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Hyperkalemia: Inpatient PaniK

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EDITORIAL

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INTRODUCTION

In this issue, Guest Editor Jeffrey Kraut determined to "go back to the basics" of nephrology and assembled an august group of authors whose expertise spans the gamut of electrolytes and acid-base disorders. The table of contents represents a carefully curated compilation of articles, each of which is a minireview and state-of-the-art appraisal of the literature on a particular topic. In alignment with this familiar group of topics, I have chosen to concentrate on inpatient hyperkalemia. Rather than opining on the panoply of potassium abundance disorders, I devote my time and yours to matters of all things done wrong when confronted with inpatient hyperkalemia, a common finding that evokes a "PaniK" disorder.

MINIMALLY INCREASED POTASSIUM CONCENTRATIONS

Minimally increased serum potassium levels, defined as 5.0 to 5.5 mmol/L, generally can be treated nonurgently. A potassium-restricted diet is generally all that is required. In patients with CKD with lower serum potassium levels, potassium restriction may not even be required with adherence to the correct diet. In fact, patients with CKD stages 3 and 4 with serum potassium levels <5 mmol/L and metabolic acidosis have been treated with diets of fresh fruits and vegetables without aggravation of hyperkalemia.[1,2]

Most non-nephrologists are concerned when serum potassium levels are ≥5.5 mmol/L—an operational definition for hyperkalemia. In a patient with CKD, such a level brings foreboding. Internal Medicine housestaff are currently deceived into believing that an emergency is forthcoming—a potassium portent of some sort. Echoes of past attending teachers ring clearly—"A person with hyperkalemia can develop ventricular fibrillation as the first sign of hyperkalemia"—but this belief is "fake news." Most mildly hyperkalemic patients with serum potassium concentrations of 5.5 to 6.0 mmol/L will not encounter such dire circumstances. No one will die at these potassium levels.[3] The most important thing to determine first is the verity of the potassium level and, then, if replicated, to rule out pseudohyperkalemia. If ruled out, one must subsequently determine the pathophysiology driving the increase in serum potassium concentration to facilitate the prudent management of hyperkalemia.

PSEUDOHYPERKALEMIA

Pseudohyperkalemia must always be ruled out. A clue to this finding is that the patient never had hyperkalemia before or always has hyperkalemia. Nearly 40 years after Farber and colleagues[4] associated skeletal muscle exercise with increases of potassium levels from 0.3 to >1.0 mmol/L, Don and colleagues[5] showed that fist clenching produced ex vivo hyperkalemia in association with lactic acid production. Forearm- and occasionally upper arm-induced skeletal muscle depolarization from fist clenching releases intracellular potassium into the extracellular space and increases the local downstream plasma potassium concentration. This leads to downstream vasodilation of vascular beds that must deliver increased oxygen content to exercising muscle. The locally increased potassium concentration is subsequently dissipated by dilution when the relatively small blood volume returns to the much larger cardiopulmonary circulation. This kind of pseudohyperkalemia is the most common form and follows exhortations from venipuncturists who encourage patients to "pump up that arm" to increase the success of venous blood draws. Many chronically ill hospitalized patients who develop hyperkalemia have poor veins, progressively destroyed by repetitive blood drawing. These are

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the individuals most susceptible to pseudohyperkalemia as fist clenching may be the only recourse to obtain the blood sample.

Reform is necessary here because venipuncturists are trained to obtain the blood within 30 seconds of tourniquet application, which invariably leads to pseudohyperkalemia from regional exercise. Note that the phenomenon of fist-clenching or exercise-induced pseudohyperkalemia is not truly pseudohyperkalemia, defined as an ex vivo phenomenon, that is, in the former case, the potassium concentration in the blood vessel and in the vacutainer tube are equally increased. This equality differentiates this form of pseudohyperkalemia, which is actually pseudopseudohyperkalemia, from "true" pseudohyperkalemic states, such as the hereditary stomatocytoses (includes genetic disorders of cryohydrocytosis, dehydrated stomatocytosis, familial pseudohyperkalemia) or xerocytosis, abnormal red cell morphologies, and membrane disorders that lend themselves to destruction and release of erythrocyte potassium during venipuncture,[6,7] thereby increasing the potassium concentration in the blood collection tube by extravascular hemolysis—an out-of-body in vitro experience.

Nephrologists, untrained in erythrocyte rehydration via gradient ektacytometry, will not be making the initial diagnoses of these hereditary red cell disturbances anytime soon, but a pathologist or hematologist will when examining a peripheral blood smear. The pseudohyperkalemias that transpires with myeloproliferative syndromes in conjunction with extreme leukocytosis as with chronic myelogenous leukemia (white blood cells >70,000 per mm^3) and thrombocytosis (platelets >700,000 per mm^3) are classical. Serum potassium concentrations greatly exceed corresponding plasma levels, when potassium ions are released from "fragile" white cells or platelets during the clotting process. In a remarkable case of "reverse" pseudohyperkalemia, heparin-induced damage of white cells in plasma produced potassium levels greater than the serum levels and resulted in dialysis after hyperkalemia was shown refractory to treatment.[8] No electrocardiographic changes were detected at plasma potassium levels of >8 mmol/L. For pseudohyperkalemia from leukocytosis, the height of the leukocyte increase is the obvious clue. However, distinguishing between reverse pseudohyperkalemia and true pseudohyperkalemia may require whole blood analysis of potassium concentration via an arterial blood gas in a heparinized nonlithium syringe. For pseudohyperkalemia from thrombocytosis, the simple maneuver of obtaining blood in a heparinized tube, with subsequent prevention of clotting by exposure to ethylenediaminetetracetate is curative. Although this "cure" has been known for decades, no one prescribes it anymore, although no special equipment is required. Recall that the normal clotting of platelets results in an approximately 0.3 mmol/L differential between the serum and plasma potassium concentrations.[9]

Occasionally, pseudohyperkalemia occurs in erythrocytosis (hematocrit >55%) when a normal platelet count releases potassium into a smaller plasma volume during clotting.[10] With repetitive refrigerated centrifugation, another unusual form of true pseudohyperkalemia of modest degree may occur.[11] This circumstance was detected in Japan in 2 patients errantly diagnosed with hyperkalemia. The cause was recentrifugation of refrigerated plasma in gel-separator tubes. After disclosure of this finding, replication and validation were conducted in a time-series of 5700 samples during a 6-month interval. The other forms of true pseudohyperkalemia that result from mishandling of blood samples are primarily related to mechanical injury of erythrocytes. These are reviewed by Avelar.[8]

I wonder how many times my colleagues and I have been asked to consult on a patient for pseudohyperkalemia and/or consider the patient for hemodialysis. The easiest way to determine whether fist-clenching hyperkalemia has occurred is to examine the patient's bruised arm for multiply "missed" venipuncture sites and to ask him/her about fist clenching. The answer should not surprise. In a value-based environment, pseudohyperkalemia represents extra laboratory work, consultations, extra payments, and, worst of all, injury to the patient.

In summary, fist-clenching pseudohyperkalemia is pseudopseudohyperkalemia because there is no ex vivo hemolysis—bilirubin concentration is normal—and the plasma potassium is increased. It is simply a patient-induced higher potassium concentration in the forearm that is nonrepresentative of the rest of the circulation.

MILD HYPERKALEMIA

For inpatients with true but mild hyperkalemia of 5.5 to 6.0 mmol/L who have not experienced acute hyperkalemia previously, the diet should be scrutinized. Perhaps the patient has been restricted from sodium but not potassium intake in hospital—a frequent occurrence on dedicated cardiac floors where the predominant logic is to prevent heart failure from excess sodium and to maintain potassium levels at ≥4.0 mmol/L in fear of hypokalemia in a cardiac-compromised patient with lower ejection fraction. The reduction in dietary sodium in an individual loathe to adhere to a sodium-restricted diet may result in hyperkalemia from diminished epithelial sodium channel–mediated sodium reabsorption and, consequently, less potassium secretion via the renal outer medullary K^+ channel. The cardiac dietitian may accidentally aggravate this scenario by increasing dietary potassium and decreasing dietary sodium.

At moderate levels of hyperkalemia, panic often sets in, unleashing a cavalcade of tests and procedures including urinary and serum potassium levels and osmolalities to calculate transtubular potassium gradients, electrocardiograms, kidney-pelvic ultrasonograms to rule out obstruction, administration of insulin and/or glucose, and inpatient polystyrene sulfonate prescription. Insulin and/or glucose treatment, if conducted with disregard to the level of insulin sensitivity, may result in the adverse effects of hypoglycemia, particularly when insulin sensitivity is high as in patients with CKD, and/or

hyperkalemia when glucose level rise from insulin insufficiency and osmotically drive plasma potassium levels upward. As recorded by studies from Putcha and Allon,[12] insulin/glucose therapy for hyperkalemia results in a mean potassium reduction of 0.8 mmol/L in hemodialysis patients after 60 minutes, a typical response of normal control subjects.

All the aforementioned tests and procedures may be ordered and executed without first obtaining a repeated serum potassium test, which represents bad medicine at its best. If the serum potassium level remains 5.5 to 6.0 mmol/L after dietary potassium restriction—the most important step in controlling hyperkalemia—a loop diuretic or bicarbonate therapy may be used to augment renal elimination of potassium in concert with additive measures such as elimination of hidden sources of potassium and discontinuation of agents that increase potassium levels. Hemodialysis should not even be contemplated at this juncture.

The question of whether a diuretic or bicarbonate represents the first-line agent has been bandied about in academic circles. Withholding my own opinion, I offer a pragmatic solution. Diuretic therapy is favored if hyperkalemia is accompanied by edema or suboptimally controlled hypertension, usually volume-dependent, and bicarbonate therapy may be used otherwise. If edema occurs during bicarbonate treatment, more aggressive sodium restriction is required because sodium bicarbonate therapy generally does not result in edema in nondialysis-dependent patients with CKD. The absence of edema formation with sodium bicarbonate treatment was clearly delineated by de Brito-Ashurst and colleagues[13] in a 2-year randomized open-label clinical trial (total $n = 134$) in which the experimental group was treated with 1800 mg (19 mmol) of sodium bicarbonate daily. Loop diuretic or bicarbonate treatments, applied correctly, should increase the serum bicarbonate concentration to the normal range. With loop diuretic therapy, serum total carbon dioxide concentrations exceeding ≥28 mmol/L with hypochloremia signify extracellular fluid contraction, an indication for dose reduction.

Recently, Agarwal and colleagues[14] demonstrated that chlorthalidone at 25 mg daily provoked hypokalemia in patients with CKD stages 3b to 4 with uncontrolled hypertension and an average estimated glomerular filtration rate (GFR) of 28 mL/min/1.73 m^2 (range, 20 to 45 mL/min/1.73 m^2). Single-dose chlorthalidone represents a convenient and well-tolerated substitute for loop agents that nearly always require multiple daily dosing to exert their salutary effect(s). In a small study, 4 of 7 participants treated with a single 25-mg dose developed hypokalemia, while lowering their blood pressures by nearly 10 mm Hg, attributable to extracellular fluid reduction. Overall, potassium-binder therapy succeeds dietary potassium restriction and diuretic or sodium bicarbonate administration as treatment of hyperkalemia.

A kidney and pelvic ultrasonogram should always be considered after hyperkalemia of any degree is established, irrespective of the absence of urinary symptoms. Occult obstruction when sustained invariably produces pressure-related renal tubular damage, and all of us have been surprised by the unexpected and incidental finding of bilateral hydronephrosis. An important clue to urologic obstruction as causative of hyperkalemia is depression of the venous total carbon dioxide content to <20–22 mmol/L, that is, the presence of hyperkalemic distal renal tubular acidosis.

HEPARIN AND ANTI–RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM ANTAGONISTS

Many hospitalized heart failure patients receive heparin to prevent deep venous thrombosis. Treatment of only a week's duration may instigate hyperkalemia via interruption of angiotensin II–mediated aldosterone release and expression by the zona glomerulosa. Again, the clinical clue is the absence of hyperkalemia before hospitalization, thereby implying an iatrogenic but unplanned provocation of hyperkalemia.

Drugs that inhibit the renin-angiotensin-aldosterone system and typically raise serum potassium levels by an average of 0.3 mmol/L are habitually stopped in hospital, blamed for inducing an episode of hyperkalemia that was absent before admission when the patient was taking the same dose of anti–renin-angiotensin-aldosterone system agents. Automatic discontinuation of anti–renin-angiotensin-aldosterone system agents during potassium increases is *de rigeur*, but this should not be a standard practice. These abrupt unnecessary stoppages of anti–renin-angiotensin-aldosterone system therapies have no immediate effect on the plasma potassium concentration. Furthermore, reduction of anti–renin-angiotensin-aldosterone system medications may prove injurious to the patient by potentially reducing right and/or left ventricular function, thereby lowering the GFR to a level (<15-20 mL/min/1.73 m^2) insufficient to excrete potassium in amounts sufficient to avert hyperkalemia, resulting in a paradoxical outcome of hyperkalemia from the absence of anti–renin-angiotensin-aldosterone system therapy. Nonsteroidal anti-inflammatory agents should be avoided in patients with CKD, particularly in diabetic and elderly patients who may harbor subclinical or fully manifest hyporeninemic hypoaldosteronism. As chronically ill individuals and those undergoing recent steroid therapy may have hypoadrenalism, this diagnostic entity must always be considered in the differential diagnosis of hyperkalemia and is nearly always a diagnosis of exclusion.

MODERATE HYPERKALEMIA

Potassium levels of 6.0 to 6.5 mmol/L and higher merit serious consideration. However, such potassium levels are not fatal and can be tolerated for hours. Marathon running is associated with an increase in potassium concentration of 2.5 mmol/L, with rapid resolution on cessation of exercise.[15] Patients who are chronically

hyperkalemic are thought to develop adaptive cardiac mechanisms, but the precise physiology is unknown. The kidneys and bowel demonstrate adaptive behaviors and enhance their respective potassium-secreting abilities after prolonged exposure to higher plasma potassium concentrations.

Potassium-binding resins are not suitable for rapid reduction in serum potassium increases, at least not yet. Polystyrene sulfonate has been available for 5 decades and is a venerated treatment for chronic outpatient hyperkalemia, yet this potassium-binder does not work well, if at all.[16] Polystyrene has no place in urgent settings of hyperkalemia where it is often prescribed. Unfortunately, to add insult to injury, the potassium-binder dose prescribed is often subtherapeutic for fear of success with hypokalemia. The hypopotassemic effect of polystyrene sulfonate emanates from bowel-induced losses of potassium, stemming from the production of watery diarrhea.[17] Diarrheal effluent activates MaxiK (Big K [BK], slo1, KCNMA1) large-conductance, voltage, and calcium-sensitive potassium-secretory channels in the bowel.[18] These channels generate the hypokalemia of colonic pseudo-obstruction (Ogilvie's syndrome) and can produce potassium losses of >100 mmol daily.[19]

Patients with hepatorenal syndrome or acute kidney injury superimposed on extensive, pre-existing liver damage often develop hyperkalemia, reflective of true GFRs far less than the value determined from GFR-estimating equations. Lactulose therapy in such patients serves a dual purpose, precluding hyperammonemia and hyperkalemia. The osmotic prowess of lactulose could also be deployed therapeutically as could those of mannitol or sorbitol, as adjunctive therapy for hyperkalemia in lieu of other orally administered more expensive potassium-binder therapies such as polystyrene sulfonate and patiromer.

SEVERE HYPERKALEMIA

Generally, patients with truly life-threatening hyperkalemia denoted by serum potassium levels of ≥6.5 to 7.0 mmol/L may have signs or symptoms of neuromuscular transmission aberration such as weakness or electrocardiographic changes. In the latter circumstance, I see true confirmation bias. Physicians *want* to see diffusely enlarged and peaked "hyperkalemic" T waves, and they do even when these electrocardiographic changes are absent. Sans calipers, few will confirm that the height of the T wave is >60% of the RS wave amplitude. Even fewer are the individuals who will confirm that the T wave is broader at the base than its prehyperkalemic counterpart. This criterion has been lost in the literature. In a clinical survey from 1998, just 14% of reported hyperkalemic episodes revealed adjudicated electrocardiographic changes.[3] Fulfilling both criteria remains unconvincing unless electrode placement between premorbid and morbid electrocardiograms was consistent. Education and/or relearning essential neuromuscular physiology serves a dual purpose here: self-edification and the avoidance of unnecessary testing and treatments as well as potential harm to patients.

Hyperkalemia affects excitable tissues such as muscle and nerve by altering the resting membrane potential. The product of Nernst's careful experimentation, the potassium resting membrane potential is defined principally by the ratio of intracellular-to-extracellular potassium concentrations. However, due to inward movement of sodium from the extracellular milieu, the Goldman-Hodgkin-Katz voltage equation more accurately reflects the resting membrane potential in per se excitable cardiac tissues, that is, the latter equation correctly predicts a lesser resting membrane potential than the Nernst equation.[20] At the normal baseline resting membrane potential for potassium, the conductance of this ion is far greater than for sodium, thereby diminishing the latter's contribution to the resting membrane potential. Because chloride has essential minimal driving force into the cell, it becomes a null factor in calculation of the resting membrane potential. In brief, hyperkalemia depolarizes the cell membrane, and hypokalemia hyperpolarizes the membrane. With severe hypokalemia, the capacity to generate an action potential is stymied by the increased absolute difference between the threshold potential and resting membrane potential, now much more negative.

The ionized calcium concentration governs the threshold potential, underlying the utility of imposing relative or absolute hypercalcemia, albeit transiently, as therapy of hyperpotassemia. Ionized hypocalcemia lowers the threshold potential and is boosted upward and away from the resting membrane potential during calcium therapy of hyperkalemia that should only be administered in the face of documented electrocardiographic changes. Clearly, calcium treatment stabilizes no conductance membranes, the inaccurate belief of most practitioners. If cardiac tissue membranes were stabilized, why are repetitive rounds of intravenous calcium required at 10- to 20-minute intervals? Moreover, repeated electrocardiograms, not 3-lead monitoring, should accompany each delivery of a calcium bolus, but are a rarity today. Worse yet, intravenous calcium is frequently underdosed. Calcium chloride is noxious to peripheral veins and muscle and should only be instilled into large veins with rapidly flowing blood. Moreover, calcium gluconate, which can be delivered in peripheral veins only, contains one-third of the amount of elemental calcium per ampule. Not adjusting for this 1:3 ratio of calcium gluconate-to-calcium chloride can seriously underdose the hyperkalemic patient whose threshold potential is colliding with a more-depolarized resting membrane potential. Treatment of hyperkalemia for severe hyperkalemia is the same as for moderate hyperkalemia, and hemodialysis with a dialysate potassium concentration of 2.0 to 3.0 mmol/L is reserved for patients with electrocardiographic changes that persist despite appropriate measures to restore plasma potassium levels to normal.

FASTING HYPERKALEMIA

Patients with ESRD frequently experience hyperkalemia in hospital, much more than the published frequency of 1% to

10% for the general population.[3] In ESRD, "fasting hyperkalemia" may be observed from intracellular potassium translocation into the plasma attributable to lack of carbohydrate intake–mediated insulin secretion. Putcha and Allon have indicated that this relatively unrecognized clinical entity may be exacerbated by nonselective beta-adrenergic blockade, with relative overactivation of alpha-adrenergic receptors.[12,21] Fasting hyperkalemia in patients with ESRD is easily managed with intravenous dextrose, which induces secretion of insulin, the hypokalemic action of which is dissociated from glucose transporter–mediated glucose uptake. Perhaps hospitalized patients with ESRD subjected to fasting before procedures and operations should be protocolized to intravenous 5% dextrose-containing solutions, which may lower potassium levels,[12] and preclude ill-advised cancellations of operations and procedures by surgeons and anesthesiologists conducting preoperative evaluations and concerned about succinylcholine-induced skeletal muscle depolarization. These postponements and cancellations are costly to health systems, delay diagnosis, and vex patients. A 1-L intravenous solution of 5% dextrose in water that costs less than 1 dollar could avoid these unfavorable circumstances.

SUMMARY

To sum up, inpatient hyperkalemia therapy is fraught with hazards, not because they exist but because we have made them worse by simply ignoring our knowledge of the pathophysiology that produces it. PaniK is an acquired and self-treatable disorder, but only if we listen to what we already know. The nephrology community must make the time to take the panic out of PaniK through appropriate and timely education and re-education of providers who confront this disorder with us.

Sometimes the questions are complicated and the answers are simple.

—Dr Seuss

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Disclosures: Dr Jerry Yee has served as a consultant to Relypsa and ZS-9, manufacturers of potassium-binder therapies.

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