Routine Cyclosporine concentration - C2 level Monitoring. Is it helpful during the early post Transplant Period?

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Abstract

Background : Pre dose or trough blood cyclosporine (CSA) concentration is routinely monitored and the result is used to alter patient's drug dosing. Patients with identical pre dose blood CSA may have very different systemic exposure to the drug. Recently CSA 2 hour post dose level [C2] has been reported to correlate better with drug exposure. We undertook this study to evaluate the influence of trough and C2, CSA concentration monitoring on short-term renal allograft outcomes.

Methods : 25 patients of renal transplant receiving a triple drug regimen of CSA micro emulsion (Panacea Biotec) 8mg/kg, azathioprine 1mg/kg and prednisolone 0.5mg/kg were analyzed prospectively for graft outcomes. CSA levels were monitored in whole blood by radioimmunoassay using monoclonal antibodies, at 72 hours after the transplant.

Results : The mean age of patients was 37.08 + 9.1 years. There were 20 males and 5 females. The mean age of donors was 40.2 + 8.2 years. There were 11 related donors with at least a haplomatch, 4 spousal and 10 unrelated donors with a nil antigen match. The mean pre dose CSA concentration was 289.22 + 171.9ng/ml; range (98.8 + 783.41ng/ml). The CSA concentration at 2 hours after the CSA administration was 838 + 310.87ng/ml (range, 169 + 1268ng/ml). 3 (12%) patients had acute rejection. In these patients the mean pre dose CSA concentration was 328.67ng/ml and the mean C2, CSA concentration was 1006.26ng/ml. CSA induced hemolytic uraemic syndrome was diagnosed in one patient. The trough and C2, CSA concentration levels were 174 and 870.83ng/ml respectively in this patient.

Conclusion : In our study CSA levels, trough and peak showed significant inter patient variability. The trough and C2 concentration levels did not correlate with the episodes of acute rejection. We conclude that in a triple drug regimen with fixed dosing schedules routine trough CSA level monitoring is not helpful in the acute post renal transplant period.

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Introduction

The introduction of CSA was a major advance in the prevention and treatment of allograft rejection. One of the challenges in CSA management is the narrow therapeutic window that allows adequate T cell immunosuppression with minimum risk of adverse effects. Therefore, there has been a concerted effort in the clinical transplant community to explore and test CSA monitoring tools and techniques that will allow blood concentration of CSA to be maintained within the narrow therapeutic window, in order to maximize efficacy and minimize toxicity. In this study, we evaluated the influence of pre dose or trough CSA blood concentration and 2 hour post dose CSA concentration on clinical outcomes like acute rejection and CSA nephrotoxicity.

Material and Methods

The study population consisted of 25 kidney transplant patients undergoing transplant between January 1999 and February 2001. Patients on drugs like rifampicin, isoniazid, diltiazem or fluconazole were excluded from this study. All

patients received CSA based immunosuppression with Panimmune (Panacea Biotec). None received antibody induction. All patients were followed up for at least 6 months.

Immunosuppressive protocols: All patients received CSA, prednisolone and azathioprine. CSA and azathioprine were started 48 hours prior to the transplant at 8mg/kg/day in two divided doses and 1mg/kg/day respectively. CSA was tapered by 1mg/kg per month till a maintenance dose of 3mg/kg/day, was reached. The blood CSA C2 concentration estimation though done, was not used as a guide to change the dose of CSA. The dosage of CSA was reduced at fixed intervals. Injection methylprednisolone 500mg was given intravenously on the evening prior to the transplant and 500mg was repeated before releasing the clamps at surgery. Injection dexamethasone 24mg was given on the first day of surgery and tapered to 8mg by the seventh day; this was followed by tablet prednisolone 0.5mg/kg/day and reduced by 5mg/month till a maintenance dose of 10mg/day was achieved.

CSA monitoring: CSA blood concentration levels were estimated on day 5 of starting CSA. A sample of venous blood was drawn for pre dose or trough CSA concentration before the morning dose of CSA, and it was repeated at 2

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hours after the CSA dose was given. Whole blood CSA assays were carried out using monoclonal radioimmunoassay. The recommended therapeutic levels were: trough 250-350 ng/ml up to 3 months after transplant; single point sampling at 2 hours post dose viz: C2 levels-1700 ng/ml up to 1 month.

Acute rejection [1] was diagnosed when there was an increase in serum creatinine by at least 25% above base line, not explained by urological or vascular compromise, with a positive response to anti rejection therapy and/or histological examination.

Cyclosporine nephrotoxicity [2] was defined as >25% increase in serum creatinine levels not attributed to any other identifiable cause and which improved with a decrease in CSA dosages.

Results

The mean age of patients was 37.08 ± 9.1 years. There were 20 males and 5 females. The mean age of donors was 40.2 ± 8.2 years. There were 11 related donors with at least a haplomatch, 4 spousal and 10 unrelated donors with a nil antigen match. The mean pre dose CSA concentration was 289.22 ± 171.9 ng/ml; range (98.8 to 783.41 ng/ml). The CSA concentration at 2 hours after the CSA administration was 838 ± 310.87 ng/ml (range, 169 to 1268 ng/ml). There was no correlation between the trough and C2 concentration of CSA (coefficient of correlation; $r > 1$). Three patients had a diagnosis of acute rejection in the first month after transplant. The mean trough and CSA C2 concentration levels were 328.67 ng/ml and 1006.26 ng/ml. There was no significant difference in CSA concentration levels between the groups of patients who had acute rejection and those who did not. One patient had CSA induced hemolytic uraemic syndrome, which improved on reducing the dose of CSA. The trough and C2 blood concentration levels in this patient were 240 ng/ml and 966 ng/ml respectively.

Discussion

The adequacy of early immunosuppression is perhaps of greater importance in live related donors where ischaemic injury and primary graft dysfunction are uncommon consequences. The graft dysfunction is a direct consequence of immunological insult to the graft and the intrinsic function of the donor kidney. Hence, optimization of immunosuppressive therapy continues to be a major priority in the management of organ transplant recipients. Absorption profiling is a sensitive and practical approach for optimizing the dosage of CSA micro emulsion and can further extend the benefit of CSA immunosuppression in individual patients [3]. The parameters often used to guide therapy are, trough CSA concentration, area under the curve and one point measurement at 2 hours after the CSA dose [4]. A commonly followed strategy is an event related monitoring in response to graft dysfunction episodes or dosage reduction points in a fixed dose drug schedule [1]. Event related CSA monitoring during graft

dysfunction episodes would be expected to stress a bias towards maintaining higher doses or levels in a bid to prevent further rejections. Therefore we conducted this study prospectively to evaluate the role of CSA level monitoring in the acute post transplant period to correlate it to episodes of graft dysfunction.

CSA trough level is widely used to monitor CSA treatment even though the correlation between CSA trough level and post transplant adverse events is poor. Mahalati K et al [2] studied 156 first renal transplant recipients who received CSA based immunosuppressive therapy with micro emulsion formulation, which was initiated at 8-10 mcg/kg and adjusted to keep CSA trough level in the target range of 250-400 ng/ml in the first month after transplant. Mean CSA trough levels were not different in patients with and without rejection (293 ± 21 vs 294 ± 11 ng/ml, respectively; $p=0.98$). In our study, we also could not define a correlation between CSA trough levels and episodes of acute rejection. The poor predictability of CSA trough levels was further substantiated by the fact that 12% of study patients with CSA trough levels maintained within the therapeutic range of 250-350 ng/ml had an acute rejection episode.

Further research into the correlation between pharmacokinetics and clinical outcomes with CSA immunosuppression found drug exposure, the area under the concentration - time curve (AUC) to be a sensitive predictor of acute rejection [3,4]. However, AUC monitoring of CSA is not widely accepted because of the impracticability of repeated sampling and the cost involved [5,6]. Many studies have reported that besides AUC, the maximum blood concentration of CSA (C_{max}) plays a key role in determining the clinical response to CSA [7]. Unfortunately C_{max} is not a practical monitoring tool because it is a value extrapolated from multiple measurements. A simple measurement at 2 hours after the CSA dose C2 concentration level is reported to be an effective surrogate marker of C_{max} and drug exposure and a predictor of acute rejections [7,8]. Baramma et al [9] did routine renal graft biopsies at 6 to 9 months post transplant in 56 patients and found sub clinical rejections in 18% of them. The mean C2 levels were significantly lower in this group at the time of biopsy compared with the group without evidence of sub clinical rejections. The major drawback of this study was that it did not establish how many patients actually went on to develop clinical acute rejections. Moreover, the significance of histologically diagnosed sub clinical rejections in clinical practice is controversial.

In our study, we found there was no difference in CSA, C2 concentration levels in the groups with and without acute rejection. This prompts us to suggest that in triple drug immunosuppressive therapy, with the

present fixed dose drug schedules in which drugs are reduced at fixed points, routine monitoring of CSA levels in the early post renal transplant period is not useful. This monitoring should be an event related monitoring, restricted to episodes of graft dysfunction. This is further supported by the observation that there is a marked inter patient variability in the CSA blood concentration, in the early post renal transplant period. The levels may vary from sub therapeutic to near maximal levels. This variability in CSA concentration levels does not adversely affect graft outcome. This may be related to the overriding effect of the other two immunosuppressive drugs viz azathioprine and prednisolone in preventing acute rejections and the fact that in about half our patients there was a haplomatch donor. The adverse effects of CSA on the graft function were not seen in our study, perhaps because the CSA concentration levels achieved were lower than that recommended for that period of renal transplant. However we would like to caution that this was a small pilot study. It was done at a time when the concept of C2 levels was at its infancy and the standard laboratory methods are being established. A larger study would now be required to arrive at a statistically significant conclusion.

References

1. Rao M, Iman A, Jacob CK. Event related Cyclosporine monitoring: Pitfalls in practice. *Indian J Nephrology* 2001;11:17-24.
2. Mahalati K, Belitsky P, Sketris I, West K, Panek R. Neoral monitoring by simplified sparse sampling area under the concentration-time curve. Its relationship to acute rejections and cyclosporine nephrotoxicity early after kidney transplantation. *Transplantation* 1999;68:55-62.
3. Belitsky P, Dunn S, Johnston A, Levy GA. Impact of absorption profiling on efficacy and safety of cyclosporine therapy in transplant recipients. *Clin Pharmacokinet* 2000;2:117-25.
4. Belitsky P, Levy GA, Johnston A. Neoral absorption profiling: An evolution in effectiveness. *Transplantation Proceedings*. 32:45 S-52 S.
5. Cantarovich M, Barkun JS, Tchervenkov JI, Besner JG, Aspeslet L, Metrakos P. Comparison of Neoral dose monitoring with cyclosporine trough levels versus 2-hour post dose levels in stable liver transplant patients. *Transplantation* 66:1621-7.
6. Meyer MM, Munar M, Udeaja J, Bennet W. Efficacy of area under the curve monitoring in renal transplant recipients. *J Am Soc Nephrol* 1993;4:1306-9.
7. Belitsky P. Neoral use in the renal transplant recipient. *Transplant Proceedings*;32:10 S-19 S.
8. Cantarovich M, Besner JG, Barkun JS, Elstein E, Loertscher R. Two cyclosporine level determination is the appropriate tool to monitor Neoral therapy. *Clin Transplant* 1998;12:243-6.
9. Baramma AA, Yilmaz S, Gough J, Belitsky P. Lower cyclosporine exposure increases the risk for sub clinical rejection in renal transplant recipients (abstract). *Transplantation* 2000;69:S 225.

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