

Review Article

Mechanism and management of diuretic resistance in congestive heart failure

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Abstract

Diuretic drugs are used almost universally in patients with congestive heart failure, most frequently the potent loop diuretics. Despite their unproven effect on survival, their indisputable efficacy in relieving congestive symptoms makes them first line therapy for most patients. In the treatment of more advanced stages of heart failure diuretics may fail to control salt and water retention despite the use of appropriate doses. Diuretic resistance may be caused by decreased renal function and reduced and delayed peak concentrations of loop diuretics in the tubular fluid, but it can also be observed in the absence of these pharmacokinetic abnormalities. When the effect of a short acting diuretic has worn off, postdiuretic salt retention will occur during the rest of the day. Chronic treatment with a loop diuretic results in compensatory hypertrophy of epithelial cells downstream from the thick ascending limb and consequently its diuretic effect will be blunted. Strategies to overcome diuretic resistance include restriction of sodium intake, changes in dose, changes in timing, and combination diuretic therapy.

Many of the clinical features of congestive heart failure (CHF) result from retention of sodium and fluid. Although diuretics have not been shown to improve survival in patients with CHF, they do improve symptoms of congestion very effectively. It should also be borne in mind that diuretics have been part of standard CHF therapy in all recent survival trials of beta-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers¹. Only loop diuretics are effective as single agents in moderate to severe heart failure². Removal of excessive fluid is usually achieved by a combination of salt restriction and loop diuretics, but in some cases oedema persists despite adequate diuretic therapy. This has been termed diuretic resistance. The prevalence of diuretic resistance in the heart failure population is unknown. In a recent retrospective analysis of 1153 patients with advanced CHF 402 patients had diuretic resistance (defined in this study as requirement of furosemide (frusemide) > 80 mg or bumetanide >2mg daily). Diuretic resistance was independently associated with total mortality, sudden death, and pump failure death³.

Causes of sodium retention in congestive heart failure

Activation of the rennin-angiotensin system occurs in moderate to severe cardiac failure and after initiation of diuretic therapy. Angiotensin II causes vasoconstriction of both afferent and efferent renal arterioles and stimulates release of aldosterone from the adrenal gland. Increased sympathetic activity is

responsible for stimulation of sodium reabsorption in the proximal tubule, renal vasoconstriction, and renin-angiotensin system activation. Increased levels of antidiuretic hormone lead to increased water reabsorption in the collecting duct, thereby predisposing to hyponatraemia.

Most patients with CHF have some degree of renal impairment, due to intrinsic renal disease, some degree of prerenal azotaemia or a combination of both. Loop diuretics inhibit the reabsorption of sodium, chloride, and potassium in the thick ascending limb of Henle's loop. Their site of action is the luminal surface of epithelial cells and therefore they have to reach the urine to be effective. Loop diuretics are firmly bound to serum proteins, they reach the tubular lumen predominantly by active secretion and not by glomerular filtration or passive diffusion. In renal insufficiency secretion of furosemide and other loop diuretics is reduced because of accumulation of endogenous organic anions competing with loop diuretics for the receptor sites of the organic anion transporter². Higher doses are required to overcome this competitive inhibition and to obtain therapeutic urinary concentrations. The bioavailability of loop diuretics is unaltered in CHF, but peak urinary concentrations are reduced and tend to occur later, resulting in a less powerful diuretic effect². This is a second pharmacokinetic mechanism that interferes with a satisfactory diuresis. When a short acting diuretic like furosemide is administered, it will result in natriuresis as long as its

concentration in tubular fluid is high enough to block the Na⁺/K⁺/2Cl⁻ cotransporter. When urinary concentrations decline below the diuretic threshold about six hours later, compensatory sodium retention occurs during the rest of the day. This is called postdiuretic salt retention. If sodium intake is high, postdiuretic salt retention can completely abolish the effect of the diuretic and a negative sodium balance is not achieved. If sodium intake is low, compensatory sodium retention in the postdiuretic phase is incomplete and there is a net loss of sodium⁴.

Chronic administration of loop diuretics results in a diminished natriuretic effect ("the braking phenomenon") Major determinants of this braking phenomenon are functional and structural adaptations that occur in downstream nephron segments. Studies in rats have shown that chronic administration of a loop diuretic induces hypertrophy and hyperplasia in epithelial cells of the distal convoluted tubule, leading to an increased reabsorption of sodium in this segment, thereby blunting the natriuretic effect. These adaptations also occur in humans^{5,6,7}.

Management of diuretic resistance

(A) Rule out non-compliance

Non-compliance with either salt restriction (sodium intake <100 mmol/day) or medication intake should first be excluded. Dietary non compliance is suspected when daily salt excretion is high (>100 mmol/day) without concurrent weight loss⁴. Use of non-steroidal anti-inflammatory drugs (NSAIDs) is a major cause of apparent diuretic resistance. These drugs interfere with prostaglandin synthesis by inhibiting cyclooxygenase and thereby antagonize the natriuretic response to loop diuretics. Administration of prostaglandin E2 has been shown to restore the natriuretic response to furosemide in indomethacin treated rats. Consumption of NSAIDs is associated with an increased risk of hospital admission because of heart failure in patients with pre-existing heart failure⁸.

(B) Dose adjustment -

Both diminished renal blood flow and reduced activity of the organic anion transporter (due to raised levels of endogenous organic anions) interfere with furosemide secretion in patients with renal impairment. This results in lower concentrations in the renal tubule. Since many patients manifest some degree of renal impairment, increasing the dose will be necessary to deliver appropriate amounts of diuretic to the urinary site of action. Few investigators have studied the use of high dose furosemide in the treatment of refractory CHF. Gerlag and van Meijel demonstrated the efficacy and safety of high dose furosemide (250-4000 mg/day, given orally or intravenously) in 35 patients with severe CHF and significantly reduced renal function

refractory to conventional diuretic therapy. No significant side effects were noted and weight reduction and relief of symptoms were achieved in all patients^{9,10}.

Since most loop diuretics are short acting, postdiuretic salt retention is an important mechanism contributing to diuretic resistance, particularly when salt intake is not sufficiently restricted. More frequent administration of the diuretic (two to three times a day) overcomes the effect of postdiuretic salt retention by reducing the drug-free interval.

Urinary concentrations that induce an adequate diuresis in healthy persons may fail to achieve the desired effect in patients with CHF, for dose-response curves are shifted down-ward and rightward in CHF¹¹. Therefore, it is often necessary to increase the dose of a loop diuretic, even in the absence of pharmacokinetic abnormalities.

Some clinicians consider bumetanide to be more effective than furosemide in patients with CHF because of its better oral bioavailability. Both in normal subjects and in patients with CHF bumetanide has an 80% bioavailability compared to 40% for furosemide¹². Although bumetanide is 40 times more potent than furosemide on a weight basis, both drugs are equally effective when equipotent doses are administered¹³.

(C) Intravenous bolus injection or continuous infusion of a loop diuretic

Impaired absorption of loop diuretics in subjects with CHF results in decreased and delayed peak concentrations in the urine, although the absolute bioavailability does not change significantly when compared with normal subjects. A moderate increase in dose or switching to intravenous administration may obviate this problem¹⁴.

Ototoxicity may occur after rapid intravenous injection of a high dose of a loop diuretic, usually in patients receiving other ototoxic drugs, particularly aminoglycoside antibiotics. Hearing loss and tinnitus are usually transient¹⁵.

Continuous intravenous infusion of a loop diuretic may be effective when other strategies to overcome diuretic resistance have failed. It will prevent postdiuretic salt retention completely and has been demonstrated to be a safe and effective treatment in patients with CHF refractory to 250 mg furosemide given orally or intravenously. Several controlled studies have compared the efficacy of intermittent intravenous bolus administration of a loop diuretic with continuous infusion in patients with advanced heart failure¹⁶⁻¹⁹. The dose of continuous infusions of furosemide ranged from as low as 3 mg/hour to as high as 200 mg/hour, with most patients receiving 10-20 mg/hour. The same daily dose caused excretion of a higher volume of urine and electrolytes

when given as a continuous infusion. The maximal plasma furosemide concentration was significantly lower and this resulted in a reduced risk for ototoxic side effects.

(D) Combination diuretic therapy

Several combinations with loop diuretics are possible. Proximal diuretics should be avoided in patients with heart failure because they cause metabolic acidosis. However, the evidence in favour of spironolactone is rather limited and its use in the treatment of diuretic resistance in CHF is not recommended. Thiazide diuretics proved to be highly effective in establishing a diuresis in patients resistant to high doses of loop diuretics. Side effects included hypokalaemia, hyponatraemia, dehydration and renal failure. All patients had a very short life expectancy; failure to respond to thiazide therapy was associated with an even more ominous prognosis^{20,21}.

Traditionally metolazone has been used in combination with loop diuretics, although there is no theoretical advantage of one thiazide over another. Addition of 25-100 mg of hydrochlorothiazide, another thiazide diuretic proved to be very effective in patients with severe CHF and impaired renal function showing diuretic resistance²².

Thiazide diuretics block the reabsorption of a mere 5%-10% of filtered sodium, whereas loop diuretics are able to block the reabsorption of about 25% of filtered sodium. Consequently, thiazide diuretics have a weak natriuretic effect and they are ineffective as monotherapy in patients with advanced heart failure. However, when the sodium load in the distal tubule increases chronically, this segment of the nephron can increase its salt transport capacity. Combining loop and thiazide diuretics in patients with CHF and diuretic resistance is a very elegant and logical treatment option because it takes into account this pathophysiological mechanism²³.

Conclusion :

The vast majority of patients presenting with acute symptoms of fluid overload are responsive to diuretic drugs, at least initially. However, after chronic exposure to loop diuretics, some patients will require increasing doses and eventually develop diuretic resistance. After excluding compliance problems, higher doses and more frequent administration should be tried. Switching to the intravenous route bypasses the gastrointestinal tract and can overcome problems associated with delayed absorption. Continuous intravenous infusion has been shown to be more efficient than intermittent bolus administration. The addition of a thiazide diuretic to treatment with loop diuretics will usually establish a diuresis even in patients not responsive to other diuretic regimens.

When diuretic resistance has been treated successfully, heart failure treatment should be

optimized according to the most recent guidelines in order to reduce mortality.

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