ABSTRACT

The activation of the renin-angiotensin-aldosterone system leads to secretion of aldosterone. The elevated aldosterone leads to elevation of blood pressure. The angiotensin-converting-enzyme inhibitors decrease aldosterone levels initially but it again returns to the pre-treatment levels despite good compliance with this therapy. This difficulty can be overcome by the using aldosterone antagonists eplerenone and spironolactone. This article reviews the pharmacokinetics, pharmacodynamics as well as effectiveness and tolerability differences of eplerenone and spironolactone with each other as antihypertensive agents. Both these agents reduce high blood pressure and cause increase in potassium levels, but the high incidence of sexual side effects limits spironolactone use as compared to eplerenone. At the same time high cost of eplerenone also limits its uses as an antihypertensive agent.

KEYWORDS: Aldosterone, blood pressure, eplerenone, spironolactone, potassium, hyperkalemia.

INTRODUCTION

The aldosterone of renin-angiotensin-aldosterone system (RAAS) when elevated causes high blood pressure (BP). By giving angiotensin-converting-enzyme inhibitor (ACEI) many clinicians assume aldosterone formation is prevented by inhibiting RAAS. But aldosterone levels again returns to pre-treatment level which decreases initially with ACEI treatment,
Despite good compliance with continued drug administration, this problem can be overcome by the availability of eplerenone and spironolactone which inhibit aldosterone at the mineralocorticoid receptor (MR). The aldosterone effects are mediated through genomic (slow) or nongenomic (rapid) mechanisms.\textsuperscript{[1,2]}

**Renin-Angiotensin-Aldosterone System**

The RAAS in the body is one of the most important systems regulating BP. A schematic representation of the RAAS is illustrated in Figure 1. The angiotensin converting enzyme (ACE) causes conversion of the inactive angiotensin I (Ang I) peptide to the active angiotensin II (Ang II) molecule. Ang II by itself can elevate BP by producing vasoconstriction. Ang II acts on adrenal cortex to initiate the aldosterone secretion from adrenal zona glomerulosa cells. The released aldosterone promotes sodium reabsorption and potassium excretion by acting on renal epithelial cells in the distal tubule and collecting duct which is an indirect BP elevation effect of Ang II. The reabsorption of sodium and water caused by aldosterone elevates BP indirectly by expanding intravascular volume. The ACEI block the conversion of Ang I to Ang II. The angiotensin receptor antagonists block the action of Ang II by blocking the AT\textsubscript{1} receptor which is an isoform of the Ang II receptor known to mediate the primary biologic effects of Ang II.\textsuperscript{[3,4]}

![Figure 1: Schematic representation of the RAAS\textsuperscript{[5]}](image-url)
Chemistry

**Figure 2: Structure of Eplerenone**[^6]

**Figure 3: Structure of spironolactone**[^6,7]

**Eplerenone IUPAC Name:** pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, γ-lactone, methyl ester (7α, 11α, 17α)

**Molecular formula:** C_{24}H_{30}O_{6}

**Mol.Wt:** 414.50

**Spironolactone IUPAC Name:** 7α-acetyltio-3-oxo-17α-pregn-4-ene-21,17-carbolactone or 17-hydroxy-7α-mercapto-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone acetate

**Molecular formula:** C_{24}H_{32}O_{4}S

**Mol.Wt:** 416.574

**Pharmacology**

The aldosterone antagonist eplerenone which is similar to diuretic spironolactone binds to the MR and thereby blocks the binding of the component of the RAAS i.e. aldosterone binds to the MR which are present in both epithelial (e.g., kidney) and nonepithelial (e.g., heart, blood vessels and brain) tissues and thereby increases BP through induction of sodium reabsorption and possibly other mechanisms.[^6,10]

Spironolactone is a steroid chemically related to aldosterone and acts at the aldosterone dependent sodium-potassium exchange site in the distal convoluted renal tubule and inhibits aldosterone by competitive binding of receptors. Spironolactone shows antihypertensive action by increasing the amount of sodium and water being excreted while potassium is retained.[^5,8]

Pharmacodynamically eplerenone as compared to spironolactone does not possess any antiandrogen, progestogen or estrogenic effects and hence is devoid of sexual side effects of spironolactone or there are very rare chances of their occurrence.[^6,10]
Table 1: Pharmacokinetics differences of Eplerenone and Spironolactone

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Eplerenone</th>
<th>Spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Not affected by food [6,8]</td>
<td>Bioavailability of unmetabolized spironolactone increased almost 100% by food. [6,8]</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>About 50% [6,8]</td>
<td>Spironolactone and its metabolites are more than 90%. [6,8]</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Predominantly and extensively metabolized by cytochrome P450 (CYP) 3A4 in the liver with no active metabolites. [6,11]</td>
<td>Rapidly and completely metabolized in liver with sulphur containing 7- α- (thiomethyl) spironolactone (TMS), 6-β-hydroxy-7-α(thiomethyl) spironolactone (HTMS) and canrenone (nonsulphur) are the predominant metabolites [5,8]</td>
</tr>
<tr>
<td>Half-life</td>
<td>4 to 6 hours [5,6]</td>
<td>1 to 2 hours for spironolactone while that of canrenone is ~18 hours. [5,6]</td>
</tr>
<tr>
<td>Excretion</td>
<td>In urine (67%), in feces (32%). [6]</td>
<td>Mainly excreted in urine, minimal biliary excretion, some in the feces as metabolites. [7,8]</td>
</tr>
</tbody>
</table>

CLINICAL EFFICACY

Hypertension trials

Eplerenone monotherapy in essential hypertension

Various clinical studies have shown the effectiveness of eplerenone monotherapy as compared to other drugs used in hypertension. Eplerenone at various doses causes dose dependent reduction in mild to moderate BP as compared to spironolactone. The BP reduced by eplerenone was 50% to 75% to that of spironolactone. [12] Eplerenone has been reported to reduce both ambulatory and clinical BP in a dose dependent manner at various doses (25, 50, 100 and 200mg once daily). [13]

Eplerenone has been shown to be efficacious in reducing DBP as compared to losartan in hypertensive black and white patients. It is more effective in reducing DBP in black patients as compared to white patients. Eplerenone is superior to losartan in reducing systolic blood pressure (SBP) and diastolic blood pressure (DBP) in hypertensive black and white patients. [14]

Compared to eplerenone monotherapy, eplerenone/enalapril combination reduces SBP more effectively, whereas eplerenone monotherapy is more efficacious in BP reduction as compared to enalapril monotherapy. [15,16] Regardless of the baseline active plasma renin level, eplerenone consistently and more effectively reduces BP than losartan. [17]
Eplerenone offers better vascular protection and outcomes when normalizing BP as compared β-blocker atenolol.\textsuperscript{[18]} Eplerenone also shows benefit in hypertensive children. Eplerenone short term treatment in hypertensive children reduces BP.\textsuperscript{[19]}

**Eplerenone in resistant hypertension**

Apart from being used as monotherapy in hypertension, eplerenone can be used as an add on therapy in resistant hypertension for management of BP. Eplerenone has an established additive effect when used along with ACEIs, angiotensin receptor blockers (ARBs), calcium channel blockers and hydrochlorothiazide causes dose related reduction in SBP and DBP.\textsuperscript{[20,21]} For the first line treatment of hypertension, low doses of thiazide type drug and eplerenone could be better than thiazide alone.\textsuperscript{[22]}

Clinic BP control rates of upto 60% and ambulatory BP control rates of upto 40% were achieved by eplerenone in resistant hypertensive patients. Another advantage is that the addition of eplerenone results in reduction in number of antihypertensive drugs prescribed.\textsuperscript{[23]} Eplerenone also offers advantages in reducing BP in non-diabetic chronic kidney disease patients who were on stable standard antihypertensive treatment including RAAS blockade.\textsuperscript{[24]} Elderly patients also get benefit of reduction in office as well as 24 h BP by eplerenone whose BP is uncontrolled by ACEIs or ARBs.\textsuperscript{[25]}

**Spironolactone in resistant hypertension**

In refractory or resistant or uncontrolled hypertensive patients, spironolactone as an add on agent in lower dose (12.5-25mg/day) as well as in higher doses (25-100mg/day) causes a reduction in BP as well as significant decrease in number of antihypertensive agents. The BP reduction in both primary aldosteronism (PA) and without PA was found to be similar but the PA subjects required a higher dose of spironolactone. Spironolactone is also effective in non chronic kidney disease (CKD) as well as in CKD patients in reducing BP.\textsuperscript{[26-33]}
Figure 4: Biochemical pathway of RAAS

TOLERABILITY
Dose-dependent gynecomastia of 6.9% at doses of <50mg/day and 52% at daily doses of >150mg has been observed with spironolactone. As compared to spironolactone, eplerenone has only 0.1% binding affinity to androgen receptors and <1% binding affinity to the progesterone receptors. The 9, 11-epoxide group is also responsible for reduced sexual effects of eplerenone.\textsuperscript{[11,34]}

Eplerenone is associated with increase in potassium level ≥ 5.5mEq/L but <6 mEq/L. No complications or clinical symptoms are observed due to this. The occurrence of
gynecomastia, menstrual abnormalities, increased incidences of impotence, female breast pain were very low as compared to those reported with the use of spironolactone. Liver functions were also not changed. The increase in serum uric acid level with eplerenone was observed but within normal range. Eplerenone along with ACEIs or ARBs causes significant increase in serum uric acid level. The incidence of coughing observed is more with enalapril as compared to eplerenone. Serum creatinine levels were also found to be increased but renal function has well preserved with eplerenone.[12-18,20,23-25,33]

Increase in potassium level >5mEq/L were also observed with spironolactone and patients either required discontinuation or dose reduction of spironolactone. The hyperkalemia observed is higher in CKD patients as compared to non-CKD patients. The significant kidney function deterioration observed with spironolactone causes reduction in glomerular filtration rate while uric acid, creatinine and potassium increase.[26-29,32-33]

CONCLUSION
Both aldosterone antagonist eplerenone and spironolactone are effective in reducing high BP. Eplerenone as a monotherapy as well as combination therapy is effective in reducing BP. But spironolactone is not commonly used as a monotherapy because the higher affinity of spironolactone for androgen and progesterone receptors leads to sexual side effects like gynecomastia, impotence, decreases libido, breast tenderness and menstrual irregularities that limits its use compared to eplerenone. At the same time high cost of eplerenone also limits its uses as an antihypertensive agent.[35] Direct comparative study/s of eplerenone and spironolactone will be required to demonstrate superiority on each other.

REFERENCES


