Curr Heart Fail Rep (2015) 12:107–111
DOI 10.1007/s11897-014-0248-y

PHARMACOLOGIC THERAPY (WHW TANG, SECTION EDITOR)

Oral Sodium and Potassium Binders in Heart Failure

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Published online: 28 December 2014

Abstract Significant improvements in the morbidity and mortality associated with chronic heart failure have been gained with the use ACE inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and diuretics. However, the use of these agents is often limited by their propensity to precipitate worsening renal function and hyperkalemia, particularly in patients with chronic kidney disease. Several pharmacologic agents have been developed in recent years that utilize the gastrointestinal tract as an alternate route for drug absorption, electrolyte exchange, and drug and electrolyte elimination. The existing data establishing the safety and efficacy of these novel agents will be the focus of this review.

This article is part of the Topical Collection on *Pharmacologic Therapy*

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Keywords Heart failure · Chronic kidney disease · Hyperkalemia · RLY5016 · CLP · Potassium-binding polymer · Sodium-binding polymer

Introduction

Heart failure (HF) progression occurs through neurohormonal activation of the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), and the arginine-vasopressin system, augmented as a compensatory response to support worsening circulatory function. The cardiac output and peripheral vascular resistance, often compromised in chronic HF, are the predominant determinants of renal sodium and water excretion [1]. In patients with HF, there is paradoxic sodium and water retention by the kidneys despite an increase in intravascular fluid volume. This excess fluid volume in the setting of ventricular dysfunction contributes to the clinical symptoms of congestion, including lower extremity and pulmonary edema.

Multiple self-care techniques and pharmacologic agents are recommended to patients to achieve fluid balance in HF. Dietary sodium restriction is commonly recommended to patients with HF despite the fact that the data for which this recommendation is based upon is modest at best [2, 3•]. Oral diuretics inhibit the reabsorption of sodium at specific sites in the renal tubules and are recommended in patients who have evidence of fluid retention. Despite their ability to increase urinary sodium excretion and to improve symptoms of congestion, diuretics are known to activate neurohormones and can worsen renal function [4••]. Furthermore, chronic diuretic use can result in diuretic resistance in the kidney, making congestion more difficult to control [5].

Inhibition of the neurohormonal cascade and RAAS with ACE inhibitors (ACEi), angiotensin receptor blockers

(ARB), and mineralocorticoid receptor antagonists (MRA) has significantly impacted the mortality associated with HF [6–11]. However, treatment of chronic stable HF with these drugs can also contribute to worsening renal function and hyperkalemia, leading to frequent hospitalizations, longer lengths of stay, and increased morbidity and mortality for patients already suffering from chronic kidney disease (CKD) [12•, 13•, 14, 15]. Adding to this conundrum, HF exacerbations are often accompanied by acute kidney injury, leading to fluctuations in serum electrolytes that make the management of HF more difficult. For instance, in the Randomized Aldactone Evaluation Study (RALES trial), 19 % of participants experienced moderate hyperkalemia (serum K ≥5.5 mmol/L) while another 3.9 % of participants experienced severe hyperkalemia (serum K ≥6.0 mmol/L) [16]. Patient factors that were independently associated with hyperkalemia in multivariable models included the dose of spironolactone; age; history of diabetes mellitus; worse functional capacity; worse renal function; and background therapy with ACEi, ARBs, and β-blockers. Subsequent rates of death were highest in patients with the lowest (<3.5 mmol/L) and highest (>6.0 mmol/L) potassium values. However, the benefit of spironolactone was maintained, with lower mortality rates in the spironolactone group than in the placebo group at any given level of potassium over the study period. Moreover, the absolute benefit of spironolactone has been shown to be greatest in patients with reduced creatinine clearance, with the mortality benefit maintained even in those patients who experience worsening renal function [17•]. Similar results have been shown in data examining ARBs and ACEi, with clinical trials consistently showing a mortality benefit with the use of these agents despite rates of hyperkalemia that range from 2.7 to 9 % [18–20]. Increased attention to the potential risks associated with these life-saving drugs has lead to suboptimal usage of these agents at clinically proven doses, particularly in patients with CKD [21••]. The opportunity to improve outcomes with the use of RAAS inhibitors without compromising safety in HF patients is tightly linked to appropriate patient selection, appropriate dosing, and attentive laboratory monitoring in accordance with established guidelines [2, 22].

Due to the challenges of balancing the risks and benefits of pharmacologic agents that affect the neurohormonal cascade, alternative therapies have been evaluated that can be safely used to manage fluid retention, without causing adverse effects on electrolyte levels and renal function in HF patients. The gastrointestinal (GI) tract provides a large surface area for drug absorption into the circulation, ion exchange, as well as drug elimination into fecal matter. Although venous congestion and fluid retention can affect absorption of drugs through the GI tract, optimizing the pharmacokinetics and bioavailability of potential agents may render the GI tract an advantageous route that can be used to bypass the kidneys. In recent years, several pharmaceutical agents have been tested to take advantage of the GI tract for the management of HF.

Potassium Binders

RLY5016 is a non-absorbent polymer that binds potassium in the GI tract and was developed for the management of elevated serum potassium levels. The 100-μm polymer bead binds soluble potassium that is excreted into the GI lumen, effectively preventing serum hyperkalemia. The safety and efficacy of RLY5016 was evaluated in a double-blind, placebo-controlled trial (PEARL-HF) in patients with chronic heart failure and CKD [21••]. Eligible patients had a history of chronic HF on optimal medical therapy and either (1) CKD with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2) or (2) a history of hyperkalemia leading to discontinuation of ACEi, ARB, MRA, or beta-blocker in the last 6 months. Patients were initiated on spironolactone at 25 mg/day and randomized 1:1 to RLY5016 or placebo in a blinded fashion. The primary end point was the mean change of serum K+ from baseline to the end of the study (day 28). Secondary end points included the proportion of patients with hyperkalemia (serum K+ >5.5 mEq/L) at any time during the trial and the proportion of patients whose spironolactone dose could be increased to 50 mg/day.

One hundred twenty patients were enrolled with 105 actually receiving the study drug or placebo. Patients treated with RLY5016 had less hyperkalemia (7 v. 25 %, P= 0.015) and were more likely to have their spironolactone (91 vs. 74 %, P=0.019) increased to the target dose of 50 mg compared to those treated with placebo. Interestingly, more hypokalemia (serum K^+ <4 meq/L) occurred in patients receiving the polymer compared to placebo (47 v. 10 %, P<0.001), perhaps due to the inclusion criteria requiring patients to have a serum potassium level of 4.3–5.1 meq/L. This level may be lower than what is ideal for the use of this polymer; however, this will need to be tested in further studies. Hypomagnesemia (serum Mg 2+ <1.8 mg/dL) also occurred more often in patients receiving RLY5016 compared to placebo (24 vs 2.1 %). However, there was no increase in the incidence of ventricular arrhythmias associated with either the development of hypokalemia or hypomagnesemia. Other adverse events including GI upset were seen more often in the group receiving RLY5016 (54 vs. 31 %) compared to placebo; however, a similar percentage of patients in both groups discontinued the study drug (7 % vs. 6 %).

Use of RLY5016 proved to be beneficial by decreasing potassium levels and allowing care providers to increase spironolactone to therapeutic target doses. However, the small sample size, short study period, and lack of discrimination with regards to ejection fraction are shortcomings of this study. More studies will be needed to determine the exact role for this agent in the management of hyperkalemia in patients with chronic HF.

Sodium Binders

Oral sodium binders are another emerging therapeutic strategy in HF and a promising alternative to diuretics. These agents target sodium absorption in the GI tract, preventing sodium and fluid accumulation without influencing hemodynamics. Importantly, their eventual elimination in the feces makes these agents safe for use in patients with CKD. Cross-linked polyelectrolyte (CLP)-1001 is a polymer that was developed to target fluid overload in HF patients. When given orally, the polymer binds and entraps both water and sodium in the GI tract, resulting in water removal through the fecal route without causing diarrhea or electrolyte imbalances (Fig. 1). In phase I trials, CLP showed dose-related increases in fecal sodium content with concomitant dose-related decreases in urinary sodium [23]. The agent was well tolerated, with a low frequency of GI adverse events or alternations in serum electrolyte concentrations.

These data gave way to a double-blind, randomized, parallel, placebo-controlled trial to evaluate the effects of CLP-1001 on serum electrolytes and measures of congestion in patients with HF and CKD [24••]. Study subjects had advanced HF with clinical evidence of fluid overload: New York Heart Association (NYHA) class III/IV with recent hospitalization, N-terminal pro brain natriuretic peptide (NT-proBNP) >1000 pg/mL, and eGFR <60 mL/min/1.73 m^2. Importantly, patients could not be receiving the indicated MRA therapy based on the degree of HF. Patients were randomized to an 8-week fixed-dose treatment period of 15 g/day of CLP-1001 or placebo. In addition, spironolactone was initiated at 25 mg/day and, if the serum K+ was ≤5.1 mEq/L, the dose was increased to 50 mg/day at week 4. The primary end point, change in serum potassium over time, was achieved with similar serum potassium values in the CLP-1001 group (N=59) and placebo group (N=52) throughout the 8-week study. The incidence of hyperkalemia (K+ ≥5.5 mEq/L) was similar in the two groups (22.4 vs. 21.2 %, P=NS), including hyperkalemia prompting discontinuation of study drug (10.2 vs. 9.3 %, P=NS). The ability to reach a target dose of spironolactone 50 mg daily was also similar in the CLP-1001 and placebo groups (64.4 vs. 73.1 %, P=NS).

A number of secondary end points were also examined that focused on volume status and functional capacity. Weight loss was significantly greater in the CLP-1001 group compared to the placebo group at week 1 (−0.7± 1.5 vs. –0.1±2.0 kg, P=0.014) and week 2 (−0.8±1.8 vs. –0.3±2.3 kg, P=0.004), and a trend towards greater weight loss in the CLP group continued at week 4 (P= 0.066) (Fig. 2). Fewer patients in the CLP-1001 group had NT-proBNP levels >1000 pg/mL at week 4 (91.5 vs. 100 %, P=0.039) and week 8 (87.8 vs. 97.8 %, P= 0.066). Patients in the CLP group were also more likely

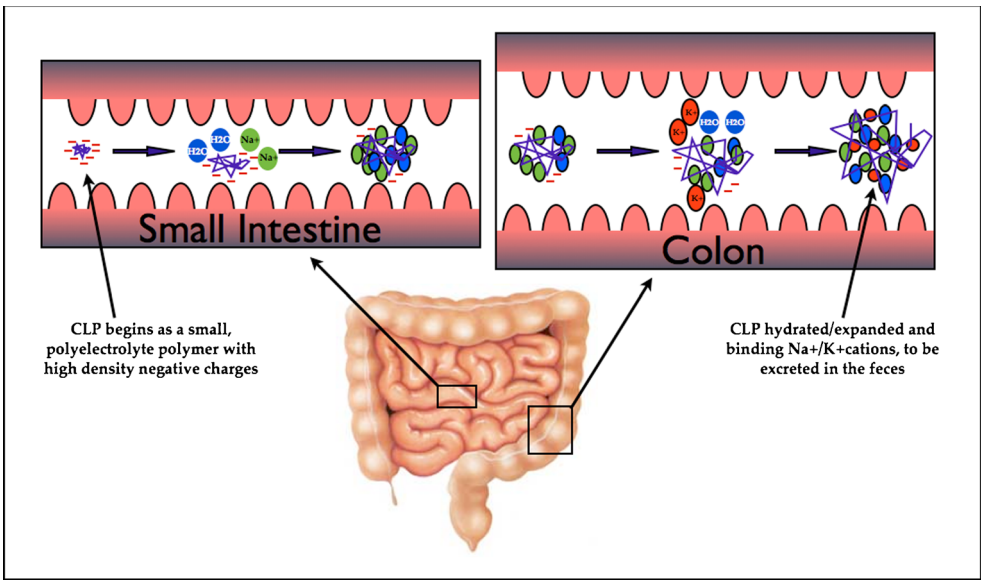

Fig. 1 Mechanism of action of the CLP molecule. In the dry form, CLP is a small, condensed molecule made of super-absorbent, cross-linked polyelectrolyte polymers. As CLP moves through the gastrointestinal tract, it absorbs water and expands accordingly. The molecule's high density of negative charges also attracts cations: predominantly sodium (Na+) in the small bowel and potassium (K+) in the colon. The polymer is not absorbed systemically and is ultimately eliminated in feces. H_2O water, *Na+* sodium, *K+* potassium, *CLP* cross-linked polyelectrolyte

to improve by at least one NYHA functional class (48.8 vs. 17.4 %, P=0.001) and had a greater increase in their six-minute walk test (6MWT) distance (39.3±53.4 vs. 19.7±39.2 m, P=0.07). Finally, improvement in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score was greater in the CLP group at the end of week 4 (13.5±12.2 vs. 6.4±12.3, P=0.005) and week 8 (18.3±17.4 vs. 12.5±13.6, P=0.06).

Four patients, all in the CLP-1001 group, experienced adverse events leading to study discontinuation, including constipation, nausea and vomiting, bloating, loss of appetite, and generalized weakness. In addition, four deaths occurred during the study, all in the CLP-1001 group. All deaths were reviewed by the attending investigator or an independent group of HF experts, and none was attributed to the use of the study drug. However, this signal will mandate cautious safety monitoring in future investigations with this agent. A phase IIb, randomized, double-blind, multicenter study comparing CLP-1001 with placebo is scheduled to be completed in June 2014. This 8-week trial will examine primary end points including time to first occurrence of death, HF or renal hospitalization, or unscheduled outpatient therapy (intravenous or mechanical) for HF, as well as end points including 6MWT, KCCQ Score, and NT-proBNP levels.

Conclusions

As the population of patients with HF and concomitant CKD continues to grow, so too must the efforts to find new and alternative therapies for the management of congestion and electrolyte imbalances. While diuretics have been the mainstay of treatment of congestion for decades, these agents upregulate neurohormones, ultimately contributing to and stimulating HF disease progression. A change in treatment strategy that incorporates the binding of sodium and water in the GI tract could bypass the involvement of the kidney altogether and potentially avoid this adverse upregulation, leading to safer decongestion. Additionally, many standard therapies used in the treatment of HF (ACEi and MCA) are contraindicated or underutilized in patients with significant renal disease due to the potential for dangerous hyperkalemia. The use of oral potassium binders could potentially eliminate unwanted potassium excesses by using the gut and facilitate the use of these important agents in patients previously declared ineligible. It is unclear if they should be used routinely in HF patients, as oral electrolyte binders have the potential to cause hypokalemia or hypomagnesemia that might cause adverse events when their use is incorporated into community practice. However, for patients who have CKD or higher potassium values at baseline, these agents could be used for both the prevention and the treatment of adverse events related to electrolyte imbalances. Ultimately, while both potassium and sodium binders have shown great promise thus far in small trials, there remains much work to be done before they can be incorporated into clinical practice. We eagerly await the results of ongoing clinical trials of these agents, as they could inform a potential paradigm shift in the management of congestion and electrolyte imbalances in the ever tenuous group of patients with HF and CKD.

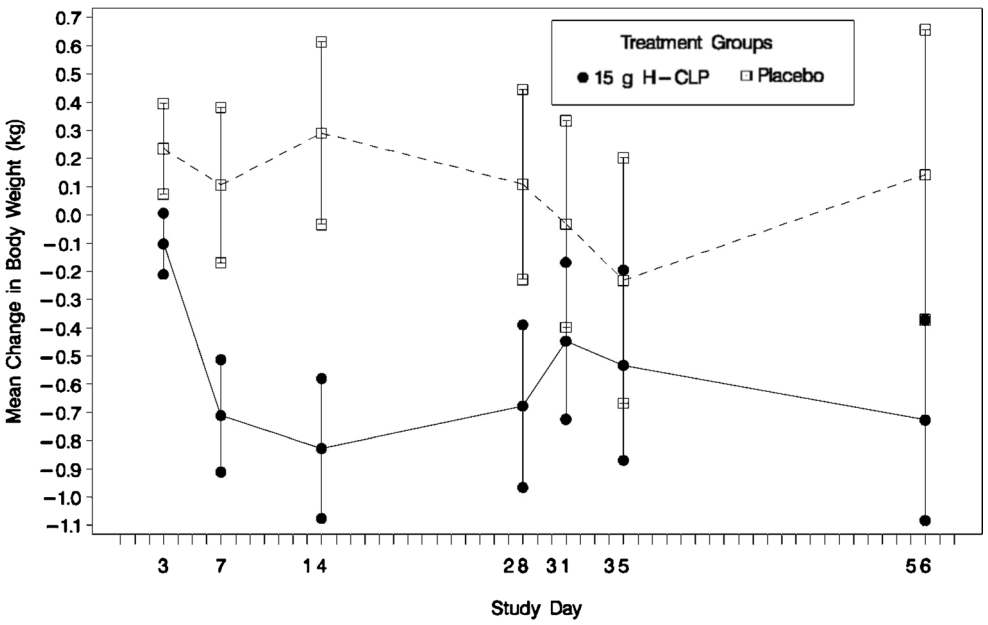

Fig. 2 Changes in body weight during the follow-up period of the randomized control trial to evaluate the effects of CLP-1001 on serum electrolytes and measures of congestion in HF patients. There was a statistically significant difference in body weight at weeks 1 and 2 (P= 0.0140 and 0.0039, respectively). These changes were not significant at weeks 4 and 8 (P values were 0.0660 and 0.2116, respectively). *CLP* cross-linked polyelectrolyte. Reprinted from [24••], with permission from John Wiley and Sons

Compliance with Ethics Guidelines

Conflict of Interest Alanna A. Morris declares that she has no conflict of interest.

Robert T. Cole declares that he has no conflict of interest.

Javed Butler serves as a consultant to Bayer and Relypsa.

Divya Gupta declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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