Diuretic Use and Subsequent Electrolyte Supplementation in a Level IV Neonatal Intensive Care Unit

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OBJECTIVES To evaluate the relationship between diuretic use, serum electrolyte concentrations, and supplementation requirements in infants admitted to the neonatal intensive care unit.

METHODS This was a single-center retrospective cohort study conducted in a freestanding children's hospital Level IV NICU. Data were collected for all infants younger than 6 months, admitted to the NICU between January 2015 and May 2017, who received 2 or more consecutive doses of furosemide, chlorothiazide, hydrochlorothiazide, and/or hydrochlorothiazide/spironolactone. The primary outcome was the composite of the incidence of electrolyte abnormalities and/or electrolyte supplementation requirement within 30 days of diuretic exposure.

RESULTS A total of 72 patients met inclusion criteria, with a median gestational age of 30 weeks. Overall, 92% of patients exposed to diuretics experienced derangement in at least 1 serum electrolyte and/or required electrolyte supplementation during diuretic therapy. Patients born at 36 to 41 weeks' gestational age, receiving thiazide diuretics, experienced a significantly lower rate of the primary outcome (37%, $p \leq 0.001$). The most common electrolytes affected by diuretic use were potassium and bicarbonate, with the highest incidence of the primary outcome for potassium occurring in patients receiving furosemide ($p = 0.0196$). Last, the median total daily dose of chlorothiazide in patients with an adverse event was 15 mg/kg/day, compared with 10 mg/kg/day in patients without an adverse event ($p = 0.0041$).

CONCLUSIONS Use of diuretics in young infants is likely to cause electrolyte derangements and/or require electrolyte supplementation. Patients born at earlier gestational ages may be at higher risk for developing such adverse effects.

ABBREVIATIONS GA, gestational age; GFR, glomerular filtration rate; IV, intravenous; NICU, neonatal intensive care unit; PN, parenteral nutrition

KEYWORDS derangement; diuretic; electrolyte; neonate; supplement

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Introduction

Diuretics are frequently prescribed in the NICU to improve pulmonary mechanics and oxygenation in infants diagnosed with disorders such as bronchopulmonary dysplasia, despite limited evidence regarding the benefit of these medications.¹ Clark and colleagues² found that furosemide was the seventh most commonly prescribed medication in the NICU, reporting furosemide use in 8% of all patients included in the study. In addition to loop diuretics such as furosemide, other diuretics commonly encountered include thiazide diuretics (hydrochlorothiazide, chlorothiazide), and potassium-sparing diuretics (spironolactone). Infants exposed to diuretic medications are at risk of a variety of adverse effects, the most acute being electrolyte abnormalities affecting serum sodium, potassium, chloride, calcium, magnesium, and phosphorus.¹

Loop diuretics target the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ symporter on

the ascending loop of Henle, thus increasing urinary excretion of sodium, chloride, and potassium. Passive reabsorption of potassium, calcium, and magnesium is also inhibited owing to effects on the nephron's apical membrane. Known adverse effects that should be monitored include hyponatremia, hypokalemia, hypomagnesemia, hypocalcemia, and hypochloremic metabolic alkalosis.³ To mitigate alkalosis, chloride supplementation is often required. Hypochloremia has also been shown to decrease the efficacy of loop diuretics, which frequently leads to diuretic dose escalation and increased adverse effects without an improved diuretic response.⁴ Furthermore, the half-life of furosemide is prolonged in the premature infant, likely related to decreased protein binding and a low rate of tubular secretion. This could lead to accumulation of furosemide in the preterm infant and increase the risk of adverse effects and toxicities related to medication exposure.^{5,6} Furosemide is also thought to have a direct effect on

lung fluid dynamics separate from the diuretic effects of the medication, a quality that increases the likelihood of use for some respiratory or cardiac disease states.^{7,8}

Although not as potent as loop diuretics, thiazide diuretics are also commonly used in infants with bronchopulmonary dysplasia.³ They exert their effects at the distal tubule by binding to the Na⁺/Cl⁻ transporter, thus inhibiting the reabsorption of sodium and chloride. Given their site of action at the main diluting site of the nephron, they are also more likely to cause hyponatremia than loop diuretics.⁹ Additionally, thiazide diuretics create a gradient that favors increased potassium secretion, which is associated with the loss of potassium and hydrogen ions.^{10,11} In contrast to loop diuretics, thiazide diuretics are less likely to cause hypocalcemia, which is beneficial for neonates who are already calcium deficient and at an increased risk of osteopenia of prematurity.³ However, thiazide-induced hyponatremia may require sodium supplementation in order to safely continue therapy. This may lead to increased luminal sodium concentrations, which in turn impairs calcium reuptake, thus resulting in calcium urinary loss and negating a possible overall benefit.¹² Furthermore, some studies have found that both loop diuretics and thiazides can cause hypercalciuria in low-birth-weight infants, which Atkinson et al¹³ postulated may be related to renal immaturity and/or excessive sodium intake.¹³

Given the extensive role the kidney plays in diuretic effect, it is worth noting the differences in the full-term infant kidney compared with a premature infant kidney. Fetal nephrogenesis is complete at 34 to 36 weeks' gestation, with over 60% of nephrons developed after 27 weeks' gestation.¹⁴ If an infant is born prematurely, their nephron volumes will continue to develop *ex utero*, but are unlikely to reach the nephron volumes of their term counterparts.¹⁵ While some interindividual variation in nephron volume exists, the glomerular filtration rate (GFR) of a term neonate starts at about 30% of adult values at birth and then doubles within the first 2 weeks of life, reaching adult levels by 2 years of age.^{16,17} Since glomerular function is dependent on gestational age (GA), premature infants have a lower initial GFR at birth than term infants, and reduced GFR rates have been noted in premature infants at corrected ages of up to 1 to 2 years.^{16–18}

Previous studies have described diuretic use in infants, but limited data exist on the specific electrolyte derangements that occur. In addition, infants born at younger GAs and lower birth weights are surviving longer than previously encountered, thus making adverse effects of drugs difficult to predict. The goal of this study is to evaluate the relationship between diuretic use, serum electrolyte concentrations, and supplementation requirements in NICU infants younger than 6 months. The authors hypothesized that there would be a high incidence of electrolyte derangements and/or supplementation requirements in diuretic-exposed

neonates, with an inverse relationship between GA and the primary outcome.

Materials and Methods

This was a retrospective chart review of the electronic medical record conducted from January 1, 2015, to May 31, 2017. Patients were included if they were admitted to the NICU, were younger than 6 months of chronological age, and received 2 or more consecutive doses of diuretic therapy by intravenous or oral route of administration. Patients were excluded if they required extracorporeal membrane oxygenation or continuous renal replacement therapy at any point during admission; had a diagnosis of an inborn error of metabolism, chronic renal dysfunction, or hemodynamically significant congenital heart disease; or received indomethacin or angiotensin converting enzyme inhibitors concurrently with diuretics. Of note, infants with renal dysfunction related to prematurity were not excluded. The diuretics studied, based on institutional usage, were furosemide, chlorothiazide, hydrochlorothiazide, and hydrochlorothiazide-spironolactone. This study was focused on short-term adverse effects of diuretic use, so data were collected for the first 30 days after diuretic exposure.

The primary outcome was the composite of the incidence of electrolyte abnormalities and/or electrolyte supplementation requirements during diuretic therapy. When one or both occurred during an infant's diuretic course, it was defined as an "adverse event." Secondary outcomes were the overall incidence of electrolyte supplementation, effect of each diuretic group on specific electrolyte derangements from baseline, and the association between GA, diuretic exposure, supplementation requirements, and serum electrolytes.

Data collected included diuretic medication, total daily dose, dosing interval, duration of use, demographics, serum electrolytes, enteral or parenteral electrolyte supplement doses, supplement dosing interval, supplement duration of use, and enteral and/or parenteral nutrition (PN) requirements. Serum electrolytes studied were sodium, chloride, potassium, bicarbonate, and calcium. Supplements included in the analysis were sodium chloride, potassium chloride, sodium phosphate, potassium phosphate, calcium gluconate, calcium carbonate, calcium chloride, sodium bicarbonate, sodium acetate, potassium acetate, and arginine hydrochloride. With regard to nutrition, the type of nutrition (PN and/or enteral nutrition) was recorded.

Electrolyte supplementation for patients receiving full enteral nutrition was defined as any additional enteral or parenteral electrolyte given within the study time-frame. In patients receiving PN, the percentage of PN received daily was used to calculate the total electrolytes received from PN each day. Standard parenteral electrolyte requirements for age were defined from ASPEN guidelines and used as a baseline measure.

Figure. Patient inclusion.

ACEI, angiotensin converting enzyme inhibitor; ECMO, extracorporeal membrane oxygenation

Any electrolyte requirement in PN above the standard for age was defined as electrolyte supplementation in this group. In patients receiving partial enteral and partial PN, electrolyte supplementation was defined as any enteral supplementation of electrolytes and/or any parenteral requirement above ASPEN requirements for age.

The first day a patient received a diuretic was considered diuretic day 1 and each consecutive daily dose, within the following 30 days, was counted towards days of diuretic exposure. Serum electrolytes and supplementation of electrolytes were recorded 48 hours before diuretic day 1, during diuretic therapy, and 48 hours after diuretic therapy was completed. The incidence of electrolyte abnormalities was evaluated by observing serum electrolyte concentrations above or below the normal range for age as defined by the hospital inpatient laboratory. Total daily doses of medications available in both IV and enteral formulations were converted into IV equivalents for analysis. Enteral chlorothiazide and furosemide were converted by using a 2:1 ratio, and enteral hydrochlorothiazide was converted by using a 5:1 ratio to IV chlorothiazide equivalents.

Baseline demographic characteristics were summarized with means and SDs, medians with IQRs, and proportions. Medications were grouped into 3 categories: thiazides (chlorothiazide, hydrochlorothiazide, and hydrochlorothiazide-spirolactone), furosemide, and both thiazides and furosemide. For further analysis, infants were also grouped into GA categories based on expected kidney ontogeny. Chi-squared and Fisher exact tests were used to compare the proportion of adverse events between the 3 diuretic groups. Median dose on the previous day was compared between ad-

verse events and non-events by using Wilcoxon rank sum tests. Baseline-as-covariate models were used to test the association between nadir electrolyte levels and diuretic. Significance was set at 0.05. R version 3.4.1 software (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>) was used.

Results

A total of 141 patients were screened for study inclusion; of these, 69 were excluded and 72 patients were included in the final analysis (Figure). Table 1 summarizes baseline cohort demographics. Patients had a median GA of 30 weeks and median birth weight of 1 kg, and median age at study inclusion was 47 days. The median duration of diuretic therapy was 13.5 days (range, 2–30 days). Thirty-six percent of patients were

Table 1. Baseline Demographic Characteristics

Characteristic	All (N = 72)
Gestational age, wk, median (IQR)	30 (23–41)
Male, %	56
Birth weight, kg, median (IQR)	1 (0–4)
Race, %	
White	50
Hispanic	26.4
Black	11.1
Asian	2.8
Other	1.4
Not available	8.3
Age at inclusion, days, median (IQR)	47 (3–136)

Table 2. Adverse Event Outcome for Entire Cohort

	Adverse Event, n (%)				p value
	All (N = 621)	Thiazide (n = 411)	Furosemide (n = 181)	Both (n = 29)	
No	50 (8)	30 (7)	20 (11)	0 (0)	0.0825
Yes	571 (92)	381 (93)	161 (89)	29 (100)	

born at less than 28 weeks' GA and 39% of patients were born at a birth weight of less than 1 kg.

Table 2 summarizes the occurrence of the primary outcome in the entire cohort. Overall, there was a high proportion of "adverse events" in all diuretic groups. There was not a statistically significant difference between type of diuretic ($p = 0.0825$). All the patients who received both furosemide and a thiazide diuretic ($n = 29$) experienced an adverse event. Table 3 stratifies the incidence of adverse events in each diuretic group by GA. Patients born at 36 to 41 weeks' GA experienced a significantly different incidence of electrolyte abnormalities and/or supplementation between diuretic groups ($p < 0.001$), with the lowest proportion of adverse events occurring with exposure to thiazide diuretics alone (37%).

Overall, 47% ($n = 34$) of patients required electrolyte supplementation. For supplements administered outside of PN, the most commonly used electrolyte supplement was enteral arginine hydrochloride (35.8% of total supplement days). In this study, patients required an average dose of 2.9 ± 1.1 mEq/kg/day (range, 1–4). Dosing ranged from 0.25 mEq/kg/dose to 1 mEq/kg/dose given every 3 to 12 hours. However, the most common frequency was every 6 hours. Overall, this aligned with the usual dosing range of 0.5 to 4 mEq/kg/day used at our institution. It was also found that most patients required arginine hydrochloride supplementation for an extended period as maintenance therapy, with an average duration of therapy of about 18 days (although data were only collected for 30 days).

Sodium chloride was the second most commonly used supplement (23.2% total supplement days) at an average dose of 2.4 ± 1.6 mEq/kg/day. Average doses of other supplements encountered were as follows: calcium gluconate (116.7 ± 51.6 mg/kg/day), calcium chloride (31.7 ± 11.8 mg/kg/day), calcium carbonate (34.3 ± 23.6 mg/kg/day), magnesium sulfate (35 ± 12.2 mg/kg/day), potassium chloride (1.3 ± 0.6 mEq/kg/day), potassium phosphate (0.3 ± 0 mEq/kg/day), and sodium phosphate (0.8 ± 0.3 mEq/kg/day). The most commonly

used diuretic, based on days of diuretic exposure, was enteral chlorothiazide at an average dose of 10.9 ± 5.6 mg/kg/dose (range, 3.5–20) most commonly given every 12 hours.

The occurrence of electrolyte derangement or supplementation between diuretics was compared for each electrolyte (Table 4), where "n" is the number of laboratory days with multiple days per subject. Overall, electrolyte derangement and/or supplementation of potassium (57%) and bicarbonate (62%) were/was the most commonly observed in all patients. The proportion of potassium adverse events was significantly different between the diuretic groups ($p = 0.0196$), with the highest proportion in those exposed to furosemide (64%) and the lowest in patients exposed to both a thiazide and furosemide (35%). Of note, 17.5% (72/411) of patient data from the thiazide group and 6.9% (2/29) from the "both" group were collected from patients on the combination product hydrochlorothiazide-spiroglactone. The proportion of calcium adverse events was also different between the diuretic groups ($p = 0.0023$), with the highest proportion seen in patients exposed to furosemide (12%) and lowest in patients exposed to a thiazide (2%).

The average total daily dose of chlorothiazide and furosemide was examined in patients with and without an adverse event (Table 5). The median total daily dose of chlorothiazide in patients with an adverse event was 15 mg/kg/day, compared with 10 mg/kg/day in patients without an adverse event, which reached statistical significance ($p = 0.0041$). There was no difference observed in patients taking furosemide.

Nadir electrolyte levels were also compared between thiazides and furosemide for the 32 patients with available baseline laboratory data (Table 6). The baseline electrolyte level was used as a covariate in a multivariable model. Overall, there was not a significant difference in nadir electrolyte levels between the 2 diuretics. On average, nadir electrolyte levels were lower in patients exposed to a thiazide diuretic than to furosemide for all electrolytes except calcium.

Table 3. Adverse Event Outcome Based on Diuretic Exposure and Gestational Age, n (%)

Gestational Age, wk	Thiazide	Furosemide	Both	p value
23–27	247 (97)	28 (93)	15 (100)	0.28
28–35	127 (92)	94 (89)	11 (100)	0.54
36–41	7 (37)	39 (87)	3 (100)	<0.001

Table 4. Incidence of Adverse Event Outcome by Electrolyte Abnormality and Diuretic, n (%)

Electrolyte	All	Thiazide	Furosemide	Both	p value
Sodium (n = 419)					
No	287 (68)	157 (67)	118 (71)	12 (71)	0.6143
Yes	132 (32)	79 (33)	48 (29)	5 (29)	
Chloride (n = 411)					
No	264 (64)	143 (62)	112 (68)	9 (53)	0.2802
Yes	147 (36)	87 (38)	52 (32)	8 (47)	
Potassium (n = 418)					
No	178 (43)	108 (46)	59 (36)	11 (65)	0.0196
Yes	240 (57)	127 (54)	107 (64)	6 (35)	
Bicarbonate (n = 408)					
No	157 (38)	82 (36)	70 (43)	5 (29)	0.2763
Yes	251 (62)	146 (64)	93 (57)	12 (71)	
Calcium (n = 301)					
No	281 (93)	150 (98)	120 (88)	11 (92)	0.0023
Yes	20 (7)	3 (2)	16 (12)	1 (8)	

Discussion

Diuretics are commonly encountered in the neonatal population, but they often result in electrolyte abnormalities that require supplementation. This may be more pronounced in premature infants, since fetal nephrogenesis is not complete until 34 to 36 weeks' gestation. Overall, limited data exist on the specific electrolyte derangements that occur in premature neonates. To our knowledge, this study was the first to evaluate the relationship between diuretic use, serum electrolyte concentrations, and supplementation requirements in infants younger than 6 months.

In this single-center study, there was a high incidence of electrolyte derangements and/or supplementation requirements across diuretic exposure groups. These findings confirmed our expectation that electrolyte derangements and supplementation would occur frequently in diuretic-exposed neonates. This study also sought to evaluate the association between GA and diuretic exposure on supplementation requirements and serum electrolytes. Overall, there was a lower incidence of the primary outcome in infants born at 36 to 41 weeks' gestation when exposed to a thiazide diuretic. Clinically, this has the potential to reduce the frequency

of serum electrolyte monitoring in these patients.

To further understand which electrolytes are most commonly wasted by the neonatal kidney with each diuretic, the incidence of the primary outcome was examined within each electrolyte. Most patients exposed to any diuretic had a potassium or bicarbonate derangement or required supplementation for these electrolytes. Additionally, calcium derangement/supplementation was more common in patients on furosemide versus thiazide diuretics, which was expected given the documented calcium-sparing effect of thiazides. As a surprise to the research group, the proportion of potassium adverse events was significantly lower in patients exposed to both a thiazide and furosemide. This could possibly be explained by the inclusion of patients on hydrochlorothiazide-spironolactone in the thiazide group. Owing to limitations in sample size, patients on the combination product were included in the study, but further evaluation of this finding is worth investigating.

All patients exposed to both a thiazide and furosemide experienced an electrolyte derangement and/or required supplementation. Interestingly, after further analysis for each individual electrolyte there was a low incidence of the primary outcome for sodium, potas-

Table 5. Total Daily Dose (mg/kg/day) of Chlorothiazide and Furosemide in Patients With and Without an Adverse Event^{*,†}

	All	No Adverse Event	Adverse Event	p value
Thiazide (n = 204)	10 (3–23)	10 (3–20)	15 (4–23)	0.0041
Furosemide (n = 126)	2 (1–4)	2 (1–3)	2 (1–4)	0.1519

* Chlorothiazide and furosemide presented in IV equivalents.

† Data presented as median (IQR).

Table 6. Difference in Nadir Electrolyte Levels Between Thiazides and Furosemide (n = 32)

Electrolyte (mEq/L)	Nadir, Mean $\pm$ SD	Difference (95% CI)	p value
Sodium	134 $\pm$ 4	-0.27 (-3.45–2.91)	0.864
Chloride	95 $\pm$ 6	-0.04 (-4.54–4.47)	0.987
Potassium	4 $\pm$ 1	-0.33 (-0.98–0.31)	0.302
Bicarbonate	26 $\pm$ 5	-1.96 (-5.09–1.17)	0.209
Calcium*	9 $\pm$ 1	0.75 (-0.33–1.82)	0.165

*mg/dL.

sium, and calcium, with derangements in bicarbonate and chloride values most commonly observed. These results do not provide definitive evidence owing to the small sample size, but these findings warrant further evaluation. If this finding is further substantiated, it may prompt providers to consider earlier or more frequent serum electrolyte monitoring and earlier initiation of electrolyte supplementation in patients receiving concomitant loop and thiazide diuretics. When evaluating thiazide diuretics, there was also a higher incidence of the primary outcome when patients received IV chlorothiazide equivalent doses at or greater than 15 mg/kg/day. Clinically, this information may prompt the clinician to be more diligent regarding electrolyte monitoring for patients receiving higher doses of chlorothiazide.

Although hypochloremia was not predominantly encountered, the high use of enteral arginine hydrochloride at our institution is worth mentioning. Both metabolic alkalosis and hypochloremia can be caused by diuretic use. Therefore, supplemental chloride is often used to correct metabolic alkalosis, since chloride administration promotes bicarbonate secretion through chloride-bicarbonate exchange pumps in the nephron.^{19,20}

Overall, the decision to use arginine chloride versus sodium chloride or potassium chloride supplements at our institution is provider dependent. Sodium chloride was the second most commonly used supplement, but patients were on arginine chloride for more days while on diuretic therapy compared with sodium chloride. Arginine chloride is an appealing option to treat hypochloremia, since it does not affect other electrolytes and the intravenous formulation can be given enterally. This may explain the high use at our institution, especially since most patients used arginine chloride for an extended period as maintenance therapy.

A previous study by Sierra et al¹⁹ also reported on arginine chloride use and found that arginine chloride was effective in resolving both hypochloremia and metabolic alkalosis in pediatric patients. In addition, oral arginine was more effective than intravenous arginine in normalizing chloride levels. However, the optimal dose, route, and frequency of arginine chloride in pediatric patients remains unclear.

Limitations of this study are, first and foremost, its retrospective nature. Additionally, this was a single-

center analysis with a relatively small sample size. There was often limited availability of laboratory data. Some patients had missing baseline data prior to diuretic initiation, and timing of electrolyte monitoring throughout diuretic therapy was inconsistent. This made it difficult to examine the relationship between diuretic initiation, dose, and onset of electrolyte disarray and is an area for future investigation. Owing to limitations in sample size, patients on the combination product hydrochlorothiazide-spironolactone were included in the thiazide group, which could confound the results. Provider and patient variability and differing prescribing practices across the physician group were additional confounding factors. Owing to the limited scope and timeframe of the project, electrolyte supplementation via arterial line and other IV fluids were not accounted for, but should be included in future studies. Finally, this evaluation only assessed the first 30 days of diuretic exposure, and further assessment of long-term diuretic exposure is warranted.

This study provides specific information regarding diuretic use in infants. Quantifying common electrolyte derangements in infants receiving diuretic therapy could help predict monitoring needs and supplementation requirements. Furthermore, reducing unnecessary blood draws and focusing monitoring efforts would not only improve care, but also reduce overall health care costs related to diuretic use. While this evaluation did not demonstrate many statistically significant differences, the clinically interesting patterns reported add to the body of literature around diuretic use in the neonatal population. Furthermore, it is encouraging to note a lower rate of adverse outcomes in the older GA population with thiazide diuretic exposure. Future studies evaluating a larger sample size would be beneficial to further characterize the findings of this study. Overall, such information has the potential to guide clinical management and could lead to the development of treatment guidelines for diuretic use in infants.

Conclusions

Use of diuretics in young infants is likely to cause electrolyte derangements and/or prompt the need for electrolyte supplementation. Overall, patients of older GA had a lower incidence of electrolyte derangements

and/or supplementation requirement with thiazide diuretics. The highest rates of adverse outcomes were observed in the youngest patients. Future studies are needed to validate these observations.

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