Treatment with patiromer decreases aldosterone in patients with chronic kidney disease and hyperkalemia on renin-angiotensin system inhibitors

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Elevated serum aldosterone can be vasculotoxic and facilitate cardiorenal damage. Renin-angiotensin system inhibitors reduce serum aldosterone levels and/or block its effects but can cause hyperkalemia. Patiromer, a nonabsorbed potassium binder, decreases serum potassium in patients with chronic kidney disease on renin-angiotensin system inhibitors. Here we examined the effect of patiromer treatment on serum aldosterone, blood pressure, and albuminuria in patients with chronic kidney disease on renin-angiotensin system inhibitors with hyperkalemia (serum potassium 5.1–6.5 mEq/l). We analyzed data from the phase 3 OPAL-HK study (4-week initial treatment phase of 243 patients; 8-week randomized withdrawal phase of 107 patients). In the treatment phase, the (mean ± standard error) serum potassium was decreased concordantly with the serum aldosterone (−1.99 ± 0.51 ng/dl), systolic/diastolic blood pressure (−5.64 ± 1.04 mm Hg/−3.84 ± 0.69 mm Hg), and albumin-to-creatinine ratio (−203.7 ± 54.7 mg/g), all in a statistically significant manner. The change in the plasma renin activity (−0.44 ± 0.63 μg/l/hr) was not significant. In the withdrawal phase, mean aldosterone levels were sustained with patiromer (+0.23 ± 1.07 ng/dl) and significantly increased with placebo (+2.78 ± 1.25 ng/dl). Patients on patiromer had significant reductions in mean systolic/diastolic blood pressure (−6.70 ± 1.59/−2.15 ± 1.06 mm Hg), whereas those on placebo did not (−1.21 ± 1.89 mm Hg/+1.72 ± 1.26 mm Hg). Significant changes in plasma renin activity were found only in the placebo group (–3.90 ± 1.41 μg/l/hr). Thus, patiromer reduced serum potassium and aldosterone levels independent of plasma renin activity in patients with chronic kidney disease and hyperkalemia on renin-angiotensin system inhibitors.

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Because of the increased prevalence of hyperkalemia (HK) in patients with renal dysfunction, novel agents have recently been developed to reduce serum potassium (sK) levels by binding potassium in the gastrointestinal tract.[1] Although these agents have produced the intended beneficial effect of reducing potassium levels,[2] there may be added benefits from this form of therapy—a reduction in aldosterone production.

Higher levels of serum aldosterone are associated with increased mineralocorticoid receptor stimulation; this ligand-receptor interaction has been well demonstrated to promote cardiovascular and renal disease progression in experimental and clinical studies.[3-9] By blocking this interaction, mineralocorticoid receptor antagonists have demonstrated benefits in patients with heart failure and post-acute myocardial infarction.[7] Moreover, blocking the mineralocorticoid receptor is associated with reductions in blood pressure (BP) and albuminuria,[8] suggesting that this type of therapeutic approach may reduce the rate of renal disease progression. Recent studies have also suggested that mineralocorticoid receptor activation may lead to metabolic dysregulation and susceptibility to type 2 diabetes mellitus and atherosclerosis.[10-13]

Consequently, there is great interest in reducing the adverse effects of aldosterone, which can be accomplished with mineralocorticoid receptor antagonists.[7,14] Yet, the use of mineralocorticoid receptor antagonists in patients with renal dysfunction is associated with a substantial incidence of HK, which limits their use either alone or combined with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[15-19] For example, in 2009, Khosla *et al.*[20] reported a rate of HK (potassium >5.5 mEq/l) of 34.7% in patients treated with a mineralocorticoid receptor antagonist who had a baseline serum potassium level >4.5 mEq/l and a glomerular filtration rate ≤45 ml/min per 1.73 m^2. This limitation is a concern, especially in patients with congestive heart failure, with or without renal dysfunction, in whom the

effects of aldosterone reduction provide the greatest benefit.[5-8]

Aldosterone production is not only regulated by the renin-angiotensin-aldosterone system (RAAS), but also by potassium,[5,21,22] which is equally potent in modulating aldosterone secretion.[23-28] Thus, the possibility exists that agents that lower potassium levels may also reduce aldosterone secretion and may provide an added benefit beyond potassium reduction in patients with renal dysfunction.

To test this hypothesis, we performed a prespecified exploratory analysis of the OPAL-HK clinical trial in which patiromer, a novel potassium-binding polymer that uses calcium rather than sodium as the cation for exchange with potassium, was shown to decrease potassium levels in patients with chronic kidney disease (CKD) and HK who were being treated with a RAAS inhibitor (RAASi).[2] Based on the pivotal OPAL-HK study,[2] patiromer was recently approved by the US Food and Drug Administration for the treatment of HK. The unique design of the OPAL-HK study allowed us to evaluate changes in aldosterone, BP, and albuminuria according to baseline potassium level and in a placebo-controlled fashion to determine whether there are additional beneficial effects of patiromer beyond sK reduction.

RESULTS

Patient disposition and demographics

Overall, 243 patients were enrolled in the initial treatment phase, and 107 patients participated in the randomized withdrawal phase of the study (55 continued patiromer and 52 switched to placebo). The majority of patients had hypertension, diabetes mellitus, and advanced CKD. The baseline characteristics of patients in these analyses are shown in Table 1.

Table 1 | Baseline demographic and clinical characteristics

Characteristic	Initial treatment phase Overall (N = 243)	Randomized withdrawal phase	
		Placebo (N = 52)	Patiromer (N = 55)
Male sex, *n* (%)	140 (58)	30 (58)	28 (51)
Age, yr, mean ± SD	64.2 ± 10.5	65.0 ± 9.1	65.5 ± 9.4
White race, *n* (%)[a]	239 (98)	52 (100)	55 (100)
Type 2 diabetes, *n* (%)	139 (57)	33 (63)	34 (62)
Heart failure, *n* (%)	102 (42)	22 (42)	27 (49)
NYHA functional class, *n* (%)			
I	19 (19)	4 (18)	5 (19)
II	66 (65)	14 (64)	18 (67)
III	17 (17)	4 (18)	4 (15)
Myocardial infarction, *n* (%)	60 (25)	14 (27)	18 (33)
Hypertension, *n* (%)	236 (97)	50 (96)	54 (98)
Serum potassium, mEq/l, mean ± SD[b]	5.6 ± 0.5	5.9 ± 0.4	5.9 ± 0.6
Estimated GFR, ml/min per 1.73 m^2, *n* (%)[c]			
Stage 2: 60 to <90	22 (9)	4 (8)	8 (15)
Stage 3A: 45 to <60	49 (20)	11 (21)	11 (20)
Stage 3B: 30 to <45	63 (26)	14 (27)	15 (27)
Stage 4/5: <30	109 (45)	23 (44)	21 (38)
RAASi use, *n* (%)[c]	243 (100)	52 (100)	55 (100)
ACE inhibitor	170 (70)	38 (73)	37 (67)
Angiotensin II receptor blocker	92 (38)	16 (31)	24 (44)
MRA	22 (9)	4 (8)	4 (7)
Renin inhibitor	2 (1)	0	0
Dual RAAS blockade[d]	41 (17)	6 (12)	10 (18)
Receiving maximal dose[e]	106 (44)	21 (40)	21 (38)
Non-RAASi diuretic use, *n* (%)[c]	132 (54)	27 (52)	28 (51)
Thiazide	70 (29)	11 (21)	16 (29)
Loop	77 (32)	20 (38)	16 (29)
Serum aldosterone, ng/dl, mean ± SD[b]	11.86 ± 11.31	11.83 ± 12.40	13.36 ± 12.14

ACE, angiotensin-converting enzyme; GFR, glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RAAS, renin-angiotensin-aldosterone system; RAASi, renin-angiotensin-aldosterone system inhibitor.
[a]Race was determined by the investigators.
[b]The values in this row refer to baseline values at the start of the study.
[c]The values for patiromer and placebo in this row refer to baseline values at the start of the randomized withdrawal phase.
[d]Dual RAAS blockade refers to any combination of ≥2 of the following: ACE inhibitor, angiotensin II receptor blocker, aldosterone antagonist, or renin inhibitor.
[e]The maximal dose was determined according to the judgment of the investigator in accordance with the local standard of care.

Initial treatment phase

Over the 4-week initial treatment phase, mean ± SE serum aldosterone levels decreased (−1.99 ± 0.51 ng/dl, $P = 0.0001$) in parallel with decreases in sK (Figure 1). When examined by baseline sK levels, only patients with moderate to severe HK had significant changes from baseline in mean ± SE serum aldosterone levels at week 4 (mild HK: −0.67 ± 0.80, P = not significant [NS]; moderate to severe HK: −3.32 ± 0.63, $P < 0.0001$) (Table 2). As previously reported,[2] patients with moderate to severe HK (5.5 to <6.5 mEq/l) at baseline had greater changes from baseline in sK compared with patients with mild HK (5.1 to <5.5 mEq/l) at baseline. Patients with mild HK had a mean decrease in sK from baseline to week 4 of −0.65 (0.05) mEq/l compared with −1.23 (0.04) mEq/l in patients with moderate to severe HK at baseline; both were statistically significant.

BP decreased over the initial 4-week treatment period in patients receiving patiromer (Figure 2). The mean ± SE systolic BP (SBP) change from baseline in patients with mild HK was −5.7 (1.6) mm Hg ($P = 0.0005$) and −5.5 (1.3) mm Hg ($P < 0.0001$) in patients with moderate to severe HK (Table 2). Mean diastolic BP (DBP) changed from baseline by −3.2 (1.1) mm Hg in patients with mild HK ($P = 0.003$) and by −4.5 (0.9) mm Hg in patients with moderate to severe HK ($P < 0.0001$) (Table 2).

In the extended multivariate mixed model for repeated measures (MMRM) model, decreases in mean ± SE aldosterone level were associated with baseline serum aldosterone levels ($P < 0.0001$), age 65 years or older ($P = 0.04$), the presence of type 2 diabetes mellitus ($P = 0.02$), and the absence of heart failure ($P = 0.04$). There was no significant effect of sex and CKD stage on aldosterone reduction (Supplementary Table S1). After adjustment for baseline aldosterone and the previously cited covariates, reduction in