Treating Interdialytic Hyperkalemia with Fludrocortisone

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ABSTRACT

Hyperkalemia is a frequent and dangerous problem in dialysis patients. Many factors contribute to potentially life-threatening potassium elevation and most remedies used to treat hyperkalemia are handicapped by the consequences of the separate pools of intra- and extracellular potassium. Besides the kidney, the colon has the ability to excrete potassium, which can help lower total body potassium. Several prior authors have addressed the colon's ability to up-regulate potassium secretion, including the effect of aldosterone on fecal potassium content. Potentially dangerous intradialytic maneuvers to lower potassium levels may be avoidable with the use of the mineralocorticoid agonist fludrocortisone.

Hyperkalemia in hemodialysis (HD) patients is a frequent problem. Several factors render these patients susceptible to hyperkalemia including chronic metabolic conditions (e.g., acidosis, progressive nephron loss (1), mineralocorticoid deficiency (2)), medications (e.g., angiotensin converting enzyme [ACE] inhibitors (3), potassium sparing diuretics (4), nonselective β-adrenergic blockers (5,6), nonsteroidal anti-inflammatory drugs [NSAIDs] (7), unfractionated heparin (8)), and difficulty adhering to dietary potassium restrictions, as well as extreme fasting (9). It is therefore not surprising that most, if not all, nephrologists care for a subset of patients who consistently develop high serum potassium levels in the interdialytic period. Many of these patients, despite attempts to treat and control these levels with potentially dangerous potassium-free dialysate baths or unpleasant oral ion exchange resins, require urgent treatment for hyperkalemia or die at home of the problem. The purpose of this article is to briefly discuss the basis for, feasibility of, and experience with aldosterone agonists in regulating interdialytic potassium levels in patients on maintenance HD.

Potassium Homeostasis

About 80% of a potassium load is initially transferred from the extracellular to the intracellular compartment, avoiding excessive potassium levels in the smaller extracellular fluid compartment. There are various factors that are implicated in effecting the intracellular shift, including insulin, β-adrenergic agonists (epinephrine), aldosterone, and other factors, all of which are believed to affect the transmembrane transport of potassium. Whatever the underlying mechanism and regulation of this shift, it is critical to recognize that it is only useful for buffering potassium loads, and does not provide homeostasis, which necessarily requires excretion (10). Within hours 80–90% of the potassium load is excreted by the kidneys, due to the probable interplay of aldosterone (11), epinephrine (12,13), antidiuretic hormone (ADH) (14,15), glucocorticoids (16), actual potassium load (17), urine flow rate (18), and residual renal function (1). The remainder of the potassium load is removed mostly by the colon (19–21). Loss of potassium by sweat glands is negligible except under conditions of heat acclimatization (22).

It is thought that intracellular potassium shifts are impaired in renal disease (9), contributing to the development of hyperkalemia in renal insufficiency (23). In anuric patients, intracellular transfer of potassium loads is slower than that found in the presence of normal renal function (24). This deficiency may also result in an inadequate response to certain treatments of hyperkalemia in dialysis patients (25).

Managing Hyperkalemia in the Dialysis Patient

Several strategies have been devised for removing potassium from patients with end-stage renal disease (ESRD). It is likely that all of the strategies are handicapped by the separate pools of intracellular and extracellular potassium leading to variability in its dialytic removal (26). Both bicarbonate infusions and the β-adrenergic agonist, epinephrine, have little to no effect on shifting potassium to the intracellular pool and lowering plasma potassium in dialysis patients (27). The basis for these defects is not known, but a derangement in sodium-potassium-ATPase activity, the presence of an inhibitor of this enzyme, acid-base imbalance, or inadequate β-adrenergic receptor activation have all been suggested as contributors to the observed decrease in

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transcellular potassium shifts. As previously mentioned, the interventions favoring intracellular buffering of potassium loads cannot contribute to homeostasis and do not assist in the management of interdialytic potassium levels since net negative potassium balance is not achieved (10).

Intradialytic attempts to achieve net negative potassium balance rely on shifting potassium out of cells into the extracellular space in an effort to preserve the concentration gradient-dependent potassium removal during the treatment. Compared to glucose-containing baths, glucose-free dialysate decreases circulating insulin levels and increases potassium efflux from cells during dialysis with enhanced total body potassium removal (28). Symptomatic hypoglycemia may develop during glucose-free dialysate treatment. During the interdialytic period, serum potassium "rebounds" as potassium now exits the intracellular pool, reestablishing the intracellular/extracellular potassium gradient (29).

Potassium-free dialysate is effective in enhancing potassium removal but can be associated with life-threatening arrhythmias, especially in patients being treated with digitalis (30). Low-potassium dialysate has been identified as a potentially hazardous dialysis-specific practice, a practice that might increase the risk of intradialytic cardiac arrest (31,32). Morrison et al. (30) demonstrated decreased ventricular ectopic activity (VEA) in four of six patients whose dialysate potassium concentration changed from 2.0 to 3.5 mEq/L.

Potassium Secretion by the Colon

Several findings make the colon a potential target for controlling interdialytic potassium levels. The electrolyte transport processes and the response to aldosterone develop in the colon before those in the kidney, and the colon is a major site for electrolyte and fluid homeostasis in neonates (33). It is well known that the epithelial cells of the mammalian colon have the same (or similar) transmembrane transport elements for potassium secretion as do the cells of the kidney collecting tubule. Both respond to aldosterone to increase potassium secretion by the induction of apical membrane potassium channels and basolateral sodium-potassium-ATPase activity (34–36).

Humans can tolerate increments in potassium loading to accommodate what otherwise could be a lethal ingestion, and this phenomenon of "potassium adaptation" includes an enhanced colon secretion of potassium (37). In animal models of renal insufficiency, aldosterone up-regulates the mRNA for potassium channels in the colon in parallel with the ability to secrete potassium to maintain serum potassium levels (38). In adults with severe renal insufficiency, the gut has been demonstrated to be an important excretory pathway for potassium homeostasis. Fecal potassium content is proportional to plasma aldosterone and colon potassium secretion adapts to potassium loads (39). Measuring fecal sodium and potassium with in vivo ingested dialysis capsules, Wilson et al. (40) demonstrated that mineralocorticoid stimulation of potassium secretion occurs and contributes to potassium balance in renal failure. In harmony with this conclusion is the clinical finding that patients with both adrenal and renal failure are at the highest risk for hyperkalemia (41). It is therefore clear that the colon has secretory processes for potassium, and that this activity is up-regulated in response to potassium loads, aldosterone, and during renal insufficiency.

Mineralocorticoids in the Treatment of Hyperkalemia Without Renal Failure

Fludrocortisone is a synthetic glucocorticoid possessing potent mineralocorticoid activity and moderate glucocorticoid activity. The latter is equivalent to 15 times the potency of hydrocortisone (42) such that 0.3 mg of fludrocortisone is equivalent to about 4.5 mg hydrocortisone or 1 mg prednisone. When used in the dose range of 0.1–0.3 mg/day fludrocortisone reduces serum potassium in hyporeninemic hypoaldosteronism (43), in renal insufficiency due to lupus erythematosus (44), and in heparin-induced hyperkalemia (45). The decrease in serum potassium in these studies was attributed to mineralocorticoid-induced increased renal tubular potassium secretion. However, balance studies were not performed and it is not known if enhanced colonic potassium secretion contributed to the effect.

Mineralocorticoids in the Treatment of Hyperkalemia With Renal Failure

Whether or not dialysis patients have true secondary hyperaldosteronism is unclear, and reported values for aldosterone in these patients are generally normal or near normal. Nevertheless, an increase in colonic excretion of potassium has been reported in chronic renal failure (9,46).

More direct evidence of a role for aldosterone in extrarenal potassium excretion, regardless of the basal level, is provided by a crossover study of unfractionated heparin vs. low molecular weight heparin for anticoagulation in maintenance HD patients (47). Unfractionated heparin is known to suppress adrenal zona glomerulosa production of aldosterone. Changing from unfractionated heparin to low molecular weight heparin resulted in a concomitant increase in aldosterone and a decrease in serum potassium. Since those patients were essentially anuric, it is reasonable to assume that the increase in aldosterone resulted in lower serum potassium by increasing colon excretion of potassium.

Nyman et al. (48) used fludrocortisone to treat symptomatic hypotension in five anuric dialysis patients; they noted a decrease in serum potassium from 4.7 to 4.0 mEq/L during the 3- to 9-month treatment period and suggested that this was due to increased bowel secretion and/or increased cellular uptake of potassium. The specific and chronic use of oral fludrocortisone to lower interdialytic potassium was reported by Singhal et al. (49), who found that 0.1–0.3 mg/day decreased mean serum potassium by 0.7 mEq/L during a 3- to 6-month period in 21 dialysis patients. Since the measured urinary

excretion of potassium in the oliguric patients did not change, it is likely that the exogenous mineralocorticoid decreased interdialytic potassium due to an increased colon potassium secretion.

In summary, the effectiveness of fludrocortisone in decreasing serum potassium in patients with renal insufficiency and those on maintenance HD has been demonstrated both by clinical and basic physiologic investigations. Despite the effectiveness of fludrocortisone in managing interdialytic hyperkalemia, it is not widely used. As a result, dialysis patients are at increased risk for both hyperkalemia and intradialytic hypokalemia as we attempt to decrease the potassium burden during a 3- to 4-hour HD session with low or potassium-free dialysate. A potentially safer approach to the problem of the potassium burden of dialysis patients would be to minimize the positive potassium balance in the interdialytic period, allowing a more physiologic dialysate potassium concentration during dialysis treatments. It is clear from the above mentioned studies that a mineralocorticoid agonist can safely provide relief from interdialytic hyperkalemia.

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