

## EDITORIALS

## Appropriate Diuretic Dosing: Closed Loop Communication

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Injectable furosemide was first approved for use by the US Food and Drug Administration in 1968.<sup>1</sup> For more than 40 years, loop diuretics have been the mainstay of therapy for relief of congestion and fluid removal in patients admitted with acute decompensated heart failure (ADHF). Despite the widespread use of loop diuretics in clinical practice, robust data supporting their role is scarce. Furthermore, the optimal approach to the management of the patient with acute volume overload has not been well defined.

In this issue of the *Journal of Hospital Medicine*, Amer et al.<sup>2</sup> present a meta-analysis of randomized controlled trials comparing continuous infusion to bolus doses of furosemide in hospitalized patients with ADHF. The study demonstrates that continuous infusion is superior to bolus in terms of weight loss and urine output over 24 hours. Specifically, patients receiving a continuous infusion of furosemide had 240 mL/day (95% CI, -462.42 to -18.66) more urine and lost an additional 0.78 kg (95% CI, -1.54 to -0.03) in their hospital stay compared with patients receiving a bolus infusion. The heterogeneity in study designs for urine output and wide confidence intervals for urine output and weight loss create uncertainty about the superiority of continuous infusion. The small difference in daily urine output questions the clinical significance of the results. Many of the studies evaluated in the meta-analysis lacked rigorous design and/or appropriately dosed furosemide.

Despite the shortcomings of the available studies, the authors have published a sound and reasonable meta-analysis. This is the first meta-analysis comparing the use of furosemide alone as a continuous infusion versus bolus dose in patients with ADHF. Additionally, Amer et al. are the first to include recent data from the DOSE trial,<sup>3</sup> which showed no difference in volume loss between heart failure patients receiving bolus versus continuous infusions dosing of loop diuretics. Although the benefits of continuous infusion in the meta-analysis

by Amer et al. represent only a modest clinical advantage over bolus infusions, the authors should be commended for addressing an important controversy in the management of patients with volume overload.

Although the method of dose delivery is an important issue in the management of such patients, we believe that a number of critical factors must be taken into consideration to assure sufficient fluid removal and quick relief of congestion. Ensuring the delivery of an adequate loop diuretic dose is critical. Additionally, the dose response must be assessed at an appropriate interval so adjustments can be made in a timely manner. Using this method, diuretic dosing can be individualized based on response.

Current guidelines jointly published by the American Heart Association (AHA) and American College of Cardiology (ACC) do not provide clinicians with specific details about the optimal approach to volume-overloaded patients.<sup>4</sup> In a 2009 update, the ACC and AHA recommend diuretic use to “optimize volume status and relieve signs and symptoms of congestion without inducing excessively rapid reduction in intravascular volume.”<sup>4</sup> They further recommend that patients already receiving a loop diuretic who present with volume overload should receive a dose of diuretic equal to or higher than the outpatient dose. Urine output and congestion should be reassessed serially, and diuretics should be titrated accordingly. Current guidelines do not adequately address several topics, including: (1) appropriate urine output in 24 hours, and how frequently urine output should be assessed; (2) optimal frequency of diuretic dosing; and (3) appropriate choice of diuretic.

An understanding of the pharmacokinetics of loop diuretics helps answer these questions. Intravenous furosemide and bumetanide have similar elimination half-lives of 1 to 2 hours and peak intravenous action at 30 minutes.<sup>5,6</sup> Intravenous torsemide has not been widely available, but has a longer half-life of 3 to 4 hours, with peak action in 1 to 2 hours.<sup>5,6</sup> The magnitude of a patient's diuretic response compared with the amount of drug administered is best represented by a sigmoid curve.<sup>5</sup> Therefore, after a specific dose threshold, further natriuresis is not achieved. Based on the elimination half-life, proper bolus dosing of furosemide or bumetanide should be every 4 to 8 hours in patients with volume overload and adequate blood pressure.<sup>6</sup> The administration of a loading dose of loop diuretic is of paramount importance to rapidly

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achieve therapeutic levels immediately before initiating a continuous infusion. Without a proper loading dose, it can take up to 20 hours to achieve steady state serum levels of diuretic during continuous infusion.<sup>5</sup> The ACC and AHA acknowledge this point in their guidelines for chronic heart failure by recommending a bolus dose before initiation of continuous infusion.<sup>7</sup> The negative results of the DOSE trial may have been due to lack of a loading dose before infusion initiation.<sup>3</sup> Additionally, the total volume loss during continuous infusion compared with bolus dosing might be greater if loading doses were consistently given before starting infusions in published studies. Overall, individual patient response to a diuretic dose is variable and dependent on several factors, including serum albumin level, renal and liver function, and diuretic resistance.<sup>5</sup>

Teamwork and collaboration are essential to overcome barriers to proper diuretic dosing and provide patients with safe and effective care. Closed loop communication between nurses, physicians, and pharmacists in structured daily interdisciplinary rounds appears to reduce adverse drug events in hospitalized patients.<sup>8</sup> The increased mortality<sup>9,10</sup> associated with high doses of diuretic, as well as registry data suggesting that over 50% of patients are discharged with significant heart failure symptoms and minimal weight loss,<sup>11</sup> call for a more structured approach toward fluid removal. A team-based protocol that directs titration of medication, monitors response, and clearly outlines communication channels to adjust doses allows for more efficacious medication administration with lower rates of serious events. This method was used with a dosing algorithm for the administration of opioids for patients with acute pain syndromes.<sup>12</sup> Serious or fatal opioid-related adverse drug events were reduced to zero using this communication-enhancing approach.<sup>12</sup> A similar approach should be used for diuretic dosing in patients who are admitted with ADHF.

We believe frequent follow-up of diuretic response is critical in the successful treatment of the volume-overloaded patient. Many clinicians who treat hospitalized patients with ADHF prescribe a fixed daily diuretic dose and evaluate the natriuretic response based on 24-hour urine output and weight loss. This can lead to unnecessary increases in length of hospital stay. We recommend using a protocol for diuretic administration that includes more frequent assessment and follow-up of dose response. After a diuretic dose is given, nurses communicate with the physician about the amount of urine output after a prespecified time based on an understanding of the pharmacokinetics of the medication administered. If the urine output is not within the desired range, then the diuretic dose can be increased and immediately administered. If the urine output is above a desired range, doses can be decreased, delayed, or held. With optimal protocol dosing for loop diuretics, continuous infusion may be

superfluous. In one study, Peacock et al.<sup>13</sup> evaluated a diuretic protocol used to treat patients with ADHF who were admitted to an observation unit. This protocol set 2-hour urine output goals after loop diuretic bolus doses were administered. If the urine output goals were not met, the diuretic dose was doubled and 2-hour urine measurements were repeated.<sup>13</sup> Limits were set on maximum dosing to ensure patient safety, and electrolytes and renal function were monitored. Using this protocol with other ADHF multidisciplinary interventions, 90-day heart failure readmission rates decreased by 64% ( $P = 0.007$ ) with a trend toward decreased 90-day mortality.<sup>13</sup> Although the multidisciplinary approach may have been the major contributor to these outcomes, the diuretic protocol allowed rapid achievement of “euvoemia” in an observation unit patient population with ADHF. Future investigation needs to specifically evaluate dosing protocols and patient safety because of the association between high doses of diuretics and increased mortality. However, studies showing that high diuretic doses are harmful may simply reflect the fact that patients who require high doses of diuretic have more advanced cardiac or renal disease. In such situations, the clinician needs to be aware of the possibility of decreased cardiac output, hypotension, and intrinsic renal disease as potential barriers to diuresis.

Currently, clinicians have no clear evidence-based strategies for using diuretics to safely reduce congestion in patients with ADHF. As shown by Amer et al.,<sup>2</sup> continuous furosemide infusion may provide more effective weight and volume loss than bolus injections. More rigorous studies comparing effectively dosed diuretics regimens are needed. These studies should optimize diuretic use by accounting for individual patient characteristics and drug pharmacokinetics, using a protocol that monitors response in an appropriate interval, and facilitates care team communication. Ultimately, the mode of diuretic administration is only 1 part of developing a process to remove fluid in patients with ADHF.

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