Aldosterone and Volume Management in Hypertensive Heart Disease

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Summary: Aldosterone-receptor antagonists dose-dependently reduce both the epithelial and nonepithelial actions of aldosterone. These compounds are used commonly in the treatment of hypertension, with or without aldosteronism, and in the volume-overload periods of various forms of heart failure, cirrhosis, and renal failure. In this regard, the relevant site of action for these compounds is compartmentalized to the distal nephron. The cardiac benefits of aldosterone-receptor blockade now are sufficiently well established to warrant routine use of these compounds for their survival benefits in moderate to advanced stages of heart failure. Aldosterone-receptor antagonists spironolactone and eplerenone commonly are used in the treatment of resistant forms of hypertension. Spironolactone, but not eplerenone, is a commonly used add-on diuretic that provides incremental benefit for salt-and-water excretion in excess of what may be seen with a loop diuretic given together with a thiazide-type diuretic. The dose-response relationship for natriuresis with spironolactone has not been explored completely as to its combination therapy responses. The quite high doses of spironolactone used in patients with cirrhosis and ascites would infer that the overall treatment effect with this compound exceeds simple receptor blockade and may include a nervous system effect that operationally reduces renal sympathetic nerve traffic. The adverse electrolyte and renal function side effects with aldosterone-receptor antagonists are not uncommon in at-risk patients, such as those with chronic kidney disease, and require that dosing be mindful of the tendency of these drugs to importantly increase serum potassium levels.
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Aldosterone is classified as a mineralocorticoid hormone based on its capacity to effect sodium (Na^+) retention and facilitate potassium (K^+) excretion. This occurs mainly at the renal tubular level and to a lesser extent at other epithelial sites such as the salivary glands and the gastrointestinal tract. These effects on vectorial Na^+/K^+ exchange are designated as classic or "epithelial" and are mediated via the binding of aldosterone to the mineralocorticoid (type 1 glucocorticoid) receptor, interaction of the ligand-receptor complex with DNA, and ensuing changes in gene expression. Recent evidence suggests that aldosterone also has a variety of "nonepithelial" effects, a finding that became obvious with the discovery of mineralocorticoid receptors in multiple nonepithelial locations. The nonepithelial effects of aldosterone appear to be mediated by a second messenger system that involves activation of the Na^+/H^+ transporter.[1,2]

Aldosterone-receptor antagonists (ARAs), such as spironolactone and eplerenone, are capable of dose-dependently limiting both the epithelial and nonepithelial actions of aldosterone.[2] These compounds are used commonly in the management of hypertension, with or without primary hyperaldosteronism, and in the volume-overload phases of heart failure (HF), cirrhosis, and nephrotic syndrome.[3–5] In this regard, the pertinent site of action for these compounds is localized to the distal nephron. More recently, the identification of aldosterone receptors in locations such as the heart has prompted use of ARAs to control the deleterious cardiac effects of aldosterone, which ostensibly are volume-independent (Fig. 1). The cardiac benefits of aldosterone-receptor blockade now sufficiently are well established to justify routine use of these compounds in moderate to advanced stages of HF.[6,7]

ALDOSTERONE RECEPTOR ANTAGONISTS AS DIURETICS

Pharmacokinetics

Spironolactone

An important consideration in the diuretic action of ARAs relates to the pharmacokinetics of these compounds. Spironolactone is poorly soluble in aqueous fluids and an intravenous formulation is not available for routine clinical use. The absolute bioavailability of spironolactone has not been determined in human beings; however, balance experiments would suggest that the extent of absorption is in the 80% to 90% range for most commercial preparations. Food increases the absorption of spironolactone and possibly reduces its first-pass metabolism; however, taking

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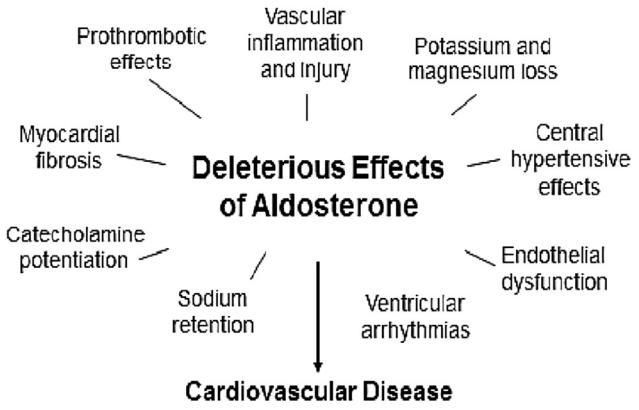

Figure 1. Adverse effects of aldosterone in cardiovascular disease.

spironolactone with food in hypertensive patients results in similar therapeutic effects as when the drug is given in the fasted state.[8]

Spironolactone is both rapidly metabolized into a series of active metabolites as well as being an inducer of hepatic microsomal drug-metabolizing enzymes in human beings. Spironolactone (88%) and its canrenone metabolite (99%) are bound extensively to plasma proteins at therapeutic concentrations. Canrenone originally was thought to be the major metabolite of spironolactone; however, this was disproven when more sensitive analytic methods for metabolite determination became available.[9] By using high-performance liquid chromatography, the 7α-methylspironolactone (TMS) metabolite,[10] was found to account for approximately 80% of the K^+-sparing effect of spironolactone.

In normal volunteers taking spironolactone (100 mg/d) for 15 days, the mean half-lives ($t_{1/2}$) for spironolactone, canrenone, 7α-TMS, and 6β-hydroxy-7α-TMS were 1.4, 16.5, 13.8, and 15 hours, respectively. Thus, although intact spironolactone can be detected, it is cleared quickly from the serum. In patients with cirrhosis, pharmacokinetic studies have indicated that the $t_{1/2}$ of spironolactone and its metabolites are increased markedly. The $t_{1/2}$ for spironolactone, canrenone, 7 α-TMS, and 6β-hydroxy-7α-TMS are 9, 58, 24, and 126 hours, respectively.[11] The pharmacokinetics of spironolactone and its metabolites have not been studied specifically in the setting of renal insufficiency or end-stage renal disease.[12]

Class Considerations

The first compound in a class of medications is generally well-defined mechanistically but oftentimes ends up being given in a suboptimal dosing form and/or carries with its use burdensome side effects; thus, classes of medications generally evolve along the lines of more efficient delivery systems and/or that of increased mechanistic specificity to reduce the side-effect rate. The calcium-channel blocker (CCB) class of medications illustrates how such progression occurs in the pharmaceutical field. For this medication class sustained and/or delayed-release delivery systems notably have improved dosing flexibility; moreover, more evolved CCBs, characterized by reduced CCB side-effect rates, have become available. In the instance of the evolution of the ARA class, eplerenone has emerged as a more specific receptor antagonist with reduced sexual side effects compared with the more common progestogenic and antiandrogenic adverse effects seen with spironolactone; however, as will be discussed later in this article it has not been studied formally as to its capacity to subserve a diuretic role.

Eplerenone

The feature of the eplerenone molecule conferring selectivity for the mineralocorticoid receptor is the presence of the 9,11-epoxy in the lactone ring (Fig. 2). In vitro studies have shown this structural difference to produce an approximate 10- to 20-fold lower affinity for the mineralocorticoid receptor compared with spironolactone.[13,14] The most conspicuous distinction between eplerenone and spironolactone resides in their differing affinity for androgen/progestin receptors. Compared with spironolactone, eplerenone has up to a 500-fold lesser affinity for these receptors, which may translate into a several-fold decrease in adverse effects of a progestogenic and/or antiandrogenic nature.

The absolute bioavailability of eplerenone is not known; however, balance studies have shown that it is absorbed rapidly from the duodenum, jejunum, colon, and rectum with a maximum concentration (C_{max}) at 1.3 hours.[15] There are no known food–drug interactions with eplerenone and it is moderately (33%–60%) protein bound, primarily to α1-acid glycoprotein. The

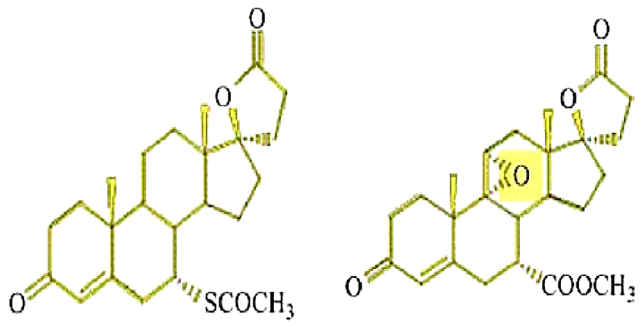

Figure 2. Chemical structure and gram molecular weight of spironolactone and eplerenone.

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