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Review Article

Continuous Intravenous Infusion of Bumetanide to Achieve Diuresis in Patients with Congestive Heart Failure and Chronic Kidney Disease: A Rapid Review

Deepak Goyal[1,2]*, Michael Talalaev[2], Prerana Upadhyaya[3], George Yatzkan[2], Javier Perez-Fernandez[2] and Marcos Sanchez-Gonzalez[1,2]

[1]*College of Biomedical Science, Larkin University, Miami, Florida, USA*

[2]*Larkin Community Hospital, Miami, Florida, USA*

[3]*International American University, Vieux Fort, Saint Lucia*

Abstract

Bumetanide falls in the class of loop diuretics like furosemide. The effects of both have been extensively researched and are well documented. In medical practice furosemide is more widely used in patients both orally and through intravenous administration. Limited information is available regarding the use of bumetanide through continuous intravenous infusion therapy in patients suffering from congestive heart failure and chronic kidney disease with an endpoint of maximal or average diuresis. A summary of what is available and key findings are presented here for rapid review. We do not make any recommendations apart from further research that needs to be conducted using bumetanide continuous infusion therapy to achieve diuresis in patients suffering from congestive heart failure and chronic kidney disease. Even more specifically, one that could estimate the amount of diuresis that can be achieved with a given rate of infusion within a set of parameters to match patient population.

Keywords: Bumetanide; Chronic kidney disease; Congestive heart failure; Diuresis; Furosemide; Intravenous infusion

Abbreviations

CHF: Congestive Heart Failure
CKD: Chronic Kidney Disease
IV: Intravenous
IM: Intramuscular
cFI: Continuous Furosemide Infusion
cBI: Continuous Bumetanide Infusion
BUN/Cr: Blood Urea Nitrogen/Creatinine
eGFR: Estimated Glomerular Filtration Rate
BNP: Brain Natriuretic Peptide

***Corresponding author:** Deepak Goyal, M.D, College of Biomedical Science, Larkin University, Miami, Florida, USA, E-mail: dgoyal@myularkin.org

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Introduction

Bumetanide is a medication used in the treatment of patients for Edema (Pulmonary, peripheral, or generalized) as it is a potent loop diuretic [1]. The potency of 1mg bumetanide is close to the equivalent of 40mg of Furosemide or 20mg Torsemide respectively [1-4]. The profound diuretic effects of the medication are well known. Many of the studies conducted show its use either as a bolus or continuous intravenous infusion but with some conflicts [5]. The authors wish to show the superior efficacy of bumetanide as a continuous infusion in patients with Congestive Heart Failure (CHF) and Chronic Kidney Disease (CKD). Current practices indicate the use of furosemide to achieve diuresis however we think bumetanide will achieve a greater response in these patients warranting further investigation into its potential use over other medications. The article will summarize key findings from various studies and present them here for analysis as a rapid review.

Understanding the Mechanism of Action of Bumetanide

Bumetanide is part of the same drug family as other loop diuretics such as furosemide, torsemide and ethacrynic acid [3]. This entire class has an effect in thick ascending limb of the loop of Henle in the medullary segment [2-4]. More specifically they compete for the sodium-potassium-chloride cotransporter located along the membrane [2,3]. Ultimately leading to an excretion of water and solutes such as magnesium phosphate, calcium, and sodium chloride [3]. These solutes being excreted in certain patient populations can become extremely concerning as they play an important role in numerous different physiologic mechanisms that are not discussed here.

Holazo A et al. [6], evaluated the pharmacokinetics of bumetanide by administering 1mg of the drug in different forms to 12 different subjects in a random crossover design study. They recorded the mean maximum plasma concentration, time to reach maximum plasma concentration, half-life and the amount of drug excreted in the urine. From their findings, pharmacokinetics based on the routes of administration were described as having first-order absorption and elimination for the oral and IM routes of administration. For the IV route, the authors concluded the two phases were: An initial rapid disposition with half-life of 5.1 minutes and a slower elimination phase with half-life of 44 minutes. Bioavailability, as expected, was higher in the IM/IV routes versus the oral route. Their summary findings are presented in table 1.

Felker G et al. [7], has summarized pharmacokinetic properties of bumetanide while comparing it to furosemide and torsemide.

Properties such as bioavailability, half-life, metabolism, onset time, and average cost are all found within table 2.

Bumetanide vs. Furosemide in Congestive Heart Failure

In a study done by Tein Ng et al. [8], dealing with Acute Heart Failure, they found that between continuous furosemide infusion at the median dose of 7mg/hr (cFI) and continuous bumetanide infusion at the median dose of 1mg/hr (cBI), there was a significant increase in the mean hourly urine output for both the regimens when compared to baseline.

However, there was an even larger amount of urine produced when looking at cFI vs. cBI. They did conclude that greater urine output may have occurred with cBI however at the cost of greater electrolyte disturbances. They did not specifically mention the degree of the disturbance, but this author would recommend the provider be cognizant of these changes.

Wargo and Banta [5], conducted a comprehensive review of loop diuretics specifically asking the question if furosemide should be first line. They did look at torsemide, furosemide, and bumetanide and how they compared. In summation of their findings, symptoms of dyspnea were significantly more improved with bumetanide over furosemide. Furthermore, they found two trials that did compare the agents however, there were conflicting results. One of the trials analyzed showed that bumetanide was more effective but a direct comparison to furosemide could not be made due to a small sample size. The second trial also had a small sample size, and the comparison groups were not similar. Finally, the authors concluded that the oral bioavailability of bumetanide is considerably higher, and the time of onset is similar regardless of the route of administration (oral versus intravenous).

Adverse Reactions of Bumetanide

Many adverse events are due to the direct effect of solutes lost in the urine and concentration of several electrolytes within the blood. All these changes are related to pharmacologic action of the medication [1,3]. These disturbances can lead to the patient having symptoms of weakness, lethargy, confusion, muscle cramps, headache, and nausea [1,4]. Like other diuretics, we recommend the provider be cautious when choosing this powerful drug and closely monitor electrolytes by ordering a complete metabolic panel and monitor urine output. When treating these symptoms, simply replace the electrolytes and fluids [1,3].

Route	Mean ± SD Maximum Plasma Concentration (ng/mL)	Amount of Time after Dosing to Reach Mean Max Plasma Concentration	Half Life Range (minutes)	Amount of Intact Drug Excreted in Urine between 0 and 24 hours
IV	*	*	24-86 (62) min	70%
IM	38.2 ± 9.8	0.34 ± 0.23 hr	47-139 (92) min	
Oral solution	34.0 ±10.6	0.76 ± 0.27 hr	27-71 (44) min	60%
Oral tablet	0.9 ±14.6	1.8 ±1.2 hr	26-99 (73) min	

Table 1: Bumetanide bioavailability summary.

Property	Furosemide	Bumetanide	Torsemide
Relative IV potency, mg	40	1	20
Bioavailability, %	10-100 (average, 50)	80-100	80-100
Oral to intravenous conversion	2:1	1:1	1:1
Initial outpatient total daily oral dose, mg	20-40	0.5-1	5-10
Maintenance outpatient total daily oral dose, mg	40-240	1-5	10-200
Maximum daily intravenous dose, mg	400-600	10	200
Onset, min			
Oral	30-60	30-60	30-60
Intravenous	5	2-3	10
Peak serum concentration after oral administration, h	1	1-2	1
Affected by food	Yes	Yes	No
Metabolism	50% renal conjugation	50% hepatic	80% hepatic
Half-life, h			
Normal	1.5-2	1	3-4
Renal dysfunction	2.8	1.6	4–5
Hepatic dysfunction	2.5	2.3	8
Heart failure	2.7	1.3	6
Average duration of effect, h	6-8	4-6	6-8
Approximate cost for oral 30-day supply (community pharmacy), $	4	4	19-23

Table 2: Pharmacokinetic properties of loop diuretics.

Role of Bumetanide with severe Congestive Heart Failure and Chronic Kidney Disease

In clinical medicine, bumetanide, like furosemide and torsemide, is used to treat fluid overload in conditions such as congestive heart failure, cirrhosis with ascites, and other highly edematous states to provide symptomatic relief [1,9-14]. Parameters like shortness of breath, generalized swelling are usually described together with an improvement of renal function and the overall hemodynamic status of the patient [9,10,12]. It can be administered orally in an outpatient setting, or IV bolus or continuous intravenous infusion over a set time frame [3,4,9].

Mandal AK [9], illustrated a female patient with severe CHF and stage 5 CKD where an infusion of bumetanide was started. Strict input and output were measured, along with several other parameters such as symptoms, BUN/Cr, eGFR and the serum Potassium. Prior to infusion, this patient had a BUN/Cr of 50/3.28 and eGFR of 14. The infusion was given over a period of 5 days at an undefined rate but believed to be titrated up to approximately 1mg/hr. In that duration the patient's urine output increased between 100ml-200ml/hr which improved her BUN/Cr to 23/1.25, eGFR to 44, and improved her CHF symptoms to the point where she was no longer having shortness of breath. This patient had a BNP of 1514 prior to infusion and at the end it decreased substantially to 352. The author did mention that while her renal function was poor to start, her urine output did not increase as much as expected given her eGFR improvement. With this information on a single patient, a causal relationship could not be fully established as this requires further review as to why the urine output did not increase as expected when compared to an improving eGFR.

Conclusion

Very few studies exist that can credibly show the effect of bumetanide in patients with CHF and CKD during a continuous intravenous infusion. It may partially be because finding similar baselines proves to be too difficult in this delicate patient population. For example, while some of them have stage 3 CKD they may all have different degrees of heart failure. It may also be associated with a cost factor of the medication as furosemide is much more readily available than bumetanide. After a comprehensive literature review, this author would suggest further studies be done into bumetanide. Especially one that could explore the average expected urine output in mL/hr directly correlated to the mg/hr infusion of bumetanide.

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