Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Mineralocorticoid Receptor Antagonists in Heart Failure***

-May 2017-

Background:

The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed heart failure (HF) at the May 2017 meeting. One of the drug classes reviewed in the treatment of HF was the mineralocorticoid receptor antagonists (MRAs). The MRAs are also referred to as aldosterone receptor antagonists (ARA) or aldosterone antagonists (AA). The two agents in this class, spironolactone and eplerenone, were reviewed. Spironolactone has been in use since the 1960s, originally for hypertension and as a potassium sparing diuretic for volume overload in HF.[1] As knowledge of mineralocorticoid receptors (MRs) increased, the use of spironolactone in HF became more common. Eplerenone was developed through chemical modification of spironolactone to enhance binding MRs while reducing binding to progesterone and androgen receptors to decrease side effects of gynecomastia, impotence, and menstrual irregularities.[2] It was FDA-approved in 2002 for use in HF.

Current American College of Cardiology Foundation/American Heart Association (ACCF/AHA) heart failure guidelines recommend the use of MRAs in patients already receiving an ACEI (or ARB) and beta blocker for NYHA class II-IV with LVEF ≤35% unless contraindicated to reduce morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF). MRAs are also recommended to reduce morbidity and mortality following acute myocardial infarction (MI) in patients with LVEF ≤40% who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated. Inappropriate use of MRAs is potentially harmful in patients with potassium levels of >5.0 mEq/L (life-threatening hyperkalemia) or serum creatinine levels ≤2.5 mg/dl in men or ≤2.0 mg/dl in women (renal insufficiency).[3]

The European Society of Cardiology (ESC) also recommends the use of MRAs in patients with HFrEF and LVEF ≤35% already taking ACEI (or ARB) and beta blockers to reduce mortality and HF hospitalization. These guidelines recommend using MRAs with caution in patients with impaired renal function and serum potassium >5 mmol/L (or >5 mEq/L). The ESC, unlike ACCF/AHA, addressed MRA use in heart failure with preserved ejection fraction (HFpEF) by suggesting that treating hypertension in HF is important and MRAs are an appropriate choice along with ACEI, ARB, and diuretics.[4]

Discussion:

Three landmark trials established the use of MRAs in treating HF. The Randomized Aldactone Evaluation Study (RALES) included patients with NYHA class III or IV HF, LVEF ≤35%, and already receiving an ACEI. The study group found that treatment with spironolactone resulted in a 30% reduction in death (RR 0.7; 95% CI: 0.60-0.82; p<0.001), a 35% reduction in hospitalizations (RR 0.65; 95% CI: 0.54-0.77; p<0.001), and significant improvement in symptoms of HF (p<0.001). The spironolactone group did show significant (p<0.001) increases in serum creatinine and potassium, but these were not clinically important. Gynecomastia or breast pain was reported by 10% of the men in the spironolactone group versus 1% in the placebo group (p<0.001).[5]

The Eplerenone Post-Acute MI Heart Failure Efficacy and Survival Study (EPHESUS) was an international, multi-center, randomized controlled trial that evaluated eplerenone versus placebo. Use of eplerenone resulted in decreased death from any cause (RR 0.85; 95% CI: 0.75-0.96; p=0.008) and death or first hospitalization from cardiovascular (CV) causes (RR 0.87; 95% CI: 0.79-0.95; p=0.002). Patients were on optimal pharmacotherapy (ACEI or ARB, possibly diuretics and beta blockers) and had LVEF <40%. Incidence of hyperkalemia was significantly higher in the eplerenone group (p<0.001).[6]

The Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (EMPHASIS-HF) study evaluated patients with NYHA class II (mild HF) and a LVEF ≤35%. This randomized, double-blind, placebo controlled trial showed a significant decrease in death from CV cause or first hospitalization for heart failure in the eplerenone-treated group (HR 0.63; 95% CI: 0.54-0.74; p<0.001). Again, hyperkalemia was found to be significantly higher with the eplerenone group.[7]

There are no large studies of spironolactone in mild or asymptomatic HF. A small study suggested that spironolactone use (in addition to optimal therapy) may reduce risk of HF and slow progression of disease in those with less advanced symptoms. A study with larger sample size is needed to determine if the effect seen in the EMPHASIS-HF study is a class effect.[8]

The use of MRAs in HFpEF may be beneficial. The 2014 TOPCAT (Treatment Of Preserved Cardiac function with an Aldosterone anTagonist) study evaluating spironolactone did not show significant reduction in the primary outcome, a composite of death from CV causes, aborted cardiac arrest, and hospitalization for management of HF. A post-hoc analysis suggested MRAs may be a potential treatment for HFpEF, but further prospective, adequately powered, randomized, controlled studies are needed.[9]

Findings:
Spironolactone is currently listed on the IHS National Core Formulary (NCF). **After reviewing the MRA class, no modifications were made to the NCF.** Current guidelines do not recommend either agent over the other at this time. Both MRAs are currently approved for use in HF and have similar safety concerns in regard to renal function and hyperkalemia. Spironolactone at a dose of 12.5 to 50 mg/day is a reasonable choice to add to ACEI (or ARB) and beta blocker therapy in the treatment of HFrEF. Caution is advised in patients with reduced renal function. Close monitoring of potassium is recommended in both ESC and ACCF/AHA guidelines. The ACCF/AHA guidelines have more stringent recommendations, suggesting that potassium be monitored at 2-3 days and 7 days after initiation of therapy, then at least monthly for 3 months, then every 3 months thereafter.[3] Eplerenone may be an option for those patients experiencing gynecomastia while taking spironolactone.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References:

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