Review

ISSN 1738-5997 (Print) • ISSN 2092-9935 (Online)
Electrolyte Blood Press 13:17-21, 2015
http://dx.doi.org/10.5049/EBP.2015.13.1.17

Loop Diuretics in Clinical Practice

Se Won Oh, M.D.
and Sang Youb Han, M.D.
Department of Internal Medicine, Inje University College of Medicine, Goyang, Korea

Received: June 25, 2015
Accepted: June 30, 2015
Corresponding Author: Sang Youb Han, M.D., Ph.D.
Department of Internal Medicine, Inje University Ilsan-Paik Hospital, Joowha-ro 170, Ilsanseo-gu, Goyang-si, Gyunggi-do 411-706, Korea
Tel: +82-31-910-7200, Fax: +82-31-910-7219
E-mail: hansy@paik.ac.kr

Diuretics are commonly used to control edema across various clinical fields. Diuretics inhibit sodium reabsorption in specific renal tubules, resulting in increased urinary sodium and water excretion. Loop diuretics are the most potent diuretics. In this article, we review five important aspects of loop diuretics, in particular furosemide, which must be considered when prescribing this medicine: (1) oral versus intravenous treatment, (2) dosage, (3) continuous versus bolus infusion, (4) application in chronic kidney disease patients, and (5) side effects. The bioavailability of furosemide differs between oral and intravenous therapy. Additionally, the threshold and ceiling doses of furosemide differ according to the particular clinical condition of the patient, for example in patients with severe edema or chronic kidney disease. To maximize the efficiency of furosemide, a clear understanding of how the mode of delivery will impact bioavailability and the required dosage is necessary.

Key Words: Loop diuretics, Furosemide, Chronic kidney disease

Introduction

Diuretics are commonly used to control edema in a number of clinical fields. Diuretics reduce sodium (Na^+) reabsorption in specific renal tubules, resulting in an increase in urinary sodium and water excretion. The thick ascending limb of the loop of Henle reabsorbs about 25% of the Na^+ of the glomerular filtrate. The distal convoluted tubule reabsorbs approximately 5% of the Na^+ through a thiazide-sensitive sodium-chloride (Na^+-Cl^-) co-transporter. About 1-2% of the Na^+ is transported at the distal segment of the distal convoluted tubule and the collecting duct. Loop diuretics can inhibit the largest amount of Na^+ reabsorption by acting on the thick ascending limb of the loop of Henle. Furosemide inhibits the sodium-potassium-chloride (Na^+-K^+-$2Cl^-$) co-transporter in the apical membrane of tubular epithelial cells in the thick ascending limb[1].

In this article, we review five important aspects of loop diuretics that we must be aware of when we prescribe this medicine: (1) oral versus intravenous treatment, (2) dosage, (3) continuous versus bolus infusion, (4) application in chronic kidney disease (CKD) patients, and (5) side effects.

Oral versus Intravenous Treatment

The bioavailability of furosemide is extremely variable (10-90%). The bioavailability can be improved if it is taken before meals because food can disrupt its absorption[2]. Furosemide is absorbed from the gastrointestinal tract, and its peak diuretic effect occurs between 1 and 1.5 hours after oral administration, and between 10 and 30 minutes after intravenous administration. Furosemide (>95%) binds to plasma proteins. Protein-bound furosemide is delivered to the proximal tubule, and secreted via organic transporters that are expressed at the luminal site of action[1-3]. Approximately 50% of the furosemide load is excreted unchanged in urine, and the rest is metabolized into glucuronide in the kidney. Thus, patients with renal dysfunction show a decreased response and increased plasma half-life of furosemide due to the reduction of urinary excretion[1-3].

In patients with severe edema, the effect of furosemide

may be altered due to inadequate gastrointestinal absorption. Patients unresponsive to oral furosemide should be switched to intravenous therapy or oral torsemide. The bioavailability of torsemide is predictable. It is extremely well absorbed (80-90%), regardless of the presence of edema, because it undergoes substantial hepatic elimination. The dosage of intravenously administered furosemide is usually half of that of the oral dose; oral bioavailability is approximately 50% (10-90%)[2-4].

Dosage of Loop Diuretics

Loop diuretics have a threshold dose; no diuretic effect is shown when the dose is lower than the threshold dose. They also have a dose-responsive effect. The threshold dose of furosemide differs according to the clinical condition of the patient. For example, the threshold dose of intravenous furosemide is 10 mg in a population with normal renal function. This increases to 80-160 mg in patients with declining renal function[5]. Therefore, furosemide doses lower than 80 mg are not effective in advanced CKD patients.

Loop diuretics have a ceiling dose; this is the dose that shows the maximum fractional sodium excretion. Although loop diuretics display dose-response curves, doses above the ceiling dose are only moderately effective. Repeated infusions with the ceiling dose are more effective than increasing the dose of furosemide[4]. The ceiling dose of intravenous furosemide also varies in different diseases; this dose is 80-200 mg in patients with CKD or nephrotic syndrome, and 40-80 mg in patients with congestive heart failure or liver cirrhosis.

The half-life of the various loop diuretics are not the same: 1-1.5 hours for furosemide and 3-4 hours for torsemide. The half-life of furosemide is prolonged in advanced renal dysfunction, and the half-life of torsemide is doubled in hepatic dysfunction. Torsemide can be administered once daily while furosemide needs to be administered two or three times a day[4].

Continuous versus Bolus Infusion

The bolus therapy of furosemide rapidly increases sodium excretion. However, this excretion is at its maximum for the first 1-2 hours and then it progressively declines[1]. The peak natriuretic effect with the second dose is 25% less than that of the first dose. Post-diuretic renal sodium and fluid retention are inevitable[6]. This compensatory sodium retention occurs along the other segments of the nephron that are not related to furosemide. To avoid this compensation, furosemide should be injected at short intervals or infused continuously.

Continuous intravenous infusion is more effective than, or in some cases, similar to, intravenous bolus therapy[7-9]. It maintains an effective rate of furosemide excretion and inhibition of Na^+ reabsorption over time. A continuous infusion of furosemide tends to increase urine output and is associated with less ototoxicity, a significant side effect associated with furosemide, in patients with acute decompensated heart failure[10]. Continuous infusion of bumetanide results in a 30% increase in sodium excretion compared with bolus infusion[11]. Recently, a randomized double-blind multicenter study was published, which reported on the comparison between bolus and continuous infusions without loading doses in patients with acute decompensated heart failure[12]. There was no difference between the groups. However, meta-analysis showed that the continuous infusion of loop diuretics preceded by a loading dose was more diuretic than intermittent dosing[13].

The maximum diuresis occurs 3 hours after continuous infusion has begun[14]. Therefore, when furosemide is administered by continuous infusion, an intravenous loading dose of furosemide is required to increase the initial intratubular concentration of furosemide[4,7]. The recommended loading dose of furosemide is 40-200 mg according to renal function. The infusion rate is 10-20 mg/hr, which can be increased to hourly 40 mg[1].

Chronic Kidney Disease and Nephrotic Syndrome

Extracellular fluid volume increases by up to 30% in patients with advanced CKD and severe edema. Loop diuretics are the recommended diuretics for patients who have an estimated glomerular filtration rate (eGFR)<30

mL/min/1.73 m^2 because other diuretics, including thiazide, are less effective in advanced CKD[15]. The natriuretic response to furosemide is also reduced in patients with CKD[4]. This is because Na^+ reabsorption in the downstream segment is increased, and the renal delivery of furosemide is reduced according to the decrease in the GFR. Compared with the general population, only about 15-20% of the furosemide dose is delivered into the tubular fluid in stage 5 CKD patients[1]. This diminished tubular secretion is due to the elevated level of endogenous organic anions that interfere with furosemide secretion via organic acid transporters in the proximal tubule[4,16]. Therefore, to achieve the desired effect, higher doses or an increased frequency of furosemide treatment is required to increase tubular secretion.

Patients with nephrotic syndrome also experience decreased furosemide activity. The tubular secretion of furosemide is reduced in patients with hypoalbuminemia, because the delivery of furosemide is dependent on the level of plasma albumin[1-3]. Moreover, Na^+ reabsorption is increased in the proximal and/or more distal segments due to an activated renin-angiotensin system[3,17]. Additionally, furosemide can bind to albumin within the tubular lumen, which reduces the level of active and unbound drug that is capable of binding to the tubular receptor[2]. Consequently, a furosemide dose two to three times greater than the usual dose is required to maintain an effective concentration of free drug at the action site.

In patients with CKD or nephrotic syndrome, higher doses and/or frequency of administration are needed, as described above. If the response of furosemide is inadequate, a combination of diuretics that act at different tubules, such as thiazide or potassium-sparing diuretics, can be considered for the downstream inhibition of Na^+ reabsorption[18]. Angiotensin-converting enzyme inhibitor or angiotensin II receptor blockade reduces renal albumin excretion. Salt and water intake must be limited to prevent post-diuretic sodium retention. In patients with severe hypoalbuminemia, albumin infusion may be considered, although the efficacy of this approach is, to date, undetermined[19].

Excessive weight gain between dialysis sessions induces high blood pressure and edema. Such patients can be considered for furosemide administration if residual renal function remains. Large doses or combination therapy are essential to attain the desired effect in dialysis patients. In one study, furosemide (250-2,000 mg daily) increased urine volume in hemodialysis patients, however, this response gradually declined during the one year follow-up period. Patients with residual renal function who receive diuretic therapy are twice as likely to have sustained residual renal function one year later, compared with patients without diuretics[20]. Additionally, less than 10% of furosemide is removed by hemodialysis or hemofiltration because of its high plasma protein binding affinity. Therefore, it is not necessary to change the dosing strategy in patients undergoing hemodialysis[21].

Adverse Events

There are three major types of adverse events associated with furosemide: hypovolemia and electrolyte imbalance due to diuresis, hypersensitivity, and ototoxicity. Excessive diuresis due to high doses of the drug can induce extracellular fluid volume contraction, resulting in contraction alkalosis. This side effect occurs more commonly in the elderly, CKD patients, and patients taking nonsteroidal anti-inflammatory drugs (NSAIDs)[22-24]. NSAIDs reduce the vasodilation and natriuretic effects of furosemide by inhibiting the synthesis of prostaglandins, resulting in Na^+ retention, azotemia, and hyperkalemia[25].

Furosemide induces various electrolyte imbalances including hypokalemia, hypomagnesemia, hypocalcemia, hyponatremia, and hyperuricemia[3,16]. Hypokalemia is caused by the increased distal delivery of potassium and secondary mineralocorticoid excess[26]. Caution should be taken when prescribing furosemide to patients taking digoxin. Although furosemide does not change the plasma level of digoxin, furosemide-induced hypokalemia increases the risk of digitalis-induced arrhythmias[16].

Furosemide is a sulfonamide, and can therefore induce hypersensitivity reactions such as rash or acute interstitial nephritis. In patients who develop allergic reactions, furo-

semide can be replaced with ethacrynic acid, which is a loop diuretic but not a sulfonamide[3,16]. However, ethacrynic acid has been shown to be more ototoxic[16].

Furosemide can lead to reversible ototoxicity, although permanent deafness had also been reported. Ototoxicity is related to both the peak serum drug concentration and the rate of infusion. However, lower doses can also cause ototoxicity in patients with renal dysfunction or those undergoing concurrent aminoglycoside therapy[27]. Therefore, one must be cautious when considering a bolus infusion of a high furosemide dose. It is recommended that the maximum rate of furosemide infusion should be 4 mg/min to avoid this complication[27]. To avoid an abrupt increase in peak serum concentration, doses higher than 80 mg of furosemide need to be infused slowly.

Finally, furosemide can displace warfarin from its binding sites on blood proteins. Therefore, a lower dose of warfarin may be needed when warfarin is administered with furosemide. Furosemide increases the risk of gout when co-administered with cyclosporine, which reduces renal urate excretion[26].

Conclusion

Loop diuretics, especially furosemide, are widely used in various conditions. The bioavailability of furosemide differs between oral and intravenous therapy. The threshold and ceiling doses of furosemide differ according to the clinical condition. Furosemide also has several side effects, especially in CKD patients. To maximize the efficiency of furosemide, a solid understanding of its bioavailability and dose adjustment kinetics associated with each route of administration is necessary.

References

1. Brater DC: Diuretic therapy. N Engl J Med 339:387-395, 1998
2. Shankar SS, Brater DC: Loop diuretics: from the Na-K-2Cl transporter to clinical use. Am J Physiol Renal Physiol 284:F11-21, 2003
3. Sica DA: Diuretic use in renal disease. Nat Rev Nephrol 8:100-109, 2012
4. Brater DC: Update in diuretic therapy: clinical pharmacology. Semin Nephrol 31:483-494, 2001
5. Wilcox CS: New insights into diuretic use in patients with chronic renal disease. J Am Soc Nephrol 13:798-805, 2002
6. Wilcox CS, Mitch WE, Kelly RA, Skorecki K, Meyer TW, Friedman PA, et al.: Response of the kidney to furosemide. I. Effects of salt intake and renal compensation. J Lab Clin Med 102:450-458, 1983
7. Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P: Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol 28:376-382, 1996
8. van Meyel JJ, Smits P, Dormans T, Gerlag PG, Russel FG, Gribnau FW: Continuous infusion of furosemide in the treatment of patients with congestive heart failure and diuretic resistance. J Intern Med 235:329-334, 1994
9. Thomson MR, Nappi JM, Dunn SP, Hollis IB, Rodgers JE, Van Bakel AB: Continuous versus intermittent infusion of furosemide in acute decompensated heart failure. J Card Fail 16:188-193, 2010
10. Salvador DR, Rey NR, Ramos GC, Punzalan FE: Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Cochrane Database Syst Rev; doi:10.1002/14651858.CD003178.pub3.Cd003178, 2005
11. Rudy DW, Voelker JR, Greene PK, Esparza FA, Brater DC: Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. Ann Intern Med 115:360-366, 1991
12. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al.: Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 364:797-805, 2011
13. Alqahtani F, Koulouridis I, Susantitaphong P, Dahal K, Jaber BL: A meta-analysis of continuous vs intermittent infusion of loop diuretics in hospitalized patients. J Crit Care 29:10-17, 2014
14. Copeland JG, Campbell DW, Plachetka JR, Salomon NW, Larson DF: Diuresis with continuous infusion of furosemide after cardiac surgery. Am J Surg 146:796-799, 1983
15. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3:1-150, 2013
16. Tamargo J, Segura J, Ruilope LM: Diuretics in the treat-

ment of hypertension. Part 2: loop diuretics and potassium-sparing agents. Expert Opin Pharmacother 15:605-621, 2014
17. Kirchner KA, Voelker JR, Brater DC: Tubular resistance to furosemide contributes to the attenuated diuretic response in nephrotic rats. J Am Soc Nephrol 2:1201-1207, 1992
18. Wollam GL, Tarazi RC, Bravo EL, Dustan HP: Diuretic potency of combined hydrochlorothiazide and furosemide therapy in patients with azotemia. Am J Med 72: 929-938, 1982
19. Chalasani N, Gorski JC, Horlander JC Sr, Craven R, Hoen H, Maya J, et al.: Effects of albumin/furosemide mixtures on responses to furosemide in hypoalbuminemic patients. J Am Soc Nephrol 12:1010-1016, 2001
20. van Olden RW, van Meyel JJ, Gerlag PG: Acute and long-term effects of therapy with high-dose furosemide in chronic hemodialysis patients. Am J Nephrol 12:351-356, 1992
21. Sica DA, Gehr TW: Diuretic use in stage five chronic kidney disease and end-stage renal disease. Curr Opin Nephrol Hypertens 12:483-490, 2003
22. Smith WE, Steele TH: Avoiding diuretic related complications in older patients. Geriatrics 38:117-119, 1983.
23. Kaufman AM, Levitt MF: The effect of diuretics on systemic and renal hemodynamics in patients with renal insufficiency. Am J Kidney Dis 5:A71-78, 1985
24. Heerdink ER, Leufkens HG, Herrings RMC, Ottervan ger JP, Stricker BHC, Bakker A: NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. Arch Intern Med 158:1108-1112, 1998
25. Dormans TP, Pickkers P, Russel FG, Smits P: Vascular effects of loop diuretics. Cardiovasc Res 32:988-997, 1996
26. Wilcox CS, Mitch WE, Kelly RA, Freidman PA, Souney PF, et al.: Factors affecting potassium balance during frusemide administration. Clin Sci 67:195-203, 1984
27. Rybak, LP: Ototoxicity of loop diuretics. Otolaryngol Clin North Am 26:829-844, 1993