

Retrospective Evaluation of Dosing Effects of Bumetanide Continuous Infusions in the Pediatric Cardiac Intensive Care Unit

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OBJECTIVE Bumetanide is commonly used to achieve diuresis and alleviate fluid overload in pediatric cardiac intensive care unit (PCICU) patients. This study aims to describe the dosing, efficacy, and safety of bumetanide continuous infusion (CI) regimens used in PCICU patients.

METHODS This single center, retrospective study included patients <6 years of age, admitted to the PCICU who received a bumetanide CI for at least 6 hours. The primary outcome was identifying doses and the total duration of bumetanide CI regimens. Secondary efficacy outcomes were determined by the ability to achieve negative fluid balance within 24 hours and the time to reach negative fluid balance. Secondary safety outcomes were based on the prevalence of electrolyte imbalances and renal impairment.

RESULTS Data from 90 pediatric patients represented 106 hospital encounters in this study. The median age of our study population was 137 days, with a median weight of 4.3 kg. The dose ranged from 0.005 mg/kg/hr to 0.3 mg/kg/hr, with a median dose of bumetanide of 0.046 mg/kg/hr and a median duration of 5.8 days. The change in serum electrolytes and creatinine during baseline and peak infusion rates was not clinically significant.

CONCLUSION This study remains the largest pediatric study to date describing the dosing, efficacy, and safety concerns of bumetanide CI in the PCICU population. However, using a high-dose bumetanide drip >0.1 mg/kg/hr may not improve the overall outcome, and future studies can explore specific advantages of its use in neonates undergoing cardiac surgery.

ABBREVIATIONS AVSD, atrioventricular septal defect; CI, continuous infusion; CRRT, continuous renal replacement therapy; CV, cardiovascular; ECMO, extracorporeal membrane oxygenation; HLHS, hypoplastic left heart syndrome; IV, intravenous; PCICU, pediatric cardiac intensive care unit; PD, peritoneal dialysis; SCr, serum creatinine; VA, venoarterial; VAD, ventricular assist device

KEYWORDS bumetanide; cardiac intensive care unit; continuous infusion; critically ill; pediatrics

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Introduction

The pediatric cardiac intensive care unit (PCICU) plays a critical role in managing pediatric patients with complex congenital heart defects and those undergoing cardiac surgery. One challenge often encountered in these patients is fluid overload, which can lead to compromised cardiac function, respiratory distress, and other adverse clinical outcomes.¹ Effective fluid management strategies are essential to achieving optimal hemodynamic stability and improving patient outcomes in the PCICU setting.¹

Loop diuretics, such as bumetanide, are commonly used to achieve diuresis and alleviate fluid overload in these patients owing to their rapid onset of action

and potent diuretic effects. These agents are indicated in various clinical conditions, including generalized edema, heart failure, and oliguria.² Owing to inadequate response to furosemide or furosemide plus a thiazide diuretic and limited intravenous (IV) drug compatibility seen with furosemide, bumetanide continuous infusions (CIs) have been increasingly used at our institution, particularly within our PCICU. While bumetanide is often administered intermittently, CI administration has gained increasing attention as a potential strategy to provide more constant and predictable drug exposure, potentially leading to more controlled diuresis and fewer fluctuations in fluid balance.³ Currently, bumetanide is not approved by the US Food and Drug Administration

for administration in pediatric patients, even though it has been used consistently for more than a decade. Compared with furosemide, bumetanide has greater bioavailability and potency, with a conversion rate of 20:1 for IV furosemide to IV bumetanide and 40:1 when converting oral furosemide to IV bumetanide.⁴ Based on the established furosemide CI doses of 0.05 to 0.4 mg/kg/hr and having this conversion in mind, bumetanide CI dosing regimens generally range from 0.00125 to 0.01 mg/kg/hr.⁴ We started at a slightly higher dose given resistance of loop diuretics over time, inadequate response to increasing furosemide doses, and propensity for renal insufficiency in patients with significant cardiac disease.

Bulkley and colleagues⁵ were the first to evaluate bumetanide CIs in critically ill neonates and children and reported mean doses of 0.05 mg/kg/hr. McCallister and colleagues⁶ also reviewed the use of bumetanide CI in critically ill pediatric patients, where 58% of patients were admitted to the PCICU, and mean doses up to 0.01 mg/kg/hr were used. These studies reported significant variations in mean doses of bumetanide CI. Owing to the limited data available to support a definitive dosing regimen of bumetanide CI, specifically in the pediatric patient population, the purpose of this study was to describe the dosing, efficacy, and safety of bumetanide CI regimens used in PCICU patients.

Materials and Methods

Study Design. This was a single center, descriptive, retrospective study performed at the University of Florida (UF) Health Shands Hospital in Gainesville, FL. Our PCICU unit is a quaternary care center with 23 beds for patients with complex congenital heart disease. Electronic health records were used to identify pediatric patients admitted to the PCICU who received a bumetanide CI.

Inclusion criteria were met if patients were younger than 6 years, admitted to the PCICU, and received bumetanide CI for at least 6 hours as part of their clinical management between January 1, 2018, and September 1, 2022. The age cutoff 6 years was used to allow for a more homogenous patient population and to evaluate the dosing effects in younger children, because previous studies that included pediatric patients up to 18 years of age have reported significant variations in dosing regimens.⁵ Patients with incomplete or missing medical records were excluded from the study. If a patient had multiple admissions during the study time frame, each encounter with bumetanide CI was assessed as an individual occurrence.

Data Collection. A comprehensive review of medical records was conducted. Historical patient data were collected by manual chart review, and bumetanide CI was determined by clinical documentation on the medication administration record. Data collection included relevant demographic information

(i.e., age, sex, weight); admitting cardiac problem or diagnosis; dosing regimens, including doses and duration of CI; previous use of furosemide; concomitant diuretics; fluid balance measurements (every 12 hours); weight measurements obtained 24 hours before and after bumetanide infusion and laboratory parameters (i.e., serum electrolytes; renal function biomarkers, namely blood urea nitrogen and serum creatinine every 12 and 24 hours); hemodynamic or mechanical circulatory support; and respiratory support and oxygen requirements, defined as any support other than room air to mechanical ventilatory and circulatory support requirements. Inadequate response to furosemide is defined as not reaching negative fluid balance.

Outcomes. The primary outcome was identifying doses and total duration of bumetanide CI regimens. Secondary efficacy outcomes were determined by the ability to achieve negative fluid balance within 24 hours and time to reach negative fluid balance defined as the net cumulative balance of inputs and outputs with variables including but not limited to oral/IV fluids, medications, blood products, daily urine output, stool, and other bodily output (e.g., chest tube, gastrostomy, gastric or ostomy outputs) as recorded after initiation of bumetanide infusion. Secondary safety outcomes were based on the prevalence of electrolyte imbalances and renal impairment. Electrolyte imbalances were predefined as serum potassium concentration less than 3 mEq/L, serum chloride concentration less than 90 mEq/L, and serum bicarbonate concentration greater than 35 mEq/L. Renal impairment was predefined as increased serum creatinine (SCr) by 0.3 mg/dL within 48 hours or 1.5 times the baseline, or urine output <0.5 ml/kg/hr for at least 6 hours.^{7,8} Laboratory values were obtained upon admission (or within 1 week of life for neonates) and within 12 hours of bumetanide peak infusion rates.

Subgroup analyses were performed to evaluate bumetanide regimens, based on patients' overall cardiovascular (CV) history and risk. This evaluation included patients who required extracorporeal membrane oxygenation (ECMO) and those with an implanted ventricular assist device (VAD). Exploratory outcomes in the *post hoc* analysis included survival to discharge, mortality rates observed from peak bumetanide infusion rates, and dosing regimens used at the time of death.

Statistical Analysis. Descriptive statistics (e.g., medians, IQRs, and frequencies) were used to summarize the study population's patient demographic and clinical characteristics. The Wilcoxon signed rank test was used to test the statistical significance of continuous variables, and a chi-square test was used to analyze categorical data. All tests were 2-tailed, with an overall alpha level of 0.05 for statistical significance. To generate these findings, statistical analyses were performed by using appropriate statistical software, JMP Pro 17.

Results

Baseline Characteristics. Ninety-four patients were identified for study eligibility; however, 4 patients were excluded because they received continuous bumetanide infusions for less than 6 hours. Ninety patients were included in the final analysis; however, to account for patients having multiple hospital admissions, the total number of 106 hospital encounters was analyzed (Figure). Baseline patient demographics for all encounters, including age, sex, weight, and admitting cardiac problems, are summarized in Table 1. Most patients included were female and younger than 8 months (65 patients making up 72%). Eighty-six percent of the patients receiving bumetanide CI transitioned from furosemide with inadequate response to furosemide as defined by no negative fluid balance (Supplemental Table S1). Of note, 91% of patients received concomitant diuretics during bumetanide CI, with the highest use seen with chlorothiazide, followed by acetazolamide and spironolactone (Supplemental Figure). The most common admitting cardiac problem was hypoplastic left heart syndrome (HLHS), followed by cardiomyopathy and atrioventricular septal defect (AVSD).

Primary Outcome. Table 2 highlights bumetanide dosing regimens observed in the PCICU during the study period. The median initial starting dose of bumetanide was 0.03 mg/kg/hr, ranging from 0.005 to 0.2 mg/kg/hr. The median dose of bumetanide was 0.046 mg/kg/hr, with a median duration of CI of 5.8 days. Median maximum doses of bumetanide were 0.075 mg/kg/hr, with doses as high as 0.3 mg/kg/hr being used in 2 patients.

Efficacy Outcomes. The secondary efficacy endpoints for optimal diuresis are displayed in Table 3, with 83% of patients achieving negative fluid balance within 24 hours of bumetanide CI initiation and a median time to reach negative fluid balance of 13.4 hours.

Figure. Study inclusion flow diagram.

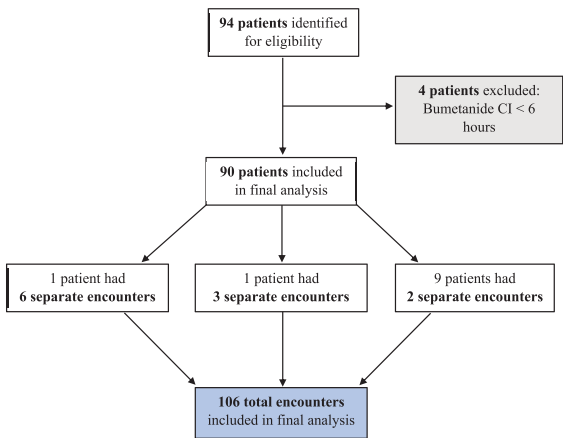


Table 1. Baseline Patient Demographics for All Encounters (N = 106)*	
Age, days	137 [49, 276]
Female	57 (53.8)
Weight, kg	4.3 [3.2, 7.0]
Hypoplastic left heart syndrome	47 (44.3)
Cardiomyopathy	15 (14.2)
Atrioventricular septal defects	7 (6.6)
Other diagnosis	37 (34.9)
Other diagnosis breakdown	
Double outlet right ventricle	6
Tetralogy of Fallot	5
Tricuspid atresia	5
Ventricular septal defects	4
Coarctation of aorta	3
Truncus arteriosus	2
Transposition of great arteries	2
Total anomalous pulmonary venous return	2
Partial anomalous pulmonary venous return	2
Pulmonary atresia intact ventricular septum	2
Aortic stenosis	1
Double inlet left ventricle	1
Interrupted aortic arch	1
Pulmonary stenosis	1

* Categorical data reported as counts (%); continuous data reported as median [IQR].

Table 2. Bumetanide Dosing Regimen*	
Initial dose, mg/kg/hr	0.03 [0.01, 0.05] (0.005–0.2)
Maximum dose, mg/kg/hr	0.075 [0.05, 0.1] (0.01–0.3)
Median dose, mg/kg/hr	0.046 [0.03, 0.07] (0.005–0.16)
Cumulative dose, mg/kg	6.02 [2.07, 21.82] (0.2–40)
Duration of CI, hrs	140 [51, 381] (9–585)

CI, continuous infusion

* Continuous data reported as median [IQR] or median [IQR] (range).

The urine output was collected for 24 hours for our study population with a median of 1.36 mL/kg/hr. To account for inconsistent or incomplete documentation on 18 encounters concerning weight, a weight comparative analysis was performed on 88 individuals before and 24 hours after starting a bumetanide CI. Before bumetanide initiation, the median weight was 5.0 kg compared with 4.9 kg after the start of bumetanide, which was statistically significant ($p = 0.009$).

Safety Outcomes. Safety was analyzed by using the previously defined criteria for electrolyte imbalances and renal impairment. Seventy-three percent of patients experienced hypokalemia, 32% experienced hypochloremia, and 36% experienced hypercarbia (Table 4). Based on SCr elevations, 51% of patients had some renal impairment. Significant changes in serum electrolytes and renal function biomarkers were noted between all laboratory values measured at baseline and during median peak infusion rates but were not clinically significant (Table 5).

Exploratory Outcomes. Epinephrine (45.2%), milrinone (34.4%), dopamine (8.6%), vasopressin (7%), norepinephrine (3.2%), and phenylephrine (1.6%) were the choices of vasopressor and inotropic support that required hemodynamic support for hemodynamic

stability. Supplemental Table S2 includes additional clinical characteristics that were analyzed to assess patients' CV history and risk. Eighteen percent of individuals were supported while on venoarterial (VA) ECMO, whereas 19% of patients had an implanted VAD using the Berlin Heart (Woodlands, TX, USA) EXCOR for additional mechanical circulatory support. When looking at heart transplant status, 34% of patients were awaiting heart transplants, whereas 12% had a history of heart transplants. Seventeen patients were supported by dialysis: 9 patients needing continuous renal replacement therapy (CRRT) and 8 patients requiring peritoneal dialysis (PD). Of the 17 patients, 13 were non-survivors, 8 received CRRT, and 5 were on PD. Of the 4 survivors, 1 was on CRRT, and 3 were on PD. Respiratory support and oxygen requirements varied substantially, with 75% of patients needing mechanical ventilation at some point during a bumetanide CI.

When assessing survival to discharge, 31 non-survivors were reported at the time of discharge. Of the non-survivors, 61% were receiving maximum bumetanide doses of 0.1 mg/kg/hr or greater (Supplemental Table S3). When stratifying this group further, based on maximum bumetanide doses (<0.1 vs ≥ 0.1 mg/kg/hr), there was a significant increase in deaths recorded with doses ≥ 0.1 mg/kg/hr (12 vs 19 patients; $p = 0.0085$). Doses observed at the time of death were 0.1 mg/kg/hr, ranging up to 0.3 mg/kg/hr (Supplemental Table S3).

A subgroup analysis of bumetanide regimens and survival to discharge, based on the CV history and risk, is presented in Supplemental Table S4. Patients with HLHS received higher doses of bumetanide and had

Table 3. Efficacy Secondary Endpoints (N = 106)*

Negative fluid balance within 24 hr	88 (83)
Overall net negative volume, mL	151.5 [83.8, 257.8]
Urine output over 24 hr after initiation, mL/kg/hr	1.36 [0.74, 2.35]
Time to reach negative fluid balance after initiation, hr	13.4 [9.5, 19.1]

* Categorical data reported as counts (%); continuous data reported as median [IQR].

Table 4. Prevalence of Safety Secondary Endpoints (N = 106)*

Electrolyte Imbalances	
K ⁺ <3 mEq/L	77 (72.6)
Cl ⁻ <90 mEq/L	34 (32.1)
CO ₂ >35 mEq/L	38 (35.9)
Renal Impairment	
SCr increase ≥ 0.3 mg/dL within 48 hr or $\geq 1.5 \times$ baseline	54 (50.9)
BUN ¹⁵ >20 mg/dL	83 (78.3)

BUN, blood urea nitrogen; Cl⁻, chloride; CO₂, carbon dioxide; K⁺, potassium; SCr, serum creatinine

* Categorical data reported as counts (%).

Table 5. Comparison Between Laboratory Values at Baseline and During Peak Infusion Rates*

	Baseline	During Peak Infusion Rate	p value [†]
K ⁺ , mEq/L	4.0 [3.6, 4.6]	3.3 [2.9, 3.6]	<0.0001
Cl ⁻ , mEq/L	104 [100, 107]	100 [94, 105]	0.0028
CO ₂ , mEq/L	24 [21, 26]	28 [24, 32]	<0.0001
SCr, mg/dL	0.36 [0.25, 0.48]	0.42 [0.28, 0.70]	0.0006
BUN, mg/dL	16 [11, 21]	22 [14, 35]	0.0008

BUN, blood urea nitrogen; Cl⁻, chloride; CO₂, carbon dioxide; K⁺, potassium; SCr, serum creatinine

* Continuous data reported as median [IQR]

[†] Wilcoxon signed rank test.

higher mortality than those with cardiomyopathy and AVSD. Patients with a VAD in place received higher doses and had higher mortality rates than those without a VAD. This finding was also consistent among individuals on VA ECMO. Because several patients had multiple admissions, we analyzed these data from the number of encounters. For patients with multiple encounters, compared with those with a single encounter, we observed shorter durations of bumetanide CI (92 vs 161 hours; $p = 0.3032$) and increased survival to discharge (78% vs 68%; $p = 0.3527$). However, these results did not reach statistical significance.

Discussion

In this single center retrospective study, we reviewed 106 encounters of patients admitted to the PCICU who received a bumetanide CI for at least 6 hours. This review provides valuable insights and real-world evidence into bumetanide's dosing, efficacy, and safety in managing fluid overload in critically ill pediatric cardiac patients. The findings of this study demonstrate that bumetanide CI led to improvements in diuresis and fluid balance in pediatric patients undergoing or awaiting cardiac surgery within the PCICU. We suggest a starting dose of 0.005 mg/kg/hr and a maximum dose of 0.1 mg/kg/hr to maximize benefits with a minimal side effect profile that can be easily managed. The reason for choosing this maximum dose is that in our subgroup analysis no patient survived when the doses were above 0.1 mg/kg/hr, suggesting that a patient's underlying condition and hemodynamic profile cannot be reversed with high-dose diuretics.

The analysis of urine output, weight, and fluid intake/output records revealed favorable responses to treatment, suggesting that bumetanide CI provides a sustained diuretic effect. This aligns with the rationale for using bumetanide CI in this patient population, because it allows for more precise titration and potentially avoids the rapid fluctuations in diuresis that may be experienced with intermittent dosing. Bumetanide offers additional potential benefits when compared with furosemide. Previous adult studies have suggested that bumetanide may potentially cause less potassium excretion,⁹ ototoxicity,¹⁰ and bilirubin displacement¹¹ when compared with furosemide and may have a reduction in seizure burden.¹² These last 2 findings are significant and beneficial to consider in the neonatal patient population, who typically present with hyperbilirubinemia in the first few days of life and have a higher propensity for seizures with neonatal cardiac surgery.¹³ We had 18 neonates in our study, but we did not focus on evaluating these and hope to explore this in future studies.

It is crucial to note that our analysis also identified electrolyte imbalances and renal impairment in patients receiving bumetanide CI. These findings are consistent with previous studies highlighting the potential risks and complications of loop diuretic therapy in critically ill

patients.¹⁴ Electrolyte imbalances, including hypokalemia and hyponatremia and resulting contraction alkalosis, can have significant clinical consequences and require careful monitoring and management in these patients.

Additional key findings indicate that sicker patients received higher doses of bumetanide CI. The subgroup and exploratory analyses found higher doses were being used with longer duration of infusions, specifically in patients on ECMO and those with an implanted VAD. However, it should be noted that the observed increased mortality risk may be attributed to several factors, including but not limited to the severity of illness, underlying cardiac pathology, or the development of treatment-resistant fluid overload.

These adverse effects highlight the need for close monitoring and cautious administration of this treatment approach. The risks observed in this retrospective review underscore the importance of considering individual patient factors, such as baseline renal function, electrolyte status, and overall clinical condition, when deciding on the appropriateness and dosage of bumetanide CI. Furthermore, a multidisciplinary approach involving collaboration between the PCICU team, pediatric cardiology specialists, and pharmacists is crucial to ensure adequate patient selection, appropriate dosing strategies, and proactive management of potential complications.

Limitations of Study

By analyzing a comprehensive set of patient data, this study contributes to our understanding of the use of bumetanide CI and its implications for clinical practice. However, it is essential to consider the limitations inherent in a retrospective chart review when interpreting these results. The study's retrospective nature introduces the risk of selection biases and limitations in the data collection process due to incomplete documentation of medical records. The lack of a control group hinders the ability to directly compare the outcomes of bumetanide CIs with alternative treatment strategies, such as intermittent dosing or other loop diuretic agents. Considering all this, it is challenging to attribute these findings directly to continuous bumetanide infusions. Therefore, these findings should be interpreted cautiously and considered hypothesis generating rather than definitive evidence of causality.

A large percentage of patients receiving concomitant diuretics may also confound the results. However, this can be expected in clinical practice with critically ill patients. Patients who are admitted to the PCICU often have poor heart function at baseline, which can contribute to hypoperfusion to vital organs and worsening clinical outcomes. Additionally, electrolyte replacement and supplementation data were not included or analyzed owing to variable provider practices. Lastly, the inclusion of patients who received bumetanide CI may introduce a bias toward patients with more severe fluid overload or those who were deemed less responsive to

intermittent dosing. This could potentially overestimate the efficacy of bumetanide CI as compared with a randomized controlled trial or prospective study.

Despite these limitations, this study remains the largest pediatric study describing dosing, efficacy, and safety concerns of bumetanide CI in this specific patient population. Our comprehensive data collection and analysis provide detailed insights into the clinical outcomes and highlight existing knowledge gaps in the literature.

Conclusion

This study contributes to the growing body of evidence on bumetanide CI regimens in pediatric patients admitted to the PCICU. We identified positive outcomes in diuresis and fluid balance by comprehensively analyzing bumetanide CI in our population. However, using a high-dose bumetanide drip >0.1 mg/kg/hr may not improve the overall outcome, and there may be advantages to specific use in neonates undergoing cardiac surgery, which needs to be explored. We emphasize the importance of further research, including prospective, randomized controlled trials, to assist clinicians in making informed decisions, aiming to improve patient outcomes and enhance care in this critical setting.

Article Information

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Ethical Approval and Informed Consent. This retrospective chart review evaluated existing data using interventions that have already occurred. There was no risk to the patients involved, nor were there any associated costs. The study protocol was approved by the University of Florida Institutional Review Board (IRB), and patient informed consent was waived owing to the retrospective design of the study.

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