Spironolactone

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Introduction

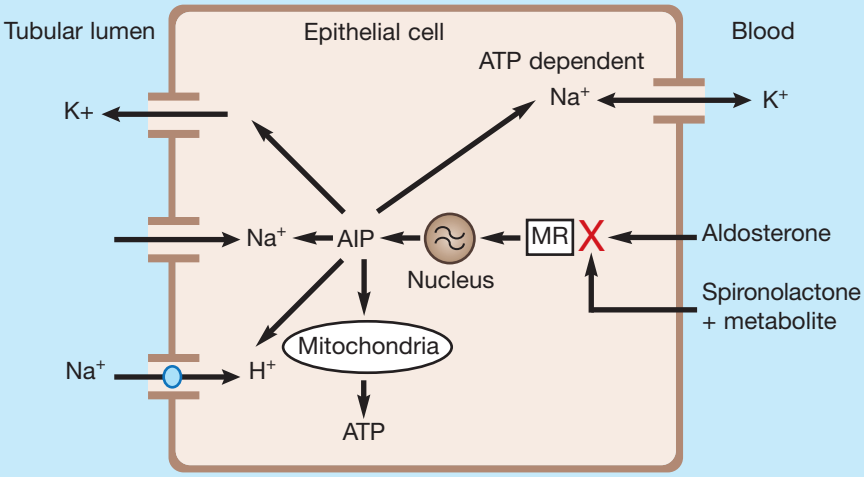
Spironolactone is a competitive aldosterone antagonist with weak antiandrogenic effects, which inhibits the physiologic effects of aldosterone, including cellular hypertrophy, interstitial fibrosis and endothelial dysfunction, on the distal renal tubules, myocardium and vasculature. Spironolactone was first extracted from pig adrenal glands and then synthesised in the 1950s before being developed as a novel diuretic in 1963.

Pharmacology

Figure 1 outlines the pharmacological action of spironolactone. It has a four ring structure characteristic of steroids and binds to the mineralocorticoid receptor in the renal tubules blocking the synthesis of aldosterone induced proteins (AIP). This reduces Na^+ reabsorption and K^+ and H^+ secretion by various mechanisms. The magnitude of diuresis produced by spironolactone depends on the plasma level of aldosterone. Spironolactone is well absorbed orally, is highly protein bound and extensively metabolised in the liver. It undergoes enterohepatic recirculation and has a short half-life of 1.3 hours. Its metabolite canrenone with a half-life of 16.5 hours is pharmacologically active, prolonging the diuretic effect.

The main adverse effects of spironolactone are hyperkalaemia, gynaecomastia, impotence, menstrual irregularities and diarrhoea. Careful monitoring for hyperkalaemia is required with concurrent administration of ACE inhibitors, angiotensin receptor blockers and K^+ sparing diuretics. Spironolactone increases the serum levels of digoxin and interferes with digoxin assays. NSAIDs decrease the potency of spironolactone. In animal models it produces feminisation of male fetuses due to its antiandrogenic effect and is tumourogenic when administered in high doses over a prolonged period.

Figure 1. Mechanism of action of spironolactone



NOTES. Spironolactone and its active metabolite bind to the mineralocorticoid receptor (MR) in the renal tubules blocking the synthesis of aldosterone induced proteins (AIP). This reduces Na^+ reabsorption and K^+ and H^+ secretion by various mechanisms illustrated, resulting in a diuresis and the potential for hyperkalaemia. (ATP = adenosine triphosphate.)

Spironolactone is used in the treatment of secondary hyperaldosteronism produced by decompensated liver disease. It is used at a dose of 50–400mg and combined with furosemide in the context of significant peripheral oedema. The minimum effective dose is calculated by the ratio of urinary Na^+/K^+ excretion.

Spironolactone is also used in low doses of 25mg in the management of severe heart failure (NYHA class III and IV) in addition to other standard agents, where it produces significant improvement in morbidity and mortality.

It is useful in the treatment of primary hyperaldosteronism when preparing the patient pre-operatively and for long-term medical management in those situations where surgical treatment is not indicated or unsuitable.

Although it is not licensed for this indication in the UK, it is used as an add-on therapy in resistant hypertension and in the treatment of accelerated hypertension.

Its weak antiandrogenic action by binding to the androgen receptor as well as inhibiting testosterone synthesis is utilised in the treatment of female hirsutism in doses of 100–200mg daily but needs to be proven in large scale studies.

Trials of safety and efficacy

The Randomised ALdactone Evaluation Study (RALES) was a landmark study in the use of spironolactone in heart failure.[1] It was a large, double-blind, randomised study involving more than 1600 patients with recent or severe heart

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failure (NYHA class III or IV) and having a left ventricular ejection fraction of 35% or less. Patients were already on the usual standard therapies including ACE inhibitors, loop diuretics and digoxin in most cases. Patients were assigned to either 25mg of spironolactone or placebo. The primary end-point was death from cardiac causes, and the trial was terminated early in August 1998 after a mean follow up of 24 months due to significant efficacy noted in the spironolactone arm. There was a 30% reduction in mortality which was attributed to death from progressive heart failure as well as sudden death from cardiac causes. There was also a 35% reduction in frequency of hospitalisation secondary to heart failure as well as significant improvement in symptoms of heart failure.

TOPCAT is an ongoing multicentre, international, randomised, double-blind, placebo-controlled trial involving 4500 adults looking at the effectiveness of low dose spironolactone in patients with diastolic heart failure.

The Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA) involved the addition of spironolactone as the fourth agent in 1411 patients with hypertension not appropriately controlled with three antihypertensive drugs.[2] The mean age was 63 years; 77% were men and 40% had diabetes. The median duration of treatment was 1.3 years and the dose was 25–50mg (median 25mg). The mean reduction in systolic BP was 21.9mmHg (95% CI 20.8–23.0mmHg) and diastolic BP was 9.5mmHg (95% CI 9.0–10.1mmHg; both p<0.001). The BP reduction was largely unaffected by age, sex, smoking, and diabetic status. Although spironolactone was initiated after a mean of 3.2 years after randomisation and not placebo controlled, the above data published in 2007 support the use of spironolactone as a fourth line agent in resistant hypertension.

Specific evidence for use in diabetes

In the RALES study 25% of the patients had a history of diabetes at baseline.[1] The mortality benefit with spironolactone was seen in those with diabetes (HR 0.70 [0.52–0.94], p=0.019) and without diabetes (HR 0.70 [0.60–0.82], p<0.001). The ASCOT-BPLA showed the similar efficacy of spironolactone in resistant hypertension in patients with diabetes (40%) compared with the rest of the study population as mentioned above.

A smaller randomised, double-blind, cross-over study involving 50 patients with type 2 diabetes and poorly controlled hypertension by Swaminathan *et al.* in Ninewells Hospital (trial duration four weeks) showed the effectiveness of spironolactone (25–50mg) in controlling BP in addition to other agents as well as improvement in QTc, but was shown to worsen endothelial function, glycaemic control (increase in HbA_{1c} +0.21%; p=0.01; 95% CI 0.05, 0.37) and cortisol levels.[3]

A trial in 81 patients with diabetic nephropathy (trial duration 48 weeks) demonstrated that the addition of spironolactone (25mg once daily) afforded greater renoprotection with significant reductions in proteinuria than the addition of losartan to patients on a maximally dosed ACE inhibitor based regimen.[4] Compared with a placebo group the urine albumin-to-creatinine ratio decreased by 34.0% in the group assigned to spironolactone, and by 16.8% with losartan. The patients were adequately controlled for BP, renal function, ACE inhibitor dose, dietary sodium and protein intake and glycaemia. The exact mechanism by which spironolactone reduces proteinuria in humans has not been elucidated.

ALDODN is an ongoing randomised, double-blind, placebo-controlled study looking at the effect of 25mg spironolactone daily in reducing albuminuria and diastolic dysfunction in patients with diabetic nephropathy.

Discussion

Spironolactone has been shown to be effective in the management of severe heart failure due to left ventricular systolic dysfunction, including patients with diabetes. The effectiveness and risks of treatment with spironolactone in patients with less severe heart failure need to be evaluated prospectively. Although it is proven to be effective in resistant hypertension, the detrimental effect of spironolactone on glycaemia may limit its use for this indication in patients with diabetes.

However, smaller studies have shown its beneficial effects in reducing albuminuria in diabetic nephropathy, although the exact mechanism in humans has still to be elucidated by further research.

Hyperkalaemia and gynaecomastia are problematic side effects in a small percentage of patients with heart failure and diabetes, necessitating discontinuation in spite of the smaller doses used in these situations.

Key points

- Spironolactone is a competitive aldosterone receptor antagonist acting on the renal collecting ducts
- A large double-blind study (RALES) reported that addition of low dose spironolactone to standard therapy in patients with severe heart failure showed a 30% reduction in risk of death and a 35% reduction in risk of hospitalisation
- The additive renoprotective effect of spironolactone in addition to ACE inhibition and its effect on glycaemic control in diabetic nephropathy need further evaluation in large scale trials

Conflict of interest statement

There are no conflicts of interest.

References

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