DOES RENAL FAILURE INDUCE A DECREASE IN CYCLOSPORINE BLOOD CONCENTRATIONS?

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Summary

Blood Cys concentrations were monitored twice weekly by RIA in nine patients undergoing renal transplantation. The Cys dose was adapted to obtain blood values between 100–400ng/ml. A negative correlation was found between plasma creatinine and blood Cys, even in those patients in whom the oral dosage was not changed \( r = -0.65, n = 23, p < 0.001 \). In vitro studies showed no effect of uraemic blood on Cys measurement. It seems probable that uraemia induces changes in distribution volume and/or gastrointestinal absorption of the drug. Careful monitoring of Cys during uraemia is therefore warranted.

Introduction

Among the side effects described during cyclosporine (Cys) treatment one of the most serious is its potential nephrotoxicity [1,2]. After renal transplantation this nephrotoxicity could be easily confused with acute rejection and some authors avoid Cys when the renal allograft is not functioning primarily [3]. In patients receiving bone marrow transplantation – with previously normal renal function – a positive correlation between blood urea nitrogen and blood Cys suggested that the higher the blood Cys the greater the nephrotoxicity [2].

The present report concerns the follow-up of renal function and blood Cys in nine renal transplanted patients and shows that during renal failure Cys blood concentrations are decreased and that they increase in parallel with the improvement of renal function.

Patients and methods

All nine patients, four male and five female aged between 25 and 51 years, received a cadaveric renal allograft. Four patients started Cys intravenously before transplantation at a dose of 5mg/kg/day and continued orally 48 hours later with a dose of 10mg/kg/day. The other five patients were changed from
conventional therapy to Cys 10mg/kg/day orally at the time their renal function was normal. Cys was adapted individually depending on blood concentrations to obtain values between 100 and 400ng/ml. Blood Cys was measured in duplicate twice weekly using the radioimmunoassay kit provided by Sandoz (Basel, Switzerland). Blood samples were drawn before the morning dose, 12 to 14 hours after the previous evening dose. Immunosuppression was completed with 0.5g methylprednisolone per-operatively followed by oral prednisone at the dose of 0.7mg/kg/day. This dose was decreased stepwise by 5mg every two weeks. Treatment of acute rejection consisted of daily doses of 0.5g methylprednisolone intravenously while Cys was continued.

An in vitro study was performed to test the effect of uraemia on the measurement of Cys by the RIA technique. Blood was drawn from five uraemic patients before dialysis and from five normal controls not treated with Cys. The blood of each patient was divided into three samples in which a fixed dose of either 500, 250 or 125ng/ml of Cys was added. All samples were then measured in duplicate.

Statistics: Statistical analysis was performed using linear and logarithmic correlations. Results are given as mean ± SEM.

**Results**

*Data analysis*

Standard deviations (SD) of blood Cys measurements were evaluated during steady state periods. A steady state period was defined as a fixed oral dose of Cys over more than four days and variations of plasma creatinine of less than 20 per cent. One SD of Cys measurements was at 18.5 ± 9 per cent (mean ± SD). The observed changes in Cys during variations of renal function always exceeded 2 SD. During the steady state periods, the Cys blood concentrations were always correlated to the oral dose either when data were analysed individually or as a group (n = 105, r = 0.48, p<0.001). In the subgroup of patients who developed an episode of acute renal failure due to acute rejection or tubular necrosis, the same correlation was found during the steady state periods but the correlation was lost during renal failure (n = 34, r = 0.036, p = NS).

When the patients received a fixed oral dose of Cys between nine and 12mg/kg/day, negative logarithmic correlations were found between blood Cys and plasma creatinine (n = 23, r = -0.65, p<0.001) and urea (n = 23, r = -0.72, p<0.001). Interestingly, in this group the higher oral Cys dosage of 11 and 12mg/kg/day did not result in higher blood Cys. Moreover, the correlations were even better when the analysis was restricted to patients receiving Cys nine and 10mg/kg/day: Cys vs creatinine n = 16, r = -0.72, p<0.001 and Cys vs urea n = 16, r = -0.85, p<0.001.

*In vitro study*

The in vitro study did not show any influence of uraemia on Cys measurements by RIA. The plasma urea and creatinine of the uraemic patients were respectively at 35.4 ± 6.1mmol/L and 932 ± 188μmol/L. Dosages obtained in
blood of uraemic patients and their controls were not significantly different: 116 ± 8 (mean ± SEM) and 113 ± 4 for 125ng/ml added, 258 ± 16 and 266 ± 12 for 250 and 534 ± 18 and 538 ± 10 for 500ng/ml added.

Discussion

Our study shows a constant increase in blood Cys occurring simultaneously with the improvement of renal function when the daily Cys dose is maintained. Similarly blood values fall when renal failure reappears or gastrointestinal disturbances occur.

The variations in blood Cys induced by fluctuations of renal function are significantly different from the baseline variability of Cys measurements in patients with stable renal function. The loss of correlation between blood Cys and the oral dose when renal failure appears and the good correlation between Cys and creatinine in patients receiving a fixed oral dose of Cys strongly suggest an effect of renal function on Cys blood concentrations.

The in vitro study demonstrates that the low values found during renal failure are not due to a direct effect of uraemia on the assay method. The decrease of blood Cys during uraemia cannot be ascribed to dialysability of the drug since two out of five patients were not dialysed during their renal failure period and the same fluctuations were observed. Moreover, it has been shown that the dialysis rate of the drug is less than 2ml/min [4].

Acute changes in the hepatic metabolism of Cys appears unlikely since no signs of hepatic dysfunction were observed simultaneously. A modification in hepatic clearance of Cys which has been suspected to occur after administration of methylprednisolone does not explain our results since Cys decreased and did not increase during the occurrence of renal failure and also occurred in patients with acute tubular necrosis who did not receive methylprednisolone [5].

Our observations could be due to decreased gastrointestinal absorption. Indeed Cys values less than the therapeutic range were measured when diarrhoea appeared. In the course of uraemia, three patients developed diarrhoea. Barrett et al reported low blood concentrations of Cys after bone marrow transplantation in patients with severe gastrointestinal disturbances due to chemotherapy, radiotherapy or graft rejection with severe diarrhoea [2]. Kahan et al observed an increase in bioavailability from five to 25 per cent of the drug after one month in their patients except in those having gastrointestinal complications [6].

Acute changes in renal function could also modify the distribution volume of Cys and induce variations of blood Cys, similarly to those shown for various other drugs [7]. This hypothesis implies that drug dosage should not necessarily be increased when low values are measured during uraemia.

In conclusion, our observation strongly suggests that renal function modulates blood Cys. The clinical implications of this observation appear important in renal as well as in other types of organ transplantation. Indeed when renal function decreases or recovers careful monitoring of blood Cys is mandatory.
References

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