Tacrolimus-Induced Hyponatremia in Lung Transplant Recipients: A Case Series

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Background. Lung transplant recipients are treated with a 3-drug immunosuppressive regimen that consists of a calcineurin inhibitor, an antiproliferative agent, and a corticosteroid. Calcineurin inhibitors are the backbone of this regimen, and tacrolimus is used more often than cyclosporine, because tacrolimus is the more potent of the two agents. Tacrolimus-induced hyponatremia has been described among kidney transplant recipients, but not among lung transplant recipients. Methods. We conducted a retrospective chart review of patients who underwent lung transplant at our institution and went on to develop severe hyponatremia. Results. We identified 5 lung transplant recipients who developed severe hyponatremia after lung transplantation (median nadir, 117 mEq/L; interquartile range, 116-119 mEq/L). Time to development of hyponatremia ranged from 3 to 85 days posttransplant. Hyponatremia persisted in these patients despite fluid restriction, salt tablets, diuretics, and fludrocortisone therapy. Hyponatremia resolved in 3 patients and significantly improved in 2 patients after they were switched from a tacrolimus-based immunosuppressive regimen to a cyclosporine-based regimen. Conclusion. Transitioning from a tacrolimus- to a cyclosporine-based immunosuppressive regimen may resolve or improve severe hyponatremia in lung transplant recipients.

Lung transplantation is a lifesaving procedure for patients with advanced lung disease. Survival after lung transplant is largely dependent on aggressive immunosuppression to prevent acute rejection and chronic lung allograft dysfunction (CLAD). A typical immunosuppressive regimen consists of corticosteroids, an antiproliferative agent (eg, mycophenolate mofetil or azathioprine), and a calcineurin inhibitor (CNI) (eg, tacrolimus or cyclosporine). CNIs serve as the immunosuppressive backbone; tacrolimus is used more commonly than cyclosporine, because tacrolimus is associated with lower rates of CLAD.1 In this report, we describe 5 lung transplant recipients who developed severe hyponatremia that either improved or resolved after they were transitioned from a tacrolimus-based to a cyclosporine-based immunosuppressive regimen.

CASE DESCRIPTION

Five patients with advanced lung disease underwent bilateral lung transplant at our center. The median age was 56 years (interquartile range [IQR], 53-63 years), 4 patients were female, and 4 had underlying obstructive lung disease. Three patients underwent perioperative induction therapy, 2 with basiliximab and 1 with anti-thymocyte globulin; 2 patients had elevated pretransplant panel-reactive antibodies and were treated with rituximab at the time of transplant. All 5 patients were treated with a tacrolimus-based immuno-suppressive regimen and were transitioned to cyclosporine after developing severe hyponatremia. In addition, all 5 patients were alive at the time of chart abstraction (median posttransplant survival, 27 months; IQR, 22.3-36.9 months). Twenty-two months after transplant, 1 patient developed bronchiolitis obliterans syndrome (BOS), which is a variant of CLAD. This patient was started on extracorporeal photophoresis with gradual improvement in lung function.

Acute cellular rejection (ACR) was identified on surveillance bronchoscopy in 3 of the 5 patients, with 1 patient developing grades A1 and A2, whereas the other 2 only developed grade A1. None of these episodes were clinically
significant, and none of the three patients developed BOS. Donor-specific antibodies (mean fluorescence intensity, >2000) were identified in 3 patients, 1 of whom was diagnosed with possible antibody-mediated rejection and went on to develop BOS (Table 1). Four patients, including the patient who developed BOS, tolerated an immunosuppressive regimen consisting of cyclosporine, mycophenolate mofetil, and prednisone; 1 patient (patient 3) was transitioned from mycophenolate mofetil to everolimus due to nausea and continued to have stable lung function.

All patients had normal serum sodium (>135 mmol/L) before transplant (Table 1), and all were treated with tacrolimus starting on postoperative day 0 (median tacrolimus trough at the time of hyponatremia diagnosis, 8.5 ng/mL; IQR, 7.9-9.7 ng/mL). Two patients developed hyponatremia within 2 weeks of starting tacrolimus, whereas 3 had normal sodium concentrations for several weeks posttransplant. Hyponatremia was severe in all 5 patients (median nadir, 117 mEq/L; IQR, 116-119 mEq/L), and all 5 patients were symptomatic (Table 2). Gastrointestinal complaints were

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**TABLE 1.**

**Patient characteristics**

| Variable                                      | Patients |
|-----------------------------------------------|----------|
| Pretransplant diagnosis                       |          |
| Age at the time of transplant, y              |          |
| Sex                                           |          |
| Pretransplant serum sodium concentration (135-145), mmol/L |          |
| Induction agent                                |          |
| Lung transplant type (double vs single)       |          |
| Alive at time of chart abstraction            |          |
| Number of episodes of ACR (grade)             |          |
| CLAD development (grade)                      |          |
| Time to CLAD development, mo                  |          |
| Posttransplant survival, mo                   |          |
| Elevated DSA (MFI > 2000)                     |          |

**TABLE 2.**

**Clinical outcomes of lung transplantation**

| Variable (normal level), (unit of measure) | Patients |
|-------------------------------------------|----------|
| Nadir serum sodium concentration (135-145), mmol/L |          |
| Time to development of hyponatremia, d     |          |
| Tacroslim trough, ng/mL                    |          |
| Symptomatic hyponatremia                   |          |
| Time to resolution of hyponatremia after stopping tacrolimus, d |          |
| Tacroslim trough at resolution of hyponatremia, ng/mL |          |
| Naranjo Adverse Drug Reaction Probability Scale |          |
| Serum osmolality (275-295), mOsm/kg        |          |
| Serum bicarbonate (22-29), mmol/L          |          |
| Serum potassium (3.5-5.0), mEq/L           |          |
| Serum blood urea nitrogen (5-20), mg/dl    |          |
| Serum creatinine (eGFR) (mL/min per 1.73 m²) |          |
| Urine osmolality (300-900), mOsm/kg        |          |
| Urine sodium (40-220), mEq/L per day        |          |

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2 Tacrolimus was stopped the day after tolvaptan administration, by which time serum sodium concentration had already normalized.

6 Naranjo adverse drug reaction probability scale.

eGFR, estimated glomerular filtration rate; N/A, nonapplicable.---

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common, with the majority of patients complaining of nausea and poor appetite. In addition, all patients reported generalized weakness, and 1 patient had altered mental status.

At the time of presentation, all 5 patients had hypoosmolar hyponatremia and radiographic infiltrates were common (4 patients). None of the patients were treated with thiazide diuretics or hypotonic fluids, none were cirrhotic, and none had echocardiographic evidence of heart failure. All patients were euthyroid, had normal serum blood urea nitrogen, and had blood glucose of less than 300 mg/dL. Serum cortisol was not routinely measured; however, all patients were on at least 10 mg of prednisone at the time of presentation. One patient developed hyponatremia 3 days after transplant, but she left the operating room with a normal serum sodium.

**FIGURE 1.** Serum sodium concentration over time. Used with permission from Norton Thoracic Institute, Phoenix, Arizona.
concentration. Urine osmolality was available in 4 of 5 patients (median urine osmolality, 573.5 mOsm/kg; IQR, 496.5-647.8 mOsm/kg); all 4 showed evidence of impaired water excretion (defined as urine osmolality >100 mOsm/kg), and only 1 had a relatively elevated urine sodium concentration suggestive of salt wasting (defined as urine sodium level, >40 mEq/L per day). Patients’ volume status could not be reliably ascertained from medical records; however, hypervolemic hyponatremia was considered in 4 of the 5 patients because they were treated with furosemide. Although hyponatremia did not resolve with diuresis alone, it may still be possible that volume overload played a role in sodium mismanagement.

One patient (patient 3) was treated with tolvaptan, a competitive vasopressin receptor 2 antagonist, which led to rapid sodium correction and resultant seizure. The rapid elevation in serum sodium was driven by supertherapeutic serum tolvaptan levels due to underlying azole-mediated CYP3A4 inhibition. This patient was concurrently treated with fludrocortisone, so the effects of each drug could not be individually assessed. In addition, all patients were treated with free water restriction (<1.2 L/d) and sodium chloride tablets, 4 were diuresed with furosemide, 3 were given 3% hypertonic saline, and 1 received urea powder (Figure 1).

Most patients were able to maintain a normal serum sodium concentration after stopping tacrolimus, with 2 notable exceptions. Stopping patient 3’s tacrolimus coincided with initiation of tolvaptan and fludrocortisone. Hyponatremia persisted once tolvaptan and fludrocortisone were stopped; however, serum sodium concentration increased with cyclosporine and salt tablets alone, which led to resolution of hyponatremia-related symptoms. Patient 5’s serum sodium concentration initially increased with stopping tacrolimus; however, hyponatremia recurred after hospital discharge due to high free water and low solute intake at home. Cyclosporine was continued, and she was treated with fluid restriction, salt tablets, and urea powder. She elected to discontinue the latter 2 therapies after returning home, but was able to maintain normal serum sodium concentration with only cyclosporine and fluid restriction. The combination of tacrolimus with salt tablets and/or fluid restriction did not improve hyponatremia in either patient; in contrast, the combination of cyclosporine with salt tablets and/or fluid restriction improved hyponatremia in both.

DISCUSSION

Hyponatremia is commonly seen early after lung transplantation, but it is usually mild (>130 mmol/L) and not associated with significant morbidity. In contrast, the 5 patients included in this case series presented with severe and symptom-atric hyponatremia that improved or resolved after transitioning from tacrolimus to cyclosporine. CNI-mediated hyponatremia has been previously described in kidney transplant recipients, and hyponatremia was more common among patients treated with tacrolimus than with cyclosporine. This report is the first to describe tacrolimus-mediated hyponatremia among lung transplant recipients. Our experience strengthens the role of tacrolimus in sodium mismanagement by eliminating the confounding effects of underlying renal allograft dysfunction. However, we are limited by the retrospective nature of this analysis, an incomplete understanding of sodium mismanagement among early and late developers of hyponatremia, and the confounding effects of multiple interventions made in a short period.

The mechanism of CNI-induced hyponatremia is not fully understood; however, a number of theories have been suggested. CNIs can damage distal renal tubules and cause type IV renal tubular acidosis (RTA). Type IV RTA is characterized by aldosterone resistance with impaired reabsorption of sodium and impaired secretion of potassium and hydrogen; none of our patients had electrolyte abnormalities suggestive of type IV RTA. Hyponatremia may also be caused by syndrome of inappropriate antidiuretic hormone (SIADH); 1 of our patients had concurrent hyponatremia and elevated urine sodium levels (>40 mEq/L per day) consistent with SIADH. CNIs can also constrict the afferent arterioles, causing renal hypoperfusion and prerenal state; 3 of our patients had concurrent hyponatremia and low urine sodium (>40 mEq/L per day) consistent with renal hypoperfusion. Lastly, CNIs also augment the activity of the Na-K-2Cl cotransporter and Na-Cl cotransporter, with resultant increase in sodium and potassium reabsorption. This increased sodium absorption may lead to aldosterone resistance and resultant hyperkalemic hyponatremia, which was seen in one of our patients. We speculate that the variation in sodium handling between tacrolimus and cyclosporine may result from a difference in extent of antiuretic hormone secretion, arteriolar constriction, aldosterone resistance, and Na-K-2Cl cotransporter/Na-Cl cotransporter activation; for example, hyponatremia due to arteriolar vasoconstriction may play a larger role in the early postoperative period due to concurrent hemodynamic shifts, whereas distal tubular injury with resultant aldosterone resistance may dominate several weeks after transplant.

Hyponatremia after lung transplant is challenging to treat, particularly because its etiology is often unclear and multifactorial. We initially treat hyponatremia with fluid restriction and salt tablets, which mitigates the severity of hyponatremia in the majority of patients. If this regimen fails, and if the electrolyte profile is consistent with type IV RTA, fludrocortisone can be used; however, this drug is difficult to tolerate due to volume overload. Tolvaptan is effective for patients with SIADH, but dosing is difficult due to previously described azole-mediated CYP3A4 inhibition with resultant risk of rapid sodium correction. We avoid the adverse effects of fludrocortisone and tolvaptan by transitioning from a tacrolimus-based to a cyclosporine-based regimen for patients who do not respond to volume restriction and salt tablets. Notably, transitioning to cyclosporine may be insufficient in some patients, and some may require ongoing salt supplementation or fluid restriction.

CNIs serve as the backbone of most immunosuppressive regimens after lung transplantation. In vitro, tacrolimus is fiftyfold more potent than cyclosporine and has been proven to be an effective rescue agent for patients with recurrent or refractory acute allograft rejection. Treede and colleagues found a twofold higher risk for BOS 3 years after lung transplantation in patients on cyclosporine-based regimens compared with patients on tacrolimus-based regimens. However, treatment with tacrolimus did not lead to a survival advantage. Our patients have fared well on cyclosporine-based regimens, although 1 did develop BOS (which responded well to extracorporeal photopheresis). Thus, although transitioning from tacrolimus to cyclosporine is not without risk, it is an option for patients with severe hyponatremia that is unresponsive to other therapeutic interventions.
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