HEART FAILURE AND TRANSPLANTATION

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REVIEW:

Diuretic Resistance in heart failure

Introduction

Acute heart failure (HF) is a leading cause of hospitalizations and is associated with significant morbidity and mortality.[1] Congestive symptoms of acute heart failure are generally treated with loop diuretics, and the overall mortality increases with increasing doses of loop diuretics[2]. Poor response to diuretics, as evidenced by inability to attain decongestion despite escalating doses, constitutes diuretic resistance(DR). While DR is associated with higher rates of readmission and mortality[3,4], this condition is not clearly defined and hence the true incidence is unknown. Prior to attempting to define DR, it may be prudent to begin by quantifying diuretic response. Some of the recent studies have made some initial attempts at this, and incorporated metrics such as weight loss[4], net fluid loss[3] or natriuretic response[5] indexed to furosemide dose to quantify diuretic response. While these metrics simplify assessment of diuretic response, DR is a complex phenomenon involving mechanisms contributed by heart failure, renal failure and their intricate interaction with altered pharmacokinetics and pharmacodynamics of diuretics. Better definition of DR will enable us to understand if it is the cause or merely a marker of overall poor prognosis. In above quoted studies, poor diuretic response was associated with other markers of poor prognosis such as more advanced HF, diabetes, and atherosclerotic disease[3,4]. Management of DR depend on the etiology, so identifying contributing factors will be helpful in guiding therapy. In this brief review, we will present the pathophysiology of DR and the currently available literature on therapeutic options.

Pharmacokinetics and Pharmacodynamics of Loop Diuretics

Loop diuretics are the first line therapies to relieve congestion. The most commonly used loop diuretic, furosemide, has poor and somewhat erratic bioavailability when compared to bumetanide and torsemide. The bioavailability of furosemide is further impaired due to gut edema in HF. The half-life of furosemide and bumetanide is around 1-2 hours and it is prolonged in patients with HF and CKD. Torsemide, which is metabolized in the liver, has a longer half-life (of about 3-4 hours), that is prolonged significantly in the presence of concomitant cirrhosis[6].

The dose response curve of loop diuretics is sigmoid shaped with a minimum dose required to reach the threshold effect, a steep curve, followed by a ceiling effect after which increasing single dose will cause minimal increase in urinary sodium excretion. This dose response curve is shifted to the right in HF and renal failure and the maximum effective natriuresis is reduced in HF[7]. Impaired gut absorption in HF results in increased time to peak concentration and reduced peak plasma concentration of oral diuretics[8]. Due to these alterations, a higher initial dose, using drugs with better bioavailability (ie: bumetenide or torsemide), using intravenous (IV) diuretics and more frequent dosing of diuretics should be considered when treating patients with decompensated HF[6]. After loop diuretics enter the vascular space, they are protein bound and are actively secreted into the proximal convoluted tubule by organic anion transporters (OAT-1).[9] In chronic kidney disease (CKD), the accumulation of endogenous organic acids compete with loop diuretics for the OAT-1 transporter, which can cause up to a 90% reduction in the amount of diuretic entering the nephron.[6,9]. Hence much higher doses of diuretics are necessary for those who have concomitant CKD.

Physiologic and Pathologic basis of Diuretic Resistance

Braking phenomenon is a physiological response to volume reduction caused by diuretics. Volume contraction causes increased sodium reabsorption in the proximal renal tubules and increased renin release contribute to the braking phenomenon[7]. This causes progressive decline in the extent of natriuresis as euvolemia ensues[10]. Chronic loop diuretic treatment causes non-physiological distal tubular hypertrophy and upregulation of sodium transport in the distal convoluted tubule and collecting duct, enhancing sodium retention and contributing to DR[11,12]. Addition of thiazide diuretics (ie: metolazone, hydrochlorothiazide) increases distal tubular sodium excretion and augments diuresis[13]. In small trials, sequential nephron blockade with drugs that act at the proximal convoluting tubules and collecting ducts, such as acetazolamide and spironolactone respectively, have shown some benefit[14-16]. Recent data suggests that hypochloremia may play a key role in the pathophysiology of DR. Chloride plays an important role in renin angiotensin-aldosterone system and regulates diuretic sensitive tubular sodium transporters [17]. Chloride supplementation resulted in restoration of diuretic responsiveness in a small hypothesis generating study[17]. Elevated intra-abdominal pressure seen in decompensated HF, can increase renal vein pressure, reduce the renal perfusion gradient, and contribute to DR as well[18]. In patients with ascites, large volume paracentesis can improve renal function and DR[19].

Therapies for refractory cases

Some patients have poor response despite above interventions. Management of these refractory cases is difficult with limited data to guide therapies. Expansion of solute with mannitol and hypertonic saline along with high dose loop diuretics has been suggested as a method to mobilize extracellular fluid and improve diuretic response in the setting of acute HF; however, this needs further validation in patients with true DR[20-23]. Renal vasodilation with low dose dopamine can improve renal perfusion in acute HF. While renal dose dopamine has not shown to enhance diuresis in randomized trials of patients in HF, this has not been systematically studied in those with DR.[24,25] While low output heart failure may contribute to worsening renal function and inadequate diuresis, improving cardiac output does not reliably improve renal function or overall survival, suggesting that the etiology of DR in these patients maybe more complex and multifactorial and may involve factors other than just poor forward

flow[26,27]. Lastly, ultrafiltration should be considered in patients who are refractory to medical therapy; while this may improve hemodynamics, the overall prognosis of these patients remains poor.[28]

Conclusion

Overall management of DR remains challenging. DR needs better definition, better understanding of the pathophysiologic mechanisms, and improved treatments. Better definition of DR and insights into causative factors will enable clinicians to individualize therapies for these patients. Recently reported metrics for quantification of diuretic responsiveness maybe the first steps towards defining DR. Most studies evaluating diuretic use in HF do not specifically look at DR; this limits their interpretation and application in the treatment of DR.

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