Is it time for spironolactone therapy in dialysis patients?

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Aldosterone in chronic kidney disease

Aldosterone has been identified in the last decade as an important contributor to the progression of both kidney and heart disease. In elegant experimental studies, Rocha and co-workers [1] demonstrated that aldosterone is responsible for inflammation and fibrosis in the kidney. According to very recent experimental data, spironolactone may induce a regression of existing glomerulosclerosis [2]. In humans, there are few and small studies confirming the beneficial effect of aldosterone antagonism on proteinuria reduction [3–5]. Thus, aldosterone blockade has the theoretic advantage of addressing both heart and kidney damage, a frequent deadly duo.

Cardiomyopathy in chronic kidney disease

Congestive heart failure (CHF) has been recognized recently as the first cause of cardiovascular death in chronic kidney disease (CKD) [6]. Once established, CHF in dialysis subjects is associated with a catastrophic survival [7]. Moreover, cardiac abnormalities are early (and progressive) events in CKD patients, often precluding clinical signs of heart failure.

There are sufficient arguments for a standard optimal medical therapy for patients with CHF on dialysis. Unfortunately, patients with significant renal dysfunction and cardiovascular disease are definitely under-diagnosed and undertreated [8]. The reasons for this ‘renalism’ are unclear, but may be related to insufficient data from large well-conducted trials and the perception that what is true in the general population may not be equally efficient in renal patients. Particularly in the case of aldosterone antagonism, the fear of life-threatening hyperkalaemia (and of endocrine side effects) with spironolactone in dialysis patients may severely limit the large-scale clinical usage of this antialdosteronic drug. However, the same fears arise with angiotensin-converting enzyme (ACE) inhibition and angiotensin-receptor blockade years ago, whereas ACE inhibitors (ACEI) and angiotensin-receptor blockers (ARB) are nowadays well accepted in routine clinical practice in chronic uraemia subjects. Nevertheless, combining aldosterone with ACEI may further increase the hazard of life-threatening hyperkalaemia in patients of older age, with diabetes, prone to dehydration and with worsening heart failure [9]. We will discuss later the issue of safety of spironolactone in dialysis populations.

The RALES lesson

The seminal data of the Randomized Aldactone Evaluation Study (RALES) published in 1999 [10] gave new hope to the therapy and outcome of patients with CHF. Indeed, there was an impressive reduction in mortality, hospitalization and symptoms in the low-dose spironolactone arm compared with placebo. The incidence of severe hyperkalaemia was minimal in both arms, despite concomitant use of ACE inhibitors in the vast majority of patients. However, as serum creatinine of >2.5 mg/dl was an exclusion criterion, we do not have to date large-scale data on the efficacy and safety of aldosterone antagonism in patients with severe renal failure. The publication of the RALES data was associated with an abrupt increase of hyperkalaemia-related morbidity and mortality, but not with all-cause mortality or risk of hospital readmission [11]. More recently, it has been confirmed that low-dose spironolactone reduces effectively ACE activity and improves vascular function and other markers of prognosis (brain natriuretic peptide, collagen markers and QT interval length).
even in patients with mild or asymptomatic heart failure [12].

Eplerenone, a selective aldosterone antagonist, seems to have similar beneficial effects on cardiovascular outcomes, with fewer adverse reactions compared with spironolactone. The EPHESUS trial showed a reduction of death risk by 15% in patients with myocardial infarction treated with eplerenone compared with those on standard therapy alone [13]. Subjects with a serum creatinine of >2.5 mg/dl were again excluded, but probably at least one-third of patients had CKD. Eplerenone is associated with similar rates of hyperkalaemia episodes in comparison with spironolactone, but with less gynaecomastia [13].

To date, according to manufacturer information, eplerenone is contraindicated in patients with a glomerular filtration rate of <30 ml/min; however, a very recent study on the pharmacokinetics of eplerenone showed similar pharmacokinetics for the active drug in patients with various degrees of renal impairment, including haemodialysis (HD) patients [14].

Despite ongoing concerns related to significant side effects [11], low-dose spironolactone was, in 2005, a part of the standard medical therapy for patients with CHF and without severe renal failure. Is it reasonable to extrapolate the data on the efficacy of spironolactone from the non-renal population with CHF to the dialysis population? While this question is still open, we will further review existing information on spironolactone usage in end-stage renal disease (ESRD).

**Aldosterone and the genesis of uraemic cardiomyopathy**

Anatomic abnormalities, including left ventricular hypertrophy and myocardial fibrosis – strong predictors of cardiac death in uraemic patients with heart failure [15] – are more pronounced in dialysis patients compared with non-renal controls. The activation of the renin–angiotensin–aldosterone (RAA) axis plays a central role in abnormal cardiac remodelling, according to both experimental and clinical evidence. Excessive activation of the RAA axis leads to myocardial hypertrophy and cardiac fibrosis; aldosterone mediates and potentiates the deleterious actions of angiotensin II (Figure 1). A detailed discussion of the pathophysiological pathways has been presented elsewhere – for a comprehensive discussion, please see Struthers et al. [16].

In animal models, Weber has shown convincingly that aldosterone is responsible for extensive scarring in the myocardial tissue – for a review of the evidence the reader is referred to [17]. Further seminal experimental data from Rocha and co-workers [1] have clearly documented the favourable impact of aldosterone antagonism on uraemic cardiomyopathy. Finally, it has been demonstrated that aldosterone may play a central role in mediating increased arterial stiffness [18], a frequent feature of ESRD patients and a major determinant of the uraemic cardiomyopathy [19,20].

Moving to clinical studies, in ESRD patients, there seems to be a direct relationship between plasma aldosterone concentration and left ventricular hypertrophy both before and after the HD session [21]. However, solid clinical data, linking aldosterone to the genesis of uraemic cardiomyopathy and aldosterone blockade to improvement in left ventricular parameters, are scarce.

### The threat of hyperkalaemia in ESRD

The major site of potassium excretion is the kidney, whereas only 10–20% of daily losses are excreted by the large bowel. In advanced renal failure, there is some increase in colonic excretion, but the absolute amounts of adaptive losses through the bowel remain low [22]. Colonic excretion can be increased in some patients with renal failure ≤30 mmol/day, significant enough to avoid dangerous hyperkalaemia [23]. Aldosterone promotes potassium colonic excretion so that aldosterone inhibition in oligoanuric patients may be, in this respect, hazardous, as illustrated by the case published by Colussi and Dossi [24].

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**Fig. 1.** Inhibition of the RAA axis by various medications, including spironolactone. BB, beta-blockers; LVH, left ventricular hypertrophy.
Hyperkalaemia in dialysis patients is frequent and may account for a significant proportion of serious arrhythmias and sudden deaths. One large study in Okinawa, Japan found that hyperkalaemia at initiation of renal replacement therapy is a predictor of mortality [25]. However, the precise relationship between hyperkalaemia and the risk of death is poorly documented and may be still discussed. Karnik and co-workers [26] were not able to find a direct relationship between pre-dialytic hyperkalaemia and the risk of sudden death, whereas dialysing against a low-potassium dialysate was hazardous. Furthermore, it has been postulated that there is an increased tolerance of hyperkalaemia in dialysis patients compared with non-renal subjects [22].

**Aldosterone blockade in HD patients**

Concerns about the safety of administering a potassium-sparing agent are justified in patients prone to chronic, and sometimes acute and life-threatening, hyperkalaemia. The potential hazardous effect of spironolactone on plasma potassium levels was recognized as early as 1979 [27]. However, low-dose spironolactone (25 mg/day) has been shown to be relatively safe in a small series of HD patients (Table 1). Just one out of 15 patients experienced significant (7.5 mEq/l) hyperkalaemia; moreover, serum potassium levels were similar to pre-study average values. Side effects were infrequent overall during the 28 days of follow-up [28]. Another investigation [29] also demonstrated that low-dose spironolactone (initially 12.5 followed by 25 mg three times a week, each regimen for two weeks) + low-potassium diet was safe. Serum potassium did not change significantly during a study period of 4 weeks, compared with baseline and with controls, despite the fact that all patients were anuric and over half of them were concomitantly treated with ACEI or ARB.

Finally, a very recent randomized double-blind cross-over study [30] in a small number of oligoanuric HD patients examined the effect of 50 mg spironolactone twice daily on blood pressure (BP) and RAA axis. When administered for 2 weeks, spironolactone was effective in lowering pre-dialysis systolic BP (from 142 to 131.4 mmHg) without causing significant hyperkalaemia. There was no effect on plasma aldosterone concentration or renin activity [30]. Interestingly, the daily dose of spironolactone was identical to the RALES pilot study, where it was associated with a high risk of hyperkalaemia in non-renal patients [31]. Although encouraging, these data on spironolactone use in HD patients (for an overview see Table 1) should be confirmed clearly by large randomized placebo-controlled trials, analysing both well-defined outcomes and safety issues. Additionally, spironolactone therapy may still be unsafe in the setting of high-potassium dietary intake, exertional hyperkalaemia, hyperglycaemia or digoxin toxicity.

### Table 1. Clinical studies on spironolactone in dialysis patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Design</th>
<th>Results</th>
<th>Observations</th>
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<tbody>
<tr>
<td>Saudan et al. 2003</td>
<td>20 patients, 14 study patients, 21 controls, half of them on ACEI or ARB</td>
<td>14 study patients, 21 controls, half of them on ACEI or ARB; 8 in each group on ion-exchange resin</td>
<td>Mean serum K similar in the two groups (4.9 mmol/l)</td>
<td>No changes from baseline K levels, 4.9 to 4.6 at end of 2 weeks</td>
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<tr>
<td>Hussain et al. 2003</td>
<td>25 patients without hyperkalaemia in the preceding 4 months</td>
<td>Mean serum K similar in the two groups (4.9 mmol/l)</td>
<td>Mean K levels not significantly modified by spironolactone administration</td>
<td>No changes from baseline K levels, 4.9 to 4.6 at end of 2 weeks</td>
</tr>
<tr>
<td>Gross et al. 2005</td>
<td>8 oligoanuric patients, not on ACEI or ARB</td>
<td>Randomized double-blind, placebo-controlled, crossover study for 2 weeks, 2+2 weeks, with a 3 week wash-out</td>
<td>No effect of spironolactone on plasma aldosterone concentration or renin activity</td>
<td>Significant drop of systolic BP BP effect independent of the diuretic effect</td>
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Aldosterone blockade in peritoneal dialysis

Spironolactone use in peritoneal dialysis (PD) patients is even less studied than in HD-treated subjects. A first case report was published by Hausmann and Liel-Cohen [32], claiming the safety of aldosterone antagonism (25 mg spironolactone daily) in a 73-year-old diabetic patient with CHF on cycling PD. During 10 months of therapy, serum potassium did not exceed 5.1 mmol/l and both systolic and diastolic function significantly improved; however, the patient developed gynaecomastia. This finding has been confirmed by Azar and colleagues [33], who reported a series of 15 patients with a ‘certain degree of renal failure’ treated for CHF with continuous ambulatory PD. In this small series, ACE inhibitors, beta-blockers and loop diuretics were also used. No hyperkalaemic episode was noticed during the 24 month follow-up. The lack of hyperkalaemic episodes was attributed to the continuous character of PD treatment. Indeed, hypokalaemia may be rather a clinical issue in PD patients, due to efficacious dialysate potassium disposal and, possibly, malnutrition [34].

None of these assumptions may be appropriate in anuric PD patients with inadequate dialysis, low-transporter status and/or dietary non-compliance [35]. In fact, the opinion that aldosterone blockade may be safe in PD patients was heavily criticized [36], the extrapolation of the RALES findings in ESRD patients being considered preposterous. It is true that there is a desperate need for randomized controlled trials examining both safety profile and cardiovascular and general outcome of aldosterone (with or without ACEI or ARB) therapy in HD and PD patients.

Perspectives

A large-scale trial of low-dose spironolactone in dialysis patients is unlikely, due to several factors, although we are in urgent need of more consistent data from well-conducted class A investigations on the effect of spironolactone on cardiovascular and general outcome. It is probable, based on extrapolations from the general population, that spironolactone may have a significant (or even more pronounced) effect on abnormal cardiac remodelling and, therefore, on cardio-vascular hazard, compared with non-renal populations. The issue of safety of spironolactone in dialysis is far from being solved and should be examined in larger trials, for longer periods, with and without concomitant ACE inhibition. Based on current knowledge, we can conclude that at least in selected dialysis patients, low-dose aldosterone blockade may be safe. However, peculiar situations like dehydration, dietary incompliance, hyperglycaemia, etc. may add an additional hazard for hyperkalaemia. Concomitant use of bowel chelation of potassium with resins may be beneficial in addition to spironolactone, but has never been studied properly.

References


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