Transplant Int (1992) 5 [Suppl 1]: S 190–S 192

TRANSPLANT
International

Cholestasis and kidney dysfunction in liver transplant patients reduces cyclosporine metabolite excretion

A. Tötterman, M. Lalla, K. Salmela, and K. Höckerstedt

Fourth Department of Surgery, University of Helsinki, Helsinki, Finland

Cyclosporin A (CsA) is metabolized principally by the hepatic cytochrome P 450-dependent microsomal enzyme system and eliminated virtually entirely as metabolites, mainly in the bile [1, 4, 6]. Only less than 1 % of the oral dose is excreted unmetabolized in the urine or bile [5, 7]. Metabolites account for 50–70% of the total CsA in whole blood [3, 5, 8]. Some of the metabolites have been shown to possess an immunosuppressive and even toxic effect but the role of this effect remains uncertain [2, 9].

In order to evaluate the effect of liver and kidney failure on the metabolism of CsA, we studied twelve patients who had undergone liver transplantation. The samples were collected during the first 4 postoperative weeks.

The aim of the study was threefold: to evaluate (1) whether an impairment of liver function, as measured by standard biochemical liver function tests, decreased the metabolism or excretion of CsA; (2) whether an induction of either the CsA metabolites or the parent compound took place in the first postoperative period; and (3) whether kidney failure, as measured by serum creatinine, correlated with blood levels of CsA or its metabolites.

Key words: Liver transplantation – Cyclosporine – Cholestasis – Kidney dysfunction

Patients and methods

Between August 1989 and January 1991 blood samples from twelve adult patients who had undergone liver transplantation in the Fourth Department of Surgery, University of Helsinki, were studied retrospectively. Samples taken during the first four postoperative weeks were included. The patients comprised eight women (age range 38–65, mean 50 years) and four men (42–62 years, mean 53.5 years). The indications for liver transplantation in the recipients were primary biliary cirrhosis (n = 6), sclerosing cholangitis (n = 2), liver cancer (n = 2), chronic active hepatitis (n = 1) and polycystic liver disease (n = 1).

Whole-blood CsA was measured with two test, a polyclonal FPIA using polyclonal antibody (polyclonal FPIA, TDx, Abbott) and a radioimmunoassay using a monoclonal specific antibody (SRIA, Sandoz), the latter being more specific for the parent compound. These results (FPIA, n = 87; SRIA, n = 101) were correlated with standard biochemical liver function tests (s-ASAT, s-ALAT, s-ALP, s-albumin, s-GT, s-bilirubin and plasma thromboplastin time) and with renal function as measured by serum creatinine.

During the follow-up period, nine patients suffered an episode of acute rejection. Five of the patients had a slight rejection, three had a moderate rejection and one had a severe rejection. Rejection was determined by the clinical picture, biochemical parameters and biopsy findings, and treated predominantly with an increase in corticosteroid dose. None of the patients died during the observation period.

In the postoperative period all patients received as immunosuppressive treatment a combination of methylprednisolone, azathioprine and CsA. CsA was administered as a continuous IV dose for 2 weeks postoperatively commencing on the first postoperative day in a dose starting at 1 mg/kg per day and titrated to maintain blood levels at 600 ng/ml measured by RIA. The drug was continued orally when absorption was stabilized. Results are given as the ratio between CsA blood level and CsA dose (mg).

All correlations were calculated with the use of a simple regression analysis, the confidence interval being 95%.

Results

Neither liver synthesizing capacity, as measured by s-albumin and s-thromboplastin time, nor hepatic cellular injury, as measured by s-ASAT, s-ALAT, and s-GT, showed any significant correlation with blood CsA levels.

With increasing values of s-BIL, blood levels of CsA (FPIA)/CsA input showed a statistically significant rise (r = 0.631, P = 0.0001) whereas the change in blood CsA (RIA)/CsA input-levels were not significant (r = 0.271, P = 0.0477). There was a positive correlation between s-bilirubin and blood CsA (FPIA)/CsA input (r = 0.611, P = 0.0001), a correlation which was not seen with blood CsA (RIA)/CsA input (r = 0.244, P = 0.084). S-ALP did not correlate clearly with blood CsA levels.

In the follow-up period there was no statistically significant correlation between blood CsA/CsA input, as

Offprint requests to: K. Höckerstedt, M.D., Fourth Department of Surgery, University of Helsinki, Kasarmikatu 11, SF-00130 Helsinki, Finland

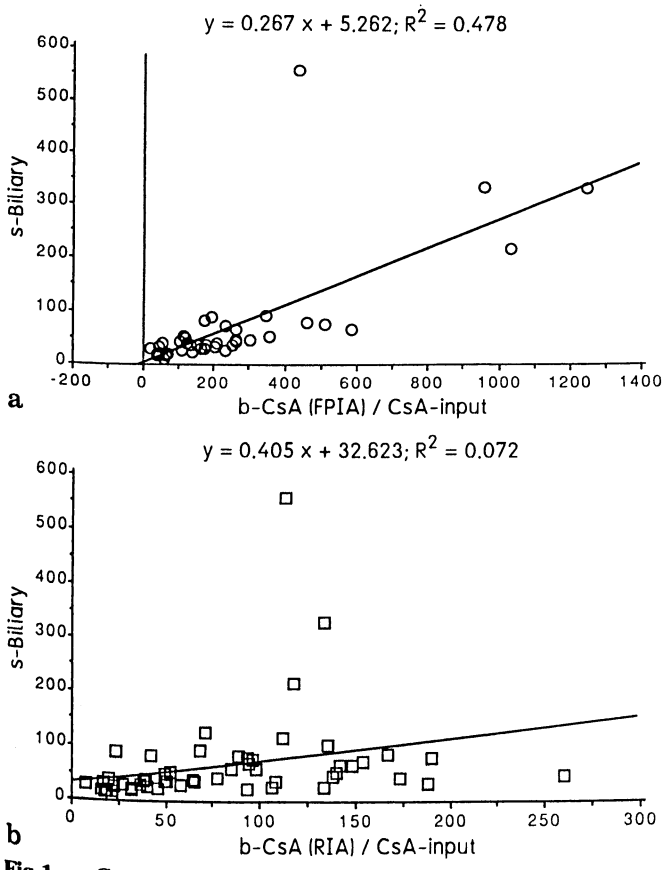

Fig. 1. **a** Correlation between serum bilirubin and blood CsA (FPIA)/CsA input. **b** Correlation between serum bilirubin and blood CsA (RIA)/CsA input

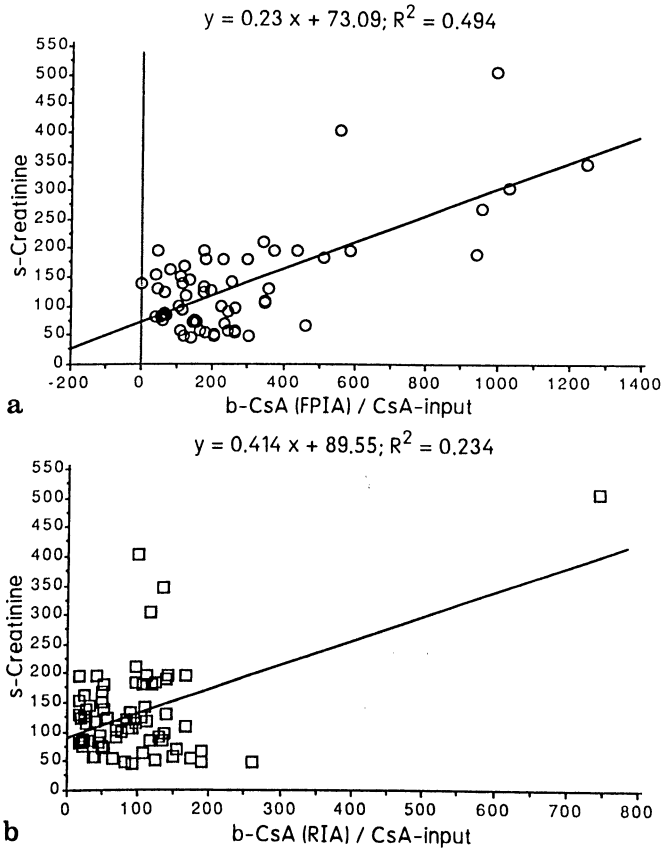

Fig. 2. **a** Correlation between serum creatinine and blood CsA (FPIA)/CsA input. **b** Correlation between serum creatinine and blood CsA (FPIA)/CsA-input

measured with either test, and the duration of medication.

With increasing values of serum creatinine, levels of both blood CsA (FPIA)/CsA input and blood CsA (RIA)/CsA input rose significantly, implying a decrease in excretion of both the parent compound and metabolites with renal failure. The correlation was seen both with the FPIA values ($r = 0.7$, $P = 0.0001$) and with the RIA values ($r = 0.48$, $P = 0.0001$).

Conclusions

The following conclusions were drawn on the assumption that the FPIA test was more specific for measuring whole blood CsA metabolites, whereas the RIA was more specific for blood levels of the parent compound.

This study did not show any correlation with impaired liver cell function and blood levels of CsA or its metabolites. Thus, an impairment in liver function did not decrease the transformation of CsA to its metabolites. Neither was there any reduction in CsA elimination in liver failure, except in cholestasis. With increasing cholestasis we saw a rise in blood levels of especially the CsA metabolites. The concentration of the CsA parent compound was not increased. This implies that cholestasis influences, in particular, the excretion of the CsA metabolites. However, a toxic effect of CsA or its metabolites on the bile duct system resulting in cholestasis, as seen in cholestasis liver failure, cannot be ruled out.

Short-term administration of CsA did not significantly increase absorption of the drug, in contrast to long-term administration [2].

Despite minor excretion of CsA through the kidneys, we found increasing blood levels of both CsA and its metabolites in kidney dysfunction. CsA is known to be nephrotoxic, thus high blood CsA levels leading to kidney failure cannot be ruled out as an explanation of the correlation.

As further knowledge of the role of the CsA metabolites is gained, the significance of the reduced excretion of CsA in kidney failure and cholestasis will become apparent, and the need for separate blood level monitoring of the metabolites for improved CsA dose adjustment will become necessary.

References

1. Berthallet-Peres P, Bonfils C, Fabre G, Just S, Cano J-P, Maurel P (1987) Metabolism of cyclosporin A. II. Implication of the macrolide antibiotic inductible cytochrome P 45 3c from rabbit liver microsomes. Drug Metab Dispos 15: 391–398
2. Kahan BD (1989) Cyclosporine. N Engl J Med 321: 1725–1738
3. Lensmeyer G, Wiebe D, Carlson I (1988) Deposition of nine metabolites of cyclosporin in human tissues, bile, urine and whole blood. Transplant Proc 20 [Suppl 2]: 614–622

4. Mauer G (1985) Metabolism of cyclosporine. Transplant Proc 17 [Suppl 1]: 19–26
5. Mauer G, Lemaine M (1986) Biotransformation and distribution in blood of cyclosporine and its metabolites. Transplant Proc 18 [Suppl 5]: 25–34
6. Shaw LM (1989) Advances in cyclosporine pharmacology, measurement and therapeutic monitoring. Cl Chemin 85: 1299–1308
7. Venkataramanan R, Starzl TE, Yang S, Burckart GJ, Platchcinski RJ, Shaw BW, Iwatsuki S, van Thiel DH, Sanhui A, Seltman H (1985) Biliary excretion of cyclosporine in liver transplanted patients. Transplant Proc 17: 286–289
8. Wagner O, Scheier E, Heitz F, Maurer G (1987) Tissue distribution, disposition, and metabolism of cyclosporine in rats. Drug Metab Dispos 15: 377–383
9. Yee GC, McGuire TR (1990) Pharmacokinetic drug interactions with cyclosporin (Part I). Clin Pharmacokinet 19: 319–332