Review

Diuretic usage in heart failure: a continuing conundrum in 2005

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Several large well-designed clinical trials have shown that the use of diuretics is beneficial in patients with hypertension. However, similarly robust data regarding their role in chronic heart failure are lacking. Historically, diuretics were developed for treatment of sodium and water retention in oedematous disorders and clinically, they remain the most potent drugs available to relieve symptoms and eliminate oedema in the congested patient with heart failure. In the non-congested patient, however, diuretics continue to be used on a purely clinical basis without sufficient characterization of benefits, adverse effects, and potential influence on mortality. There are also concerns that chronic diuretic usage can cause adverse vascular effects, unfavourable neuroendocrine activation, electrolyte imbalances, and life-threatening arrhythmias. In this article, we review the limited evidence available regarding the benefits and perils of using diuretics in heart failure.

KEYWORDS
Diuretics; Heart failure; Prognosis

Introduction

Diuretics remain a major component of drug therapy in both hypertension and heart failure. Thiazide diuretics interfere predominantly with sodium reabsorption in the central part of the distal tubule and are often used clinically as first line therapy in hypertension or mild chronic heart failure (CHF) in ambulatory patients. Loop diuretics work by blocking the sodium–potassium–chloride transporter in the ascending loop of Henle. They tend to be more potent, have a shorter duration of action, and are used in the treatment of acute pulmonary oedema and severe CHF. Loop diuretics are also the diuretics of choice in patients with milder CHF and concomitant renal dysfunction.1

The use of thiazides in the management of hypertension is well established. Hypertension remains the most common risk factor for heart failure and thiazides have been shown in several large scale trials to be effective in controlling blood pressure and reducing the incidence of left ventricular hypertrophy and heart failure in hypertensive patients.2,3

Despite being used in the first line management of CHF for several decades, diuretics have not been scrutinized as carefully as the other drugs used in the treatment of this condition. This is partly because they were introduced before the advent of large clinical trials with mortality end points and at a time when the pathophysiology of CHF was less well understood. Activation of the neurohormonal system is now known to be closely linked to prognosis in CHF. Angiotensin-converting enzyme (ACE)-inhibitors and β-blockers, block neuroendocrine activation, and have been shown to improve prognosis.4,5 As the majority of the patients in trials evaluating ACE-inhibitors and β-blockers were also on background diuretic therapy, it is unclear what effect the presence of concomitant diuretic therapy may have had on the observed results.

In the congested patient with CHF, diuretics are extremely effective in relieving symptoms, reducing...
intracardiac pressures, and improving cardiac performance. However, patients often continue to be treated with diuretics even after congestion has been relieved despite the fact that in many cases it may be possible for patients to avoid the need for a diuretic by limiting salt intake and maintaining themselves at dry weight. The continued use of diuretics avoids this need, but it is unclear as to whether there are any advantages of diuretics per se over and above salt homeostasis. Additionally, there is some evidence to suggest that the continued use of diuretics may cause potentially detrimental vascular effects\(^8\text{,}^9\) and neurohormonal activation.\(^10\text{,}^11\) Concomitant use of ACE-inhibitors is logical because they block neurohormonal activation and blunt the detrimental vascular effects seen with chronic diuretic therapy.\(^12\text{,}^13\) It is, however, now known that renin–angiotensin–aldosterone system (RAAS) blockade by ACE-inhibitors may be variable and incomplete and that some aldosterone can escape suppression in a proportion of patients. This residual aldosterone can mediate further harmful effects in heart failure\(^14\) and may have prognostic implications. Hence, questions remain as to whether the beneficial haemodynamic effects of chronic diuretic usage outweigh the potentially noxious neuroendocrine stimulation in the compensated patient who is already on ACE-inhibitors and β-blockers. In this article, we review the beneficial and potentially hazardous effects of diuretics in CHF and their effects on morbidity and mortality from the limited data available.

**Search strategy**

A search of published literature in the last 30 years was performed using the MEDLINE database using the following search terms: diuretics, heart failure, left ventricular dysfunction, and prognosis. Reference lists from identified studies were also reviewed to identify other potentially relevant references.

**Haemodynamic effects of diuretics**

The acute haemodynamic actions of diuretics reflect immediate direct or indirect vascular actions and those of diuresis and volume redistribution.\(^15\) Haemodynamic responses to diuretics are variable and dependant on which diuretic is used, whether the patient has acute pulmonary oedema or chronic compensated heart failure, the degree of baseline neurohormonal activation, and presence of concomitant medications, such as ACE-inhibitors.\(^13\)

This article predominantly focuses on the role of diuretics in systolic heart failure. Diuretics may be used to relieve oedema in isolated diastolic heart failure which may be due to impaired myocardial relaxation or rarely infiltration of the myocardium, but as cardiac output and blood pressure are dependent on high filling pressures, patients are more prone to the adverse consequences of dehydration, and diuretics should therefore be used judiciously in this situation.\(^16\)

**Haemodynamic effects of introducing diuretics in congested patients**

In patients with acute pulmonary oedema, intravenous administration of frusemide results in a rapid fall in right heart filling pressures and in an improvement in symptoms before any diuresis ensues.\(^17\) Frusemide-induced venodilatation lowers right atrial and pulmonary capillary wedge pressures, which in turn reduces cardiac preload. Frusemide-mediated renin release stimulates production of angiotensin I and II. Angiotensin II, at best only a weak vasoconstrictor by itself, stimulates vasodilatory prostaglandins which cause overall venodilatation.\(^13\text{,}^15\)

**Haemodynamic effects of diuretics in non-congested patients**

In non-congested patients, administration of additional diuretic may result in disparate vascular and haemodynamic effects.\(^8\text{,}^9\text{,}^13\) Potentially detrimental arteriolar vasoconstriction seems to predominate. Francis *et al.*\(^8\) observed that the administration of intravenous frusemide to patients with CHF on chronic diuretic therapy resulted in an increase in left ventricular filling pressures, a fall in the stroke volume index, and a deterioration in pump function. Kiely *et al.*,\(^18\) assessed the response of frusemide on pulmonary vasculature and found that there was an increase in systemic and pulmonary vascular resistance. This difference may be because patients with CHF already have higher levels of angiotensin II and hence venous capacitance is already maximally increased. Administration of additional frusemide in these patients results in a further increase in angiotensin and as the veins are unable to dilate further, the arterial vasoconstrictor effects of the angiotensin II predominate.\(^8\text{,}^13\) In keeping with this hypothesis is the observation that ACE-inhibitors attenuate the peripheral vascular effects of diuretics.\(^12\)

**Haemodynamic effects of diuretic withdrawal**

In a pivotal study, Braunschweig *et al.*\(^19\) used an implantable haemodynamic monitor to continuously record right heart pressure parameters while withdrawing diuretics in a small series of four patients with CHF. All patients were on an ACE-inhibitor and a β-blocker and had been clinically stable over the preceding 3 months. Diuretic withdrawal caused significant deterioration of haemodynamic parameters and worsening of CHF. The right ventricular systolic and diastolic pressures and the estimated pulmonary artery pressures all increased and returned to baseline after reinstitution of diuretics. Body weight and B-type natriuretic peptide measurements also increased, suggesting increasing ventricular overload and increased body fluid content. The fact that the patients deteriorated is evidence supporting the notion that diuretics are needed for chronic therapy. It is possible, however, that if the
patients had strictly restricted their sodium intake, they could have avoided the observed deterioration.

**Neuroendocrine effects of diuretics**

**Neuroendocrine effects of diuretics in congested patients**

Several investigators have demonstrated that in untreated heart failure there is no significant activation of the RAAS in the absence of diuretic therapy.\(^{11,20,21}\) The main mechanism for renin release is thought to be diuretic-induced volume contraction. Bayliss et al.\(^{11}\) demonstrated that untreated heart failure patients had significantly elevated levels of noradrenaline at rest and on exercise but no significant increase in renin levels. Addition of a diuretic resulted in noradrenaline levels falling to normal at rest but remaining abnormally elevated on exercise. Additionally, there were significant increases in plasma renin activity and aldosterone at rest and on exercise. Despite this stimulation of the RAAS, there was clinical improvement and increase in exercise capacity over a period of 1 month.

**Neuroendocrine effects of diuretics in non-congested patients**

Ikram et al.\(^{10}\) studied the haemodynamic and hormone responses to acute and chronic frusemide therapy in 10 patients with oedematous heart failure. An intravenous bolus of frusemide resulted in rapid fall in mean pulmonary pressure, with no significant changes in cardiac output, urine output, plasma renin, and aldosterone concentrations. However, after the oedema had been eliminated and the patient had become euvolumic, continued oral frusemide resulted in a fall in cardiac output with significant increases in plasma renin activity and aldosterone levels, suggesting late activation of the neurohumoral axis; alternatively or in addition, it may represent a reaction to overdiuresis. To our knowledge, this question has not been adequately addressed.

Prolonged activation of the RAAS may lead to progressive salt/water retention and peripheral vasoconstriction. ACE-inhibitors block the production of angiotensin II and aldosterone and have been shown to improve prognosis, although it is still not clear whether these benefits would be seen in patients who were not on diuretic therapy and hence did not have significant RAAS stimulation. It has therefore been argued that diuretics are used in combination with ACE-inhibitors on the assumption that the ACE inhibitor would suppress the adverse neurohormonal effects of the diuretic. It is now known that inhibition of the ACE by ACE-inhibitors is neither uniform nor sustained and aldosterone levels may rise again despite chronic ACE-inhibitor therapy.\(^{14}\) The noxious effects of diuretics on the neuroendocrine system, may hence persist despite ACE-inhibitor therapy and may affect prognosis adversely.

**Important non-diuretic effects of diuretics**

Both Spironolactone and Eplerenone have powerful anti-aldosteronergic effects and have been shown to improve outcome in CHF (discussed subsequently). Use of aldosterone antagonists in CHF has been shown to result in favourable effects on heart rate variability and cardiac adrenergic tone, a reduction in cardiac fibrosis, and significant improvement in prognosis.\(^{22-24}\)

**Impact of diuretics on electrolyte balance**

Electrolyte imbalances are the most common adverse effects of chronic diuretic therapy and their incidence ranges from 14 to 60%.\(^{7}\) Possible biochemical abnormalities include hypokalaemia, hyponatraemia, hypomagnesemia, hyperuricaemia, and metabolic alkalosis. Diuretic-associated hypokalaemia may increase the risk of arrhythmic mortality in patients.\(^{25,26}\) Potassium sparing diuretics can cause hyperkalaemia particularly in patients who are also on ACE-inhibitors.

**Effects of diuretics on symptoms and quality of life**

There is considerable evidence to show that diuretics improve quality of life by providing relief from symptoms of heart failure.\(^{27}\)

**Effects of introducing diuretics on symptoms and quality of life**

In the congested patient, diuretics lower filling pressures, reduce lung water content, and are the most efficacious drugs available to relieve symptoms rapidly. Symptomatically worse patients are likely to gain the greatest improvement in quality of life from diuretic treatment.\(^{27}\) Diuretics are more effective in improving symptoms when compared with ACE-inhibitors. Cowley et al.\(^{28}\) showed that symptomatic improvement was more marked with increasing doses of frusemide than with the addition of captopril in patients with moderate CHF. Richardson et al.\(^{29}\) observed that 4 out of 14 patients who were previously stable and well compensated on diuretics developed pulmonary oedema within a few weeks of replacing the diuretic with an ACE-inhibitor.

The bioavailability of the diuretic used may also influence its effects on quality of life. Both bumetanide and torasemide, when taken orally, have a more consistent level of absorption when compared with frusemide.\(^{1}\) Torasemide is associated with less fatigue in CHF patients when compared with frusemide.\(^{30}\)

The longer-term impact of diuretic therapy on quality of life and symptom relief has also been studied using the loop diuretic, piretanide, which is no longer on the market. Piretanide monotherapy was compared with placebo in 46 patients with New York Heart Association (NYHA) class II–III CHF.\(^{31}\) After 3 weeks of therapy, the
majority of patients on piretanide reported a subjective feeling of improvement coupled with significant improvement in exercise tolerance.

Effect of withdrawing diuretics on symptoms and quality of life

Withdrawal of diuretics in stable compensated patients with CHF has been shown in several studies to result in symptoms of congestion. When diuretic treatment was discontinued in 41 patients with a history of heart failure, it was found that diuretics had to be restarted in 71% of patients after a median of 15 days, owing to worsening heart failure symptoms. A history of hypertension, baseline frusemide dose of >40 mg/day, and a low left ventricular ejection fraction (<27%) were independent predictors of diuretic reinitiation.

Effect of diuretics on morbidity and mortality

With the exception of aldosterone antagonists, diuretics have not been studied in large-scale heart failure mortality endpoint trials and this remains the major cause for uncertainty regarding their use in day-to-day clinical practice. In the Randomized Aldactone Evaluation Study (RALES), spironolactone was associated with a 30% reduction in risk of death when compared with placebo. The benefits of spironolactone, which is a very weak diuretic, are believed to be largely due to its antagonism of aldosterone, which ‘escapes’ suppression despite ACE-inhibition. A subsequent study (EPHESUS) has shown that the addition of a selective aldosterone antagonist, Eplerenone, to optimal medical therapy results in reduced morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.

In a meta-analysis of randomized controlled trials assessing the role of diuretics in heart failure, only three small placebo-controlled studies had reported on the effect of diuretic therapy on mortality. Analysis performed by the authors on the combined population of these studies (n = 221) suggested an absolute risk reduction of 8% in mortality in patients treated with diuretics compared with placebo. The studies analysed were inadequately powered and it was not possible to draw any definitive conclusions.

Some studies do not distinguish adequately between systolic and diastolic heart failure, and this may have influenced the results particularly as patients with predominant diastolic dysfunction are more susceptible to the adverse repercussions of volume depletion when compared with patients with systolic dysfunction. This is an important issue for future studies.

The effects of diuretics on cardiac function

Diuretics can reduce the dynamic functional mitral regurgitation that is frequently present in patients with advanced heart failure and consequently improve the effective forward stroke volume at rest and on exercise. Lower filling pressures reduce chronic wall stress and myocardial oxygen requirements. Lower right atrial pressure results in reduced coronary venous pressure and myocardial turgor. This may lead to improved fibre shortening. Monotherapy with piretanide, in patients with NYHA class II–III heart failure has been demonstrated to result in a fall in cardiac volumes and an improvement in fractional shortening after 3 weeks. These findings contrast with results published by Sharpe et al. who compared the effects of captopril, frusemide, and placebo in 60 patients with Q-wave infarction and asymptomatic left ventricular dysfunction. The captopril group fared best with no change in left ventricular diastolic dimensions and an improvement in ejection fraction. The frusemide and placebo groups, however, showed an increase in left ventricular dimensions and a decrease in ejection fraction. These contrasting observations may be simply due to differences in the populations enrolled in these studies, but nevertheless it still remains an unresolved question as to whether diuretic-induced improvements in echocardiographic markers of cardiac contractility seen in the other studies were caused by alteration of loading conditions rather than by ventricular remodelling or an improvement in the intrinsic performance of the heart.

The effects of diuretics on hospitalizations due to heart failure

In the Digoxin Multicenter research group trial, the placebo arm, which consisted of patients on diuretics alone, had higher rates of hospital admission when compared with patients who were taking either digoxin or captopril.

In an open label study, Murray et al. randomized 234 patients to either oral torasemide or frusemide for 1 year. Torasemide-treated patients were less likely to need hospitalization for heart failure or for all other cardiovascular causes. In addition, patients treated with torasemide had significantly fewer hospital days for heart failure when compared with those treated with frusemide (296 vs. 106 days).

The effects of diuretics on cardiac arrhythmias

Use of non-potassium-sparing diuretics was found to be associated with a significantly increased incidence of sudden, presumed arrhythmic, death in the Multiple Risk Factor Intervention Trial Research Group which randomized patients to either usual care or diuretic-based stepped care antihypertensive regime. Similar results were obtained in a retrospective analysis of patients enrolled in the Studies Of Left Ventricular Dysfunction (SOLVD). Potassium-sparing diuretics, however, were not associated with increase in arrhythmic death, suggesting that diuretic-induced electrolyte disturbances were responsible for the observed increase in mortality. Surprisingly, potassium supplementation or addition of
an ACE-inhibitor did not significantly alter the risk of arrhythmic death in contrast to the use of potassium-sparing diuretics. Potassium-sparing diuretics may therefore offer cardioprotection over and above simple potassium correction.

Are all diuretics equal in terms of prognosis?

The Torasemide in Chronic heart failure (TORIC) study was an open label post-marketing surveillance study, which compared torasemide with frusemide and other diuretics. Oral torasemide has considerably higher bioavailability when compared with oral frusemide due to its relatively consistent absorption. It has also been shown to have additional anti-aldosteronergic effects in animal studies. Although the TORIC study was not designed to be a mortality study, the results showed significantly less total and cardiac mortality in the group of patients treated with torasemide. It is yet unclear as to whether the benefits seen were purely due to the greater bioavailability of torasemide or whether its anti-aldosteronergic effects also played a role.

Conclusion

Surprisingly little information exists regarding the efficacy and safety of diuretic therapy in patients with congestive heart failure. The lack of a suitable alternative for control of symptoms of congestion means that diuretics will continue to be used as first line therapy in the treatment of congestive heart failure. The Torasemide in Chronic heart failure (TORIC) study was an open label post-marketing surveillance study, which compared torasemide with frusemide and other diuretics. Oral torasemide has considerably higher bioavailability when compared with oral frusemide due to its relatively consistent absorption. It has also been shown to have additional anti-aldosteronergic effects in animal studies. Although the TORIC study was not designed to be a mortality study, the results showed significantly less total and cardiac mortality in the group of patients treated with torasemide. It is yet unclear as to whether the benefits seen were purely due to the greater bioavailability of torasemide or whether its anti-aldosteronergic effects also played a role.

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References


