Original Article

Cyclosporine induced Nephrotoxicity in Renal Transplant Recipients: Clinical significance of fractional excretion of Sodium, Potassium and Magnesium

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Abstract

Objective: Evaluation of fractional excretion of Sodium, Potassium and Magnesium as indicators of cyclosporine (CsA) toxicity in de-novo renal transplant recipients.

Methods: A prospective study was conducted on 59 live related renal allograft recipients. Fractional excretion(FE) of sodium(Na^+), potassium(K+)and magnesium(Mg^{2+}) were calculated on day 1,3, 5 and 10 post transplant. Graft dysfunctions were evaluated by colour-doppler, CsA levels and renal biopsy. Normal ranges were determined on 30 healthy subjects.

Results: The mean creatinine on day1 was 3.1±1.3 mg/dl and declined to 1.6±1.2 on day10. FE of Na^+, K^+ and Mg^{2+} were 12±9%, 34±20% and 13±10% respectively on day 1 and reduced to 2.2±2%, 11±14% and 11±14% on day10. Of the 59 recipients, 38 (64%) had uneventful recovery (group A), 21(36%) had graft dysfunction [6 acute rejection (group B) and 15 either acute tubular necrosis or high CsA (group C)]. In group A, on day1, $FENa^+$, FEK^+ and $FEMg^{2+}$ were 5±4%, 24±12% and 6.6±3% respectively and these declined to 1.2±0.6%, 4.6±0.7% and 6±3% respectively on day10. Compared to group A, group C had significantly high values on day 1, $FENa^+$ 15±8%, FEK^+ 36±24% and $FEMg^{2+}$ 21±10% ($p<0.0001$) and on day10, $FENa^+$ 3.7± 2.7%, FEK^+ 20±15% and $FEMg^{2+}$ 15±8% ($p<0.05$). In the group B, day 1 and day10 levels were $FENa^+$ 6±3%, FEK^+ 26±13% and $FEMg^{2+}$ 7±2.8% and $FENa^+$ 1.2±0.7%, FEK^+ 4.2±0.5%, $FEMg^{2+}$ 7±4 % respectively. CsA levels and AUC did not correlate with CsA toxicity.

Conclusion: FE of magnesium is a useful marker of CsA toxicity independent of CsA blood levels. FE studies can supplement renal biopsy findings (JPMA 55:161;2005).

Introduction

Nephrotoxicity is a well known side effect of cyclosporine (CsA) therapy. It causes reduction in Glomerular Filtration Rate (GFR) by vasoconstriction of the afferent glomerular arterioles[1] and disturbs tubular function with alterations in homeostasis of electrolytes.[2] Renal allograft dysfunction in the early transplant period often causes diagnostic problems due to borderline histopathological changes where differentiation between acute cellular rejection and CsA nephrotoxicity becomes difficult. This differentiation is important since the therapeutic modalities are different for the two situations. CsA acts on the proximal tubular cells causing increased fractional excretion (FE) of sodium (Na^+), potassium (K^+), and magnesium (Mg^{2+})[3,4] and these parameters could help in this differentiation. This study was undertaken to observe changes in FE of (Na^+), (K^+) and (Mg^{2+}) in the early post transplant period and their correlation with causes of graft dysfunction.

Patients and Methods

This was a cross-sectional comparative study conducted on 59 live related renal allograft recipients. All patients received intravenous CsA at 8mg/Kg/body weight. Serum and urinary creatinine, magnesium, sodium and potassium were measured on the 1st, 3rd, 5th and 10th day post transplant. Serum and urinary creatinine and magnesium were analyzed on Hitachi 911 autoanalyzer. Magnesium was analyzed by Xylidyle Blue method and Creatinine by Jaffe-Kinetic method.[6,7] Serum and urinary sodium and potassium were analyzed on Synchron ELIS (Beckman) autoanalyzer by ion selective electrodes. Fractional excretion was calculated by the formula:

FE solute = U/P solute ÷ U/P creatinine X 100 and expressed as a percent where U is for Urine and P for plasma. CsA levels were analyzed on first day post transplant and a sparse sampling area under the curve (AUC) was undertaken in all patients on the 5th day of transplant. Cyclosporine was analyzed by a monoclonal antibody assay [Abbott]. All graft dysfunctions were assessed by colour doppler, CsA levels and renal biopsy. Statistical analysis was done by statistical package SPSS version 8.0. Comparisons between parameters were done by t-test and correlation was estimated by Pearson test. p-values less than 0.05 were considered statistically significant.

For comparison purposes, 30 healthy adults were tested for Fe of sodium, potassium and magnesium.

Results

Of the 59 de-novo renal transplant recipients, 43 were male and 16 were female. The mean age was 28.1 ± 9.8 years with a range of 12 to 53 years. The mean serum creatinine on 1st day after transplant was 3.1 ± 1.3 mg/dl. It was reduced to 2.2 ± 1.2 on the 3rd day and the tenth day mean serum creatinine was 1.6 ± 1.2 mg/dl (Figure 1 A). Serial mean ± SD % FE of sodium, potassium, and magnesium (Figure 1B, C, D) showed that there was a generalized increase in excretion of Na^+ 12.0 ± 9.0%, K^+ 34.0 ± 20.0% and Mg^{2+} 13.0 ± 10.0% on day 1 after transplant. There was reduction in the levels of sodium and potassium with reduction in creatinine levels. However % FE magnesium increased on day 3 with subsequent fall at day 5 and 10.

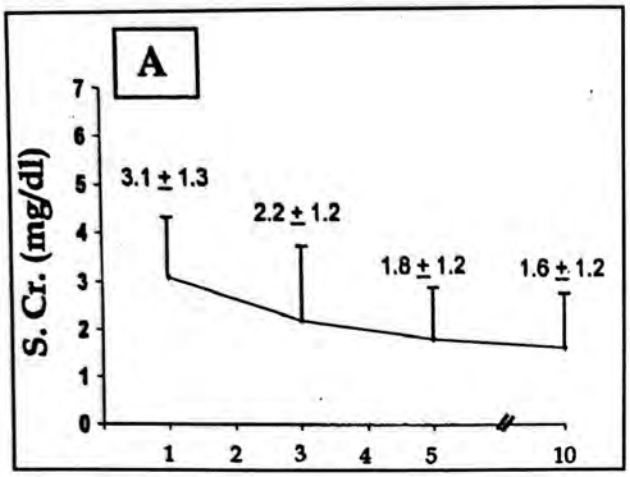
Of the 30 healthy adult controls, 20 were males and 10 females with a mean age of 33±6.7 years with a range of 22 to 50 years. In the healthy controls mean levels of FE Na^+ were 0.55 ± .34 %, K^+ 6.02 ± 2.3% and Mg^{2+} 2.84 ± 1.05%.

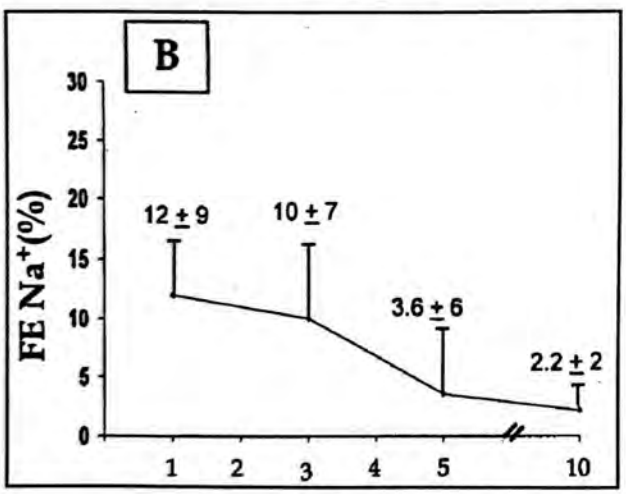
Of the 59 patients, 38 (64%) showed uneventful course with gradual decline of creatinine by day 10 (group A). Twenty one (36%) patients experienced graft dysfunction within this period. Of these 6 had biopsy proven acute rejection (group B) and in remaining 15 (group C or CsA toxicity group), 12 either had border line changes and / or acute tubular necrosis on biopsy and 3 patients had high CsA levels. Serial blood chemistry parameters in the three groups showed no significant difference in sodium, potassium or magnesium levels on day 1, 3, 5, and 10 between group A vs group B and group A vs group C. Serum creatinine was significantly increased in the two dysfunction groups B and C as compared to A (Table). Percentage FE of Na^+, K^+ and Mg^{2+} were evaluated in groups A, B and C (Figure 2 A, B, C). Increased FE Na^+ was observed in all three groups on day 1. As compared to group A and B, FE Na^+ was significantly higher in group C ($p<0.001$). On 10th day FE Na^+ declined to 1.2% in group A and B but remained significantly high 3.7 ± 2.7% ($p<0.001$) in group C. Similar to FE Na^+, FE K^+ (Figure 2B) levels were high on day 1 and remained elevated till day 10 in group C, as compared to group A and B where the levels were normalized below 6%. Mean fractional excretion of Mg^{2+} on day 1 was 6.6 % in group A and 7.0% in group B as

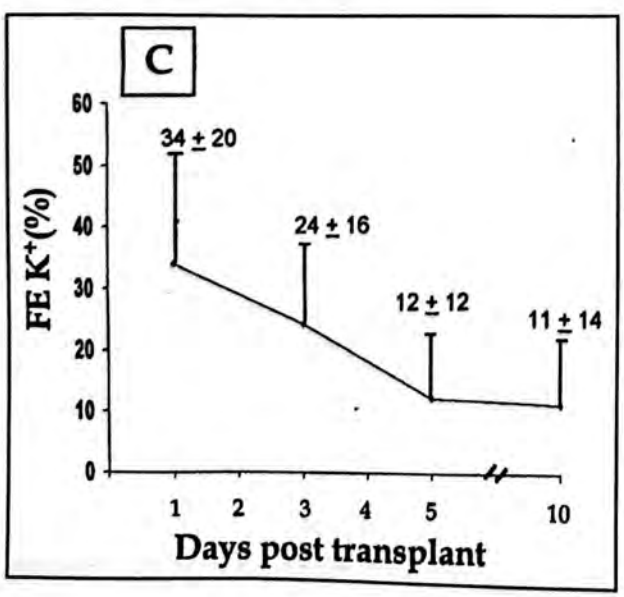
Table. Serial blood chemistry parameters in renal allograft recipients with and without graft dysfunction.

	Group A No dysfunction (n=38)	Group B Acute rejection (n=6)	P. Value	Group C CsA toxicity (n=15)	P. Value
Creatinine mg/dl					
Day 1	2.68 ± 1.3	2.50 ± 1.8	NS	3.89 ± 2.17	<0.05
Day 3	2.2 ± 1.6	1.75 ± 0.8	NS	3.10 ± 1.2	<0.05
Day 5	1.16 ± 0.43	1.7 ± 4.2	<0.05	2.58 ± 1.87	<0.05
Day 10	1.02 ± 0.32	1.38 ± 0.56	<0.05	2.86 ± 1.6	<0.05
Sodium mEq/L					
Day 1	137 ± 3.6	136 ± 5.7	NS	136 ± 5.5	NS
Day 3	137 ± 4.3	138 ± 6.3	NS	137 ± 4.9	NS
Day 5	138 ± 4.7	136 ± 4.1	NS	136 ± 6.5	NS
Day 10	138 ± 3.5	138 ± 4.5	NS	134 ± 4.4	NS
Potassium mEq/L					
Day 1	4.0 ± 0.3	3.6 ± 0.4	NS	4.1 ± 0.3	NS
Day 3	3.9 ± 0.4	3.7 ± 0.38	NS	4.0 ± 0.47	NS
Day 5	3.9 ± 0.4	3.7 ± 0.38	NS	4.0 ± 0.37	NS
Day 10	4.1 ± 0.45	4.0 ± 0.75	NS	4.0 ± 0.19	NS
Magnesium mEq/L					
Day 1	1.91 ± 0.3	1.85 ± 0.17	NS	1.92 ± 0.19	NS
Day 3	1.88 ± 0.3	1.90 ± 0.4	NS	2.0 ± 0.43	NS
Day 5	1.9 ± 0.3	1.9 ± 0.36	NS	1.95 ± 0.33	NS
Day 10	1.81 ± 0.2	1.88 ± 0.79	NS	1.88 ± 0.38	NS

compared to 21.0% in group C. This difference was statistically significant ($p<0.001$). In contrast to FE Na^+ and FE K^+, which showed decline of FE from day 1 to day 10 in group A and B (Figure 2 A, B), FE Mg^{2+} remained unchanged in these groups from day 1 to day 10 (Figure







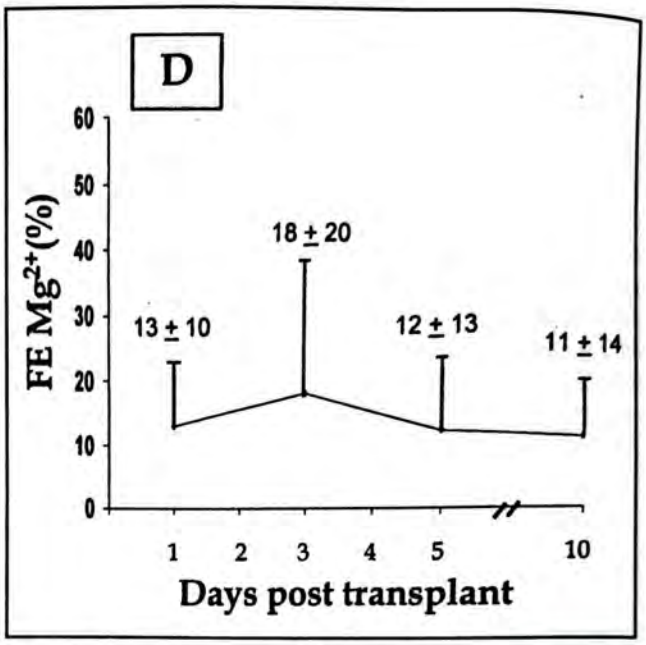
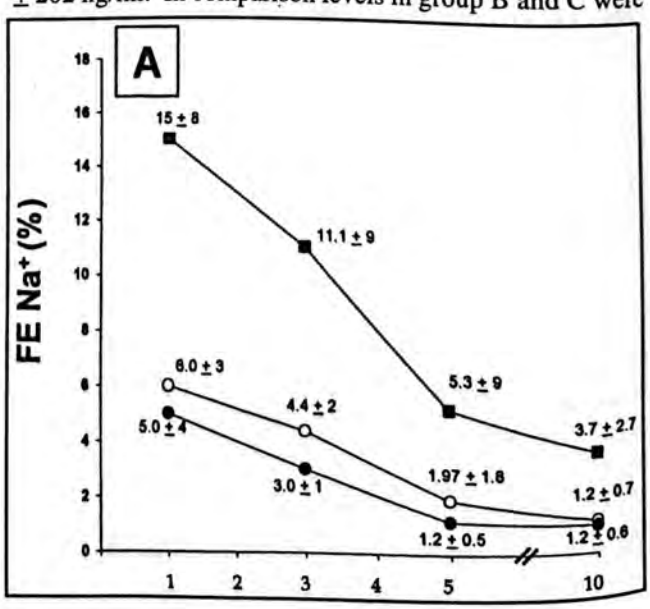


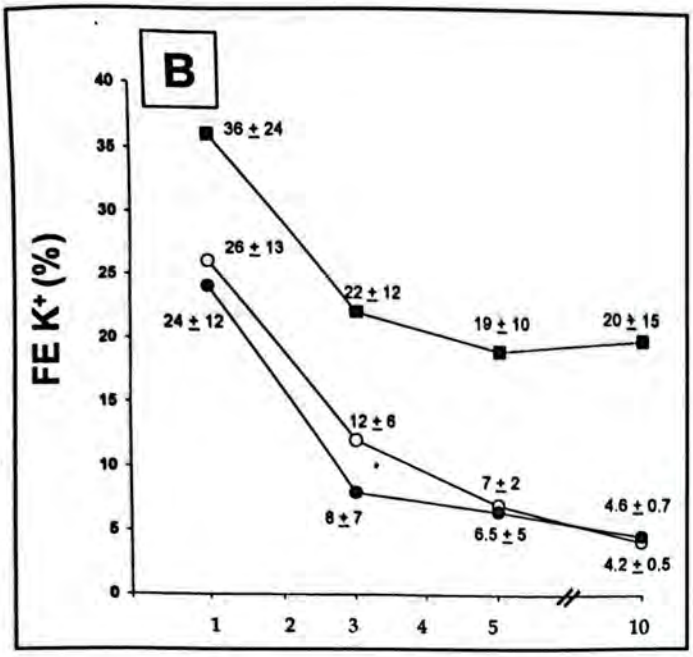
Figure 1. Mean ± SD, serum creatinine mg/dl Figure 1A, FE Na^+ % Figure 1B, FEK^+ % Figure 1C and FE Mg^{2+} % Figure 1D on post transplant day 1, 3, 5 and 10. Vertical bars show standard deviation.

2C). In group C mean % FE Mg^{2+} remained elevated from day 1 to day 10. (Figure 2C). In group C, 3 patients with high CsA levels required dose reductions during this period.

In group A, 7 patients had FE Mg^{2+} more than 10% at day 10 where mean FE Mg^{2+} was 14.3 ± 2.8% with a mean creatinine of 1.046 ± 0.264 mg/dl. At one to two week follow up there was a significant increase in serum creatinine to a mean of 1.34 ± 0.23 mg/dl (P 0.001). CsA dose reductions were undertaken in all 7 of these cases, and in all patients the serum creatinine levels reduced.

CsA levels on day 1 in group A patients were 295 ± 202 ng/ml. In comparison levels in group B and C were





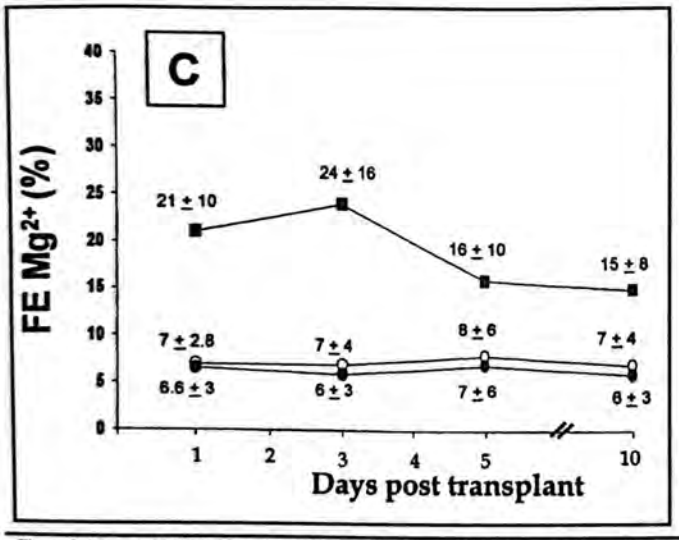


Figure 2. Mean ± SD % fractional excretion of sodium Figure 2A, potassium Figure 2B and Magnesium Figure 2C on post transplant day 1, 3, 5 and 10. Group A (uneventful recovery (○—○), group B (Acute rejection (●—●) and group C (Toxicity (■—■).

similar 270 ± 113 ng/ml (p 0.3) and 298 ± 133 ng/ml (p 0.2) respectively. A similar comparison of AUC showed levels of 5292 ± 1409 ng/ml/hr in group A, 5714 ± 1455 (p 0.5) in group B and 5907 ± 1113 ng/ml (p 0.1) in group C.

Discussion

In recent years a new diagnostic approach has been adopted to determine renal tubular transport defects by evaluating FE of a group of solutes e.g. Sodium; Potassium; Uric acid and Magnesium.[7] FE of magnesium has been shown to be the most sensitive index to detect an early abnormality of tubular structure and function.[7] In the early transplant period introduction of cyclosporine therapy can cause acute nephrotoxicity characterized by vasoconstriction, reduced G.F.R., magnesium leak and tubular injury. Our findings on the first post transplant day showed that there was increased FE of Na^+, K^+ and Mg^{2+}. A significant difference was found between the control and test population which had higher levels of FE of Na^+, K^+ and Mg^{2+}. This is in agreement with studies on acute tubular injury due to ischemia and reperfusion injuries of the transplanted kidney.[3] With improving renal function, FE of both Na^+ and K^+ return to near normal limits in patients with uneventful course and those with acute rejection. However, FE of magnesium remained high due to toxic effects of cyclosporine on tubular function.[8] Increased FE of Na^+, K^+ and Mg^{2+} in patients with ATN or high CsA levels differentiated this group from the former two categories. Our observations of FE Na^+, FE K^+ and FE Mg^{2+} in the early transplant period suggest that FE Mg^{2+} is the most reliable marker for CsA nephrotoxicity. This is of particular importance since we did not find any difference in mean spot levels of CsA on IV doses in the three groups of patients as well as AUC's on the 5th day of transplant. Similar findings have been reported in stable renal transplant recipients where CsA levels did not correlate with FE Mg^{2+}.[9] Clearly there are factors other than CsA blood levels which predispose to CsA toxicity, for example direct toxic effects of CsA on renal tubules[10] and genetic predisposition to CsA toxicity.[11]

In conclusion FE Mg^{2+} in the early transplant period appears to be an important marker of CsA toxicity. This is specially of significance, since acute toxicity can mimic acute rejection. The fact that this marker is independent of CsA dose or blood levels, a FE Mg^{2+} of more than 10% can be predictive of toxic effects of CsA. This was interestingly observed in a small group of our patients who were discharged at serum creatinine of <1.5 mg/dl and a FE Mg^{2+} of >10% and returned with renal dysfunction within 15 days. FE Mg^{2+} can be an independent important marker of CsA toxicity as well as it can be used as supportive evidence to renal biopsy findings.

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