CASE REORT

Tacrolimus Induced Hyperkalemia in Post Renal Transplantation: Chloride Shunt Mechanism- A Clinical Study

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ABSTRACT

Calcineurin inhibitors have nephrotoxicity as a common and significant adverse effect. CNI has an effect in all the components of kidney from vascular system to tubules. Calcineurin inhibitor-associated tubular dysfunction is manifested by hyperchloremic normal anion gap metabolic acidosis, hyperkalemia, calcium, phosphate, and magnesium loss. The reported incidence of hyperkalemia is 5-40% among calcineurin inhibitor treated patients. CNI can cause hyperkalemia either by direct inhibition of ROMK, Na+ K+ ATPase[3] or chloride shunt mechanism.

KEYWORDS: Renal Transplantation,Calcineurin Inhibitor,Chloride Shunt

INTRODUCTION

Calcineurin inhibitor has an effect in all component of kidney from vascular to tubules. Calcineurin inhibitor-associated tubular dysfunction is manifested by hyperchloremic normal anion gap metabolic acidosis, hyperkalemia, calcium, phosphate wasting and magnesium loss.[1] Hyperkalemia is commonly observed in renal transplant recipients, with an incidence of 44%–73% in patients maintained on calcineurin inhibitors.[2] These drugs are associated with a syndrome similar to hyporenin hypoaldosteronism with decreased aldosterone release, impairment of tubular potassium secretion via inhibition of sodium/potassium ATPase activity in the medullary thick ascending limb and collecting ducts, and decreased expression of the mineralocorticoid receptor.[1,4]

Aim Of Study: To elucidate chloride shunt hypothesis as a cause for hyperkalemia induced by CNI.

METHODOLOGY

3 patients were evaluated and worked up for hyperkalemia.

- Step 1- TTKG was calculated for a given patient. [expected TTKG >7]
- Step2- In the case of TTKG < 7, recalculate TTKG after 4 hours of administration of 100µg of fludro-cortisone .
- Step 3- If an inappropriate response to aldosterone, 250mg of acetazolamide given and dose was titrated until urine ph becomes > 7.6. Again recalculate TTKG[3].

CASE REPORT

Case A: 48- year-old ESRD secondary to diabetic nephropathy, underwent renal transplantation. Spousal donor HLA was unmatched. Immediate post- transplant was uneventful, and graft functions was normal. S.creatinine was 1.5mg/dl with triple immunosuppresion agent. 0n 7th postop day, s.creatinine at 2.3mg/dl. Kidney biopsy, showed acute t cell- mediated rejection Banff 2a corresponding c0 tacrolimus done with 5.3. He was treated with 3 doses of pulse therapy, and the dose of tacrolimus increased from 0.1mg/ kg to 0.125mg/ kg (3-0-3 to 4-0-4). POD day 19- S.creatinine 0.9mg/dl and s. potassium was progressively increased to 6.5. He was started on conservative management with k- binder, salbutamol nebulization. ABG suggestive of metabolic acidosis(anion gap – normal). TTKG calculated 2.08, repeated after administration of fludrocortisone 100 micrograms was 2.71- suggestive of aldosterone resistance. It was planned for acetazolamide challenge, with vigilant monitoring, acetazolamide 250mg administered. After one hour, urine pH done was 7.8 and TTKG were repeated and was increased from 3.12 to 9.1 (Table 1). Thus it was concluded that, replacing chloride by bicarbonate after acetazolamide administration produces a favorable electrochemical gradient for potassium secretion. we were able to demonstrate chloride shunt theory as a possible mechanism.

Interpretation	Sr.K+	Sr.Osm	Urine K+	Urine Osm	Ttkg
Before Fludrocortisone	5.8	299	12.1	301	2.08
After Fludrocortisone	5.4	296	15.1	308	2.71
Before Acetazolamide	5.5	304	12.8	216	3.12
After Acetazolamide	4.8	309	25.6	185	9.10

Table 1

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Case B- A 24- Year -old male post- renal transplant for 3 years with graft nephrectomy done for renal artery thrombosis on POD 14. Following that patient was on MHD. He underwent cadaver renal transplantation, the deceased donor (32year old no medical complication). Immediate transplantation no complication, slow graft function s.creatinine 2.5mg at the end of first -week post - transplant on triple immunosuppression with induction agent ATG (2 doses – 50mg on day 1 and 4). Kidney biopsy was done which showed acute tubular injury. c0 Tacrolimus level was 8.9ng/ml & dose was reduced from 0.15mg/kg to 0.1mg/kg. Subsequent days output improved and s.creatinine reduced to 1mg/dl. Post OP day 38 presented with renal dysfunction 1.6, 2nd kidney biopsy showed acute cell mediated rejection Banff ii A. He was treated with pulse therapy steroid 3 doses and tacrolimus dose was increased 0.10mg/kg to 0.125mg/kg. S.creatinine was reduced to 1.1 on the 3rd day; potassium was 6.2meq/dl. Evaluation for hyperkalemia step 1- TTKG was 2.58, since TTKG value was less than 7 (Table 2). Repeated TTKG after administration of 100 microgram fludrocorti-sone was 2.95. As aldosterone resistance was there followed up with step 3, acetazolamide 250mg, urine ph 8.1 after 1 hr. TTKG increased from 2.28 to 7.95.

Interpretation	Sr.K+	Sr.Osm	Urine K+	Urine Osm	Ttkg
Before Fludrocortisone	6.2	293	18.2	340	2.58
After Fludrocortisone	5.8	296	20.1	348	2.95
Before Acetazolamide	5.9	296	14.1	310	2.28
After Acetazolamide	4.5	298	25.6	265	7.95

Table 2

Case C: A 26 Year- old female known case of type 1 diabetes mellitus for 10 years, diabetic nephropathy- CKD on MHD for the past 2 years, underwent live related renal transplantation mother being the donor with steroid -free regimen had early withdrawal planned one week. POD 7 she had stable graft function on CNI (0.15mg/kg) and MMF 500mg (1-1-1). POD 10 day s.creatinine 0.9mg/ml and s.potassium 6.4meq/ml. we worked her upon hyperkalemia, ABG- metabolic acidosis (normal anion gap). Step 2 -fludrocortisone 100 microgram given TTKG value not improved. Step 3 - followed up acetazolamide challenge test ,TTKG improved.

Interpretation	**Sr.K+**	**Sr.Osm**	**Urine K+**	**Urine Osm**	**Ttkg**
Before Fludrocortisone	6.1	286	16.5	320	2.42
After Fludrocortisone	5.7	296	21.1	308	3.56
Before Acetazolamide	6.1	291	15.1	330	2.28
After Acetazolamide	4.5	293	34.8	320	7.05

Table 3

DISCUSSION

Totally 3 patients (2 live related and 1 cadaver- related renal transplantation), developed CNI induced hyperkalemia RTA. Resistance to aldosterone noted in all three cases after substituting aldosterone 100 micrograms TTKG not improved. Probable mechanism underlying is secondary pseudohypoaldosteronism.[5] Aldosterone action is mediated by MR which is bound to molecular chaperones. Chaperones are liberated when aldosterone – MR complex is translocated into the nucleus. Chaperones such as hsp 90 capable of binding to immunophilins (cyp 40, FKBP 51 and 52). CNI will bind with these immunophilins and impair the translocation of the aldosterone-MR complex into nucleus causing secondary pseudo-aldosteronism. Few weeks therapy of fludrocortisone is useful in this situation.[6] Other than above mechanism CNI can act through direct inhibition of ROMK, Na-K ATPase and Direct activation of chloride shuntmechanism.[1]

It was elucidated that the probable mechanism of inappropriate renal response to hyperkalemia and tubular insensitivity to mineralocorticoids may be in part due to inability to generate a favorable electro chemical gradient in a cortical distal nephron defect[4]. To overcome electrochemical gradient by replacing chloride by bicarbonate after acetazolamide administration produces a favorable electrochemical gradient for potassium secretion[4]. This indicates an intact intrinsic ability in these patients to secrete potassium and may point to defect in generating a favorable electrochemical gradient in CCT or to reduced conductance for potassium as the cause of this syndrome.

CONCLUSION

- Hyperkalemia caused by cni due to aldosterone resistance improved after eliminating chloride shunt mechanism by administration of acetazolamide.
- Hence chloride shunt mechanism is most likely the cause for hyperkalemia.

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