Vol 13| Issue 1| 2023 | 17-22.

e-ISSN 2248 – 9142
print-ISSN 2248 – 9134

International Journal of
Current Pharmaceutical & Clinical Research

www.ijcpcr.com

BUMETANIDE EFFICACY COMPARED TO INTRAVENOUS FUROSEMIDE (I.V): A RETROSPECTIVE STUDY

Siri *, M Lohith, Reena Abraham, G Sai Sowmya, A Sai Manasa

KLR Pharmacy College, Paloncha, Bhadradri Kothgudadm, Telangana- 507115, India.

ABSTRACT

Objective: Patients receiving 48 hours of treatment and a subgroup of patients with heart failure will be studied to determine what effect bumetanide has on urine output (UOP). (HF) after 48 hours of therapy. A comparison of bumetanide and furosemide potency was conducted using this subgroup. During therapy, electrolyte replacement was a secondary safety objective. Methods: Study design: Among patients receiving bumetanide intermittently versus continuously, the dose-response relationship was compared by measuring UOP per mg of drug received (mL/mg). An I.V. concomitant study of bumetanide and furosemide was performed in a subset of patients with congestive heart failure on the basis of pre-existing data. The safety of intravenous bumetanide was evaluated by quantifying electrolyte replacement during the study period. Results: Intermittent (I.V) groups (n=46) achieved higher primary outcomes than continual (I.V) groups (n=8) (P=0.001). For the intermittent I.V group and 24:1 for the continuous I.V group of patients with HF who received furosemide (intermittent IV n=15, continuous IV n=13), we found a potency ratio of 31:1 and 24:1 for those who received bumetanide (intermittent IV n=7, continuous IV n=2). Neither group replaced electrolytes significantly differently Conclusion: When intermittent bumetanide was administered instead of continuous infusion, there was a greater response. It is supported by this study that furosemide and bumetanide have equivalent dose equivalence ratios when administered intravenously intermittently to patients with HF.

Key words: Heart Failure, Bumetanide, Furosemide

INTRODUCTION

In order to manage patients with volume overload, intravenous loop diuretics make an important contribution to the treatment of symptoms and the optimization of hemodynamic status. In addition to their role in heart failure and chronic cirrhosis with ascites management, diuretics are also recommended in the management of renal insufficiency and pulmonary hypertension [1-6]. Historically, furosemide has been the first of its kind and the most commonly used loop diuretic [7,8]. Furosemide 40 mg to bumetanide 1 mg and torsemide 20 mg combined with bumetanide or torsemide has been reported to have equal effects on loop diuretics. [9-11].

The use of diuretics to treat a variety of diseases has consistently demonstrated the deleterious consequences resulting from these agents and no precise dosing strategy has yet been identified [6,12,13].

In addition to ototoxicity, activation of neurohormones, volume depletion and electrolyte imbalance, these agents are known to cause adverse effects. Patients with heart failure who receive high diuretic doses also have a greater hospital stay and higher mortality rates [9,10,12,14]. Hypertension, decreased renal perfusion and decreased cardiac output can be symptoms of over diuresis. During intermittent and continuous loop diuretics, serum creatinine increases by an average of 0.23 mg/dL and 0.14 mg/dL, respectively, as a result of decreased renal blood flow. [9]. All loop diuretics have been linked to ototoxicity, although bumetanide may be less likely than furosemide to cause it [10,14].

Corresponding Author: - SIRI Email: sirisiri7884@gmail.com

Arrhythmias may occur when diuretics induce electrolyte abnormalities. Although bumetanide has a slightly lower kaliuretic effect than furosemide, both drugs may work in much the same way [10, 15]. This difference may result in less arrhythmogenicity, but its clinical significance remains unclear. According to an analysis of the National Registry for Acute Decompensated Heart Failure, patients who received higher doses of IV loop diuretics during the first 24 hours of hospital admission were more likely to spend more than three days in the intensive care unit, more than four days in the hospital, and more likely to die in hospital. [17, 18]. Additionally, several studies have shown that chronic diuretic dose and mortality are positively correlated. However, inconsistencies have been reported in the conversion of loop diuretics to furosemide equivalent amounts [13]. However, it is an important consideration despite not knowing how this may affect outcomes there are slight differences between bumetanide and furosemide in their pharmacokinetic profiles, which may affect the drug's response or toxicity [10]. They both act on sodium-potassium-chloride channels within the ascending loop of Henle via active transport via active transport into the renal tubules [9]. The oral bioavailability of bumetanide is greater and more consistent than that of furosemide, which is relevant in diseases such as heart failure, in which oral absorption is often compromised. Cirrhosis, chronic kidney disease, heart failure, and ascites with ascites are all conditions characterized by a greater volume of distribution and increased extracellular fluid which may require shorter dosing interval or higher doses to achieve adequate drug concentration at the site of action. The concentration of the drug in the body increases with increased dose, whereas sodium retention can be prevented by decreasing the dosing interval because the intravascular volume decreases during the end of the dosing interval. These strategies and more aggressive doses don't guarantee a maximal diuretic effect in all edematous disease states.

Diuretics must be dose-selected carefully in light of their dose-related adverse effects in order to achieve maximum therapeutic benefit. A national shortage forced the Medical University of South Carolina to substitute an IV bumetanide for an I.V furosemide as the formulary loop diuretic. As IV bumetanide is increasingly being used, we conducted a quantitative study to evaluate the dose response of IV bumetanide when dosed continuously or intermittently, compare IV bumetanide dose response to IV furosemide in HF patients, and describe any adverse effects encountered with the drug.

Our study determined if intermittent or continuous infusions of bumetanide at our institution affected dose-response effects. Thomson and colleagues [26] previously collected data at our institution on IV bumetanide and IV furosemide potency in a subset of HF patients [27]. Moreover, this study aimed to determine whether IV bumetanide would affect electrolytes in a safe manner.

METHODS

Study Design

Observational research was conducted on patients who had received intravenous bumetanide for a minimum of 48 hours. A 20:2 ratio was implemented for orders of IV furosemide to be automatically converted to IV bumetanide at this time. This substitution was available to all hospital patients. Those under 18 years of age, those who received bumetanide for less than 48 hours, or those without urine output records were excluded from the study. Institutional review board approval was obtained for this study.

Data Collection

Patients were interviewed about their demographics, length of stay in hospital, past medical history, admission diagnosis, as well as the medications they took at home and in the hospital. It was collected daily how much bumetanide was given, whether it was intermittent or continuous infusions, how much fluid was consumed and how much urine was pumped, how much sodium, blood urea nitrogen, serum creatinine, and albumin was taken or refilled. At admission and discharge, weights and B-type natriuretic peptides were collected.

The primary endpoint of this study was determined by calculating the average daily urine output for all bumetanide doses received (mL/mg). A calculation was made for each patient by summarizing their urine output and then dividing the total amount of drug received by their urine output. By dividing this value (mL/mg) by the duration of therapy (days), we can determine the average daily urine output per mg of drug received for each patient. As a primary outcome, we looked at the mean (standard deviation; SD) of this number.

By selecting only patients with systolic HF and comparing their urine output with the preexisting data describing this outcome with IV furosemide, a more homogeneous patient population was selected to compare IV bumetanide to IV furosemide's potency. [26]. In addition to measuring safety in this study, electrolyte replacement administered while on therapy was quantified as a secondary objective.

Statistical Analysis

In addition to categorical data, continuous variables, including primary outcome and secondary outcome measuring the safety of intermittent I.V. bumetanide over continuous I.V. bumetanide, were reported as means (SDs). The Mann-Whitney-U test was used to test for significant differences. Based on the previously described measurement for bumetanide (mL/mg/day), potency ratios were calculated.

Data analysis feasibility and number of patients were taken into account in order to determine the size of the sample. The power of 80% was calculated using post-hoc power calculations. We detected independent variables

that were associated with the primary outcome by employing Spearman rank correlation with pair wise exclusion. The significance of this study was assessed using a p-value of 0.05. Data analysis was performed using SPSS 12.0 version.

RESULTS

The drugs were administered intravenously to 115 patients for a period of at least 48 hours. After exclusion of patients with no urine output recordings or doses held resulting in less than 48 hours of bumetanide therapy, 54 patients were included in the analysis of bumetanide efficacy, after excluding those with no urine output records or doses held. The patients were dosed intermittently, and eight of them were dosed continuously (14.81%). The potency of bumetanide and furosemide was compared in 16 patients (29.62%) with systolic HF.

In Table 1, we find that baseline characteristics are similar among groups. Males constituted 52.3% of the patient population. It averaged 58.2 years of age (SD=15.3). More than one third of the intermittent patients had a serum creatinine level greater than 1.5 mg/dL at baseline when compared with the continuous patients. As a result of intermittent intravenous administration, serum sodium concentrations were significantly higher. Several baseline characteristics of the patients in this study resemble those in Thomson et al's study (age, race, serum creatinine). A major difference existed, however, between the populations. In the present study, patients who were diagnosed with heart failure outside of an acute exacerbation of the disease were included in the study.

According to Table 2, the continuous I.V group had significantly higher mean daily bumetanide doses and mean daily urine output; however, the intermittent group had significantly better primary outcomes. A weight-based primary outcome was also used to analyze the data, but the results were not influenced by this method. Both continuous I.V. and intermittent I.V. groups included patients with heart failure, renal insufficiency, or both.
Bumetanide responded poorly in the HF+RI group. The average total daily dose and response to bumetanide (mL/mg) were statistically significant in a correlation analysis. I.V bumetanide and I.V furosemide were compared in HF patients based on previously published data and they showed similar dose-response effects [26].

Intermittent intravenous bumetanide and continuous intravenous bumetanide caused electrolyte disturbances measured as an average potassium and magnesium electrolyte replacement per patient per day during the research study. In terms of electrolyte replacement, none of the dosing strategies showed a significant difference. In both intermittent and continuous dosing groups, potassium replacement averaged 25.1 mEq daily compared to 14.4 mEq daily. Among 54 patients, potassium replacement averaged 11 (SD=30) mEq a day and magnesium replacement averaged 0.123 mg a day (SD=0.557).

Table 1: Patients who received intravenous bumetanide were provided with baseline demographic information and laboratory values.

Baseline demographics and laboratory values mean (sd)	Intermittent infusion (n=46)	Continuous infusion (n=8)	P- value
Age	48.8	45.1	0.419
Male in per cent	49.7	50.3	0.684
Serum creatinine [mg/dL]	1.15	1.04	0.39
Blood urea nitrogen [mg/dL]	31.74	28.78	0.478
Sodium [m Eq/L]	134	130	0.015
Albumin [g/dL]	1.97	1.87	0.104
Weight on admission [kg]	89.7	87.45	0.798
Admisssion diagnosis (N)			
Acute coronary syndrome	2	1	
Heart failure	16	0	
Subarachnoid /StrokeHemorrhage	3	3	
Cardia-othoracic surgery	2	3	
Infectious disease	4	1	
Respiratory disorder/Pulmonary hypertension	4	0	
Gastrointestinal disease	5	2	
Other	8	0	

Table 2: The primary outcome shown below shows the number of mg of bumetanide metabolized daily per patient by urine output.

	Intermittent infusion (n=46)	Continuous infusion (n=8)	P-value

Mean (SD) total daily dose [mg]	3.14	7.45	*< 0.001
Mean (SD) daily urine output [mL]	1287	1995	*< 0.001
Daily urine output per bumetanide dose (SD) [mL/mg]	636	374	*0.002

Table 3: Study comparing bumetanide and furosemide potency in patients with heart failure when both were administered intermittently and continuously

	Continuous IV infusion	Intermittent IV infusion	All patients with heart failure
Bumetanide UOP per mg drug [mL/mg] mean (SD)	537	448	505
Furosemide UOP per mg drug [mL/mg] mean (SD)	19	11	15
Furosemide: Bumetanide equivalence ratio	27:1	41:1	35:2

DISCUSSION

Using our retrospective analysis, we quantified the dose-response relationship between IV bumetanide and intermittent dosing and determined that intermittent dosing had the greater dose-response relationship. Although there was variability in response between patients with HF, RI, or otherwise healthy individuals, significant differences were not observed. Due to pharmacokinetic and pharmacodynamic changes in HF+RI patients and the difficulty of maintaining adequate diuresis, there may be a low response in the group. Finally, this study confirms the 20:2 dose equivalency between furosemide and bumetanide administered intermittently. Continuously infused patients had a lower 20:2 ratio.

Recent literature emphasizes the need to evaluate clinical outcomes using a diuretic equivalence ratio other than the well-established 20:2. An example of this is the study Eshagian et al. conducted on independent predictors of mortality in severe heart failure patients [12]. Using the equivalent of furosemide as a measure of chronic diuretic dose, mortality was independently predicted. Furosemide 80 mg and bumetanide 3 mg were considered equivalent in this study. The average daily dose of chronic bumetanide patients may have been underestimated if the bioavailability of oral furosemide is approximately 25%. The Diuretic Optimization Strategies Evaluation (DOSE) trial evaluated four different dosing strategies for acutely decompensated heart failure patients. [13] With a dose conversion method, 4 mg of furosemide were converted to 20 mg of torsemide and 1 mg of bumetanide. It is assumed that oral bioavailability of furosemide is 25%, which would yield a ratio of 40:10:1 for flurosemide: torsemide: bumetanide. [11, 22] A lower dose of IV furosemide may have been administered to patients admitted to the DOSE trial based on their home dose of torsemide or bumetanide. It is debatable whether furosemide is suitable for oral administration due to its low bioavailability

Our study has several limitations. Due to the retrospective nature of the study, acuity of illness, baseline characteristics and concurrent medicines could not be accounted for. It is important to interpret the subgroup analysis that excludes patients who received thiazide diuretics with caution given the number of patients who were excluded from the continuous intravenous group. 12% of patients receiving IV bumetanide also received thiazide diuretics.A thiazide diuretic was the only diuretic that was not well tolerated by these patients. Compared with IV furosemide, bumetanide's potency in patients with heart failure was quantified by measuring its dose-response effect. We will need to determine the true dose-response effect of continuous infusion bumetanide once the 20:2 equipotent furosemide:bumetanide ratio has been established. In addition to prospective studies, further confirmation is needed. It is important to take into consideration the ratio when analyzing data using alternative ratios. In transitioning from intravenous furosemide to intravenous bumetanide, clinicians should maintain the 20:2 dose equivalence ratio. When furosemide fails to treat edematous patients, bumetanide may be of benefit [22].

There may have been a need to administer higher doses of bumetanide to HF and RI patients to achieve similar urine output, which could explain the lower UOP per mg given in the continuous I.V. bumetanide group. Moreover, the continuous I.V group had a lower baseline serum sodium level, which may suggest a deeper volume overload, which is accompanied by a greater need for diuresis, but not a greater need for diuretics. Since there are fewer patients in the continuous I.V. bumetanide group and/or a greater proportion of diuretic resistant patients, we can only hypothesize that the difference is caused by the presence of diuretic resistant patients.

Based on this assumption, we assumed that urine output was accurately recorded in the patient's medical record. By comparing normal electrolyte levels with electrolyte replacement, we evaluated the potential for arrhythmias. Since the study was retrospective, additional potentially adverse effects of loop diuretics, including increases in myalgias, serum creatinine, hypotension, hyponatremia, and ototoxicity, could not be assessed adequately. Furthermore, the original patient population was excluded from this study. A number of factors contributed to this, including difficulties gathering

retrospective data and inadequate technology for identifying potential patients.

In retrospect, urine output monitoring was not regulated and poor records prevented many patients from being included. Due to a number of factors, such as the absence of a specific physician order, the patient's location outside of an intensive care unit, or the absence of a foley catheter, urine output for these patients may have been recorded as an "occurrence" only. Patients on bumetanide therapy for at least 48 hours were generated using an electronic pharmacy system based on the number of doses prescribed. We observed that the actual number of doses administered was sometimes less than the number dispensed, resulting in a shorter therapy period than 48 hours. Despite the large standard deviations of our results, the limitations of this study are evident. Patients receiving therapy for less than 48 hours might not be able to use these data.

According to Thomson and colleagues [26], it is also difficult to compare new data with previously collected data. Data collection and baseline control may have been improved due to the. Compared to furosemide, bumetanide's potency cannot be accurately analyzed due to different study designs and timeframes.

CONCLUSIONS

By comparing IV bumetanide potency with IV furosemide potency in patients with heart failure, we quantified the dose-response effect of IV bumetanide. The dose-response relationship between continuous infusion bumetanide and furosemide must be established once the 30:2 optimal ratio furosemide:bumetanide has been established. This needs to be confirmed in further prospective studies. The ratio should be taken into account whenever alternative ratios are used in literature for data analysis. It is important for clinicians to continue using the 20:2 intravenous dose equivalence ratio when transitioning from intravenous furosemide to intravenous bumetanide. The efficacy of bumetanide may be beneficial to edematous patients resistant to furosemide.

REFERENCES

1. Ginés P, Cárdenas A, Arroyo V, Rodés J, *et al*. Management of cirrhosis and ascites. *New Engl J Med*. 350(16), 2004, 1646- 54.
2. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. American Association for the Study of Liver Disease Practice Guidelines. *Hepatology*. 49(6), 2009, 2087-107.
3. Kidney Disease Outcomes Quality Initiative (K/DOQI). Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. *Am J Kidney Dis.* 43(5 Suppl 1), 2004, S1-290.
4. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J, *et al*. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 53(17), 2009, 1573- 619.
5. Puschett JB. Pharmacological classification and renal actions of diuretics. Cardiology. 84(Suppl 2), 1994, 4-13.
6. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW, *et al*. Focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in Collaboration with the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 53(15), 2009, 1343-1382.
7. Konecke LL. Clinical trial of bumetanide versus furosemide in patients with congestive heart failure. *J Clin Pharmacol*. 21(11-12 Pt 2), 1981, 688-90.
8. Dixon DW, Barwolf-Gohlke C, Gunnar RM, *et al*. Comparative efficacy and safety of bumetanide and furosemide in long-term treatment of edema due to congestive heart failure. *J Clin Pharmacol*. 21(11-12 Pt 2), 1981, 680-7.
9. Cleland JGF, Coletta A, Witte K, *et al*. Practical applications of intravenous diuretic therapy in decompensated heart failure. *Am J Med*. 119(12 Suppl 1), 2006, S26-36.
10. Ward A, Heel RC. Bumetanide: A review of its pharmacodynamic properties and therapeutic use. *Drugs*. 28(5), 1984, 426-64.
11. Product information. Bumex (Bumetanide). Bedford, OH: Bedford Laboratories; February 2010.
12. Eshaghian S, Horwich TB, Fonarow GC, *et al*. Relation of loop diuretic dose to mortality in advanced heart failure. *Am J Cardiol*. 97(12), 2006, 1759-64.
13. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswai A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velaquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, *et al.* O'Connor CM for the NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med.* 364(9), 2011, 797-805.
14. Whelton A. Long-term bumetanide treatment of renal edema. Comparison with furosemide. *J Clin Pharmacol*. 21(11-12 Pt 2), 1981, 591-8.

15. Hutcheon DE, Vincent ME, Sandhu RS. Renal electrolyte excretion pattern in response to bumetanide in healthy volunteers. *J Clin Pharmacol*. 21(11-12 Pt 2), 1981, 604-9.