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Clinical Research Article

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Management and Appropriate Use of Diazoxide in Infants and Children with Hyperinsulinism

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Abstract

Background: The diagnosis of hypoglycemia and the use of diazoxide have risen in the last decade. Diazoxide is the only Food and Drug Agency-approved pharmacologic treatment for neonatal hypoglycemia caused by hyperinsulinism (HI). Recent publications have highlighted that diazoxide has serious adverse effects (AEs) such as pulmonary hypertension (2–3%) and neutropenia (15%). Despite its increasing use, there is little information regarding dosing of diazoxide and/or monitoring for AEs.

Methods: We convened a working group of pediatric endocrinologists who were members of the Drug and Therapeutics Committee of the Pediatric Endocrine Society (PES) to review the available literature. Our committee sent a survey to its PES members regarding the use of diazoxide in their endocrine practices. Our review of the results concluded that there was substantial heterogeneity in usage and monitoring for AEs for diazoxide among pediatric endocrinologists.

Conclusions: Based on our extensive literature review and on the lack of consensus regarding use of diazoxide noted in our PES survey, our group graded the evidence using the framework of the Grading of Recommendations, Assessment, Development and Evaluation Working Group, and has proposed expert consensus practice guidelines for the appropriate use of diazoxide in infants and children with HI. We

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summarized the information on AEs reported to date and have provided practical ideas for dosing and monitoring for AEs in infants treated with diazoxide.

Freeform/Key Words: hyperinsulinism, diazoxide, hypoglycemia, adverse effects, pulmonary hypertension, thrombocytopenia

The frequency of neonatal hypoglycemia diagnosis has risen over the last decade, as has the use of diazoxide (1). Recommendations regarding the diagnosis and management of hypoglycemia have been published. However, none have really addressed the appropriate use of diazoxide, specifically its indications, dosing, side effects and monitoring (2–4). In 1964, the first use of diazoxide was described by Drash and Wolff when they performed a trial in a patient with hyperinsulinism (HI), then referred to as leucine-sensitive hypoglycemia (5). In both animal and human studies, hyperglycemia had previously been noted as a side effect of diazoxide, and a reversible diabetes-like syndrome had been noted to occur in dogs (6, 7). Drash found that 8 mg/kg/day of diazoxide divided twice daily ameliorated hypoglycemia and its symptoms. A subsequent trial of 15 mg/kg/day caused hyperglycemia. By 1968, Drash et al reported the use of diazoxide in 10 children treated at the Johns Hopkins Hospital and the Children's Hospital of Pittsburgh for hypoglycemia (8), and that same year Marks and Samols reported 9 patients treated with diazoxide for intractable hypoglycemia in the United Kingdom (9). Diazoxide was subsequently approved for medical use by the Food and Drug Administration (FDA) in 1973. In pediatrics, only 1 study to date has examined the frequency of diazoxide use. This retrospective study obtained data from a clinical data warehouse and included approximately 1 249 000 infants in 392 NICUs from 1997–2016. In this cohort, 15% of infants were diagnosed with hypoglycemia, while only 0.09% of all infants (1066) or 0.57% of hypoglycemic infants were treated with diazoxide (1). However, the percentage of treated infants rose significantly during the study period, as did the percentage of infants diagnosed with hypoglycemia. Among centers, the percentage of infants exposed to diazoxide ranged from 0% to 14.9%, which indicates substantial differences in practice. Most patients (92.1%) treated with diazoxide were discharged home directly without ongoing diazoxide therapy, and 75% of those were treated for < 10 days. This indicates that short-term use of diazoxide in the NICU setting is very common. The study authors, part of the Best Pharmaceuticals for Children Act–Pediatric Trials Network, noted that the prevalence of diazoxide exposure (1:1,172 babies) was much higher than the estimated incidence of either perinatal stress-induced HI (1:12 000) (1) or genetic/congenital HI (1:50 000 genetic HI, but up to 1:2500 in populations with high consanguinity rates) (10). We can only speculate that many infants were treated with diazoxide without a complete evaluation and a confirmed diagnosis of HI. Although hundreds of papers on diazoxide have been published since its approval, practices around dosing and safety monitoring still vary substantially. Diazoxide currently remains the only drug approved by the FDA for treatment of what is now known as congenital HI or familial hyperinsulinemic hypoglycemia. Given the lack of consensus on the use of diazoxide and the data on neonatal use presented by Gray et al (1), we suspected that clinical practice might vary among pediatric endocrinologists, posing a question that we wanted to query. We convened a working group through the Pediatric Endocrine Society (PES) Drug and Therapeutics Committee to assess current practices, comprehensively review existing literature, and develop best practice recommendations.

Methods

The working group of the PES Drug and Therapeutics Committee set out to address this gap in knowledge. The PES Drug and Therapeutics committee working group consisted of 12 pediatric endocrinologists, all of whom treat more than 10 patients with HI with diazoxide per year and are all familiar with the literature on diazoxide use. The grade score was determined by each of the group individually and then any score that was not unanimous was discussed and scored as a group.

To determine the current state of knowledge about diazoxide, we performed a literature search using the following terms: diazoxide, diazoxide adverse events, hyperinsulinemic hypoglycemia, congenital HI, and treatment of hypoglycemia (Fig. 1). We used PubMed for the literature search and reviewed English language articles only. After reviewing and summarizing the literature, we graded the evidence using the framework of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group. The group rated their confidence of the evidence as high (++++), moderate (+++), low (++), and very low quality (+). High quality evidence is defined as "well-performed Randomized Controlled Trial (RCTs) or very strong evidence from

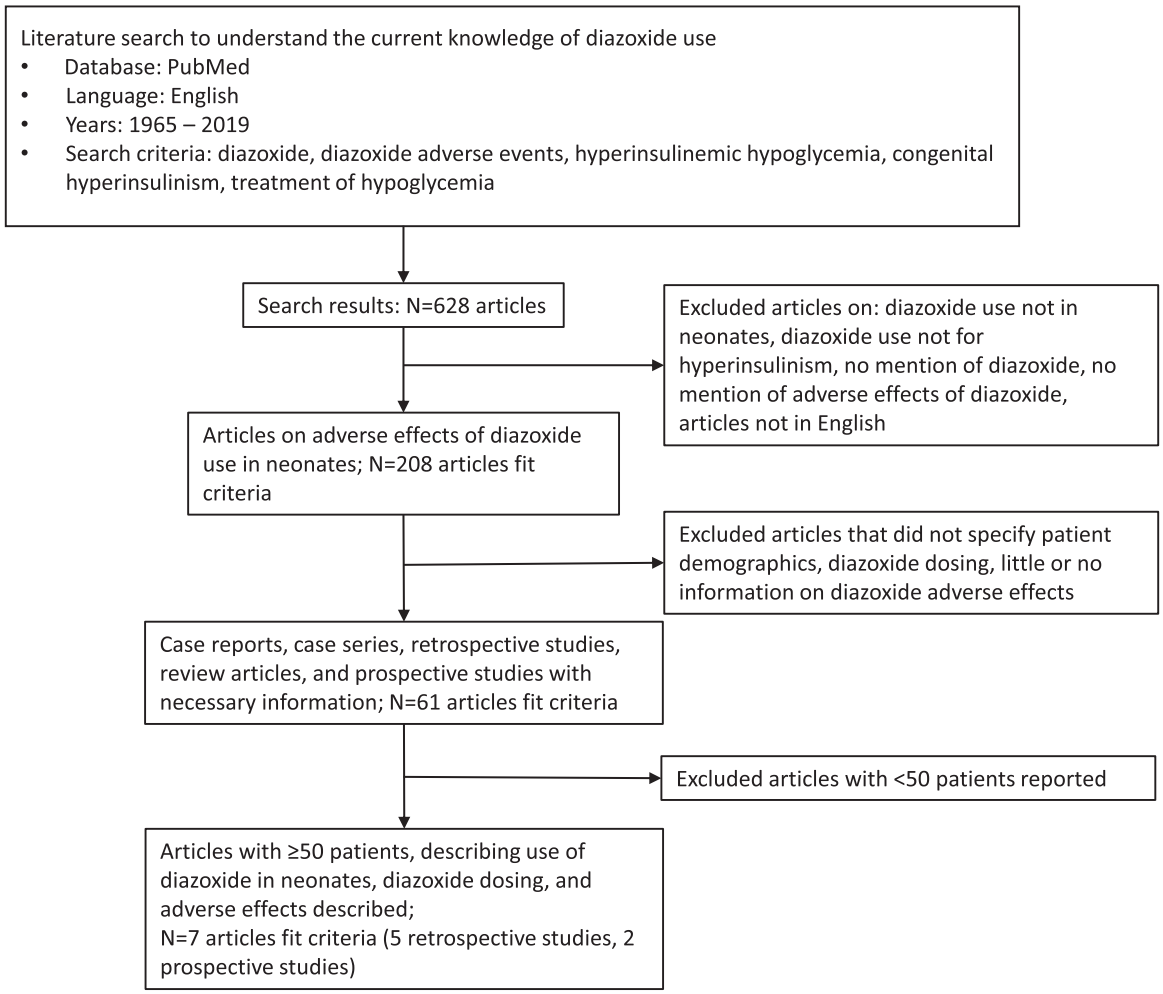

Figure 1. Literature search to understand the current knowledge of diazoxide use.

unbiased observational studies"; moderate quality is defined as "RCTs with some limitations or strong evidence from unbiased observational studies"; low quality is defined as "RCTs with serious flaws or some evidence from observational studies"; and very low quality is defined as "unsystematic clinical observations or very indirect evidence observational studies." We rated the strength of the recommendations as GRADE 1 as "we recommend" or GRADE 2 as "we suggest" (11).

Concurrently, to assess practice variability in the use of diazoxide for the treatment of HI, we conducted an online survey of pediatric endocrinologists through the PES in January 2018. Pediatric Endocrine Society members, including pediatric endocrinologists, fellows, and advanced practice practitioners, were e-mailed a short survey (estimated completion time of less than 10 minutes). The PES members include 75% of all practicing pediatric endocrinologists in the United States (45% are in academia). Members were are also from Canada and 28 other countries worldwide. Surveys sent out to the members usually have a response rate of 18% to 20%. Survey responses were collected and managed using Research Electronic Data Capture (REDCap, Vanderbilt University, Nashville, TN, USA).

Results

As shown in Table 1, our practice guidelines were graded as per the GRADE methodology based on our review of the literature. The survey response rate was 21% (319/1502 members; Table 2), which is on par with the response rate seen with surveys sent out through PES (18–20%). The results demonstrated practice heterogeneity among respondents, most of whom (88%) estimated that they were treating between 1 and 10 infants with diazoxide each year. Initial and maximum doses of diazoxide varied greatly. Additionally, 43% of respondents reported adjusting their starting dose depending on the suspected etiology of HI. Although most respondents (81%) felt knowledgeable about the potential adverse

Table 1. Practice Guidelines for Dosing and Monitoring for AEs in Infants Treated with Diazoxide

I. Indication	• Diazoxide should be strongly considered for the treatment of neonatal hypoglycemia confirmed to be secondary to persistent or prolonged perinatal stress-induced HI (**1⊕⊕⊕⊕**).
II. Dosing of diazoxide	• The recommended dose range for diazoxide is 5 to 15 mg/kg/day in 2 to 3 divided doses (**1⊕⊕⊕**). • The starting dose should be selected according to the suspected cause of HI (ie, lower doses for neonates with suspected perinatal stress-induced HI) and the risk profile of the neonate (ie, lower doses for neonates with underlying cardiac disease) (**2⊕⊕**). • The dose should be titrated to clinical effect; however, doses above 15 mg/kg/day should be avoided (**2⊕⊕**). • If transient hyperinsulinism is suspected, the dose of diazoxide may be reduced every 2 to 4 weeks if glucose levels are stable > 70mg/dL. Once off diazoxide, glucose should be monitored closely for at least 5 days and a safety fast for 15 to 18 hours should be completed to prove resolution of hyperinsulinism (**2⊕**).
III. Consultation with an endocrinologist	• Diazoxide should be prescribed in infants only after consultation with a pediatric endocrinologist to assist in the assessment of indication of use and monitoring of short- and long-term adverse effects (**1⊕**).
IV. Diazoxide use for perinatal stress-induced HI	• In infants with HI suspected to be due to perinatal stress, strong consideration should be given to avoiding the use of diazoxide until after 7 to 10 days of life if euglycemia can be maintained by other means (especially in a patient with respiratory distress, prematurity, small for gestational age, infants of diabetic mothers, and/or bronchopulmonary dysplasia) (**2⊕**).
V. Diazoxide and risk for PH	• Given the risk of PH, we suggest that cardiopulmonary health be assessed in all infants prior to initiating diazoxide. This should include a thorough cardiac examination and consideration of a baseline echocardiogram (**2⊕⊕**).
VI. Consultation with a cardiologist	• We recommend a pediatric cardiology consultation and careful consideration be given when starting diazoxide in infants with pulmonary hypoplasia, cardiomyopathy, or significant structural heart disease (**1⊕⊕**).
VII. Fluid management with diazoxide initiation	• Thiazide use: We strongly recommend that a thiazide diuretic be started concomitantly with the initiation of diazoxide due to risk of fluid retention and PH. Possibilities include chlorothiazide at 10 to 20 mg/kg/day divided once or twice daily, and hydrochlorothiazide at 1 to 2 mg/kg/day divided twice daily. Sometimes higher doses may be required (**1⊕⊕⊕**). • Fluid restriction: We suggest limiting fluid rate to less than 150 cc/kg/day and consider high glucose concentration in the intravenous fluid to avoid fluid overload in infants treated with diazoxide (**2⊕**).
VIII. Monitoring for AEs	• Infants should be monitored carefully for signs of fluid overload and/or PH (prevalence 2–3%) throughout diazoxide treatment (**1⊕⊕⊕⊕**). • Consideration should be given to performing an echocardiogram about a week after starting diazoxide, even in infants without signs of PH (**2⊕⊕⊕**). • Providers should be aware of the risks and monitor for neutropenia and thrombocytopenia (prevalence of 15%). Complete blood count with differential should be measured at baseline and 5 to 7 days after starting diazoxide and every 3 to 6 months thereafter (**1⊕⊕⊕**). • Providers should be aware of the risks and monitor for hyperuricemia. Uric acid levels should be measured at baseline and 5 to 7 days after starting diazoxide and every 6 months thereafter (**1⊕⊕**).

We graded the evidence using the framework of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group. The group rated their confidence of the evidence as high (⊕⊕⊕⊕), moderate (⊕⊕⊕), low (⊕⊕) and very low quality (⊕). High quality evidence is defined as "well-performed Randomized Controlled Trials (RCT) or very strong evidence from unbiased observational studies;" moderate quality is defined as "RCTs with some limitations or strong evidence from unbiased observational studies;" low quality is defined as "RCTs with serious flaws or some evidence from observational studies;" and very low quality is defined as "unsystematic clinical observations or very indirect evidence observational studies." We rated the strength of the recommendations as GRADE 1 stated as "we recommend" or GRADE 2 as "we suggest."

Abbreviations: AE, adverse effects; HI, hyperinsulinism; PH, pulmonary hypertension.

effects (AEs) of diazoxide, practices related to AE prevention and monitoring varied. For example, 24% of respondents reported that they always start diuretics on initiation of diazoxide, while 40% indicated that they started diuretics only if the infant had evidence of fluid retention. Similarly, 23% of respondents always obtained a baseline echocardiogram (ECHO) before starting diazoxide in an infant without a known cardiac history, while 40% reported never obtaining a baseline ECHO. Practices for monitoring electrolytes and complete blood counts of infants on diazoxide also varied.

In our comprehensive review of the literature, we found that, until recently, very little information was available other than case reports and case series. However, more

Table 2. Survey Results of Respondents From Members of the Pediatric Endocrine Society

1. Approximately how many neonates/infants do you treat with diazoxide per year?	**0**	**1–5**	**6–10**	**11–20**	**>20**
	2%	68%	20%	7%	3%
Dosing of diazoxide and chlorothiazide					
2. Typical starting dose of diazoxide in mg/kg/day?[a]	**<5**	**5–9**	**10–14**	**≥15**	
Same dose for all infants (N = 181)	3% (5)	59% (107)	34% (61)	4% (8)	
Dose for suspected stress HI (N = 138)	15% (21)	65% (90)	16% (22)	4% (5)	
Dose for suspected genetic HI (N = 138)	0% (0)	28% (39)	57% (78)	15% (21)	
3. Maximum dose of diazoxide you will try in mg/kg/day (N = 319)?	**<5**	**5–9**	**10–15**	**>15**	
	1% (2)	1% (4)	79% (252)	19% (61)	
4. When do you initiate chlorothiazide or other diuretic therapy in infants on diazoxide?[b]	**Only if evidence of fluid retention**	**If diazoxide dose exceeds a certain threshold**	**Sometimes on initiation of diazoxide, depending on clinical context**	**Always on initiation of diazoxide**	
	40%	11%	25%	24%	
Monitoring for adverse effects from diazoxide use					
	Never	**Sometimes**	**Often**	**Always**	
5. Do you obtain a baseline echocardiogram prior to starting diazoxide in infants without a known cardiac history?[c]	40%	26%	11%	23%	
6. After starting diazoxide therapy, do you obtain screening echocardiograms if the infant is otherwise stable without a known cardiac history?[c]	64%	25%	3%	8%	
7. Do you monitor electrolytes in otherwise stable infants on diazoxide?[c]	21%	41%	16%	22%	
8. Do you monitor blood counts (CBC) in otherwise stable infants on diazoxide?[c]	47%	30%	8%	15%	
Knowledge base among pediatric endocrinologist about diazoxide					
	SD	**D**	**N**	**A**	**SA**
9. I feel knowledgeable about the potential adverse effects of diazoxide.[d]	1%	4%	14%	66%	15%
10. My personal concerns about potential adverse effects of diazoxide affect my likelihood to prescribe or recommend this drug (N = 318).[d]	8%	35%	26%	26%	6%
11. Other providers' (neonatology, cardiology, pharmacy, etc.) concerns about potential adverse effects of diazoxide affect my likelihood to prescribe or recommend this drug.[d]	7%	32%	25%	30%	7%

Number of respondents on PES survey = 319, unless otherwise noted. Percentages are rounded and therefore may not total 100.

[a]A total of 56.7% (181) of respondents answered that they use the same typical starting dose for all infants, regardless of suspected type of hyperinsulinism, while 43.3% (138) of respondents answered that they use different typical starting doses for suspected stress hyperinsulinism versus genetic hyperinsulinism.

[b]The instruction was, "Please choose the response closest to your clinical practice."

[c]The instruction was, "Answer 'never' if you perform the action 0% of the time; 'sometimes' if you perform the action less than 50% of the time; 'often' if you perform the action more than 50% of the time; and '*always*' if you perform the action 100% of the time."

[d]The question asked was, "To what extent do you agree with the following?"

Abbreviations: A, agree; D, disagree; N, neutral; SA, strongly agree; SD, strongly disagree; CBC, complete blood count; HI, hyperinsulinism.

recently, several publications have shed light on the issues listed in Table 3.

Mechanism of action

Insulin secretion by the pancreatic beta cell is a tightly controlled process that is responsive to plasma glucose concentrations. When the plasma glucose concentration is above the threshold for glucose-stimulated insulin secretion (~80 mg/dL = 4.4 mmol/L), glucose uptake and metabolism in the beta cell result in an increase in the adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio, triggering the closure of ATP-sensitive potassium (K_{ATP}) channels on the plasma membrane (12). This closure, in turn, depolarizes the cell membrane and opens voltage-gated calcium channels. Calcium then enters the cell and activates insulin granules to fuse to the plasma membrane and release their contents. The beta-cell K_{ATP} channels are comprised of 4 sulfonylurea receptor 1 (SUR1) subunits and 4 inwardly rectifying potassium channel (Kir6.2) subunits (13). 4 Sulfonylurea receptor 1 and Kir6.2 subunits are encoded by the *ABCC8* and *KCNJ11* genes, respectively. The key role of the K_{ATP} channels in the regulation of glucose metabolism in humans is clearly demonstrated

Table 3. Adverse Events of Diazoxide in Infants and Children

Author	Year	Number	Male (%)	Median Age at Diazoxide Initiation (Days)	Median Diazoxide Duration	Median Diazoxide Dose (mg/kg/day)	Pulmonary HTN	Edema	Cardiac Effects	Neutropenia	Thrombocytopenia	Hyperuricemia	GI Effects	Allergic Reaction/ Anaphylaxis	Hirsutism/ Hypertrichosis
Fukutomi et al (36)	2018	384	61	4.1	239 days	6.9	2	26[a]	14[b]	4	3				
Meissner et al (45)	2003	114	52			15			1[c]					2	
Touati et al	1998	77								2					77
Martinez et al	2016	50	36			15									14
Gray et al[b]	2018	1066	62	6	6 days		24[d]						10[e]		
Herrera et al (29)[i]	2018	295	56	29	48 days	10–15	6 (2.1%)[f]	49		42	11	15			
Thornton et al (28)[j]	2019	165	58	13			8[g]			8			1		

[a]A total of 21 patients with "edema," 3 with generalized edema, and 2 with pulmonary edema.
[b]A total of 9 patients with cardiac failure, 3 with CHF, and 2 hypertrophy.
[c]Sinus tachycardia.
[d]Twelve percent required O2 and 5% required a ventilator.
[e]Necrotizing enterocolitis (9/10 patients were less than 37 weeks, 1/1 patient was at 35 weeks gestation).
[f]These infants were more likely to be premature and had 1 risk factor, such as lower gestational age, respiratory failure, or congenital heart disease. There were no sex differences in those infants who developed PH.
[g]Of these 8 patients, the average diazoxide dose was 8.5 mg/kg/day; only 3/8 patients were on hydrochlorothiazide and all 8 patients had cardiac anomaly (PFO, ASD, PDA, or VSD) on echocardiogram.
[h]Retrospective analysis of infants between 1997–2016 in 392 NICUs. Total infants were 1 249 466; 0.57% of infants were treated with diazoxide.
[i]Retrospective study of 295 infants with HI treated with diazoxide at the Children's Hospital of Philadelphia between 2003–2014.
[j]Retrospective study of 194 infants with HI of whom 165 (85.1%) were treated with diazoxide. Of those 17, serious AEs were reported with 8 cases of PH and 8cases of neutropenia.

Touati, G, et al. Long-term treatment of persistent hyperinsulinaemic hypoglycaemia of infancy with diazoxide: a retrospective review of 77 cases and analysis of efficacy-predicting criteria. *Eur J Pediatr*. 1998;157(8):628–33.1. **Martinez-Ibanez, V**, et al. Pancreatectomy extension in persistent hyperinsulinaemic hypoglycaemia: a new strategy. *Eur J Pediatr Surg*. 2002;12(4):262–266. **Gray, KD**, et al. Prevalence and safety of diazoxide in the neonatal intensive care unit. *J Perinatol* 2018;38(11):1496–1502.

Abbreviations: ASD, atrial septal defect; CHF, congestive heart failure; GI, gastrointestinal; HTN, hypertension; NICU, Neonatal Intensive Care Unit; O2, oxygen; PDA, persistent ductus arteriosus; PFO, patent foramen ovale; PH, pulmonary hypertension; VSD, ventricular septal defect.

by the effects of activating and inactivating mutations in either 1 of the 2 components of the channel, which result in neonatal diabetes and congenital HI, respectively (13).

Diazoxide acts by directly binding to the linker region of the SUR1 subunit motif of the K_{ATP} channels. This action requires the presence of Mg^{2+} and hydrolyzable nucleotides (14), forcing the channels to remain open, thereby inhibiting insulin secretion (15). Additionally, diazoxide binds to the SUR2 subunit of the K_{ATP} channel, which are expressed in the heart, smooth muscles, skeletal muscles, and brain. Diazoxide can lower blood pressure acutely when given through the intravenous route, through actions on sarcolemma cells of the arterioles, but it has little to no effect on the venous system (16). Interestingly, unlike other agents, diazoxide has both antidiuretic and antihypertensive effects (17) that are thought to be related to its actions on the vasculature rather than its direct action at the renal tubular system (18).

Pharmacokinetics and pharmacodynamics

Pruitt et al reported the pharmacokinetics and pharmacodynamics of diazoxide in 4 children in 1973 (19), and very little has been published since then. Recently, Kizu et al reported population pharmacokinetics using nonlinear mixed-effects modeling methods (20). They showed that similar steady-state concentrations were found in children dosed either 2 or 3 times a day, and that the time to steady-state concentration was 72 to 96 hours with both dosing strategies. Thus, they reported that diazoxide is equally effective with twice or three times daily dosing at an equivalent total daily dose. However, once-daily dosing caused a significant variation in levels and was not suitable. The half-life of diazoxide was 15 ± 5.3 hours (range, 5.9–27.7 hours) and there were gender differences in total body clearance of diazoxide, with females having a 39% greater total body clearance compared to males. Due to its long half-life, the response to diazoxide should be assessed after at least 5 days of therapy. Due to the small sample size, the authors could not determine if this gender difference was statistically significant. Diazoxide is excreted by the kidneys and, therefore, must be used cautiously in patients with renal impairment in whom its half-life may be increased, requiring a dose reduction, although evidence for this is currently limited (21, 22).

Diazoxide is distributed under the brand name Proglycem and can be in capsule or suspension form. The capsules are 100 mg and the suspension comes in a 50 mg/mL concentration. The 2 formulations are bioequivalent (23). A 2017 study by Behm at al compared Proglycem capsules (manufactured in Italy and distributed by Merck in Canada) with a 100 mg hard capsule called Proglicem (manufactured in France and distributed by a German supplier) and found them to be bioequivalent (24). In December 2019, the FDA approved a generic form of diazoxide suspension under the competitive generic therapy pathway. In infants and children, the suspension is used primarily since it is easily dosed and tolerated. There is no evidence available comparing the pharmacokinetics between liquid formulations and tablet/capsule formulations.

Clinical uses and efficacy

Diazoxide has limited FDA-approved indications in adults and children. In adults, it is indicated for the management of inoperable islet cell adenoma or carcinoma or extrapancreatic malignancy. In infants and children, diazoxide is indicated for the management of hypoglycemia due to HI caused by leucine sensitivity, islet cell hyperplasia, extrapancreatic malignancy, islet cell adenoma, or adenomatosis. Of note, the current labeling does not mention any of the genetic, syndromal, or perinatal

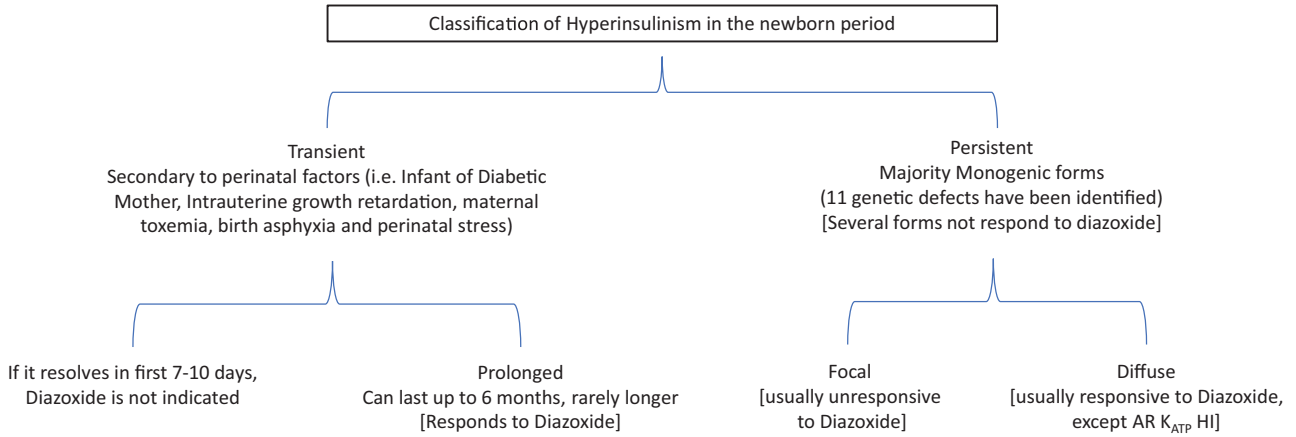

Figure 2. Classification of hyperinsulinism in the newborn period. Abbreviations: AR, autosomal recessive; HI, hyperinsulinism; KATP, Adenosine triphosphate (ATP)-sensitive potassium channel.

stress-induced causes of HI because of the changes in nomenclature that have occurred since the FDA labeling was approved. Diazoxide is considered the first-line treatment and the only FDA-approved medication for the treatment of persistent hypoglycemia caused by HI.

In this paper we classify HI into the following 2 categories: transient and persistent (Fig. 2). Transient HI refers to those causes of HI that have been shown to typically resolve by 6 months of age and persistent HI refers to those causes of HI that typically persist beyond 6 months of age and are caused by single gene mutations or associated with syndromes (eg, Beckwith-Wiedemann syndrome, Kabuki, Soto, etc.). This would also include those forms of HI in which a genetic defect has not yet been discovered. Transitional hypoglycemia is short-term hypoglycemia seen right after birth in infants, and data from the recent GLOW study indicates that for term infants (n = 67; weight = 3584 ± 349 g) a period of transitional hypoglycemia occurs, which appears to be explained by a lower threshold for glucose-stimulated insulin secretion, and it can last up to 4 days (which is longer than the 72 hours included in the PES guidelines) (3, 25). This transitional hypoglycemia is not the same as transient HI that includes short-term causes of hypoglycemia, as seen in infants of diabetic mothers and prolonged transient HI secondary to perinatal stress.

Perinatal stress HI (PSHI), a form of transient HI, is common in small-for-gestational-age babies and those exposed to perinatal stress such as intrauterine growth retardation, maternal toxemia, birth asphyxia, and peripartum stress, and it is usually responsive to diazoxide (10). Hoe et al reported that PSHI can last up to 6 months (26), but a more recent study by Raisingani et al (n = 20) showed resolution in 44.9 ± 27.9 days, although they did not do a safety fast to document the resolution of HI (27). Most babies who develop PSHI will settle spontaneously and come off intravenous dextrose treatment within 7 to 10 days of life, and only a small proportion will require long-term diazoxide treatment (1). Thornton et al reported higher rates of adverse events in infants with perinatal stress HI when compared with genetic HI (28). Herrera et al reported increased risk of pulmonary hypertension (PH) in premature babies (29). Based on the information regarding the risks of diazoxide and the fact that the majority of PSHI cases settle spontaneously, we suggest waiting to start diazoxide for 7 to 10 days in infants suspected to have PSHI, provided their glucose levels can safely be maintained > 70mg/dL with intravenous fluids in addition to feeds and as long as the glucose infusion rate required to do so is falling (GRADE 2+) (3). In those showing no sign of improvement, diazoxide may be started earlier to prevent severe hypoglycemia. We recommend that diazoxide should be prescribed in infants only after consultation with a pediatric endocrinologist to assist in the assessment of indication of use and monitoring of short- and long-term AEs (GRADE 1+).

Persistent HI is most commonly caused by monogenic forms of HI and to date 11 genetic defects have been identified. The most common form of HI, referred to as K_{ATP}-HI, is caused by gene defects in *ABCC8* and *KCNJ11*, which encode the SUR1 and Kir6.2 subunits, respectively, of the K_{ATP} channel. Recessive mutations in these genes result in the absence of K_{ATP} channels on the plasma membrane, thus causing diazoxide-unresponsive HI that may require pancreatectomy. Biallelic recessive mutations cause diffuse HI, while paternally inherited monoallelic recessive mutations in combination with a somatic loss of the maternal 11p15 chromosomal region cause focal HI, which can be cured by surgery. Dominant mutations in K_{ATP} channel genes cause variable degrees of impairment of channel activity, resulting in HI that can be either responsive or unresponsive to diazoxide. Defects that cause changes in the control of glutamate dehydrogenase (GDH) by guanosine triphosphate or by the protein–protein interaction of GDH with short chain 3-hydroxyacyl-CoA dehydrogenase cause HI and are responsive to diazoxide. Other forms of genetic HI are responsive to diazoxide, with the notable exception of activating mutations of glucokinase, which lower the threshold for glucose-stimulated insulin release (30, 31). We recommend diazoxide for the treatment of neonatal hypoglycemia confirmed to be secondary to prolonged PSHI or persistent HI (GRADE 1++++). We recommend that the dose range for diazoxide is 5 to 15 mg/kg/day in 2 or 3 divided doses (GRADE 1+++). The starting dose should be selected according to the suspected cause of HI (ie, lower doses for neonates with suspected perinatal stress-induced HI) and the risk profile of the neonate (ie, lower doses for neonates with underlying cardiac disease) (GRADE 2++). We recommend the dose be titrated to clinical effect; however, doses above 15 mg/kg/day should be avoided (GRADE 2++).

Children are generally defined as being responsive to diazoxide if they maintain plasma glucose concentrations > 70 mg/dL (3.9 mmol/L) during a prolonged fast appropriate for age (32) or if they develop ketonemia (>2 mmol/L) before the plasma glucose concentration is ≤ 50 mg/dL (2.8 mmol/L) on diazoxide (33). A dose reduction is required if hyperglycemia occurs. Hyperglycemia may occur at the higher dose range of 15 mg/kg/day when diazoxide levels reach > 100 mcg/mL (20).

Summary of AEs reported in the literature

A total of 61 publications (case reports and series) were reviewed to obtain information about reported AEs to

diazoxide in neonates, infants, and children < 18 years old who either had genetic or perinatal stress-induced HI. Some reports investigated specific AEs rather than the overall side effect profile, and some did not give specifics of the adverse events, instead stating them as "other" (Fig. 2).

Table 3 summarizes all the studies (≥ 50 subjects or more) that reported diazoxide-related AEs. These included hypertrichosis, fluid retention, pulmonary edema, hypertension, neutropenia, thrombocytopenia, hyperuricemia, and hyperglycemia. Pulmonary hypertension is the most serious side effect of diazoxide, but it is less common than other side effects. Hypertrichosis is the most commonly noted side effect of diazoxide, consistently reported at rates of 26% to 30%. The underlying pathophysiology resulting in hypertrichosis is related to the effect of diazoxide on 2 potassium-gated channels in the skin that affect hair growth, namely, SUR1/KIR6.2 and SUR2B/KIR6.1, resulting in lengthening of the anagen phase of hair growth (34, 35). The resolution of the abnormal pattern of hair growth can take up to 11 months after diazoxide has been stopped. In their cohort of 384 Japanese infants and children, Fukotomi et al reported a hypertrichosis rate of only 8.6% (36). This study was of Japanese infants and children, and ethnic differences could be postulated for the lower rates of hypertrichosis. Kizu et al did not show a significant correlation between total daily dose and hypertrichosis, though they acknowledged that their sample size was small (20). However, clinical experience suggests that hypertrichosis is worsened with doses > 10 mg/kg/day, though we acknowledge that hypertrichosis can appear at any dose. Certain features of Cantu syndrome, a genetic condition caused by gain-of-function mutations in *KCNJ8* and *ABCC9,* the genes encoding the Kir6.1 and SUR2 K_{ATP} channel subunits, resemble the nonbeta cell effects of diazoxide treatment, particularly hypertrichosis and characteristic facial changes (coarse features) (37–39). Thus, off-target effects of diazoxide through its binding to the SUR2 subunit of the K_{ATP} channel may explain these and other side effects of diazoxide, including the potential cardiac effects that are also illustrated by the Cantu Syndrome patients who may have cardiomegaly, pericardial effusion, and congestive heart failure (40).

Bone marrow suppression, or neutropenia and thrombocytopenia, have been reported in patients treated with diazoxide. Herrera et al reported a neutropenia prevalence of 15.6% with diazoxide; neutropenia resolved a few months after the cessation of treatment. Thornton et al found a neutropenia prevalence of 9.1% in those with perinatal stress HI and 2.4% in those with genetic HI (28). The different rates reported may be due to the differing definition of neutropenia, with Herrera defining this as a neutrophil count of < 1500 cells/μL and Thornton defining it as < 600 cells/μL. The pathophysiologic basis and clinical significance of neutropenia and thrombocytopenia are not well-defined in the literature. However, increased susceptibility to infections has not been noted in association with these findings (23). We recommend complete blood count (CBC) with differential should be measured at baseline and 5 to 7 days after starting diazoxide and every 3 to 6 months thereafter (GRADE 1+++).

Gastrointestinal AEs such as poor appetite and vomiting have been frequently reported as a common side effect of diazoxide. Thornton et al recently reported one case of necrotizing enterocolitis (NEC) among 66 infants treated for perinatal stress HI and no cases in 83 infants treated for genetic forms of HI (28). Gray et al reported NEC in 10/1066 (0.9%) cases following diazoxide exposure, and 9 of those infants were less than 37-weeks gestational age (1). However, the rates of NEC for all infants with hypoglycemia and all infants included in the cohort were 4755/185 832 (2.6%) and 26 064/1 249 466 (2.1%), respectively. Therefore, the rate of NEC in those treated with diazoxide was lower than in the background population (R. Greenberg, personal communication) and suggests that this is an association, rather than causation.

Hyperuricemia is another known finding associated with diazoxide therapy, with a prevalence of about 5% (30). It is thought to be a result of a decrease in uric acid excretion (23), with its clinical significance unclear. There is no evidence to date that diazoxide needs to be stopped if uric acid levels are mildly elevated. We recommend that uric acid levels be measured at baseline and 5 to 7 days after starting diazoxide therapy and every 6 months thereafter (GRADE 1++).

Cardiopulmonary AEs, including peripheral edema, pulmonary edema, pericardial effusion, and congestive heart failure, have been reported in children treated with diazoxide. Edema rates range from 5.5% to 16% (28, 36). We recommend that infants should be monitored carefully for signs of fluid overload and/or PH throughout diazoxide treatment (GRADE 1++++). Avatapalle et al reported a pericardial effusion in a patient with Down syndrome who had HI without underlying cardiac anomalies, who was started on diazoxide at 3 years of age at a dose of 10 mg/kg/day. The pericardial effusion resolved on discontinuing diazoxide and reappeared on restarting diazoxide (after a failed trial of octreotide) on an even much lower dose (4 mg/kg/day) (41). However, pericardial effusion has been reported in patients with Down syndrome without cardiac defects and without diazoxide treatment; therefore, it is difficult to draw too many conclusions from this case report (42). In a case series of 3 infants with either an *HNF1A* or *HNF4A* mutation, McGlacken-Bryne et al reported congestive heart failure in a female who was on 7.5 mg/kg/day of diazoxide (43).

Pulmonary hypertension is the most serious side effect of diazoxide, and it is hypothesized to be due to off-target effects of diazoxide on SUR2. Two recent studies have estimated the prevalence of PH to be 2.4% to 4.8% in infants treated with diazoxide (28, 29). Herrera et al suggested that patients who developed PH may have had a predisposition for developing PH at baseline. In that cohort, 14 patients (4.7%) had ECHOs with evidence of PH. Seven of those patients had evidence of PH on ECHO before initiation of diazoxide and 6/288 patients (2.1%) had echocardiographic evidence of PH after the initiation of diazoxide and within 28 days of its discontinuation (29). Thornton et al found a higher prevalence of PH in babies with perinatal stress HI (7.6%) compared with those with genetic forms of HI (1.2%) (28). Skovrlj et al reported PH in 2/29 infants treated with diazoxide, 1 of whom had a patent ductus arteriosus, an atrial septal defect, and right ventricular hypertrophy (44). The average dose of diazoxide in that retrospective review of 58 infants with HI was 7.5 mg/kg/day (44). Japanese investigators reported rates of PH at 0.5% in infants with HI (36). The study by Gray et al found PH rates of 2% in infants treated with diazoxide, compared with 3.5% in all infants with hypoglycemia and 2.8% of all infants in the cohort (R. Greenberg, personal communication). Prevalence of PH is reported as 2.4% to 4.8%, except in Japanese infants where the rate is much lower (0.5%) (36). The risk factors for PH are prematurity, small for gestational age, and underlying congenital heart disease. Thornton et al reported that PH prevalence rates were higher in infants with PSHI versus those with genetic HI (28). It is for these reasons that we suggest that a careful evaluation of cardiopulmonary health should be done prior to starting diazoxide, which should include a thorough cardiac examination and consideration of a baseline ECHO (GRADE 2++). We recommend a cardiac consult prior to starting diazoxide in patients with pulmonary hypoplasia, cardiomyopathy, or significant structural cardiac disease (GRADE 1++). We also recommend that a thiazide diuretic be started concomitantly with the initiation of diazoxide due to the risk of fluid retention and PH (GRADE 1+++) using chlorothiazide at 10 to 20 mg/kg/day divided once or twice daily, and hydrochlorothiazide at 1 to 2 mg/kg/day divided twice daily. Sometimes higher doses may be required. We also suggest limiting fluid rate to less than 150 cc/kg/day and consider high glucose concentration in the intravenous fluid to avoid fluid overload in infants treated with diazoxide (GRADE 2+).

Other rare adverse events such as macular rash have been described in 3 case reports, and anaphylaxis was reported in 2 infants in a study of 114 infants and children with genetic forms of HI treated with diazoxide (45). McGraw et al described an 8.5-month-old male born at 36 weeks who was started on diazoxide and developed ataxia at 12 months. He remained on diazoxide, as his parents refused a pancreatectomy and his symptoms improved with procyclidine. The authors reported that a wide range of extrapyramidal symptoms have been observed in 15% of adults treated with diazoxide (46).

Discussion

The recent paper by Gray et al has shown an increase in the diagnosis of neonatal hypoglycemia and a dramatic increase in the use of diazoxide over the last 10 years (1). In addition, they have shown that diazoxide is primarily used on a short-term basis and often not for an FDA-approved indication. Our survey of pediatric endocrinologists showed that, even in this group, there is significant variability in starting doses, frequency of dosing, monitoring for side effects, and concomitant therapy with diuretics. Our review of the literature revealed information regarding the pharmacokinetics of diazoxide and, more importantly, the side effect profile that is becoming clearer in recent years. Based on this literature review, the Drug and Therapeutics Committee formulated a set of best practices for the management of HI with diazoxide (Table 1), which will be useful not just for pediatric endocrinologists, but also neonatologists, cardiologists, and pediatricians caring for infants with HI. The key elements of our practice guidelines are summarized below.

Diazoxide is the first-line treatment and only FDA-approved treatment for hypoglycemia caused by persistent HI or prolonged PSHI in infants. The starting dose of diazoxide is 5 to 15 mg/kg/day, and we recommend a lower starting dose in patients with suspected PSHI or those with underlying cardiac disease. This is due to an increased risk of AEs in those with cardiac disease for PH. When doses start to increase beyond 15 mg/kg/day, there is also an increased risk of AEs; thus, we recommend avoiding larger doses. Kizu et al found that with comparable daily doses, splitting the dose 2 or 3 times daily was found to have no significant difference, but that once daily dosing led to much more variable diazoxide concentrations (20). Our recommended approach to dose titration is to watch for clinical effect by monitoring plasma glucose levels. Due to its long half-life, it can take up to 5 days to reach steady-state (20, 21). The dose should be increased by 2.5 to 5 mg/kg/day if the patient continues to have hypoglycemia after 3 to 5 days. Although there is limited evidence on dosing strategies, the expert consensus of our group is that the dose should be reduced if hyperglycemia occurs (GRADE 2+). If PSHI is suspected, the dose of diazoxide may be reduced every 2 to 4 weeks if glucose levels are stable > 70mg/dL. Once off diazoxide, glucose should be monitored closely for at least 5 days, and a safety fast for 15 to 18 hours should be completed to prove resolution. After the FDA warning of

2015 regarding the risk of PH developing in infants treated with diazoxide (available at http: //www.fda. gov/Safety/ MedWatch/ Safety Information/ Safety Alerts for Human MedicalProducts/ucm455125.htm), a pediatric cardiology group (47) recommended a baseline ECHO (in all infants) and 5 days after starting diazoxide. Recent publications by Herrera (29) and Thornton (28) provided the incidence of PH and the precipitating risk factors. Our Drugs and Therapeutics (D&T) group reached a consensus that a cardiology consultation, especially in high risk infants (eg, prematurity, small for gestational age, and underlying congenital heart disease), is prudent and that consideration should be given for a baseline ECHO and a repeat ECHO once the dose is established. Due to the risk of fluid retention and pulmonary edema, we have recommended concurrent use of a diuretic with the initiation of diazoxide, especially for those with higher risk factors (eg, underlying heart or lung disease). Use of thiazide diuretics can help reduce the risk of fluid overload and possibly PH.

There were several limitations to this study. Our goals were to review the literature, survey current practices of pediatric endocrinologists' use, and to put forth recommendations for the use of diazoxide in neonates with HI. To assess the current practices regarding the use of diazoxide, a survey was sent to the members of the PES. While this group encompasses a great proportion of pediatric endocrinologists, it may not have reached everyone who prescribes diazoxide in neonates. Furthermore, another limitation is that the response rate to the survey was only 21%, (although the average response to surveys in the PES is 18–21%). Most of the respondents only prescribed it for it up to 10 patients per year, perhaps indicating the rarity of the condition. Despite these factors it was clear that practice patterns varied greatly, and this indicated to us that some guidance was needed.

Conclusions

Diazoxide should be considered for the treatment of persistent neonatal hypoglycemia confirmed to be secondary to excess insulin secretion. In neonates with perinatal stress HI, therapy should be considered when the infant is not showing evidence of resolution by 7 to 10 days of life. Dosing of diazoxide should be titrated to clinical effect and based on the cause (genetic vs perinatal stress), using extra caution in high-risk neonates (eg, underlying heart disease, respiratory distress, and small for gestational age). Assessment for cardiovascular health is recommended, which may include a baseline ECHO. In those showing signs of PH, a follow-up ECHO is indicated. Also, monitoring for neutropenia and hyperuricemia is suggested. Finally, starting a diuretic at the time of commencing diazoxide is strongly recommended, especially in neonates on high intravenous glucose infusion rates. Infants with certain forms of HI have an excellent therapeutic response to diazoxide, and we hope our review has highlighted the importance of being cognizant of the AEs and complications associated with diazoxide use.

Additional Information

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