**Abstract**

**Objectives:** Hyperkalemia is an electrolyte disorder that may occur during the first few months after a renal transplant, in patients undergoing cyclosporine immunosuppression. We present our experience with cyclosporine-associated hyperkalemia in living-donor renal transplant recipients, with isolated clinically relevant hyperkalemia soon after surgery.

**Materials and Methods:** We report 4 living-donor renal recipients with hyperkalemia soon after transplant.

**Results:** Severe unexpected hyperkalemia (7.5-9.4 mmol/L) was noted in our patients 12, 20, 22, and 34 days after transplant. The C2 cyclosporine concentration was within recommended range or slightly greater than 1200 ng/mL. The hypertonic glucose/insulin treatment along with potassium diet was without results. A reduction in daily cyclosporine dosages, along with 1- to 2-week administration of fludrocortisone was effective. The patients became normokalemic taking a standard, triple-drug immunosuppression protocol, and were discharged home with normal renal function. There were no repeat episodes of hyperkalemia in any of the patients during 12 months of follow-up.

**Conclusions:** Cyclosporine should be considered a cause of hyperkalemia in renal transplant recipients.

Successful treatment with fludrocortisone confirms that transitional pseudohypoaldosteronism has a potential nephrotoxic effect of cyclosporine. We recommend close monitoring of the cyclosporine concentration and administering fludrocortisone when treating hyperkalemia in renal transplant recipients.

**Key words:** Kidney transplant, Cyclosporine, Hyperkalemia, Fludrocortisone

**Introduction**

Despite its wide acceptance as an essential immunomodulator in different organ and tissue transplant, cyclosporine (CyA) has clinical adverse effects.1 Dose-dependent nephrotoxicity is one of them.2,3 There are several potential mechanisms that can explain this effect. Cyclosporine increases vasoconstriction of the afferent and efferent glomerular arterioles; thus reducing renal blood flow and glomerular filtration rate (GFR) that may result in acute renal failure.4 Administering CyA can produce structural and morphologic changes in proximal tubules (eg, vacuolization of proximal tubule cells, mitochondrial swelling, and atrophy), microvascular arteriolopathy, and interstitial fibrosis.5 An extrarenal adverse effect of CyA is hypertension, owing to expansion of volume of extracellular fluid. Additionally, CyA may cause hyperchloremic metabolic acidosis.6 Hyperkalemia is a relatively common electrolyte disorder during the first months after transplant when one is undergoing CyA immunosuppression (occurrence, 44%-73% of patients).7,8 However, rarely is it life-threatening disorder requiring treatment.

The mechanisms of CyA-induced hyperkalemia appear to be related to impaired ability to excrete an
acute potassium load; impaired production of aldosterone; inhibition of Na+/K+-ATPase activity in the nephron; and inhibition of cortical collecting duct of potassium secretory channels. Additionally, hyperkalemia may be exacerbated by concomitant administration of beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, K+-sparing diuretics, phosphate supplements, and trimethoprim-sulfamethoxazole. We describe 4 living-donor renal transplant recipients with isolated relevant hyperkalemia early after surgery.

**Materials and Methods**

All patients underwent our standard surgical procedure. Grafts were preserved with Euro-Collins solution. All patients received the same quadruple sequential immunosuppressive protocol with anti–interleukin-2R monoclonal antibodies (ie, anti–interleukin-2R antagonists, mycophenolate mofetil, CyA, and prednisolone), and all received empiric antibiotic (cefuroxime), antiviral (valganciclovir), and antifungal (fluconazole) prophylaxis. Other medications given were diltiazem, dopamine, ranitidine, enoxaparin, furosemide for volume control and hydration. Cyclosporine was introduced beginning on the second day after transplant (5 mg/kg/body weight).

**Case 1**

A 38-year-old man with adult polycystic kidney disease, who had been undergoing chronic hemodialysis since June 2011, underwent a living-donor kidney transplant in November 2011. Preoperatively, he was given a bilateral nephrectomy, regular hemodialysis, and erythropoietin therapy. Warm and cold ischemia times were 3 and 270 minutes. Although standard immunosuppression dosages were given (C2 cyclosporine serum concentration, 1044-1331 ng/mL), hyperkalemia was unnoticed until 29 days after surgery. Hyperkalemia increased from 7 to 9.5 mmol/L on day 35 (Figure 1). During this time of severe hyperkalemia, neither rejection nor urinary infection was noted. Despite an increased serum potassium level, there were no clinical signs of hyperkalemia. His serum creatinine level was approximately 132.6 μmol/L (1.5 mg/dL) (Figure 1), and his GFR (Modification of Diet in Renal Disease) was 54 mL/min. On day 34, an appropriate dietary regimen (potassium arm diet), hypertonic glucose, and insulin was started. However, we saw no effects from this therapy. Thereafter, fludrocortisone therapy (0.1 mg/d) was given for 2 weeks, together with a reduction in the daily dosage of CyA (to keep CyA C2 level below 400 ng/mL). His potassium level gradually became normal 48 days after surgery. He was discharged home, under the triple-drug immunosuppression protocol, with normal renal functioning (ie, serum creatinine, 87 μmol/L (0.98 mg/dL); urea, 9 mmol/L; 24-h GFR, 83 mL/min) and normal serum potassium concentration (4.8 mmol/L). There were no repeat episodes of hyperkalemia during his 12-month follow-up.

**Case 2**

A 34-year-old man with Alport syndrome who had been undergoing hemodialysis since June 2006, underwent a living-donor kidney transplant in August 2011. Warm and cold ischemia times were 5 and 320 minutes. Because of his acute cellular rejection (Banff IA), steroid pulse therapy was begun during the second week after surgery. The CyA C2 levels were 400 and 780 ng/mL on the days 8 and 20.
During the first 2 weeks, the patient’s serum potassium concentrations were between 5 and 6.0 mmol/L (Figure 2). However, 20 days after surgery, the potassium increased to 8.0 mmol/L (Figure 2). During the same time, the urinary potassium concentration decreased from 52 to 32 mmol/L. Hyperkalemia remained until day 32 and became clinically and electrocardiographically relevant. The hypertonic glucose and insulin treatment were without results. However, reducing his daily CyA dosages and administering fludrocortisone for 2 weeks was effective. His serum potassium level became normal 33 days after surgery and remained so for 12 months’ follow-up. His CyA trough level remained below 400 ng/mL. After a slight worsening during the time of his hyperkalemia, his GFR returned to normal after treatment. The patient was discharged home, taking a standard triple-drug immunosuppression protocol, with normal renal functioning (GFR, 82 mL/min).

**Case 3**
A 66-year-old man with immunoglobulin A nephropathy since April 1997, underwent a living-donor, unrelated preemptive kidney transplant in April 2010. Warm and cold ischemia times were 4 and 220 minutes. The standard quadruple immunosuppressive protocol was used. The serum potassium increased from 5.89 mmol/L 13 days after surgery to 7.07 mmol/L 16 days after surgery (Figure 3). Hyperkalemia remained until day 23. His C2 CyA level was approximately 900 ng/mL during this same time. His urine potassium varied from 56 to 30 mmol/L during the same time. During peak potassium levels, his serum creatinine was 215.6 μmol/L (2.44 mg/dL), with a GFR from 46 mL/min. Neither rejection nor urinary infection was noted. Treatment with a potassium arm diet, hypertonic glucose, and insulin was ineffective. Additional treatment with 1 week of fludrocortisone was started, and his potassium level returned to normal 24 days after surgery. The patient underwent triple-drug immunosuppression, and was discharged home with normal renal functioning (serum creatinine, 103 μmol/L [1.16 mg/dL]) and a normal potassium level (4.8 mmol/L).

**Case 4**
A 26-year-old man with chronic glomerulonephritis since June 1989 was given hemodialysis since May...
2008. He underwent a living-related donor kidney transplant in April 2011 (the donor was his grandmother). Warm and cold ischemia times were 3 and 200 minutes. Delayed graft function and a urinary infection during the first 2 weeks after surgery were seen and treated with dialysis and imipenem.

His serum potassium level increased from 4.6 to 8.0 mmol/L from days 2 to 15 after surgery. Hyperkalemia remained until 21 days after surgery. His urine potassium level varied from 30 to 54 mmol/L during the same time. During peak potassium levels, his serum creatinine was normal, with a GFR of 70 mL/min. During the same time, his C2 CyA level went from 800 to 900 ng/mL. Treatment with a potassium arm diet, hypertonic glucose, and insulin was introduced. The addition of fludrocortisone finally returned his serum potassium level to the normal range 22 days after surgery. The patient was discharged home under triple-drug immunosuppression, with serum creatinine level of 101.6 μmol/L (1.15 mg/dL) and normal serum potassium level of 5.5 mmol/L.

Discussion

Hyperkalemia is common during the early posttransplant period after a kidney transplant and may be caused by various defects to the renal tubule owing to acute renal failure, acute rejection, acute tubular necrosis, ischemia, and drug toxicity. Drugs that lead to hyperkalemia can be divided into 3 groups: drugs that impair renin-aldosterone synthesis; drugs that alter potassium distribution; and drugs that inhibit potassium secretion.

Some authors agree that posttransplant electrolyte and acid-base disturbances should be part of global calcineurin inhibitors nephrotoxicity, and those patients treated with tacrolimus have more-severe hyperkalemia and hyponatremia with greater duration than those treated with CyA. Calcineurin inhibitors cause hyperkalemia by inhibiting potassium secretion. In the past, mechanisms of CyA-associated hyperkalemia (aside from an inadequate creatinine clearance) had been considered elusive. However, several studies have shown different mechanisms of CyA-induced hyperkalemia include an aldosterone resistance secondary to a decreased transcription of human mineralocorticoid receptor; dose-dependent inhibition of Na+/K+-ATPase activity in the cortical and outer medullary collecting ducts of the nephron segment; and a voltage-dependent defect.

We explain hyperkalemia in the described patients with hypo/pseudohypoaldosteronism as a possible mechanism (aside from those renal tubular defects secondary to resistance to aldosterone). Renal transplant recipients treated with CyA develop signs of hypoaldosteronism, despite normal plasma aldosterone levels and normal human mineralocorticoid receptor mRNA levels. This is because of the relative resistance of distal nephrons to aldosterone because of CyA. Cyclosporine also can reduce aldosterone-stimulated human mineralocorticoid receptor transcripational activity, and may inhibit human mineralocorticoid receptor transcripational activity without affecting expression of human mineralocorticoid receptors. Other studies suggest that mineralocorticoid receptor expression might be down-regulated. Cyclosporine impairs human mineralocorticoid receptor function. This induces alterations in ion transport in renal graft recipients. Several studies confirm the low (< 8 mmol/L) transtubular potassium gradient, and it could be related to aldosterone deficiency or resistance.
There is also evidence that decreased numbers of mineralocorticoid receptors (which are detected in 75% of patients treated with CyA) lead to hyperkalemia and metabolic acidosis as a result of aldosterone resistance.\(^2\) We did not see any clinically significant hyponatremia, which is understandable because of massive diuresis and hypernatriuria soon after surgery. Therapeutic levels of CyA had no significant effect on Na\(^+\)/K\(^+\)-ATPase activity, but concentrations that caused clinical CyA toxicity show a significant inhibition of Na\(^+\)/K\(^+\)-ATPase activity.\(^{10,14}\)

Although the exact mechanism is unknown, there are measures that may prevent CyA-induced hyperkalemia. One way would be to avoid concomitant administration of angiotensin-converting enzyme-inhibitors and beta-blockers, and angiotensin receptor blockers as hypotensive agents during CsA use.\(^{15}\) The most simple and important therapeutic intervention is to decrease potassium administration. Finally, if these measures give no result, one can use potassium “wasting” pharmaceuticals and/or synthetic mineral-corticoids fludrocortisone.\(^{16}\) The fludrocortisone therapy early after transplant has no significant adverse effects and can be used with safety in preventing and treating severe hyperkaliemia in renal transplant recipients.

We described 4 cases of severe CyA-induced hyperkalemia associated with hypoaldosteronism. Successful treatment with fludrocortisone in our cases confirms the hypothesis of transitional pseudohypoaldosteronism as a potential nephotoxic effect of calcineurin inhibitors. When treating severe hyperkalemia in renal transplant recipients, we recommended careful monitoring of CyA concentration and administering fludrocortisone.

References