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Pharmacoepidemiology of Furosemide in the Neonatal Intensive Care Unit

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Abstract

Background: Furosemide is commonly used off-label in the neonatal intensive care unit (NICU), but current dosing practices vary widely.

Objectives: To describe dosing practices including route, dose, and duration of exposure to furosemide in a large number of community and tertiary NICUs across North America.

Method: Using the Pediatrix Medical Group Clinical Data Warehouse, we identified all infants between 1997 and 2016 who received ≥ 1 dose of furosemide. We excluded infants with incomplete dosing data. We calculated average daily furosemide dose, cumulative dose, total days of exposure, and maximum daily dose. We compared dosing between infants born at <32 weeks gestational age (GA) and ≥ 32 weeks GA.

Results: A total of 18,572 infants had complete dosing data. The median (interquartile value) postnatal age at first exposure was 11 days (4, 26), the median maximum daily dose was 1.0 mg/kg (0.97, 1.6), the median average daily dose was 1.0 mg/kg (0.88, 1.1), and the median cumulative dose was 2.0 mg/kg (1.0, 4.5). The median total duration of exposure was 2 days (1, 4). A total of 177 (1%) infants received ≥ 4 mg/kg/day of furosemide. Infants born <32 weeks GA

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Author Contributions

Dr. Thompson contributed to the conception of the work, data analysis, data interpretation, and drafting the work. Dr. Benjamin contributed to the conception of the work, data analysis and interpretation, and critically revising the work. Drs. Greenberg, Kumar, Zimmerman, Smith, and Laughon contributed to the conception of the work, data interpretation, and critically revising the work. Dr. Clark contributed to the conception of the work, data analysis, and critically revising the work. Dr. Hornik contributed to conception of the work, data interpretation, drafting the work and critically revising the work.

Statement of Ethics

This research was conducted in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the Duke University Institutional Review Board as exempt research.

were an older age at initial furosemide exposure compared to those born ≥ 32 weeks GA: 19 versus 4 days, $p < 0.001$.

Conclusions: Most infants received short courses of furosemide within the labeled dosing parameters. Further studies are needed to assess the safety and efficacy of furosemide in the NICU.

Keywords

neonatal; diuretics; furosemide

Introduction

Neonatologists use furosemide off-label in infants to treat tachypnea and peripheral or pulmonary edema, improve respiratory status, prevent fluid overload after blood product transfusions, and wean respiratory support [1-3]. However, furosemide has potential side effects, including nephrocalcinosis, ototoxicity, electrolyte disturbances, hyperbilirubinemia, and metabolic bone disease [4-6]. Despite the drug's incompletely described risk-benefit profile, furosemide is the most commonly prescribed diuretic and among the top ten prescribed medications in the neonatal intensive care unit (NICU) [4,7,8].

Furosemide is a loop diuretic that inhibits renal reabsorption of sodium and chloride in the proximal tubule, distal tubule, and Loop of Henle. Furosemide is eliminated in the urine [9]. The pharmacokinetics and pharmacodynamics of furosemide are dependent on renal development, as well as chronological age [10,11]. Nephrogenesis begins early in gestation and is not complete until 3–4 weeks after term birth [12]. The half-life of intravenous furosemide in premature infants is twice as long as in term infants and children, and may be considerably longer [10,11]. In pediatric patients, recommended dosing of furosemide is 1 mg/kg/dose up to a maximum of 6 mg/kg/dose [4]. In premature infants, the maximum United States Food and Drug Administration label suggested dose is 1 mg/kg/day [4,13]. Despite these recommendations, current dose and frequency practice varies widely [11]. In this study, we describe dosing practices including route, dose, and duration of exposure to furosemide in a large number of community and tertiary NICUs across North America.

Materials and Methods

We identified infants who died or were discharged from NICUs managed by the Pediatrix Medical Group from 1997 to 2016 who received ≥ 1 dose of furosemide. We excluded infants with incomplete dosing data (e.g., missing route of administration, end date, or dose) and those receiving >9 mg/kg/dose, since this was believed to be a dose reporting error. Prospectively-captured demographic and clinical data generated by clinicians were extracted from electronic health records [14]. We collected demographic and dosing data, as well as surrogate markers of lung disease (exposure to prenatal steroids and mechanical ventilation), surrogate markers of illness severity (exposure to inotropes), and length of stay.

We calculated average daily dose (mg/kg/day), cumulative dose during hospitalization (mg/kg), total days with furosemide exposure, and maximum daily dose (mg/kg) and assumed

50% enteral bioavailability based on previously published enteral absorption data, reporting doses in intravenous equivalents [15]. Transfusion-related doses were those explicitly written as given with blood product. We defined mechanical ventilation as conventional or high-frequency ventilation starting prior to furosemide administration. Inotrope exposure was defined as epinephrine, dopamine, dobutamine, or norepinephrine prior to furosemide administration. Data was analyzed as a whole, and then for infants <32 weeks gestational age (GA) and ≥32 weeks GA, since this cut-off is used when defining bronchopulmonary dysplasia, a disease in which furosemide is commonly used [16,17].

We used summary statistics including counts (percentages) and medians (interquartile value [IQV]) to describe categorical and continuous variables, respectively. We used Chi-square or Wilcoxon's rank-sum tests to compare distributions of categorical and continuous study variables across groups, respectively. We conducted analyses using Stata 15.1 (StataCorp LLC, College Station, Texas) and considered a *p* value <0.05 statistically significant. The study was approved by the Duke University Institutional Review Board without need for informed consent.

Results

Demographics

Over the 19-year study period, 1,249,466 infants were identified from 392 NICUs. A total of 38,183 (19%) of 200,611 infants <32 weeks, and 21,165 (2%) of 1,047,840 infants ≥32 weeks, received ≥1 dose of furosemide with a total of 59,391 (4.8%) infants receiving furosemide. Of these, 18,572 (31%) infants had complete dosing data. Most instances of incomplete dosing data were the result of missing dosing units. The median (IQV) birthweight in our cohort was 1340 g (900, 2440) and GA was 30 weeks (27, 35). The majority of infants <32 weeks received prenatal steroids (76%) or mechanical ventilation (81%), while one-third received inotropes. Among infants ≥32 weeks, 50% were mechanically ventilated, but <25% received prenatal steroids or inotropes (Table 1). Of the 81% of infants <32 weeks GA who were mechanically ventilated prior to receiving furosemide, 35% were mechanically ventilated after completing their furosemide course. Of the 50% of infants ≥32 weeks GA who were mechanically ventilated prior to receiving furosemide, 30% were mechanically ventilated after receiving their furosemide course.

Dosing

The majority of infants with furosemide exposure were <32 weeks GA (10,868; 59%). Overall, a total of 13,208 (71%) infants received only intravenous dosing, 3541 (19%) received only enteral dosing, and 1812 (10%) received intravenous and enteral dosing. Age at first postnatal exposure for all infants was 11 (4, 26) days, maximum daily dose was 1.0 (0.97, 1.6) mg/kg, average daily dose was 1.0 mg/kg (0.88, 1.1), and cumulative dose was 2 (1, 4.5) mg/kg. Total duration of exposure was 2 (1, 4) days. A total of 177 (1%) infants received ≥4 mg/kg/day of furosemide. Transfusion-related doses accounted for 6455 doses in 3371 (18%) infants. Results were similar when transfusion-related doses were excluded: the median age at first postnatal exposure was 10 days and the median values of the maximum daily dose and average daily dose were both 1 mg/kg.

Infants born <32 weeks GA received their first dose at older postnatal ages than infants ≥ 32 weeks (day 19 versus day 4; $p<0.0001$), but average, maximum, and cumulative dosing, as well as duration of exposure, were similar (Table 2). Within each GA group, enteral doses were received at older postnatal ages and infants had more days of enteral doses compared to intravenous doses (Table 2).

Discussion/Conclusion

We report widespread furosemide dosing practices across community and tertiary NICUs. Most infants received doses of furosemide within labeled parameters. Infants treated with furosemide received a short course regardless of GA, even when transfusion-related doses were excluded, possibly due to previous evidence that single doses of loop diuretics result in short-term increases in pulmonary compliance and possible improvement of respiratory status [13]. We saw a decrease in the percentage of infants who were mechanically ventilated after completing their furosemide courses, which supports an improvement in respiratory status with furosemide, although we cannot comment on causation. Evidence is lacking for improvement in outcomes with longer exposures.

Infants born <32 weeks GA received their first furosemide dose two weeks later in life than infants born ≥ 32 weeks (median day of life 19 versus 4 days). This is consistent with a prior study describing neonatologists' use of furosemide in very low birth weight infants: 32% would not use diuretics in the first 7 days of life, whereas only 8% would not use diuretics at 28 days of life [18]. Existing studies present conflicting evidence on the safety and efficacy of furosemide; some showed decreased respiratory distress syndrome in infants receiving furosemide in the first day of life [19,20], while others showed hypovolemia and electrolyte abnormalities with no change in outcomes in infants receiving early furosemide [6,21,22]. Importantly, infants born <32 weeks and ≥ 32 weeks have different clinical scenarios prompting furosemide use, although there are currently no studies supporting use in infants for indications other than edema.

The strengths of our study include the large sample size of real-world data derived from the electronic medical record from different NICUs over a large study period. Additionally, this is the first study to describe furosemide dosing practices in the NICU. Some limitations include the retrospective nature of the data and lack of indication for furosemide use. We assumed 50% enteral bioavailability, which was supported when we analyzed our data without this assumption in infants receiving only enteral furosemide versus infants receiving only IV furosemide: median (IQV) maximum daily dose was 2 (1.2, 2.1) mg/kg enterally versus 1.0 (0.98, 1.7) mg/kg IV, average daily dose was 1.9 (1.0, 2.0) mg/kg enterally versus 1.0 (0.9, 1.2) mg/kg IV, and cumulative dose was 4 (2, 9.8) mg/kg enterally versus 1.9 (1, 3.8) mg/kg IV. These numbers support our assumption and are consistent with past pharmacokinetic studies [15]. Furthermore, many observations were without complete dosing data, which reflects our conservative inclusion criteria. We did not assume or impute dosing units or route of administration in order to give as accurate a reflection as possible of the current dosing practices. To confirm our data was representative of all infants, we analyzed dosing parameters for the six sites with the highest retention rates (complete dosing data for >75% of infants receiving furosemide) and found similar consistent results. Further

studies examining optimal dosing duration and furosemide' association with various outcomes are necessary to further guide use in the NICU.

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References

- [1]. Slaughter JL, Stenger MR, Reagan PB. Variation in the use of diuretic therapy for infants with bronchopulmonary dysplasia. *Pediatrics*. 2013;131 (4):716–23. [PubMed: 23478874]
- [2]. Iyengar A, Davis JM. Drug therapy for the prevention and treatment of bronchopulmonary dysplasia. *Front Pharmacol*. 2015;6:12. [PubMed: 25762933]
- [3]. Sarai M, Tejani AM. Loop diuretics for patients receiving blood transfusions. *Cochrane Database Syst Rev*. 2015;(2):CD010138. [PubMed: 25685898]
- [4]. Furosemide Injection, USP [package insert]. Shirley, NY: American Regent Inc; 2011 United States Food and Drug Administration Access Data web site. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/018579s0291bl.pdf. Accessed March 27, 2020.
- [5]. Shankaran S, Poland RL. The displacement of bilirubin from albumin by furosemide. *J Pediatr*. 1977;90(4):642–6. [PubMed: 839387]
- [6]. Orth LE, O'Mara KL. Impact of early versus late diuretic exposure on metabolic bone disease and growth in premature neonates. *J Pediatr Pharmacol Ther*. 2018;23(1):26–33. [PubMed: 29491749]
- [7]. Laughon MM, Chantala K, Aliaga S, Herring AH, Hornik CP, Hughes R, et al. Diuretic exposure in premature infants from 1997 to 2011. *Am J Perinatol*. 2015;32(1):49–56. [PubMed: 24801161]
- [8]. Hsieh EM, Hornik CP, Clark RH, Laughon MM, Benjamin DK, Smith P, et al. Medication use in the neonatal intensive care unit. *Am J Perinatol*. 2014;31(9):811–22. [PubMed: 24347262]

- [9]. Eades SK, Christensen ML. The clinical pharmacology of loop diuretics in the pediatric patient. *Pediatr Nephrol*. 1998;12(7):603–16. [PubMed: 9761364]
- [10]. Vert P, Broquaire M, Legagneur M, Morselli PL. Pharmacokinetics of furosemide in neonates. *Eur J Clin Pharmacol*. 1982;22:39–45. [PubMed: 7094973]
- [11]. Peterson RG, Simmons MA, Rumack BH, Levine RL, Brooks JG. Pharmacology of furosemide in the premature newborn infant. *J Pediatr*. 1980;97(1):139–43. [PubMed: 7381633]
- [12]. Ryan D, Sutherland MR, Flores TJ, Kent AL, Dahlstrom JE, Puelles VG, et al. Development of the human fetal kidney from mid to late gestation in male and female infants. *EBioMedicine*. 2018;27:275–83. [PubMed: 29329932]
- [13]. Jackson W, Taylor G, Selewski D, Smith PB, Tolleson-Rinehart S, Laughon MM. Association between furosemide in premature infants and sensorineural hearing loss and nephrocalcinosis: a systematic review. *Matern Health Neonatol Perinatol*. 2018;4:23. [PubMed: 30473868]
- [14]. Spitzer AR, Ellsbury DL, Handler D, Clark RH. The Pediatrix BabySteps Data Warehouse and the Pediatrix QualitySteps improvement project system--tools for "meaningful use" in continuous quality improvement. *Clin Perinatol*. 2010;37(1):49–70. [PubMed: 20363447]
- [15]. Brater DC. Update in diuretic therapy: clinical pharmacology. *Semin Nephrol*. 2011;31 (6):483–94. [PubMed: 22099505]
- [16]. Higgins RD, Jobe AH, Koso-Thomas M, Bancalari E, Viscardi RM, Hartert TV, et al. Bronchopulmonary dysplasia: executive summary of a workshop. *J Pediatr*. 2018;197:300–8. [PubMed: 29551318]
- [17]. Trembath A, Hornik CP, Clark R, Smith PB, Daniels J, Laughon M, et al. Comparative effectiveness of three surfactant preparations in premature infants. *J Pediatr*. 2013;163(4):955–60.e1. [PubMed: 23769501]
- [18]. Hagadorn JL, Sanders MR, Staves C, Herson VC, Daigle K. Diuretics for very low birth weight infants in the first 28 days: a survey of the U.S. neonatologists. *J Perinatol*. 2011;31 (10):677–81. [PubMed: 21394079]
- [19]. Belik J, Spitzer AR, Clark BJ, Gewitz MH, Fox WW. Effect of early furosemide administration in neonates with respiratory distress syndrome. *Pediatr Pulmonol*. 1987;3(4):219–25. [PubMed: 3658526]
- [20]. Greenberg RG, Gayam S, Savage D, Tong A, Gorham D, Sholomon A, et al. Furosemide exposure and prevention of bronchopulmonary dysplasia in premature infants. *J Pediatr*. 2019;208:134–40.e2. [PubMed: 30579586]
- [21]. Green TP, Johnson DE, Bass JL, Landrum BG, Ferrara TB, Thompson TR. Prophylactic furosemide in severe respiratory distress syndrome: blinded prospective study. *J Pediatr*. 1988;112(4):605–12. [PubMed: 3280773]
- [22]. Wang LA, Smith PB, Laughon M, Goldberg RN, Ku LC, Zimmerman KO, et al. Prolonged furosemide exposure and risk of abnormal newborn hearing screen in premature infants. *Early Hum Dev*. 2018;125:26–30. [PubMed: 30193125]

Table 1.

Demographics, exposures, and outcomes of infants receiving furosemide based on gestational age, reported as percentages.

	<32 weeks N=10,868	32 weeks N=7,693
Route		
Intravenous	64	81
Enteral	22	15
Intravenous and enteral	14	4
Median birth weight, g (IQV)	962 (760, 1220)	2660 (2084, 3200)
Gestational age, weeks (IQV)	27 (26, 29)	36 (34, 38)
APGAR at 5 minutes		
0–3	6	4
4–6	21	9
7–10	73	87
Male	55	63
Small for gestational age	15	14
Race		
White	51	50
Black	26	10
Hispanic	19	36
Other	4	4
Prenatal steroids	76	22
Mechanical ventilation prior to furosemide	81	50
Inotrope exposure prior to furosemide	33	20
Length of hospital stay, days (IQV)	68 (47, 91)	16 (11, 29)

APGAR = Appearance, Pulse, Grimace, Activity, and Respiration; IQV = interquartile value

Table 2.

Dosing parameters by gestational age group for all enteral and intravenous doses. All data are presented as medians with interquartile values.

	<32 weeks GA N=10,868	32 weeks GA N=7693
Postnatal age at time of first exposure (days)	19 (9, 36)	4 (2, 10)
Intravenous	15 (7, 28)	3 (2, 7)
Enteral	38 (24, 55)	12 (7, 20)
Maximum daily dose (mg/kg)	1 (0.99, 1.7)	1 (0.95, 1.4)
Intravenous	1.0 (1.0, 1.9)	1.0 (0.96, 1.6)
Enteral	1.0 (0.77, 1.1)	1.0 (0.54, 1.0)
Average daily dose (mg/kg)	1 (0.89, 1.1)	1 (0.86, 1.1)
Intravenous	1.0 (0.94, 1.2)	1.0 (0.90, 1.1)
Enteral	0.98 (0.54, 1.0)	0.95 (0.51, 1.0)
Cumulative dose (mg/kg)	2.0 (1.0, 5.3)	1.9 (1, 3.9)
Intravenous	2.0 (1.0, 5.4)	1.8 (1, 3.7)
Enteral	2.1 (1, 5.2)	2.0 (1, 5.2)
Total duration of exposure (days)	2 (1, 5)	2 (1, 4)
Intravenous	2 (1, 5)	1 (1, 3)
Enteral	3 (1, 6)	3 (1, 6)

GA = gestational age