The Utility of the Transtubular Potassium Gradient in the Evaluation of Hyperkalemia

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ABSTRACT

The transtubular potassium gradient (TTKG) is used to gauge renal potassium secretion by the cortical collecting duct, indirectly assessing mineralocorticoid bioactivity in patients who have hypo- or hyperkalemia. TTKG values <6 indicate an inappropriate renal response to hyperkalemia, whereas values >2 during hypokalemia point to renal loss. Hypokalemia is not addressed here. Studies supporting the usefulness of the TTKG in hyperkalemia are limited to case series. This calculation may be most useful in distinguishing hyperkalemic patients who have mineralocorticoid deficiency versus resistance by observing a change in TTKG values after physiologic or pharmacologic doses of mineralocorticoids.

Potassium is secreted by the late distal convoluted tubule, connecting segment, and cortical and outer medullary collecting tubules. This secretion depends on the K⁺ concentration gradient across the luminal membrane of principal cells, which is determined by the difference between cell and urine K⁺ concentrations. Aldosterone and high plasma K⁺ concentration promote K⁺ secretion. Other important determinants of K⁺ secretion are K⁺ permeability of the luminal membrane through K⁺ channels, sodium delivery and urine flow rate into the distal nephron, and the degree of electronegativity of the urinary lumen generated by Na⁺ reabsorption through luminal Na⁺ channels and the anion composition of the urine. Methods to gauge appropriate urinary K⁺ excretion during hypo- or hyperkalemia, such as 24-h urinary K⁺, spot urine K⁺ concentration, fractional excretion of K⁺, and urine K⁺:Na⁺ ratio may have limitations. Because water reabsorption takes place in the distal nephron as well, urine K⁺ concentration is not an accurate index evaluating distal K⁺ secretion because the effect of water is not taken into account on urine K⁺ concentrations. Also, serum and urine aldosterone levels are not readily available, and aldosterone levels may not reflect mineralocorticoid bioactivity in patients with aldosterone resistance. A popular method of measuring the appropriateness of renal K⁺ excretion during disorders of serum K⁺ concentration is the calculation of the transtubular K⁺ concentration gradient (TTKG):

\[ \text{TTKG} = \frac{[K^+]_{\text{urine}} \times \text{Osm}_{\text{blood}}}{[K^+]_{\text{blood}} \times \text{Osm}_{\text{urine}}} \]

The urine-to-plasma K⁺ concentration ratio measures the gradient for K⁺ secretion. The urine to plasma osmolality ratio adjusts for the degree of medullary water reabsorption, which increases the urine K⁺ concentration as more water is absorbed. Thus, the TTKG is intended to estimate the tubular fluid K⁺ concentration at a point at which the fluid was last isotonic to plasma, namely, the cortical collecting duct. The development of the TTKG equation was verified in vivo by micropuncture and microcatheterization studies in rats. This commentary addresses the utility of the TTKG in evaluating hyperkalemic states (often defined as serum K⁺ >5.0 mEq/L).

One premise underlying the TTKG calculation is the absence of significant solute transport in the medullary collecting duct, such that any change in the urinary K⁺ concentration that occurs after exit from the cortex derives only from water reabsorption in the medulla. If, however, sodium and urea are reabsorbed from the medulla, resulting in decreased urine osmolality, then the TTKG would overestimate the gradient for cortical collecting duct K⁺ secretion. Also, in situations with a dilute urine or high urine flow rate, the TTKG underestimates K⁺ secretory capacity in the hyperkalemic patient. Calculation of the TTKG requires that urine Na⁺ be >25 mEq/L so that sodium delivery to principal cells is not rate limiting for K⁺ secretion. This value is twice the concentration required for half-maximal rates of K⁺ secretion in the rat distal nephron. Another prerequisite for calculating the TTKG is that urine osmolality be equal to

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or greater than plasma osmolality because vasopressin is required for optimal K⁺ excretion in the distal cortical nephron.³

There is a positive correlation between mineralocorticoid activity and the TTKG,¹ but the TTKG values that represent absence or presence of this activity are variable, and the standard cutoff value indicating an inappropriately low TTKG during hyperkalemia is not precisely known.⁶,⁷ In general, when the TTKG is <6 with hyperkalemia, it suggests that the collecting tubule is not responding appropriately to the hyperkalemia and that K⁺ secretion is impaired;² however, in one study, a TTKG value >5 was believed to reflect appropriate aldosterone activity, whereas a value <3 denoted mineralocorticoid absence or resistance.⁸ Another study concluded that a value <4 was due to reduced mineralocorticoid bioactivity and a value >6 was consistent with stimulated renal potassium secretion;³ however, a TTKG >6 in the presence of hyperkalemia may be difficult to interpret unequivocally in terms of estimating aldosterone activity;⁷ perhaps because of the influence of an elevated serum K⁺ on increasing potassium secretion independent of aldosterone. In a third study, administration of 50 mEq of K⁺ to 14 normal individuals resulted in the TTKG’s increasing from 8.1 ± 1.8 to 13.1 ± 3.8 (± SD), suggesting that the expected value of the TTKG should be >10 with normal adrenal and renal function during potassium loading,⁸ and a TTKG value of >10 has been quoted as the expected TTKG during hyperkalemia.¹ It is interesting that these articles have many of the same authors. TTKG values <4.1 for children and <4.9 for infants are used as indications of low aldosterone bioactivity in the pediatric population.⁹ These TTKG values represent the third percentile for age in 473 normokalemic infants and children.⁹ This study found that 13 pediatric patients with hypo- or pseudohypoaldosteronism had TTKG values that ranged from 1.6 to 4.1. Taken together, a TTKG <6 in adults with hyperkalemia may denote inappropriately low K⁺ secretion with corresponding values of <4 in children and <5 in infants.⁹

The utility of the TTKG has been investigated in patients with medication-induced hyperkalemia. The most common medications causing hyperkalemia—often given in combination—were angiotensin-converting enzyme inhibitors, spironolactone, and potassium supplements. In one study, 10 patients with medication-induced hyperkalemia (7.1 ± 0.3 mEq/L) and chronic kidney disease (CKD; serum creatinine 2.11 ± 0.13 mg/dl) were compared with two control groups: Individuals with normal renal function (serum creatinine 1.07 ± 0.32 mg/dl) and patients with CKD (serum creatinine 1.95 ± 0.09 mg/dl) without hyperkalemia.¹⁰ In the hyperkalemic patients, the TTKG was 2.58 ± 0.36, compared with 6.68 ± 0.55 in those with normal renal function and 5.51 ± 0.87 in those with CKD and normokalemia. It is interesting that serum aldosterone levels were higher in the hyperkalemic patients compared with individuals with normal renal function but were not statistically different from patients with CKD and normokalemia.

The TTKG has also been used to assess renal transplant patients with cyclosporine-induced hyperkalemia. Twelve adult renal transplant patients who were on maintenance cyclosporine and had mild hyperkalemia (5.1 ± 0.2 mEq/L) and mild renal insufficiency (serum creatinine 1.6 ± 0.16 mg/dl) had low TTKG values (4.3 ± 0.4) that were relatively unresponsive to pharmacologic mineralocorticoid administration (5.6 ± 0.6).¹¹ Pediatric transplant patients who were treated with cyclosporine showed low-normal or reduced TTKG values;¹² however, there was a large overlap in the TTKG values in patients who had hyperkalemia (n = 11, TTKG 5.1 ± 1.5) and those who did not (n = 13, TTKG 6.0 ± 4.8).¹² In two hyperkalemic patients with low TTKG (<4), adrenal function as assessed by ACTH testing was intact. Thus, the low TTKG in cyclosporine-treated patients may reflect multiple mechanisms of increased serum K⁺ concentration in the cyclosporine-treated allograft.

The use of TTKG has been advocated to help guide spironolactone therapy in patients with cirrhosis and ascites.¹³ Spironolactone was initiated at 100 mg/d and increased by 100 mg every 5 d until either diuresis commenced or TTKG fell below 3.0, a value indicating complete blockade of aldosterone bioactivity. When diuresis was not achieved in the nonresponder group with TTKG <3, furosemide was given in addition to spironolactone. Basal TTKG correlated with plasma aldosterone concentration, and treatment with spironolactone decreased the TTKG to <3 in 20 of 23 patients (from 5.3 ± 0.5 to 2.9 ± 0.2). All patients achieved diuresis with this regimen, and only one patient had transient hyperkalemia of 6.0 mEq/L.

The impaired K⁺ excretion in patients with diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome has been studied using TTKG and other measurements of K⁺ excretion.¹⁴ Such patients can present with hyperkalemia despite high aldosterone levels as a result of volume depletion and augmented urine sodium delivery as a result of glucosuria. The TTKG value can be <6, but it increases and serum aldosterone levels fall within 24 to 48 h of fluid and insulin therapy.¹⁴ The authors concluded that there is a reversible impairment of renal K⁺ secretion during severe hyperglycemia and postulated that an initial blunted renal K⁺ response to aldosterone may be protective, because total body K⁺ stores are low and renal response to aldosterone normalizes with therapy.¹⁴

The TTKG, however, may be most helpful in discerning whether a low value in hyperkalemic patients is due to either low aldosterone levels or aldosterone resistance. One method to differentiate these scenarios is to determine whether the TTKG rises after administration of mineralocorticoid. After a physiologic dose of mineralocorticoid in patients with adrenal insufficiency, the TTKG increases to >6 within 4 h and, in most cases, within 2 h.⁶ Zettle et al.⁷ described three patients with hyperkalemia and primary adrenal disease with TTKG values <6 that increased to >6 within 4 h of physiologic doses of mineralocorticoids
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(3.1 to 6.7, 3.8 to 8.5, and 3.3 to 7.1). In contrast, Zettle et al. also described patients who had aldosterone resistance and in whom the TTKG did not increase to >6 after physiologic mineralocorticoid doses. These patients had variable or delayed responses to pharmacologic doses of mineralocorticoid. One patient eventually responded to repeated pharmacologic doses (0.2 mg of 9-α-fludrocortisone): The TTKG increased from 1.7 to 6.5 after 1 d. Another patient with hyporeninemic hypoaldosteronism had an increase in TTKG from 3.3 to 5.6 after first a physiologic then a pharmacologic dose of 9-α-fludrocortisone; the TTKG was 6.8 when measured 2 wk later on 0.1 mg/d 9-α-fludrocortisone. Another hyperkalemic patient who had a serum creatinine of 2.4 mg/dl and normal aldosterone levels had no substantial increase in TTKG after physiologic or pharmacologic doses of mineralocorticoid with a peak TTKG value of 2.6. A patient with AIDS and trimethoprim-induced hyperkalemia did not respond to 0.3 mg of 9-α-fludrocortisone (TTKG 1.9 to 2.8) but subsequently had normalization of the serum K+ concentration with an increase in the TTKG to 8.9 after discontinuation of trimethoprim. In conclusion, after a physiologic dose (0.05 mg) of 9-α-fludrocortisone, the TTKG should increase to >6 within 4 h in mineralocorticoid-deficient but not aldosterone-resistant states. There may be a delayed response (>24 h) after a pharmacologic dose (0.2 mg) of 9-α-fludrocortisone in mineralocorticoid-resistant states.

In summary, TTKG is an index of potassium secretory activity in the distal tubule. TTKG values <6 indicate impaired aldosterone bioactivity in the distal nephron as the cause of the hyperkalemia. Hyperkalemia as a result of K+ overload or intra- to extracellular shifting of K+ is associated with higher TTKG values when the renal response is intact. The calculation of TTKG may be most useful in distinguishing patients who have mineralocorticoid deficiency versus resistance by observing a change in TTKG values during a period of hours to a few days after physiologic or pharmacologic doses of mineralocorticoid.

DISCLOSURES

None.

REFERENCES