Diuretic Therapy in Decompensated Heart Failure
Position Statement, 11/2003

BACKGROUND

Duiretics decrease edema and pulmonary congestion associated with heart failure. During an exacerbation of heart failure, intravenous loop diuretics such as furosemide are required for symptomatic relief. Despite widespread use, optimal treatment strategies with furosemide for decompensated heart failure is not well defined. This is most likely due to patient variability and a lack of large, randomized, controlled trials assessing different treatment strategies. Clinical decisions regarding diuretic therapy in the decompensated state often concern assessing responsiveness to therapy, and the management of diuretic resistance. This statement addresses issues specific to intravenous administration of furosemide for heart failure. The purpose of this document is provide guidance to clinicians in managing diuretic therapy during an exacerbation of heart failure.

ASSESSING RESPONSIVENESS

Patients who present with signs and symptoms of volume overload (dyspnea, edema, elevated jugular reflex) should receive intravenous diuretics. Typically, patients will experience symptomatic improvement before urine output increases significantly. Improvement in symptoms and increases in urine output should be monitored closely and used as a guide to adjust diuretic therapy. In one prospective, randomized study, a protocol-guided strategy to manage diuretic therapy resulted in greater diuresis and shorter length of hospital stay when compared to a group of nonrandomized individuals.[1] This protocol-guided approach differed from usual care in that fluid restriction was strictly enforced, and the furosemide dose was adjusted according to hourly intakes and outputs.

DIURETIC RESISTANCE

Diuretic resistance should be suspected in patients on high doses of oral furosemide ($\geq$ 80-160 mg/dose, depending on renal function) who do not respond to therapy. These patients fail to excrete sodium and water despite high doses of diuretics and compliance with fluid and water restriction. The mechanisms of diuretic resistance are both pharmacokinetic and pharmacodynamic. Although the bioavailability of furosemide is relatively unchanged in heart failure, absorption of the oral form may be delayed, resulting in diminished responsiveness. [2,3]

The site of action of loop diuretics is the thick ascending limb of the Loop of Henle. These agents must be secreted into the tubular lumen of the nephron in order to reach their site of action. Thus the effectiveness of loop diuretics such as furosemide depends on transport across the lumen with subsequent delivery into the urine. In heart failure, less furosemide is secreted into the urine because of diminished renal blood flow and competition with other organic anions for active transport. This contributes to diuretic resistance observed in heart failure patients.

Strategies to manage diuretic resistance attempt to overcome the pharmacokinetic and pharmacodynamic alterations that occur during heart failure. These include increasing the dose or dosing frequency, initiation of a continuous infusion or addition of hydrochlorothiazide or metolazone.

Increasing the dose or dosing frequency

Increasing the diuretic dose or dosing frequency is an effective strategy to manage diuretic resistance. Indeed, Gerlag and associates found that high dose furosemide (250-400 mg/day, either orally or intravenously) was safe and effective in the management of thirty-five patients with severe heart failure and renal dysfunction. Although no significant side effects were observed in this study, patients who receive high doses of furosemide, either orally or intravenously, should be monitored for hypokalemia and other electrolyte abnormalities. Additionally, high doses of intravenous furosemide has been associated with ototoxicity, which may or may not be reversible. [6]

Increasing the dosing frequency may also overcome diuretic resistance. The duration of action of furosemide is approximately six hours so that sodium and fluid may accumulate in patients who take the drug once daily. In such cases, the patient may benefit from taking furosemide two to three times daily.

Continuous Infusion vs Bolus Therapy

The efficacy and safety of continuous infusion of furosemide has been evaluated in five clinical trials. [1,5-8] Three of these trials were specific to heart failure; another included mostly (79%) patients with heart failure. In a prospective, randomized, crossover study, nine patients with New York Heart Association (NYHA) class III or IV heart failure and normal renal function received a bolus injection followed by a 48-hour continuous infusion or 3 bolus injections daily for 48 hours.[5] The total dose of furosemide was 90-120 mg in both treatment arms. The loading dose-continuous infusion strategy resulted in significantly greater diuresis (urine output 12-26% greater, $p < 0.01$) and natriuresis (sodium excretion 11-32% greater, $p < 0.01$). No difference in adverse events were observed.

Another prospective, randomized, crossover study found similar results in a slightly different patient population.[6] Twenty patients on high doses of furosemide (mean 690 mg, range 250-2000 mg) with some degree of renal impairment (creatinine clearance 45 mL/min $\pm$ 4.8). Patients either received one bolus injection daily for 3 days or a loading dose (20% of continuous infusion) followed by and 8-hour continuous infusion. Again, urine output (approximately 21% increase, $p = 0.0005$) and sodium excretion (approximately 29% increase, $p = 0.0045$) were significantly greater with the continuous infusion. These results, however, are difficult to interpret and may not apply to practice since patients in the bolus group received just one dose of furosemide daily. Typically, patients on higher doses of furosemide will require more frequent administration of the drug for purposes previously mentioned. Of note, reversible ototoxicity was observed in 5 patients after high dose bolus therapy.

In an uncontrolled, open-label trial of ten patients with diuretic resistance, a continuous infusion of furosemide (20-160 mg/hr) was safe an effective. All patients experienced symptom relief and weight loss. [7]

In summary, the safety and efficacy of a continuous infusion of furosemide has been demonstrated in a few small clinical trials. These data suggest that a loading dose followed by a continuous infusion may be more efficacious than bolus dosing, resulting in about 20% greater diuresis and naturesis. It would be reasonable to initiate therapy with a loading dose followed by a continuous infusion of furosemide when greater diuresis and naturesis is desired.

Addition of another diuretic

Patients who are not responding to furosemide may benefit form the addition of another diuretic. Mechanistically, thiazide diuretics have a different site of action, which may explain the benefits that are observed with combination diuretic therapy. Thiazide and thiazide-like diuretics work in the distal convoluted tubule where 5-8% of sodium is reabsorbed.[3] In contrast, approximately 20-25% of sodium is reabsorbed in the Loop of Henle, the site of action of furosemide.[3] In the setting of diuretic resistance, more sodium reaches the distal tubule because of diminished efficacy of furosemide to block sodium reabsorption in the Loop of Henle. Enhanced delivery of sodium to the distal tubule actually increases the efficacy of the thiazide diuretic, such that more than 5-8% of sodium reabsorption is inhibited. In this way, thiazide and loop diuretics may exert synergistic effects in the setting of diuretic reistance.

The effects of combination therapy with a thiazide or thiazide-like agent has been examined in three clinical trials. [9-11] These trials demonstrate the beneficial effects of combination therapy in heart failure patients.

Dormans and Gerlag demonstrated that the addition of hydrochlorothiazide (HCTZ 25-100 mg) to twenty patients with renal impairment and diuretic resistance (furosemide dose at least 250 mg) resulted in greater weight loss (mean weight loss 0.6 $\pm$ 1.2 kg during 5 days prior to addition of HCTZ vs 6.7 $\pm$ 3.3 kg during treatment period, p value not provided), diuresis (approximately 38% increase in mean daily urine volume, $p < 0.001$) and naturesis (3.5 $\pm$ 3.2% to 11.5 $\pm$ 9.0%, $p < 0.001$).[9]

In another study, fifteen out of seventeen patients with severe refractory heart failure who did not respond to conventional therapy improved and were discharged after the addition of metolazone (1.25-10mg) to intravenous furosemide (mean dose 120 mg/day).[10]

Similarly, Channer and associates found that the addition of metolazone or bendrofluazide to intravenous loop diuretics resulted in weight loss and sufficient improvement to allow hospital discharge.[11] The investigators found no significant difference in the efficacy of metolazone or bendrofluazide.

The most common side effect in these trials was electrolyte disturbances, including hypokalemia and hyponatremia. In most instances, hypokalemia was successfully corrected with potassium supplementation. However, serious complications including cardiac arrhythmias and neuromuscular disorders may result from persistent hypokalemia. Therefore serum electrolytes should be monitored closely in patients receiving combination diuretic therapy.

In summary, data from 3 small clinical trials support the addition of hydrochlorothiazide, metolazone or bendrofluazide to loop diuretics in patients unresponsive to diuretic therapy.

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