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Minireview

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Mineralocorticoid receptor blockade—a novel approach to fight hyperkalaemia in chronic kidney disease

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Abstract
Hyperkalaemia continues to be a major hazard of mineralocorticoid receptor blockade in an effort to retard the progression of chronic kidney disease (CKD). In cardiac patients on mineralocorticoid receptor blockade, RLY-5016 which captures K^+ in the colon has been effective in reducing the risk of hyperkalaemia. This compound might be useful in CKD as well.

Keywords: aldosterone blockade; chronic kidney disease; hyperkalaemia; potassium binder

The management of chronic kidney disease (CKD) was revolutionized by the introduction of RAS blockade. In patients with CKD, this intervention attenuates, but usually fails to stop, progressive loss of glomerular filtration rate (GFR) [1]. There is an obvious need for further types of intervention. One promising additional target of intervention is aldosterone. So far, however, the mineralocorticoid receptor blockade has been infrequently used because of the risk of hyperkalaemia.

The role of aldosterone in CKD

The rationale to select aldosterone as a target is provided by the evidence that—apart from the renin–angiotensin system—for intervention aldosterone also plays an important role in the progression of CKD. This has been documented by experimental and clinical observations. In the study by Rocha *et al*. [2], infusion of aldosterone reversed renoprotection by Captopril in SHRsp independent of blood pressure (BP). In the seminal study by Greene *et al*. [3], combined treatment with an angiotensin converting enzyme (ACE) inhibitor and angiotensin receptor blocker caused substantial reduction of proteinuria in rats with subtotal nephrectomy; when aldosterone was administered on top of RAS blockade, a dramatic increase in proteinuria was seen pointing to a potent role of aldosterone. The importance of aldosterone as a promotor of CKD is further illustrated by the observation in subtotally nephrectomized rats that aldosterone blockade even causes regression of established glomerulosclerosis [4]. Furthermore aldosterone is one of the causes of renal fibrosis caused by epithelial-to-mesenchymal transition [5]. A reduction of aldosterone production improves renal oxidative stress and renal fibrosis as shown in diabetic rats [6]. Recent experimental studies documented that mineralocorticoid receptor blockade confers renoprotection even in the absence of elevated aldosterone concentrations; this was the result of crosstalk between the mineralocorticoid receptor and the small GTP'ase Rac1 [7].

In experimental studies, the impact of aldosterone on renal lesions is further aggravated by high salt intake [3, 8], which causes renal inflammation, fibrosis, podocyte injury and mesangial cell proliferation [9].

It has been shown in the past that plasma aldosterone concentrations are significantly elevated in CKD patients once the GFR is <70 mL/min [10]. Furthermore, recent studies showed that the plasma aldosterone concentration is a predictor of future impairment of GFR [11]. In patients with primary kidney disease, the serum aldosterone concentration correlated with deterioration of renal function [12–14]. A significant correlation was also found between serum aldosterone concentration and renal cicatrization [15]. The adverse renal effect of aldosterone is at least in part independent of BP; e.g. in primary aldosteronism proteinuria is more severe than in essential hypertension [16].

It has been known for a long time that RAS blockade decreases in renal patients, but subsequently a secondary increase, associated with more rapid loss of GFR, is frequently observed [17]. Aldosterone is the cause of such renal 'escape' in diabetic nephropathy [18] and other forms of proteinuric nephropathy and this is also true in advanced renal failure [19]. Such 'escape' can often be prevented by mineralocorticoid receptor blockade [20]. In CKD, the kidney may be particularly sensitive to the adverse effects of aldosterone because of increased expression of the mineralocorticoid receptor and of sgk-1 [15].

It is also of interest that renal injury may be provoked not only by circulating aldosterone, but also by local production of aldosterone in the kidney [21, 22]—similar to what has been shown in the heart as well [23]. In view of the importance of receptor blockade in the clinical

management, it should be mentioned, however, that some of the adverse renal consequences of aldosterone are the result of nongenomic effects [24].

The potential role of mineralocorticoid receptor blockade in kidney disease

The recent interest in mineralocorticoid receptor blockade as a strategy to interfere with the progressive loss of GFR in proteinuric CKD was mainly stimulated by an observation of Chrysostomou and Becker [25]: eight patients with CKD had substantial residual proteinuria despite RAS blockade; they received 25 mg spironolactone, and this intervention reduced proteinuria by 54% without any change in BP or creatinine clearance. Such a decrease of proteinuria is not the result of the diuretic effect of spironolactone, since it is not seen with furosemide [26]. A meta-analysis evaluating four randomized, controlled trials documented a significant reduction of proteinuria by spironolactone in proteinuric CKD patients [27]. As discussed below an important ancillary aspect in the management of CKD patients is the role of aldosterone in the genesis of cardiac abnormalities [28] and their reversal by spironolactone [29].

Apart from these classical indications for the use of spironolactone, i.e. lowering of BP, reduction of proteinuria and potentially progressive loss of GFR, recently vascular calcification has been identified as a novel additional potential target for aldosterone blockade: aldosterone induced PIT-1-dependent vascular osteoinduction in response to aldosterone in klotho-hypomorphic mice, and this was ameliorated by spironolactone [30, 31].

In the context of non-classical indications for aldosterone blockade, a recent clinical observation is also of interest: avasare (Clin Nephrol (2012) e-pub 4 December 2012) observed that patients with proteinuric renal disease developed anaemia on treatment with ACE inhibitors + ARB; anaemia was reversed when mineralocorticoid receptor blockers were substituted for ACEi + ARB.

It is an unexplored issue whether a mineralocorticoid receptor blockade interferes with the recently documented role of aldosterone in the genesis of insulin resistance and metabolic syndrome—common problems in CKD [32–35] (Feraco *et al.*, J Steroid Biochem Mol Biol (2013)e-pub February 28).

A number of studies on mineralocorticoid receptor blockade with spironolactone or eplerenone have meanwhile been performed in patients with advanced CKD and even in patients on haemodialysis [36] including anephric patients [37]. In haemodialyzed patients, a randomized controlled trial with spironolactone (50 mg 3× per week) documented a beneficial effect on carotid intima-media thickness; remarkably in this well supervised study, there was no major increase in S–K^+ [38]. In the management of CKD patients, and particularly of dialysis patients, one common difficulty is the poor correlation between (estimated) K^+ intake and serum-K^+. In contrast, a significant correlation has been found between K^+ intake and all-cause mortality [39].

Side effects of mineralocorticoid receptor blockade

One major problem with spironolactone administration in renal patients is the concern about hyperkalaemia as a frequent side effect. In CKD, the potential risk of hyperkalaemia is aggravated by the almost obligatory treatment with RAS inhibitors. The RENAAL study included type 2 diabetic patients with advanced renal disease: the risk of renal events (doubling of serum creatinine, end-stage renal disease) was significantly increased in the cohort with even minor elevation of serum K^+ (5.0–5.5 mmol/L) [40].

The major concerns, however, are the cardiac side effects of hyperkalaemia. Despite these potential side effects, the current interest in mineralocorticoid receptor blockade is reflected by the title of a recent communication [41]: 'Renal aspirin: will all patients with CKD one day take spironolactone?'.

Although in the published studies, side effects (including hyperkalaemia) were relatively infrequent, it must be emphasized that the included patients had been carefully selected. Generally, the administered doses of spironolactone or eplerenone were also relatively low. Nevertheless, the main stumbling stone for considering the blockade of the mineralocorticoid receptor in CKD patients remains the concern about hyperkalaemia with its potentially catastrophic outcome [42].

For the nephrologist, it is certainly useful to be aware of recent studies on the use of mineralocorticoid receptor blockers in cardiac patients with a reduced renal function. The cardiac benefit from the mineralocorticoid receptor blockade in cardiac disease had been documented in several breakthrough studies [43–45]. Such a benefit is the result of several mechanisms, including prevention or reversal of cardiac remodelling, antifibrotic mechanisms, reduction of arrhythmogenesis etc. Serious hyperkalaemic episodes had been reported in the major mineralocorticoid receptor antagonist trials. Although patient selection, patient education, monitoring and follow-up reduce the risk [46], nevertheless the rate of hyperkalaemia in the major clinical trials ranged from 2–11% both in controlled trials and in population surveys [47], though the figures are less frightening than suggested by early reports [48]. Worsening of renal function was reported in 8.9% of patients randomized to a mineralocorticoid receptor antagonist versus 1.6% in control patients[49]. It is important, however, that the benefit of mineralocorticoid receptor blockade persisted despite early worsening of renal function.

For the nephrologist, a look at some recent reports on aldosterone blockade is rewarding. In the RALES trial on patients with severe heart failure [50], the absolute risk reduction by spironolactone was greater in patients with an eGFR of <60 mL/min/1.73 m^2 compared with patients with a higher eGFR (10.3 versus 6.4%); importantly a decrease of eGFR was seen in 17% of patients in the spironolactone and 7% in the placebo group. Such a decrease of eGFR increased the adjusted risk of death by a factor of 1.9 in the placebo group, but an increase of risk was not seen in the spironolactone group. Remarkably, the absolute benefit from spironolactone was greatest in patients with reduced eGFR! Although worsening renal function was associated with a negative prognosis, the mortality benefit of spironolactone was still demonstrable. The Chronic Renal Impairment study in Birmingham studied 115 non-diabetic CKD patients with an eGFR of 30–89 mL/min/1.73 m^2 on spironolactone plus RAS blockade; they were followed for 40 weeks; despite rigorous follow-up, S-K^+ values >5.5 mmol/L were seen in ∼10% [51]. In a *post hoc* analysis of the EPHESUS trial [49], the following items were independent predictors of serum K+ > 6 mmol/L: eGFR < 60 mL/min/1.73 m^2, history of diabetes mellitus, baseline serum K^+ > 4.3 mmol/L and prior use of anti-arrhythmics. In a *post hoc* analysis, the decrease in eGFR was higher in the eplerenone group compared with placebo ($P < 0.001$); the

decrease appeared early on and persisted subsequently. Determinants of an early decline of eGFR were female sex, age >68 years, smoking, LVEF <35%, use of eplerenone and use of loop diuretics. Subsequently, renal dysfunction declined at a similar rate on placebo or eplerenone; the baseline severity of renal dysfunction as well as the eGFR decline predicted an adverse outcome regardless of treatment. Importantly, an early excess decline in eGFR did not attenuate the survival benefit in patients assigned to eplerenone. In the *post hoc* analysis of the RALES study [50], the absolute benefit from spironolactone was greatest in patients with a reduced eGFR. An important information is the finding that worsening renal function provided still a mortality benefit despite the association of a reduced GFR with a negative prognosis.

Novel strategies to interfere with mineralocorticoid receptor-mediated effects

On the horizon are novel compounds: on the one hand, substances inhibiting mineralocorticoid receptors [52], e.g. PF-03882845 with high affinity and selectivity for the mineralocorticoid receptor. In animal experiments, it was more potent than eplerenone or BR-4628 [53, 54]. Recently, another non-steroidal mineralocorticoid receptor antagonist has been developed, BAY 94-8862, with greater selectivity compared with spironolactone and stronger mineralocorticoid receptor binding affinity compared with eplerenone. It is currently evaluated in a randomized double-blind study of patients with chronic heart failure and mild-to-moderate CKD [55].

Another line is blockade of the biosynthesis of aldosterone; two aldosterone synthase inhibitors are currently in development, FAD286 and LC1699 [56, 57]. As recently summarized in NDT by Azizi [58], inhibition of aldosterone synthase (CYP11B2) lowered BP in an initial randomized double blind study of patients with primary hypertension [59]; in a second study it also caused significant reduction of 24 h blood pressure—although less compared with eplerenone (Amar, J.Hypertension in press).

How to cope with the risk of hyperkalaemia ?

To assess and reduce the risk of hyperkalaemia, one must not only avoid food items with a high potassium content, but one must also consider that a number of drugs tend to increase serum K^+: obviously K^+-sparing diuretics, but also K^+ salts or supplements, non-steroidal anti-inflammatory drugs, pentamidin, trimethoprim, heparin, penicillin G, tolvaptan, cyclosporine and tacrolimus.

To identify patients at a high risk for hyperkalaemia, a number of tests have been proposed, none of which are very reliable. Follow-up monitoring was required in the RALES dose-finding study in the subgroup of patients with reduced kidney function. Serum K^+ increased from baseline in the first 8 weeks of spironolactone treatment [44], but in patients on RAS blockade the risk of hyperkalaemia persisted throughout the treatment, mainly because of changes in dietary habits [60].

Mineralocorticoid receptor blockers reduce sodium and water reabsorption, but as a downside of this action the potassium excretion is reduced causing hyperkalaemia. The classical management of hyperkalaemia in patients receiving mineralocorticoid receptor antagonists has been recently summarized by Roscioni *et al*. [61].

The risk of hyperkalaemia—a novel approach

Against the background of hyperkalaemia as the limiting factor in the use of mineralocorticoid receptor blockade, it is of interest to the nephrologist that the polymeric potassium binder RLY5016 has recently become available which opens up new possibilities [62, 63]: RLY5016 is a non-absorbed polymer in the form of 100 µm beads. In the colon, RLY5016 binds preferentially to K^+, the concentration of which is much higher than the concentration of other cations. One important issue is the potential scavenging of coadministered drugs. This has so far been documented for valsartan and rosiglitazone, but this issue requires further studies.

The efficacy and safety in cardiac patients have recently been assessed in a double-blind placebo-controlled study in patients with chronic heart failure, the PEARL-HF trial [62]. One hundred and five patients on spironolactone with chronic heart failure and a history of hyperkalaemia were treated for 4 weeks with 30 g/day RLY5016 or placebo. Thirty-two of the patients had an eGFR of <60 mL/min. In the PEARL-HF trial, the patients were instructed to take 15 g of the study drug orally in the morning and in the evening (for a total daily dose of 30 g). They were also instructed to mix the study drug in powder form with water and to ingest low K^+ food. Compared with placebo, RLY5016 lowered serum K^+ levels significantly; the difference with placebo was 0.45 mmol/L ($P < 0.001$). Fewer patients on RLY5016 developed hyperkalaemia ($S\text{-}K^+ > 5.5$ mmol/L) compared with placebo, i.e. 7 versus 25%; conversely more patients on RLY5016 than on placebo developed hypokalaemia <3.5 mmol/L, i.e. 6 versus 0%, respectively.

With respect to CKD, the subgroup of patients with an eGFR of <60 mL/min is of particular interest. In this cohort, the difference of serum K^+ at the end of the study was again different between the groups −0.14 versus +0.38 mmol/L in the RLY5016 and placebo groups respectively (*P = 0.031)*. In the subgroup of patients with a baseline eGFR of <60 mL/min, the incidence of $S\text{–}K^+ > 5.5$ mmol/L was 7% in patients on RLY5016 compared with 39% of patients on placebo (*P = 0.041*). Apart from potassium, magnesium values were also significantly reduced—although minimally so (−0.11 versus 0.01 mmol/L, $P < 0.001$). Most importantly, patients on RLY5016 were able to have their spironolactone dose increased in 91 versus 74% in the placebo group; $P = 0.019$. A relevant aspect is safety: adverse events were flatulence, diarrhoea, constipation and vomiting (21% in the RLY5016 group versus 6% in the placebo group), but this was generally of mild or moderate intensity. No serious adverse events were attributable to the potassium binder.

This novel K^+ binder is obviously of definitive interest to the nephrologist.

In view of the substantial risk of hyperkalaemia in CKD patients on RAS blockade in general, this K^+ binder is obviously of interest to the nephrologist. More specifically, it may also open the possibility of using mineralocorticoid receptor blockade as an add-on treatment on top of RAS blockade in CKD patients—a perspective the efficacy and safety of which will require evidence from controlled studies.

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(See related article by Luft. The chronic kalaemia conundrum. *Clin Kidney J* 2013; 6: 455–456)

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