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ABSTRACT

Introduction: Diazoxide is the first-line treatment used to manage infants and children with hypoglycemia secondary to hyperinsulinemic hypoglycemia (HH), after initial stabilization of blood glucose. Recent changes in Pediatric Endocrine Society guidelines regarding definition of, and screening for hypoglycemia in the neonate led to an increase in the number of infants treated with diazoxide.

Previous studies have noted various side effects of diazoxide. With the increased use of this drug in neonates, our aim is to further evaluate these side effects.

Methods: We performed a retrospective case control analysis of all neonates admitted to a tertiary care center in New Jersey who were treated with diazoxide for hypoglycemia after a confirmed diagnosis of HH between 1/1/2015 and 9/1/2019. All subjects were younger than 6 months of age at treatment initiation with diazoxide. We collected data regarding general patient characteristics, diuretic dosing, findings on echocardiogram, blood counts, episodes of emesis, and quantity of feeds at time points before and after diazoxide initiation.

Results: A total of 25 infants (64% males) met inclusion criteria and were included in the analysis. Based on echocardiogram results, one baby (4%) had pulmonary hypertension (PHTN) prior to initiation of diazoxide, and 20% after, with 5 cases (20%) of reopening of the ductus arteriosus (DA). Nine patients (36%) required a diuretic dose increase after diazoxide initiation. There was increased feeding intolerance with increased number of emesis events after diazoxide initiation (p=0.006). A week after initiation of diazoxide, there was no improvement in the percent of total oral intake as would typically be expected.

Conclusion: New onset PHTN and re-opening of the DA were associated with initiation of diazoxide treatment. Significant increase in emesis after diazoxide initiation suggests that infants may be experiencing feeding difficulties associated with this medication. Larger studies are needed to further evaluate the extent and frequencies of these side effects.

INTRODUCTION

Hyperinsulinism is the most common cause of persistent or recurrent hypoglycemia in infants[1]. Appropriately treating neonates with hypoglycemia is important in reducing the risk of developing seizures, brain damage, and long-term developmental delay[2]. In hyperinsulinemic hypoglycemia (HH), an inappropriately high level of insulin has an inhibitory effect on lipolysis and ketogenesis[3]. Suppressing ketone body formation limits the brain's backup source of fuel during periods of hypoglycemia, making infants with HH especially vulnerable to developing neurologic sequelae of hypoglycemia[3].

Diazoxide, in combination with the diuretic chlorothiazide, is currently the first-line treatment used to manage those infants and children with hypoglycemia secondary to hyperinsulinism, after initial stabilization of blood glucose[3] . There is a lack of consensus regarding a specific blood glucose value that defines hypoglycemia in neonates[4]. Both the American Academy of Pediatrics and the Pediatric Endocrine Society published conflicting guidelines regarding definition of and screening for hypoglycemia in the neonate in 2011 and 2015, respectively[4] . Gray et al report that from 1997 to 2016, the percentage of infants treated with diazoxide and the percentage of infants diagnosed with hypoglycemia increased significantly, which may have been attributable to the publication of these guidelines[5]. This increased use of diazoxide in neonates has prompted heightened concern regarding the side effects of diazoxide in this specific population.

Diazoxide inhibits insulin secretion by acting as a β-cell K_{ATP} channel opener, which hyperpolarizes the membrane and prevents insulin secretion[6]. Due to its mechanism, diazoxide can lead to an increase in sodium retention and subsequent decrease in water clearance[6]. Circulatory complications such as fluid retention and, in severe cases pulmonary hypertension (PHTN), have been reported following treatment with diazoxide[7]. Both Herrera and Yoshida reported circulatory dysfunction, defined as edema, oliguria and/or reopening of the ductus arteriosus (DA), or PHTN in infants treated with diazoxide, with younger gestational age at birth and higher maximum doses of diazoxide as main risk factors[7,8]. Several other side effects have been associated with diazoxide therapy. It can cause blood dyscrasias, as demonstrated in a number of studies and case reports[7,9,10].

In addition to circulatory complications and blood dyscrasias, feeding difficulties have been observed as a possible side effect of diazoxide therapy in neonates. Hu et al reported that children were seen to have transient gastrointestinal (GI) reactions[11]. Additional data regarding gastro-intestinal (GI) disturbances and feeding difficulty in neonates receiving diazoxide is lacking and was therefore a focus of this study.

This study reports the incidence of various side effects in neonates treated with diazoxide for hypoglycemia after a diagnosis of HH. This article pays special attention to side effects within the realm of circulatory compromise, blood cell dyscrasias and feeding difficulties. This study adds to existing literature on these particular side effects and expands on them, particularly the GI side effects.

MATERIALS AND METHODS

This was an IRB-approved retrospective case series of all neonates admitted to a tertiary care hospital in New Jersey who were treated with diazoxide for hypoglycemia after a confirmed diagnosis of HH between January 1, 2015 and September 1, 2019. To be included in the study, subjects had to be younger than six months of age at treatment initiation with diazoxide for hypoglycemia. Infants were excluded if they were older than six months of age at treatment initiation, or if they were not treated with diazoxide for hypoglycemia. Information was gathered on general patient characteristics including gender, birth weight, gestational age at birth, and age and weight at treatment initiation with diazoxide. Data regarding diazoxide dosing, duration of therapy, concurrent treatment with diuretics and diuretic dosing was also collected using electronic medical records (EPIC).

Echocardiogram was performed before and after treatment initiation of diazoxide for each subject and was read by a pediatric cardiologists. PHTN was defined by a clinician diagnosis in the echocardiogram report, with supportive findings including bidirectional or right-to-left patent DA or intracardiac shunt, and/or flattening of the ventricular septum during systole.

Additional data points that were collected included platelet, neutrophil and lymphocyte values. To obtain these values, we evaluated closest complete blood count (CBC) drawn prior to the date of diazoxide initiation as the “before,” and the CBC drawn within a week post diazoxide initiation as the “after.” We also obtained the total number of emesis episodes for the three days before and after diazoxide initiation. To evaluate feeding tolerance, we recorded quantity and percent of oral (PO) intake and intake via nasogastric/orogastric (NG/OG) tube 24 hours prior, 24 hours after, and 1 week after initiation of treatment. For all variables with time points relating to treatment initiation, the treatment initiation time point was considered as 7 AM on the morning of the day the medication was started. The time periods chosen for analysis were determined based on standard time periods evaluated for the same variables in other similar studies as well as clinical experience.

Descriptive analysis was performed with means (standard deviations), medians (ranges), percentages, or frequencies reported as appropriate. To compare continuous or discrete measures before and after the administration of diazoxide, we utilized a paired t-test or repeated measures ANOVA. For categorical measures, we utilized the Chi Test or McNemar test. Statistical significance was considered for $p<0.05$.

RESULTS

A total of 25 patients (64% males) were identified as meeting inclusion criteria, with a mean gestational age of 35.65 weeks ($\pm$3.99), and mean birthweight of 2112 grams ($\pm$954). Diazoxide was initiated at mean 13.8 postnatal days (+/-12.41) and mean weight of 2376 grams (+/-827.71). Cohort characteristics

are included in Table 1.

Average length of treatment was 19.6 (±15.9) days. The mean initial dose of diazoxide was 10.9 (±2.2) mg/kg/day. The mean maximum dose of diazoxide was 12.1 (±2.7) mg/kg/day.

Circulatory Complications

Before diazoxide initiation, one patient (4%) had PHTN documented on their echocardiogram report, versus 5 cases (20%) of PHTN present after diazoxide initiation (p=0.13). Consistent with current guidelines, all but one patient was started on chlorthiazide therapy at time of diazoxide initiation (the remaining patient was started on furosemide). Nine patients (36%) required an increase in the dose of their diuretic after diazoxide initiation, with a mean maximum dose of chlorthiazide of 18.28 (median 15; 10-40 , ±9.7) mg/kg/day. There were 5 cases (20%) of reopening of the DA, defined as a patent DA that was reported on the echocardiogram performed after treatment initiation, that was not present on the echocardiogram prior to diazoxide initiation.

Blood Cell Dyscrasias

We analyzed blood cell counts from subjects who had a CBC with differential completed within a week before diazoxide initiation (n=15). The mean platelet, leukocyte, and neutrophil counts before and after diazoxide initiation are shown in Table 2.

Feeding Difficulties

The average number of episodes of emesis in the three days after diazoxide initiation was significantly higher than three days before (1.24 +/- 1.5 and 0.28 +/- 0.3 respectively, p=0.006). We collected PO intake quantity and percent compared to intake via NG/OG tube for the 24 hours prior to, 24 hours after, and 1 week after diazoxide initiation (Table 3 , Figure 1). These results did not reach statistical significance.

DISCUSSION

Diazoxide use in neonates has been increasing over the past 40 years and remains the first-line treatment used to manage infants and children with hypoglycemia secondary to HH5. Concern regarding these side effects was heightened when in 2015 the FDA issued a drug safety communication warning of the association between PHTN and diazoxide use in neonates12. In addition to circulatory complications, such as PHTN and re-opening of the DA, various other side effects have been reported, includingneutropenia, thrombocytopenia, and transient GI side effects.

PHTN remains the most concerning complication of diazoxide use in neonates, and clinically may lead to heart failure, increased oxygen requirement, ventilator requirement, or need for increased diuretic dosing5. Our study found a 20% incidence of PHTN after diazoxide initiation, which is higher than other recent studies5,7,10. Other investigators report

lower rates of PHTN after diazoxide exposure (2.0%, 2.4% and 4.8%, respectively)5,7,10. In these studies, infants that developed PHTN were more likely to be premature and have a risk factor for PHTN at the time of diazoxide initiation. Several additional published case studies demonstrate cases of cardiac failure and PHTN in infants treated with diazoxide13–15. Although we report a high incidence of PHTN after diazoxide initiation, clinically none of our subjects developed overt heart failure, and the PHTN eventually resolved with continued diuretic therapy. The severity of PHTN in our patients never necessitated cessation of diazoxide therapy. It is possible that our patients had more of the underlying factors that increased the risk of developing PHTN, compared to the other studies.

We also report a 20% incidence of re-opening of the DA after initiation with diazoxide therapy. Demirel et al report a case of an infant treated with diazoxide who developed both PHTN and reopening of the DA[16], and Yoshida et al reported 3 cases (3.8%) of reopening of the DA[8]. In our study, reopening of the DA was not exclusive to patients who experienced PHTN after diazoxide initiation, suggesting that these events can occur exclusive of one another, despite a likely similar underlying mechanism of fluid retention. The clinical significance of this finding is unclear and necessitates further studies. However, it supports the evidence that diazoxide leads to circulatory alterations in neonates.

Previous studies have reported blood cell dyscrasias in neonates after diazoxide therapy including thrombocytopenia and neutropenia. Yildizdas et al describe a four-month-old infant who developed PHTN, heart failure and neutropenia during diazoxide therapy, which resolved once the drug was withdrawn[9]. Herrera et al. report that among 295 children with HH treated with diazoxide, 15.6 % developed neutropenia and 4.7% developed thrombocytopenia[7]. Thornton et al reported that among 165 infants treated with diazoxide, 8 (4.8%) experienced neutropenia[10]. Although not statistically significant, we observed a slight thrombocytosis a week following diazoxide initiation compared to prior. We observed no significant change in the total leukocyte count or absolute neutrophil count after diazoxide initiation. Although the numbers of patients evaluated in our study is smaller, based on our data special monitoring for blood cell dyscrasias may not be necessary while on diazoxide therapy, unless indicated for other medical reasons.

Hu et al reported that out of 44 patients, 12 suffered transient GI reactions after treatment with diazoxide[11] , and no other studies have looked further into the incidence of such reactions. A study by Keyes et al of 24 neonates in the intensive care unit who received diazoxide for HH showed that 20% of the subjects developed necrotizing enterocolitis (NEC) after treatment initiation with diazoxide, which is above the baseline incidence of NEC (1% for all infants and 6% for all very low birth weight infants)[17] . None of the subjects in our study developed NEC, however we did observe a significant increase in the number of emesis events during the three days after diazoxide initiation compared to the three days before. This is important in the clinical setting, as even seemingly small amounts of emesis can affect growth and disturb fluid and electrolyte status in neonates. Typically, an improvement in PO intake in neonates learning to take oral feeds would be expected over time, with continued improvement in clinical status. However, we found a mild decrease in the percent of total PO intake (versus NG/OG tube) the week after diazoxide

initiation compared to the 24 hours before therapy was initiated. Due to lack of control, the clinical significance of this decrease could not by appreciated. However, the trend of our data suggests that diazoxide treatment may lead to feeding difficulties and clinicians may need to alter feeding route and/or amount in neonates treated with diazoxide to avoid emesis and other GI side effects. This finding is also very important when diazoxide is initiated in outpatient setting, as infants may have decreased PO intake that goes unrecognized by the caregiver, and may lead to dehydration and failure to thrive. Larger studies are needed to further characterize GI side effects and feeding disturbances in neonates treated with diazoxide.

There are several limitations to our study. Our sample size was small, especially when analyzing blood cell counts, as we had to exclude patients who did not have a CBC with differential done both before and after diazoxide initiation. Another limitation is that due to the study design, we are only able to report association, not cause and effect. Lastly, as with any chart review study, there is potential error at the time of clinical documentation by medical staff. Data points such as emesis are reliant on nursing staff accurately recording such events, and data points like echocardiogram results depend on the personnel interpreting the study.

CONCLUSIONS

Our data supports existing evidence that cardiovascular complications, such as new onset PHTN and re-opening of the DA are associated with initiation of diazoxide treatment. Clinicians should continue to follow current guidelines regarding diuretic treatment during diazoxide therapy and be vigilant for signs of fluid overload and its sequelae. We did not observe any significant side effects regarding blood cell dyscrasias in our sample, which may help decrease blood tests that are needed in monitoring of patients on diazoxide. Lastly, there were notable GI complications seen after diazoxide initiation in our sample, including a lack of improvement in PO intake and a significant increase in emesis events. Clinicians should monitor for signs of GI upset and feeding difficulty and adjust feeding amount and route accordingly. As diazoxide appears to be used more liberally among neonates, larger studies are needed to further evaluate the extent and severity of side effects seen with this medication.

Table 1 Cohort Characteristics (n=25)

Characteristic	Data
Gender, n (%) Male	16 (64)
Gestational age at birth, weeks Mean (SD)	35.65 (3.99)
Birthweight, grams Mean (SD)	2112.12 (954.17)
Postnatal age at diazoxide initiation, days Mean (SD)	13.76 (12.41)
Gestational age at diazoxide initiation, days Mean (SD)	37.61 (2.88)
Weight at diazoxide initiation, grams Mean (SD)	2375.76 (827.71)

Table 2 Select blood cell counts before and after diazoxide initiation

	Prior to diazoxide	**After diazoxide**	**p**
Platelet count (mean +/- SD, 10^3 cells/mL)	149.13 +/- 100.5	212.93 +/- 108.2	0.127
Leukocyte count (mean +/- SD, 10^3 cells/mL)	10.89 +/- 3.0	10.34 +/- 4.3	0.612
Neutrophil count (mean +/- SD, 10^3 cells/mL)	4.99 +/- 2.8	3.93 +/- 2.4	0.191

Table 3 Intake orally and via NG/OG tube prior to and after diazoxide initiation

	24 hours prior to diazoxide	**24 hours after diazoxide**	**1 week after diazoxide**
Oral Intake (mean +/- SD, mL/kg/day)	61.67 +/- 60.6	80.54 +/- 74.3	72.62 +/- 67.4
NG/OG tube Intake (mean +/- SD, mL/kg/day)	36.10 +/- 48.3	40.10 +/- 47.6	58.50 +/- 50.6
% oral intake of total (mean +/- SD, %)	56.14 +/- 44.2	55.92 +/- 44.9	52.30 +/- 41.5

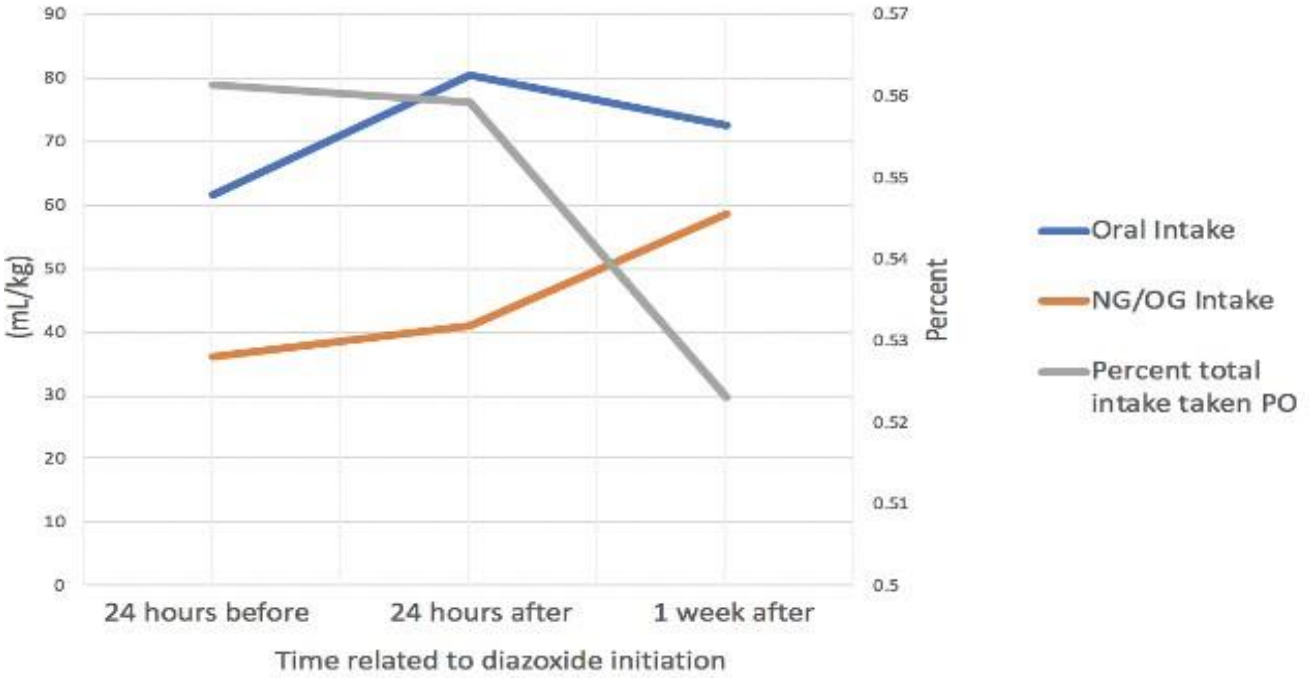

Figure 1 Oral Intake vs. Intake via NG/OG Tube

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