Hyperkalemia Risk in Chronic Kidney Disease
Deterrent to the Use of Aldosterone Receptor Antagonism or Not

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Chronic kidney disease (CKD), with or without associated comorbidities, has emerged as a global health care problem, with >1.75 million people currently being kept alive by means of dialysis or transplantation.1 This number is projected to double within the next decade. The cumulative global cost for dialysis and transplantation is predicted to exceed $1 trillion over the next decade. Preventing the development of end-stage renal disease would obviously have a significant positive impact on global health care costs, which would be of particular import for developing countries where dialysis is largely unaffordable. This economic plight is being addressed with implementation of early screening for the presence of CKD. Such screening, including measuring blood pressure (BP), serum creatinine, and urine protein excretion, carries minimal cost and is readily available.2 Once a patient is screened, cost-effective treatment measures exist that can target BP, protein excretion, smoking status, body weight, glycemic control, as well as management of hyperlipidemia.

BP reduction in CKD patients can prove particularly challenging, not uncommonly requiring ≥3 antihypertensive medications, and even then, BP is often still not at goal. Reducing urine protein excretion is another modifiable risk factor for renal failure progression that is best managed with multidrug therapy. During the past 2 decades, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and, most recently, direct renin inhibitors have emerged as preferred therapies for both the BP and proteinuria treatment aspects of CKD. Each of these drug classes, whether given individually or when combined, has a finite capacity to reduce BP/protein excretion in CKD patients; thus, it comes as no surprise that many individuals with CKD experience an unrelenting loss of renal function despite treatment with ACE inhibitors or ARBs, hence the search for primary or adjunctive therapies to support (or possibly replace) these more traditional treatment modalities.

In that regard, aldosterone has emerged as a significant determinant of BP, protein excretion, and the rate at which renal failure progresses in CKD patients. In the presence of a high salt intake, aldosterone-mediated activation of mineralocorticoid receptors localized to nonepithelial tissues promotes both inflammation and fibrotic tissue injury in the cardiovascular and renal systems. In experimental models, aldosterone administration in the setting of high salt intake produces glomerulosclerosis and heavy proteinuria independent of the BP level, evidence indicating a direct profibrotic effect of aldosterone on the kidney.3 ACE inhibitors and ARBs do not fully arrest this profibrotic/inflammatory effect of aldosterone, which may, in part, relate to the phenomenon of aldosterone breakthrough.4

In these same experimental models, mineralocorticoid receptor antagonism (MRA) decreased urinary protein excretion and attenuated, if not regressed, histological markers of glomerular injury. These findings would seem to firmly position MRA in the hierarchy of therapies for patients with CKD, not unlike what has become the case for MRA in patients with heart failure.5–8 There are 2 MRAs, eplerenone and spironolactone, currently available in the United States. Both compounds dose-dependently increase serum potassium levels, particularly when given together with either an ACE inhibitor or an ARB in the setting of renal failure,9 thus the basis of the studies by Preston et al, which set out to address the acute and chronic changes in serum potassium in a cohort of CKD patients (estimated glomerular filtration rate between 25 and 65 mL/min) receiving the ACE inhibitor lisinopril along with the MRA spironolactone.10

Preston et al thoughtfully approached what is now an increasingly common clinical question: how safe is it to give an MRA to stage-3 CKD patients already receiving an ACE inhibitor? In so doing, they have not only acquired clinically useful information but also have established a model for future study of medication-related effect on potassium homeostasis. There are multiple nuggets that emerge from these studies. First, the average increase in serum potassium to be expected with chronic dosing of an ACE inhibitor and an MRA is identified. Such a change in serum potassium could be viewed as a simple fait accompli; nevertheless, the lesson learned with chronic dosing with an ACE inhibitor and an ARB is that at a steady-state for level of renal function, dietary potassium intake, and medication doses, serum potassium values reach a higher value and thereafter do not increase continuously.10 If serum potassium values do increase, it is when steady-state circumstances no longer exist, such as when dietary potassium intake suddenly increases or there is a significant decline in renal function.

Second, and of even more interest, Preston et al cleverly used the change in serum potassium after an oral potassium load (35 mmol/L potassium) as an indicator of the internal homeostatic coping skills of CKD patients to a potassium...
challenge. In so doing, they emphasize that serum potassium values are quite dynamic in nature when a potassium load is administered. It is customary in CKD patients to measure serum potassium values at regular intervals. The value obtained then determines whether patients fall into the category of hyperkalemia (typically a serum potassium value of >6.0 mmol/L). What is missing from this time-honored approach to interpreting serum potassium values is the dynamic component or the variation around an average value as it relates to recent potassium intake or the efficiency with which potassium undergoes transcellular redistribution.

It would seem that Preston et al provide a concrete example of the importance of this peak and valley aspect of potassium homeostasis, particularly in light of the fact that they demonstrate that the internal translocation of potassium can be compromised in the CKD patient even in the absence of hyperglycemia. Peak values, which most times go unrecognized because of the vagaries of potassium value sampling, could put patients in a danger zone for a short period of time (hours) until they re-equilibrate through renal excretory mechanisms and transcellular redistribution.

There are 2 items that complicate interpretation of the findings of these studies. First, the patients were placed on a low-sodium diet before being given a potassium challenge, which would impact the potassium excretion findings of these studies. All other factors being equal, an increase in sodium intake, and therein greater distal tubular delivery, would result in additional urinary losses of potassium. Second, the CKD patients studied had an average estimated glomerular filtration rate of ~45 mL/min and seemed not to be sodium retainers. It is unclear how potassium handling would play out in CKD patients at more advanced stages of their disease, during which proteinuria might be more significant and sodium retention more prominent. Finally, the pharmacokinetics of spironolactone may also be a consideration in these findings. Spironolactone has several active metabolites and a longer pharmacodynamic effect than eplerenone. The more prolonged duration of effect for spironolactone may be the basis for its ability to reduce BP more so than eplerenone; however, in at-risk patients, this extended pharmacodynamic effect for spironolactone may also be associated with a greater risk of hyperkalemia than what is seen with eplerenone.

In summary, as enthusiasm grows for use of MRAs in CKD, the risks inherent in the use of such drugs become more pertinent. Whereas the endocrine side effects of spironolactone are, in reality, little more than a cosmetic disfigurement, the potassium-sparing effects of spironolactone (and eplerenone) can prove life threatening if hyperkalemia develops. However, for most patients, the risk of developing hyperkalemia should not dissuade the prudent clinician from use of these compounds if indicated. Hyperkalemia should be considered a possibility in any patient receiving an MRA with or without an ACE inhibitor (or ARB). Hyperkalemia is best addressed preemptively with control of dietary potassium intake, elimination (or dosage reduction) of potassium supplements, and avoidance of potassium-sparing compounds.

Disclosures

D.A.S. has served on the advisory board/consultancies for Novartis, Takeda, Glaxo Smith Kline, and CVRx and received research grants from Novartis, Takeda, and CVRx.

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