, one can infer that CS should have a low extraction ratio. In a 4-year-old child hepatic and portal venous blood samples were obtained simultaneously just before a transplanted liver was removed due to hepatic artery thrombosis. In these rather uncharacteristic circumstances an extraction ratio of 0.16 was directly measured 1 month after initiating CS therapy (3).

A better understanding of the hepatic extraction ratio can help to anticipate and to control variability in CS clearance. To this end we conducted the following pharmacokinetic experiment in rats whose portal veins were shunted from the liver to the vena cava.

MATERIALS AND METHODS

Male inbred Lewis rats weighing 350 to 450 g were purchased from Harlan Sprague Dawley (Indianapolis, Ind.). Twelve rats were subjected to an end-to-side portacaval shunt operation according to a previously published procedure (4) 3 days before the pharmacokinetic study. Another 12 rats were sham operated by opening the abdomen and clamping the portal vein for 15 min. During a 3-day recovery period the rats had free access to regular chow diet and water.

On the study day six shunted and six sham-operated rats received either 1.0 mg CS intravenously or 6.0 mg CS orally, resulting in 24 applications in 24 different rats. Prior to dosing a catheter was placed into a jugular vein under light ether anesthesia. The intravenous dose (Sandimmune i.v. diluted with saline) was given into a contralateral jugular vein shortly before the animals awoke from anesthesia. The oral dose was administered by gavage after homogenization of Sandimmune oral solution in 1 ml of chocolate milk. Blood samples were collected through the venous catheter into EDTA-containing tubes at the following times after dosing: 0, 5, 10, and 30 min and 1, 1.5, 2, 4, 6, 8, 12, 20, 24, and 28 hr for i.v. and 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 20, 24, and 28 hr for p.o. All blood samples were obtained from awake animals and they were stored refrigerated until analysis with the specific monoclonal radioimmunoassay of Sandoz, East Hanover, N.J., whose performance characteristics were recently published (5). Each rat was sacrificed after the 28-hr blood sample.

Noncompartmental pharmacokinetic analysis was performed by calculating the area under the concentration–time curve according to the trapezoidal rule. The area was extrapolated to infinity by using the rate constant obtained by fitting a straight line to the terminal part of the semilogarithmically plotted concentration–time profile. The extrapolated area was, on average, 34 ± 14% of the total AUC. Clearance (CL) or clearance over bioavailability (CL/*F*) and half-life ($t_{1/2}$) were calculated according to standard methods for each data set separately.

RESULTS

The weights of rats in the control and shunt groups were not statistically different and ranged from 350 to 450 g. However, 3 days after the operation the weight loss in the shunt group (−4.9%) was significantly larger than that in the control group (−1.5%). The administration of standard doses (1.0 mg CS i.v. and 6.0 mg CS p.o.) resulted in weight-normalized doses ranging from 2.6 to 3.1 and from 13.6 to 16.9 mg/kg for intravenous and oral dosing, respectively. Figure 1 displays four pharmacokinetic profiles (i.v. control,

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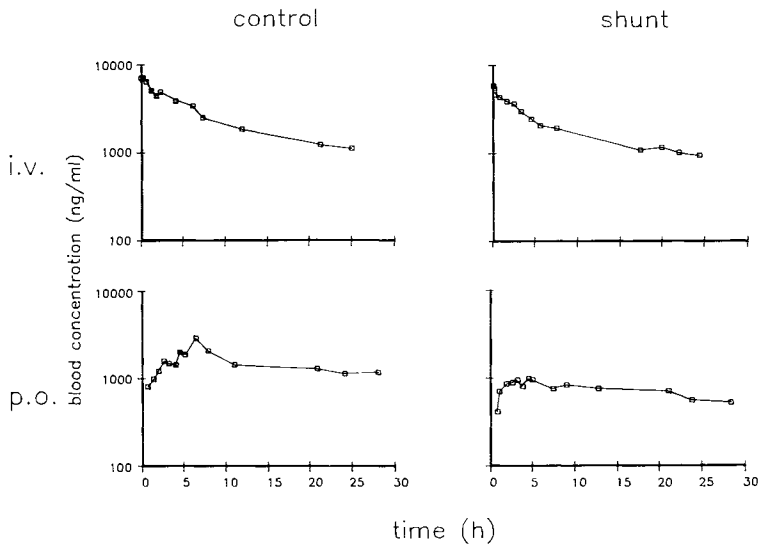

Fig. 1. Representative pharmacokinetic profiles after intravenous and oral doses of cyclosporine to sham-operated rats and rats with an end-to-side portacaval shunt. Concentrations were measured in whole blood by a specific monoclonal radioimmunoassay.

i.v. shunt, p.o. control, and p.o. shunt), each a typical example of a group of six animals, except for the i.v. shunt group, where one rat died due to unknown causes 5 hr into the experiment, leaving only five data sets for analysis. Table I summarizes the parameters under different conditions and their statistical comparison. Only CL/*F* changed significantly due to shunting. Since CL remained unchanged, *F* must have decreased, on average, from 24 to 9%.

DISCUSSION

It is well documented that rats lose weight after end-to-side portacaval shunting but at the same time they appear healthy and do not show an increased mortality rate for 25 weeks after the operation (6). It can therefore be assumed that any change in pharmacokinetics in our experiment was due to the shunt and not to a general deterioration in health.

Differences between the average CL (1.5 ml/min/kg) and the average *F* (24%) reported here for control animals and values (CL = 6.8 ml/min/kg; *F* = 99%) published previously (7) seem to be caused by the difference in concentration measurements (specific measurement in whole blood versus nonspecific polyclonal radioimmunoassay in serum).

It was reported that hepatic blood flow is reduced by 33% 3 days after the shunt operation (8). The fact that CL was not influenced by the shunt in our experiment indicates that CL of CS in rats seems to be independent of liver blood flow. Already this observation points toward a low extraction ratio for CS.

The reduction in bioavailability due to the shunt operation (*F* control = 24%; *F* shunt = 9%) is likely to be caused by a decreased absorption. Sufficient bile flow into the small intestine is a prerequisite for maximal absorption of CS (9). In shunt-operated rats it was shown that bile flow is significantly reduced (10). Thus decreased absorption seems to be a reasonable explanation for our observations. The missing peak in the p.o. profile (Fig. 1) further supports this hypothesis. The absence of the first pass through the liver in shunted animals could not compensate for the reduced absorption. It can be concluded that the first-pass effect and, for that matter, the hepatic extraction ratio of CS must be small.

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Table I. Pharmacokinetic Parameters

Dosing	Parameter	Control	Shunt	Statistics[a]
i.v.	Cl (ml/min)	0.58 ± 0.20	0.42 ± 0.04	NS[b]
i.v.	CL (ml/min/kg)	1.49 ± 0.48	1.15 ± 0.03	NS[b]
i.v.	$t_{1/2}$ (hr)	10.4 ± 4.9	12.8 ± 1.9	NS[c]
p.o.	CL/*F* (ml/min)	2.51 ± 0.97	6.87 ± 3.21	$P = 0.02$[b]
p.o.	CL/*F* (ml/min/kg)	6.07 ± 2.15	18.20 ± 8.12	$P = 0.01$[b]
p.o.	$t_{1/2}$ (hr)	17.2 ± 5.1	19.4 ± 11.9	NS[c]

[a] All groups contained six rats except for i.v., shunt with five rats.
[b] Unequal variances *t* test.
[c] Equal variances *t* test.

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REFERENCES

1. A. Lindberg, B. Odlind, G. Tufveson, B. Lindstrom, and J. Gabrielsson. *Transplant. Proc.* **18**(Suppl. 5):144–152 (1986).
2. G. Maurer. *Transplant. Proc.* **17**(Suppl. 1):19–26 (1985).
3. R. Venkataramanan, R. J. Ptachcinski, G. J. Burckart, S. Yang, and T. E. Starzl. *J. Pharm. Sci.* 74:901–902 (1985).
4. S. H. Lee and B. Fisher. *Surgery* 50:668–672 (1961).
5. P. E. Ball, H. Munzer, H. P. Keller, E. Abisch, and J. Rosenthaler. *Clin. Chem.* **34**:257–260 (1988).
6. J. R. Martin. *Physiol. Behav.* **30**:749–755 (1983).
7. R. H. Didlake, E. K. Kim, J. Grevel, L. Jarolimek, and B. D. Kahan. *Transplant. Proc.* **20**(Suppl. 2):692–695 (1988).
8. M. Secchi, B. de Hemptinne, J. B. Otte, and L. Lambotte. *Eur. Surg. Res.* **18**:361–368 (1986).
9. J. M. Tredger, N. V. Naoumov, C. M. Steward, J. G. O'Grady, J. Grevel, A. A. Niven, A. W. Kelman, B. Whiting, and R. Williams. *Transplant. Proc.* **20**(Suppl. 2):512–515 (1988).
10. G. Zsigmond, A. Bodnar, Z. Schaff, and S. Karacsonyi. *Eur. Surg. Res.* **14**:344–357 (1982).